

Review Article

The multidimensional biology of SKP2: mechanisms, pathologies, and emerging therapeutic frontiers

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ABSTRACT

S phase kinase-associated protein 2 (SKP2), the rate-limiting substrate receptor of the SKP1-Cullin1-F-box (SCF) E3 ubiquitin ligase complex, is considered a canonical gatekeeper of cell cycle progression. However, accumulating evidence indicates that SKP2 functions as a multifaceted signaling hub that orchestrates metabolic reprogramming, the DNA damage response, stem cell maintenance, and synaptic plasticity. Dysregulation of these processes contributes to the pathogenesis of many types of human diseases, including cancer. This review provides a comprehensive overview of the diverse biological roles of SKP2, beginning with detailed insights into the assembly and substrate-recognition mechanisms of the Cullin1-SKP2-CKS1 protein complex. Moreover, we explore the functional dichotomy of SKP2, expanding its classic role in K48-linked proteasomal degradation to include noncanonical roles in K63-linked signaling activation. Furthermore, we elucidate the pathogenic implications of SKP2 in malignancies such as castration-resistant prostate cancer (CRPC) and triple-negative breast cancer (TNBC), as well as neurodegenerative conditions, including Alzheimer's disease. More importantly, we evaluate therapeutic approaches targeting SKP2, highlighting the shift from first-generation protein-protein interaction (PPI) inhibitors to next-generation degraders, including the novel induced-proximity degrader SKPer1 and emerging PROTACs. Finally, to bridge the gap to clinical translation, we discuss the remaining druggability challenges and future directions for pharmacological optimization.

Keywords: SKP2, E3 Ubiquitin Ligase, Metabolic Reprogramming, Tumorigenesis, Oncogene, Cell Cycle, PROTACs

1. INTRODUCTION

The precise coordination of cellular proliferation, metabolism, stress adaptation, and differentiation depends on a series of highly dynamic protein degradation networks and signal transduction pathways [1, 2]. Among these, the ubiquitin-proteasome system (UPS) is foundational in governing cellular homeostasis [3]. Within the UPS, the SKP1-Cullin1-F-box (SCF) complex has indispensable roles in cell fate determination and key cellular processes, including the cell cycle, cell migration, and cell death [4]. S-phase Kinase-associated Protein 2 (SKP2), the rate-limiting substrate receptor (SR) of the SCF-SKP2 E3 ligase complex, has historically

been defined by its canonical role as the “gatekeeper” of the G1/S transition, by recognizing and targeting various cell cycle inhibitors, such as p27^{Kip1} and p21^{Cip1}, for ubiquitination and subsequent proteasomal destruction [5, 6].

However, a growing body of evidence over the past decade has markedly expanded the biological repertoire of SKP2 to extend beyond its classic classification in cell-cycle regulation. SKP2 has been redefined as a multifaceted signaling hub that governs diverse processes, including metabolic reprogramming [7, 8], the DNA damage response (DDR) [9], stem cell maintenance [10, 11], and autophagy [12]. This shift in understanding was underpinned by the discovery of a dual

mechanism, wherein SKP2 mediates canonical protein turnover, largely via catalyzing K48-linked ubiquitin chains, and concurrently orchestrates non-proteolytic signal activation through K63-linked poly-ubiquitin chains, through which it directly engages the Akt and mTOR signaling pathways, and consequently influences tumorigenesis [7, 13, 14]. Furthermore, recent studies have indicated that SKP2 regulates autophagy by modulating CARM1 signaling [15, 16] and epigenetic regulation by promoting JARID1B degradation [17]. This “dual-track” capability enables SKP2 to integrate multidimensional biological signals that extend far beyond simple protein elimination.

The functional versatility of SKP2 is mirrored in its pathological importance. Its dysregulation, a common feature across a spectrum of solid and hematological malignancies, correlates with tumor aggressiveness, poor survival outcomes, and therapeutic resistance [18]. For example, in castration-resistant prostate cancer (CRPC), SKP2 stabilizes Twist via ubiquitination, thereby augmenting stemness and chemoresistance [19]. However, in triple-negative breast cancer (TNBC), it mediates Akt ubiquitination and rebound activation, thereby driving intrinsic resistance to PI3K inhibitors [20]. Beyond oncology, its physiological roles in neurodegenerative conditions, such as Alzheimer's disease (AD), are emerging, particularly regarding synaptic plasticity and neuronal metabolic homeostasis [21, 22]. These cross-system findings therefore establish SKP2 as a central node in disease pathogenesis. Concurrently, the development of SKP2-targeted therapeutics is rapidly advancing. Strategies have shifted from the first-generation protein-protein interaction (PPI) inhibitors—designed to sterically block the SKP2–p27, SKP1, or CKS1 interface [23]—to next-generation proteolysis-targeting chimeras (PROTACs) [24] and the novel induced-proximity degrader SKPer1 [25], which recruits E3 ligases and subsequently induces specific destruction of the SKP2 oncoprotein itself. Consequently, SKP2 is transitioning from a basic research focus to a frontline drug target for precision medicine.

This review systematically summarizes the molecular mechanics of SKP2, dissecting its hierarchical roles in cellular homeostasis and pathology. Moreover, we provide a comprehensive assessment of current therapeutic strategies and their translational potential. By integrating current advances, we aim to construct a comprehensive, forward-looking atlas of SKP2 biology, thereby laying the theoretical groundwork for future SKP2-directed interventions for various types of human disorders, including cancer.

2. THE UBIQUITIN-PROTEASOME SYSTEM

The maintenance of proteostasis is fundamental to eukaryotic viability [26]. Notably, protein turnover is governed primarily by two distinct machineries: the lysosomal-autophagy pathway [27] and the UPS [28].

Whereas autophagy primarily mediates bulk clearance of organelles and long-lived protein aggregates, the UPS precisely executes the spatiotemporal degradation of specific regulatory proteins marked for removal after induction of certain upstream physiological cues [26, 29]. The discovery of this ATP-dependent, non-lysosomal degradation pathway in the late 1970s earned Avram Herskho, Aaron Ciechanover, and Irwin Rose the Nobel Prize in Chemistry in 2004 [30]. Historically dismissed as the cell's “waste disposal unit,” the UPS is now recognized as a sophisticated command center [31]. By selectively eliminating key regulators, such as cell cycle mediators and transcription factors, it orchestrates critical decisions regarding cell fate and function [18]. Consequently, aberrancy in this process often contributes to various human pathological conditions, including cancer and neurodegenerative diseases [1, 32].

2.1 Biochemistry of the E1-E2-E3 enzymatic cascade

Ubiquitination is a tightly regulated enzymatic process that culminates in the covalent attachment of the evolutionarily conserved 76-amino acid ubiquitin moiety to a lysine residue on a target protein [31]. This process proceeds through three sequential stages [33]. First, in the **activation step (E1)**, through an ATP-dependent reaction, the ubiquitin-activating enzyme (E1) forms a high-energy thioester bond with the ubiquitin molecule. Second, in the **conjugation step (E2)**, the activated ubiquitin molecule is transferred to the active site cysteine of a ubiquitin-conjugating enzyme (E2). Finally, in the **ligation step (E3)**, the ubiquitin ligase (E3) acts as a specific recognition module facilitating the formation of an isopeptide bond through transfer of ubiquitin from E2 to the target protein [34]. Substrates marked with poly-ubiquitin chains are trafficked to the 26S proteasome for destruction [35]. This approximately 2.5 MDa macromolecular machine comprises two functional sub-complexes: the **19S regulatory particle (RP)** and **20S core particle (CP)**. The RP, functioning as the “lid,” is responsible for recognizing ubiquitinated substrates, deubiquitinating them via intrinsic deubiquitinases (DUBs) such as Rpn11 [36], and harnessing ATP hydrolysis to unfold and translocate the protein into the core. The CP forms a central cylindrical chamber that houses the proteolytic active sites. Recent cryo-EM studies have provided atomic-resolution insights into the gate-opening mechanisms that control substrate entry [37] (Figure 1).

2.2 Classification of E3 ligases

The >600 E3 ubiquitin ligases encoded in the human genome are the primary determinants of specificity within the UPS. They are further categorized into three major superfamilies, according to domain architecture and catalytic mechanisms: Really Interesting New Gene (RING), Homologous to E6-AP Carboxyl Terminus (HECT), and RING-Between-RING (RBR) [4].

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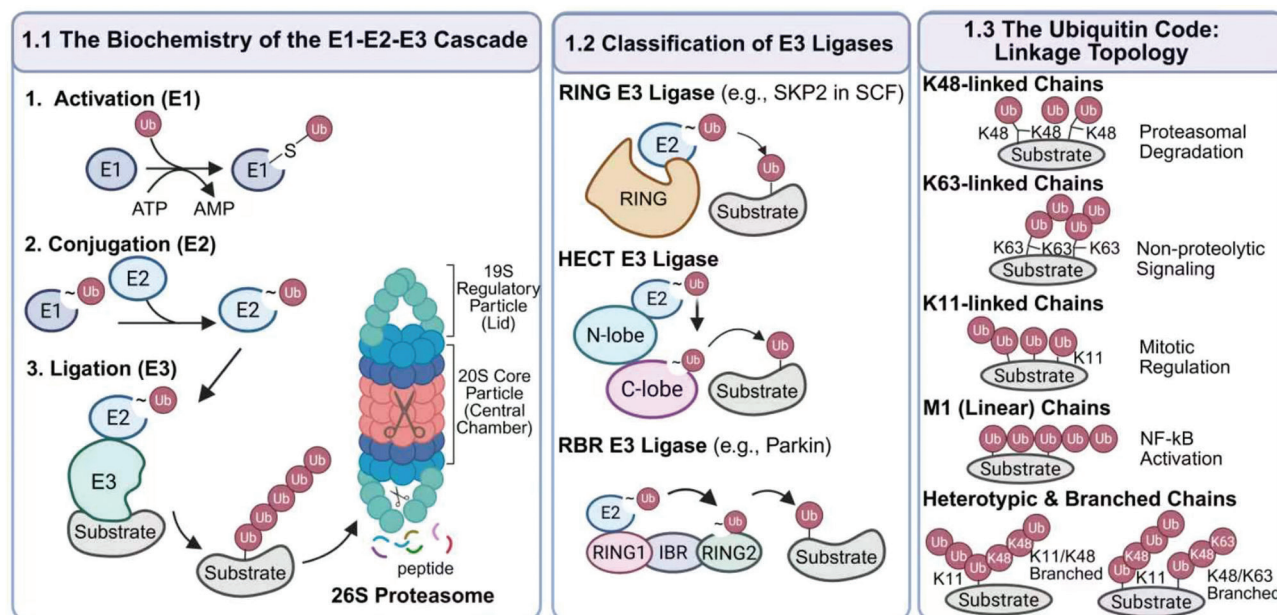


Figure 1 | The biochemistry, classification, and coding of the ubiquitin-proteasome system (UPS).

(1.1) Biochemistry of the E1-E2-E3 Cascade: Ubiquitin is sequentially activated and transferred to a substrate via an enzymatic cascade involving E1 (activating), E2 (conjugating), and E3 (ligase) enzymes. The resulting polyubiquitinated protein substrate is subsequently recognized and degraded into peptides by the 26S proteasome, comprising the 19S regulatory particle (Lid) and the 20S core particle (Central Chamber). **(1.2)** Classification of E3 Ubiquitin Ligases: E3 ligases are categorized into three major classes according to their catalytic domains and transfer mechanisms: RING E3s (e.g., SCF-SKP2) function as scaffolds facilitating direct ubiquitin transfer from E2 to substrate; HECT E3s form an obligate E3~Ub thioester intermediate; and RBR E3s (e.g., Parkin) use a hybrid mechanism combining features of both. **(1.3)** The Ubiquitin Code (Linkage Topology): Distinct ubiquitin chain topologies dictate specific substrate fates. K48-linked chains mediate proteasomal degradation, whereas K63-linked chains regulate non-proteolytic signaling. K11-linked chains largely control mitotic progression, and linear (M1) chains are essential for NF-κB activation. Furthermore, heterotypic and branched chains provide additional layers of regulatory complexity. Figure created with BioRender.com.

The RING superfamily constitutes the largest class of E3s, which function mechanistically as molecular scaffolds rather than direct catalysts [38]. As such, they do not form a covalent intermediate with the ubiquitin molecule. Instead, they bridge the E2~Ub thioester complex and the downstream protein substrate, and allosterically activate the E2, thereby facilitating direct ubiquitin transfer to the protein substrate [39]. SKP2 exemplifies this mechanism. As the substrate recognition subunit of the SCF E3 ligase complex, and a prototypical Cullin-RING ligase (CRL) [40, 41], SKP2 relies on the RING domain of the associated RBX1 subunit to recruit the E2 enzyme, thereby mediating the polyubiquitination of multiple downstream protein substrates, including p27 and p57 [42].

In contrast to the RING ligases, which have scaffolding roles, the HECT superfamily members directly catalyze ubiquitin transfer to the downstream protein substrate [43]. This mechanism involves an obligate intermediate step: ubiquitin is first transferred from the E2 to a conserved cysteine residue within the HECT domain of the E3 ligase, thereby forming a covalent E3~Ub thioester bond [44]. Ubiquitin is subsequently handed over to the protein substrate in a “relay” fashion [44, 45]. Although SKP2 does not belong to this class, understanding the

mechanistic action of HECT E3 ligase provides essential context for appreciating the functional diversity of the E3 ligase repertoire.

The third class, the RBR superfamily, uses a unique hybrid mechanism combining features of both RING and HECT enzymes. Structurally defined by a RING1-IBR-RING2 motif, RBRs use the RING1 domain to recruit the E2~Ub complex, similarly to RING E3s [46]. They then transfer the ubiquitin molecule to a catalytic cysteine present in the RING2 domain, thus forming a thioester intermediate, as in HECT E3s, before delivery to the protein substrate [47]. The characterization of Parkin as a representative RBR ligase has markedly expanded understanding of the complexity inherent in the ubiquitination machinery [48] and how misregulation of this process can lead to human pathological conditions such as Parkinson’s disease [47, 49] (Figure 1).

2.3 The ubiquitin code: linkage topology determines biological fate

Ubiquitination is not a monolithic signal but a sophisticated molecular language. The ubiquitin moiety contains seven internal lysine residues (K6, K11, K27, K29, K33, K48, and K63) alongside an N-terminal methionine

Table 1 | Functional and structural diversity of ubiquitin linkage types that compose “the ubiquitin code” governing key cellular processes.

Linkage type	Structural conformation	Biological consequence	Archetypal signaling axis
K48-linked	Closed, compact	Canonical proteasomal turnover	Cell cycle (e.g., SCF-p27)
K63-linked	Open, extended	Non-proteolytic signaling	DDR; NF-κB activation
K11-linked	Compact	Mitotic quality control; ER-associated degradation (ERAD)	APC/C-mediated cyclins
M1-linked (linear)	Head-to-tail	Inflammatory signaling	LUBAC-mediated TNFα
Mono-Ub	Single Ub moiety	Trafficking; epigenetics	Receptor endocytosis; histone modification (e.g., H2B)
Branched (e.g., K11/K48)	Heterotypic	High-priority degradation	Rapid clearance of aggregates

(M1), all of which can serve as acceptor sites for polyubiquitin chain elongation [50]. The specific topology of these linkages dictates the ultimate destiny of the downstream protein substrate [50, 51] (Table 1, Figure 1).

2.3.1 Homotypic chains. Homotypic ubiquitin chains form through specific lysine residues on ubiquitin and have distinct functions in regulating protein fate and signaling pathways. **K48-linked chains** are the canonical signal for proteasomal targeting. Substrates marked with K48 chains are recognized and degraded by the 26S proteasome [52]. A classic example is the SKP2-mediated turnover of p27^{Kip1}, which relies primarily on the assembly of K48-linked polyubiquitin chains [5, 6]. In contrast, **K63-linked chains** generally mediate non-proteolytic functions and serve as molecular scaffolds that assemble signal transduction complexes involved in DNA repair and protein trafficking [53, 54]. SKP2 uses this topology to regulate key cell-fate regulators such as Akt. By assembling K63-linked chains, SKP2 promotes recruitment of Akt to the plasma membrane, thereby triggering its activation and influencing tumorigenesis [7]. **K11-linked chains** are particularly critical for mitotic regulation; they are assembled predominantly by the APC/C E3 ligase complex and tag cell-cycle drivers, such as SKP2, Cyclin A, and PLK, for timely degradation [55]. **M1 (linear) chains**, synthesized exclusively by the LUBAC E3 ligase complex, are integral to the activation of the NF-κB inflammatory signaling pathway [56]. **Atypical chains (K27, K29, and K33)**, although relatively less understood, are increasingly recognized for their key regulatory roles in innate immunity and epigenetic regulation [57]. For example, K27-linked polyubiquitination of PTEN has recently been reported to dampen its tumor suppressor function to contribute to prostate tumorigenesis [58].

2.3.2 Heterotypic and branched chains. Recent research has illuminated the existence of complex branched ubiquitin chains. This current frontier in ubiquitin biology awaits in-depth investigation to understand the physiological roles of these ubiquitin chains in governing

various cellular processes [59]. **K11/K48 branched chains**, synthesized primarily by the APC/C complex during mitosis, function as “high-priority” degradation signals that result in markedly enhanced substrate recognition and degradation efficiency by the proteasome, in contrast to their homotypic K48 or K11 counterparts [60]. This mechanism ensures the rapid and irreversible clearance of key regulatory proteins essential for cell cycle progression [61]. Moreover, **K48/K63 branched chains**, which substantially accumulate during NF-κB activation or under proteasome inhibition, might serve as molecular switches for signal transduction cascades or as exceptionally potent degradation signals [62, 63].

The versatility of the ubiquitin code is counterbalanced by **DUBs**, which cleave specific linkages and consequently reverse the signaling cascade. The approximately 100 DUBs in the human genome, together with the approximately 600 E3 ligases, form the dynamic and reversible network of the ubiquitination coding system and govern various cellular processes [64]. For example, USP10 counteracts SKP2 auto-ubiquitination, thereby adding an additional layer of regulation [65].

2.4 Molecular determinants of substrate recruitment by SCF-SKP2

A detailed understanding of polyubiquitin chain linkages within the ubiquitin code is indispensable for decoding SKP2 biology. SKP2 has dual functions as an executioner via K48-linked chains and a signal activator via K63-linked chains [66]. This selectivity is likely to be influenced by context, depending on the availability of specific cofactors or the post-translational status of the substrate across different tissues or cell types.

As a RING-type E3 ubiquitin ligase, the SCF-SKP2 complex does not itself catalyze ubiquitin transfer but instead functions primarily as a molecular scaffold that positions a charged E2 enzyme in proximity to the protein substrate [67]. In this system, the linkage topology of the resulting polyubiquitin chain is determined principally by the recruited E2, because different E2s inherently favor distinct lysine linkages during ubiquitin transfer [68]. For example, SCF complexes typically

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engage CDC34 (also known as UBE2R1), an E2 with structural features that promote assembly of K48-linked polyubiquitin chains, the canonical signal for proteasomal substrate degradation [4]. The CDC34–SCF partnership is among the best characterized in directing degradative ubiquitination.

Beyond degradative signaling, SCF–SKP2 participates in non-proteolytic ubiquitination by cooperating with linkage-specialized E2s. The heterodimeric E2 UBE2N (formerly UBC13) together with its non-catalytic partner UBE2V1, efficiently catalyzes formation of K63-linked chains, which are typically associated with regulatory outcomes such as protein trafficking or signal activation rather than degradation [69]. K63-linked ubiquitination mediated by SCF–SKP2 has been demonstrated for substrates such as Akt, and found to enhance membrane localization and kinase activation without triggering proteasomal degradation [7].

Therefore, the functional diversity of SKP2-dependent ubiquitination, whether directing substrates toward degradation or alternative signaling fates, depends critically on which E2 enzyme is engaged by the SCF core complex. Consequently, E2 selection is important in determining the biological outcome of SKP2-mediated ubiquitination, thus expanding the conceptual framework beyond a purely degradative E3 role to encompass regulatory ubiquitin signaling.

3. THE CULLIN-RING LIGASE SUPERFAMILY

3.1 Overview

Among eukaryotic E3 ubiquitin ligases, the CRL superfamily is the most extensive and structurally intricate, and it accounts for approximately 20% of all cellular ubiquitination events [4]. The hallmark of CRL biology is an elegant “modular” assembly strategy. By using the Cullin protein as a rigid architectural scaffold, these E3 ligase complexes use specific adaptor proteins to recruit a vast library of SRs [39]. This combinatorial design endows CRLs with the plasticity to regulate biological processes as diverse as cell cycle progression, DDR, hypoxic responses, and signal transduction pathways [70].

3.2 Core architecture and classification

Regardless of their specific composition, all CRL complexes adhere to a unified topological blueprint characterized by four distinct modules [4]. At the core, the **scaffold protein** Cullin serves as the structural backbone for the E3 ligase complex. The N-terminal domain consists of a repeating helical bundle, the Cullin repeat (CR), that dictates the curvature of the multi-subunit protein complex [71]. In contrast, the C-terminus docks the catalytic core. The **catalytic core** comprises a RING domain protein (typically RBX1 or RBX2). This module recruits the E2 ubiquitin-conjugating enzyme. The RBX1–Cullin 1 (CUL1) interface is critical for positioning the E2–Ub thioester for catalysis of the ubiquitin transfer [28]. In

contrast, the **adaptor protein** acts as a physical bridge linking the rigid Cullin scaffold to the variable SR. Finally, the **SR** confers target specificity by recognizing and binding specific degron motifs on substrate proteins. SKP2 is a well-characterized example of an SR within the CRL1 complex [28].

3.3 The Cullin-RING ligase superfamily: structural diversity and functional specialization

The structural modularity of the CRL superfamily represents a pinnacle of evolutionary engineering. By using distinct Cullin scaffolds as architectural backbones, cells generate a diverse library of E3 ubiquitin ligases, each tailored to specific cellular compartments and signaling contexts. Below, we dissect the molecular architecture and distinct regulatory roles of the major CRL subfamilies (Table 2, Figure 2).

3.3.1 CRL1 (SCF complex): the paradigm of phospho-dependent ubiquitination. The CRL1 subfamily, ubiquitously known as the SCF complex, is the structural archetype for the entire superfamily [72] and is based on the CUL1 scaffold. The adaptor protein SKP1 binds the N-terminus of CUL1 and recruits one of approximately 69 human F-box proteins [73], which are structurally categorized into FBXW (WD40), FBXL (leucine-rich repeat [LRR]), and FBXO (other) subfamilies, largely according to their substrate-binding domains [74]. F-box proteins function as the variable SRs. A defining feature of SCF ligases is their reliance on phosphodegrons: substrates must typically be phosphorylated to be recognized by the F-box protein (e.g., F-box domains WD40 or LRR) [75]. Functionally, F-box proteins play diverse roles: the SCF–SKP2 E3 ligase complex acts as the master regulator of S-phase entry, partly via promoting p27 degradation [5, 6], whereas SCF– β -TrCP governs the NF- κ B and Wnt signaling pathways by targeting I κ B α and β -catenin for ubiquitination and subsequent degradation, respectively [18]. Recent structural work has revealed how β -TrCP recognizes the diphosphorylated degron of β -catenin with high affinity [76]. In contrast, FBW7 exerts its tumor suppressor role primarily by targeting various oncoproteins, including c-Myc, c-Jun, and MCL-1, for ubiquitination-mediated proteasomal degradation [40, 77, 78].

3.3.2 CRL2: the oxygen-sensing machinery. The CRL2 subfamily is defined by its use of the CUL2 scaffold and is architecturally distinguished by the Elongin B/C complex as its adaptor module. This adaptor recruits SRs containing a VHL-box motif (a domain structurally homologous to the SOCS box) [79, 80]. The most prominent member is CRL2^{VHL}, wherein the Von Hippel-Lindau (VHL) tumor suppressor acts as the SR. This E3 ligase complex functions as a cellular oxygen sensor. Under normoxic conditions, it targets hydroxylated HIF-1 α for proteasomal degradation [81]. Loss of VHL leads to constitutive

Table 2 | Modular architecture and physiological roles of Cullin-RING ligase (CRL) subfamilies.

CRL subfamily	Scaffold	Adaptor module	Substrate receptor (SR) motif	Archetypal complexes and physiological roles
CRL1 (SCF)	CUL1	SKP1	F-box (~69 members)	SCF ^{SKP2} : cell cycle progression SCF ^{β-TrCP} : NF-κB signaling
CRL2	CUL2	Elongin B/C	VHL-box	CRL2 ^{VHL} : hypoxic response (HIF-1α degradation)
CRL3	CUL3	BTB domain acts as adaptor	BTB (POZ)	CRL3 ^{Keap1} : oxidative stress response (Nrf2 regulation)
CRL4A/B	CUL4A/B	DDB1	DCAF (e.g., WD40 repeats)	CRL4 ^{CRBN} : immunomodulation; primary target of thalidomide
CRL5	CUL5	Elongin B/C	SOCS-box	CRL5 ^{ASB9} : antiviral defense; cytokine signaling regulation
CRL7	CUL7	SKP1	F-box (specifically Fbxw8)	CRL7 ^{Fbxw8} : placental development; Golgi apparatus maintenance
CRL9	CUL9 (PARC)	Atypical/integrated (contains internal RING domain)	Direct binding (lacks canonical SR motif)	CRL9 ^{PARC} : p53 regulation (cytoplasmic sequestration and turnover)

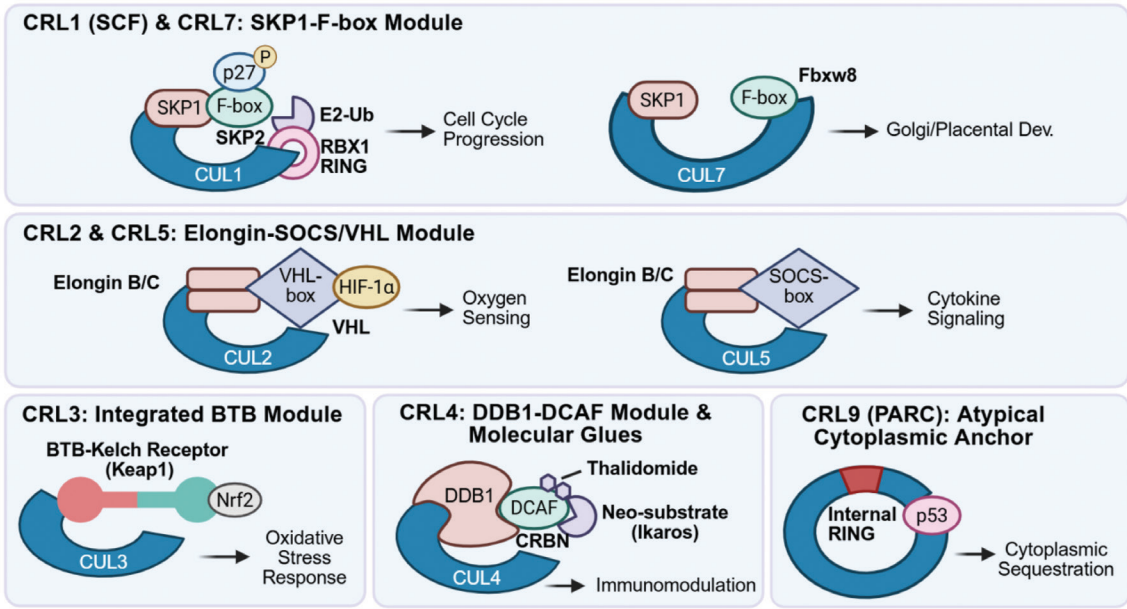


Figure 2 | Structural diversity and modular assembly of Cullin-RING E3 ubiquitin ligases (CRLs).

Structural organization of the CRL superfamily. The schematic model highlights how different Cullin proteins (blue) act as scaffolds to build specific E3 ligase complexes. **CRL1 and CRL7 (SKP1-F-box Module):** CRL1 (also known as the SCF complex) is the family archetype, comprising the CUL1 scaffold, SKP1 adaptor, and an F-box substrate receptor (e.g., SKP2) that regulates the cell cycle. CRL7 is involved in Golgi maintenance and placental development. **CRL2 and CRL5 (Elongin-SOCS/VHL Module):** These complexes share Elongin B/C as adaptors. CRL2 typically uses VHL for oxygen sensing (via targeting HIF-1α), whereas CRL5 uses SOCS-box proteins to regulate cytokine signaling. **CRL3 (Integrated BTB Module):** CUL3 uniquely uses BTB-domain proteins (e.g., Keap1), which function as both adaptors and substrate receptors, in mediating the Nrf2 oxidative stress response. **CRL4 (DDB1-DCAF Module and Molecular Glues):** Composed of CUL4 and DDB1. The diagram highlights how immunomodulatory drugs (e.g., thalidomide) act as “molecular glues,” by altering the specificity of the substrate receptor CRBN to recruit and degrade neosubstrates (e.g., Ikaros). **CRL9 (Atypical Structure):** CUL9 (PARC), a massive cytoplasmic protein with an internal RING domain, primarily sequesters p53 in the cytoplasm. Figure created with [BioRender.com](#).

HIF-1α accumulation, thus driving the angiogenic phenotype characteristic of clear cell renal cell carcinoma (ccRCC) [82].

3.3.3 CRL3: the “two-in-one” integrated system. CRL3 complexes, assembled on the CUL3 scaffold, exhibit a unique topological deviation from other CRLs. CRL3

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lacks a separate adaptor protein. Instead, it uses proteins containing a Broad-Complex, Tramtrack, and Bric-a-brac (BTB) domain [83]. The BTB domain has dual functions: it directly binds the CUL3 scaffold, and simultaneously serves as the dimerization interface and SR [84, 85]. The CRL3^{Keap1} complex is central to the oxidative stress response. Keap1 (a BTB-Kelch protein) constitutively targets the transcription factor Nrf2 for degradation [86]. Notably, under oxidative stress, cysteine modification of Keap1 disrupts this interaction, thereby allowing Nrf2 to accumulate and facilitate transcription of antioxidant genes [87]. In contrast, CRL3^{SPOP} targets various oncogenic substrates, including AR [88], ERG [89], and BRD4 [90], for protein degradation. Loss-of-function mutations in SPOP are frequently observed in prostate cancer [91].

3.3.4 CRL4: genome stability and immunomodulation. The CRL4 subfamily comprises CRL4A and CRL4B, which use the highly homologous CUL4A and CUL4B scaffolds, respectively [92]. These complexes rely on the large adaptor protein Damage-Specific DNA Binding Protein 1 (DDB1). DDB1 recruits a large family of SRs known as DDB1- and CUL4-associated factors (DCAFs), which typically contain WD40 repeats [93]. The DDB1 structure's distinct triple-beta-propeller (BPA-BPC) architecture provides a large surface area for diverse protein interactions [94]. This family is critical for DNA repair and replication. Notably, CRL4^{CRBN}, which incorporates the DCAF protein Cereblon (CRBN), has attracted considerable clinical attention as the primary target of immunomodulatory drugs such as thalidomide and lenalidomide [95]. These drugs act as "molecular glues," by altering the substrate specificity of CRBN to target neosubstrates (e.g., Ikaros or Aiolos) for degradation [96, 97]. Crystallographic data have demonstrated that thalidomide binds a hydrophobic pocket on the surface of CRBN, thereby creating a "neo-interface" that enables the recruitment of the transcription factor Ikaros (IKZF1), which does not normally bind CRBN [94, 98].

3.3.5 CRL5: cytokine signaling and viral defense. Because CRL5 complexes use the CUL5 scaffold and share the Elongin B/C adaptor module with CRL2, structural similarities exist between CRL2 and CRL5 E3 ligases [99]. The distinguishing feature of CRL5 is the recruitment of SRs containing a Suppressors of Cytokine Signaling (SOCS)-box motif [79]. This family is critical in the negative feedback regulation of cytokine signaling (e.g., JAK/STAT pathway) [100]. For example, CRL5^{ASB9} regulates creatine kinase levels. Furthermore, CRL5 is a frequent target for viral hijacking; the HIV-1 protein Vif hijacks CRL5, thus leading to degradation of the host antiviral factor APOBEC3G [101]. Structural analysis of the ASB9-CKB complex has revealed how the E3 ligase induces conformational strain and consequently promotes ubiquitination [102]. Additionally, the HIV-1 Vif

protein mimics the SOCS-box motif, thereby hijacking CRL5, in a prime example of "molecular mimicry" in pathogenesis [103].

3.3.6 CRL7: the gigantic scaffold. CRL7 is assembled on CUL7, a massive scaffold protein (>185 kDa) that is substantially larger than other Cullins. Similarly to CRL1, CUL7 binds the adaptor SKP1 [104]. However, its SR repertoire appears to be highly restricted: FBW8 is the primary and obligatory partner essential for complex stability [105]. CUL7's large size enables it to potentially scaffold multiple signaling components simultaneously, thereby functioning as a signaling hub rather than merely a degradation machine [106]. CRL7 is indispensable for placental development and the maintenance of Golgi apparatus morphology [106]. Mutations in CUL7 are associated with 3M syndrome, a disorder characterized by severe pre- and post-natal growth retardation [107].

3.3.7 CRL9 (PARC): the atypical cytoplasmic anchor. CRL9, also known as p53-associated Parkin-like cytoplasmic protein (PARC), is an atypical outlier within the superfamily [108]. Unlike canonical Cullins, CUL9 contains an intrinsic RING domain within its polypeptide chain and therefore does not strictly require a separate RBX subunit for E2 recruitment. However, it lacks a canonical SR motif and binds substrates directly [109]. CUL9 functions primarily as a cytoplasmic anchor that retains the tumor suppressor p53 in its inactive form. By sequestering p53 in the cytoplasm and promoting its turnover, CUL9 prevents unnecessary nuclear accumulation of p53 and apoptosis in the absence of stress signals [110]. CUL9/PARC contains a C-terminal RING domain that is structurally homologous to RBX1 but is fused directly to the Cullin stalk [111].

On the basis of the eight distinct Cullin proteins encoded by the human genome, the CRL superfamily is stratified into several major subfamilies, as described below.

3.4 Dynamic assembly and regulatory mechanisms of the SCF complex

As the archetype of the CRL superfamily, the SCF complex is the most extensively characterized E3 ligase architecture. Its structural integrity relies on four distinct functional modules. CUL1 functions as a rigid, arc-shaped backbone that physically bridges the complex's opposing termini. The RING-finger protein RBX1 docks at the C-terminus of CUL1 and recruits the ubiquitin-loaded E2 conjugating enzyme. In contrast, SKP1 binds the N-terminus of CUL1 and acts as an essential molecular bridge between the scaffold and the receptor. Moreover, F-box proteins anchor to SKP1 via the conserved F-box motif and simultaneously use their variable C-terminal domains (e.g., WD40 repeats or LRRs) to specifically entrap target substrates [71].

This modular design confers remarkable plasticity upon the system. By using different F-box proteins, approximately 69 of which are encoded in the human genome, cells use a single conserved CUL1–RBX1 core to recognize and degrade diverse substrates [112]. Furthermore, the spatiotemporal activity of the SCF machinery is strictly governed by the neddylation cycle and the regulatory protein Cullin-Associated Neddylation Dissociated 1 (CAND1) [113]. The covalent attachment of Nedd8 to CUL1 induces a marked conformational rearrangement that liberates the catalytic potential of RBX1 [114]. A structural comparison of neddylated vs. un-neddylated CUL1 has revealed that Nedd8 acts as a wedge forcing the RBX1 RING domain into an active, extended conformation suitable for E2 recruitment [115]. In contrast, CAND1 exclusively binds un-neddylated CUL1 and effectively sequesters the SKP1-binding interface. Cryo-EM structures of the CUL1–CAND1 complex show that CAND1 wraps around the entire Cullin scaffold, thus physically blocking the SKP1 binding site and preventing “futile” complex assembly [116]. This mechanism, known as receptor exchange, by driving the rapid recycling of F-box proteins, allows cells to swiftly remodel their E3 ligase repertoire in response to fluctuating environmental cues [117].

4. STRUCTURAL BIOLOGY DEEP DIVE: THE CULLIN1-SKP2-CKS1 INTERFACE

Elucidating the structural underpinnings of SKP2 is fundamental to decoding its functional mechanics and guiding rational drug design. SKP2, a member of the F-box protein FBXL subfamily, is structurally characterized by a domain rich in LRRs [71].

4.1 Insights from crystallography (PDB ID: 2AST)

The determination of the crystal structure of the SKP1–SKP2–CKS1 ternary complex bound to a p27 peptide was a watershed moment in understanding SCF–SKP2-mediated substrate recognition [118]. This work provided an atomic-level blueprint for understanding substrate recognition within the SCF–SKP2 complex.

4.2 The “obligate cofactor” recognition paradigm

In contrast to most F-box proteins, which directly engage their substrates, SKP2 exhibits an absolute dependency on the auxiliary protein Cyclin-dependent Kinase Regulatory Subunit 1 (CKS1) for the recognition of its canonical substrate, p27^{Kip1} [118, 119]. Moreover, structural analysis has revealed the existence of the CKS1–SKP2 interface, wherein CKS1 docks onto the concave surface of the SKP2 LRR domain. A network of hydrophobic interactions and hydrogen bonds forges a continuous composite surface essential for creating the substrate-binding pocket [118]. In contrast, the binding geometry of p27 indicates that the p27 peptide intercalates into a deep groove. According to thermodynamic studies, CKS1 binding to SKP2 increases the affinity

for phosphorylated p27 by more than 100-fold [13]. Notably, phosphorylation of p27 at T187 engages a positively charged pocket on CKS1. This phosphate recognition is highly specific: substitution with a phosphomimetic glutamate markedly decreases binding affinity, thus underscoring the need for genuine phosphorylation [120]. More importantly, the side chain of Glu185 on p27 directly inserts into the interface between SKP2 and CKS1, and simultaneously contacts residues on both proteins. Hence, this “molecular sandwich” binding mode is likely to account for the requirement of CKS1 for p27 degradation [121]. This structural architecture not only clarifies the biochemical mechanism but also highlights a compelling therapeutic vulnerability: the potential to pharmacologically disrupt the SKP2–CKS1 or SKP2–SKP1 interfaces and achieve precise substrate interference without dismantling the entire SCF machinery.

4.3 The SKP1–SKP2 interface

SKP1 engages the N-terminal F-box motif of SKP2 via its own C-terminal domain; this interaction physically anchors SKP2 to the CUL1 scaffold [122]. The F-box motif comprises approximately 40 amino acids folded into a compact helical bundle [123]. Disruption of this interface, such as with the small-molecule inhibitor SZL-P1-41, prevents SKP2 integration into the SCF E3 ligase complex and leads to loss of ubiquitin ligase activity, thus providing a primary strategy for developing pan-SKP2 inhibitors [13, 123].

5. THE MULTIDIMENSIONAL REGULATORY LANDSCAPE OF SKP2: FROM TRANSCRIPTION TO POST-TRANSLATIONAL CONTROL

SKP2 is not merely an orchestrator of cellular signaling but a participant in complex regulation itself. Its expression and activity substantially oscillate throughout the cell cycle, in a rhythm strictly governed by a convergence of transcriptional activation, post-transcriptional suppression, and post-translational modifications (PTMs) (Table 3, Figure 3).

5.1 Transcriptional regulation

Transcriptional induction of the *SKP2* gene occurs predominantly at the G1/S transition and is driven by a set of oncogenes and transcription factors [145, 146]. E2F1, a critical driver of S-phase entry, is a primary transcriptional activator of *SKP2* [145]. Concurrently, c-Myc binds E-box sequences within the *SKP2* promoter and robustly upregulates its mRNA levels. This synergy elucidates why SKP2 is frequently overexpressed in Myc-driven malignancies [124, 125]. Moreover, via the noncanonical NF- κ B pathway, the IKK α kinase facilitates nuclear translocation of the p52/RelB complex, which subsequently activates *SKP2* transcription [126]. In contrast, in T-cell acute lymphoblastic leukemia, Notch1 acts synergistically with IL-7 signaling in directly inducing *SKP2* expression,

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Table 3 | Multilayer regulation of SKP2 expression and protein stability.

Regulatory tier	Key modulator	Mechanistic action	Biological consequence	Refs.
Transcriptional	c-Myc, E2F1	Transactivation; promoter binding	Upregulation of <i>SKP2</i> mRNA driving proliferation	[124-128]
Transcriptional	FOXO3a	Recruitment of HDACs	Transcriptional silencing leading to cell-cycle arrest	[129-131]
Post-transcriptional	miR-127-3p, miR-40, miR186	3' UTR targeting; RNAi	mRNA destabilization or translational repression	[132-134]
PTM (phosphorylation)	Akt (Ser72)	Subcellular relocalization	Cytoplasmic export; glycolysis	[135, 136]
PTM (phosphorylation)	CDK2/mTORC1 (Ser64)	Protein stabilization	Evasion of APC/Cdh1 in S/G2	[137, 138]
PTM (ubiquitination)	APC/Cdh1	Proteolytic targeting	Proteasomal turnover; G1 p27 recovery	[139, 140]
PTM (ubiquitination)	USP10, USP2, CSN5	Deubiquitination	Cleavage of Ub chains; increased half-life	[65, 141-143]
PTM (acetylation)	p300 (K68/K71)	Lysine acetylation	Stability enhancement; oncogenic gain	[144]

thereby fueling leukemic proliferation [127, 128]. Furthermore, the tumor suppressor FOXO3a directly binds the SKP2 promoter and represses its transcription [129]. SKP2 mediates the ubiquitination and degradation of FOXO3a (e.g., when FOXO3a is deacetylated by SIRT1/2 [130] or in the context of Aurora-A overexpression [131]), thereby decreasing FOXO3a protein levels. Because FOXO3a is also a transcriptional repressor of SKP2, loss of FOXO3a has been found to relieve repression and indirectly facilitate SKP2 upregulation in some contexts. However, a direct demonstration of this feedback loop under physiological or oncogenic conditions remains to be fully established.

5.2 Post-transcriptional and epigenetic regulation

Recent studies have indicated that microRNAs (miRNAs) play critical roles in fine-tuning SKP2 mRNA stability. In Kaposi's sarcoma, miR-127-3p has been identified as a direct repressor of SKP2, and its downregulation after Kaposi's Sarcoma-associated herpesvirus infection coincides with a pathological increase in SKP2 levels [132]. Similarly, members of the miR-30 family have been reported to target the 3' UTR of SKP2, whereas their loss or downregulation contributes to SKP2 overexpression in tumors such as gliomas [133]. Furthermore, miR-186 has been shown to repress SKP2 in lung cancer, although the precise physiological contribution of this regulation to the oncogenic role of SKP2 remains to be fully elucidated [134].

5.3 Post-translational modifications

The protein stability, subcellular localization, and enzymatic activity of SKP2 are modulated by a complex array of PTMs, including phosphorylation, ubiquitination, and acetylation events, among others.

5.3.1 Phosphorylation: the switch for localization and stability.

Akt-mediated phosphorylation of SKP2 at

Ser72 provides a critical layer of regulation of the oncogenic role of SKP2 [135, 136]. Mechanistically, phosphorylation of SKP2 at Ser72 by Akt disrupts its interaction with Importin, thus causing cytoplasmic sequestration. In the cytoplasm, SKP2 ceases to degrade nuclear p27 and instead catalyzes K63-linked ubiquitination of Akt [136], thereby creating a "feed-forward vicious cycle" (Akt-SKP2-Akt) that amplifies glycolysis and cell migration [147].

Moreover, CDK2 and mTORC1-mediated phosphorylation of SKP2 at Ser64 protects SKP2 against recognition and degradation by APC/Cdh1, thereby stabilizing SKP2 in G1/S and probably sustaining elevated SKP2 levels through S and G2 phases; this state might help maintain suppression of p27 and p21 [137, 138].

5.3.2 Ubiquitination: cyclic turnover. SKP2 is itself a substrate for ubiquitin-mediated degradation, a process essential for cell cycle resetting. Aberrancy in the timely destruction of SKP2 leads to the elevation of SKP2 oncogenic functions, thereby facilitating tumorigenesis [139, 140]. During G1 phase, cells require p27 accumulation to maintain cell-cycle arrest. To achieve this accumulation, the APC/Cdh1 E3 ligase recognizes the N-terminal destruction box motif of SKP2, and triggers its polyubiquitination and subsequent proteasomal clearance [140]. Notably, enzymes such as USP10 and USP13 cleave ubiquitin chains from SKP2, thereby stabilizing the protein and counteracting APC/Cdh1-mediated degradation in various cancers [65, 141]. USP2 has been identified as a critical DUB that stabilizes SKP2 and prevents its circadian degradation in the liver [142], whereas CSN5 (a subunit of the COP9 signalosome) protects SKP2 against auto-ubiquitination [143].

5.3.3 Acetylation. The acetyltransferase p300 acetylates SKP2, primarily at residues K68 and K71. This modification serves a dual purpose: it not only enhances SKP2 protein stability but also promotes its cytoplasmic

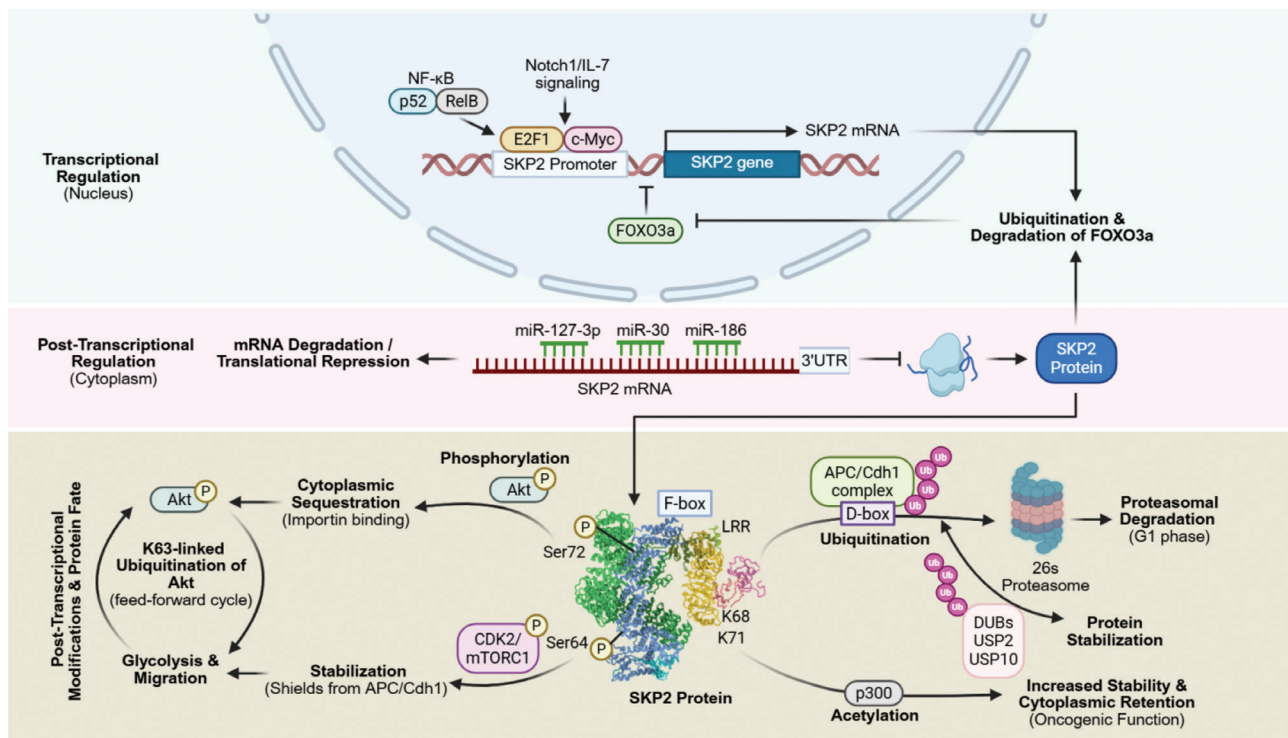


Figure 3 | The multidimensional regulatory network governing SKP2 expression and functions.

(Top) Transcriptional Regulation: In the nucleus, activators including E2F1, c-Myc, NF-κB (p52/RelB), and Notch1/IL-7 signaling drive *SKP2* gene expression. In contrast, FOXO3a recruits HDACs, thereby repressing transcription. Notably, a reciprocal feedback loop exists, wherein SKP2 promotes ubiquitin-mediated degradation of FOXO3a. **(Middle)** Post-Transcriptional Regulation: In the cytoplasm, specific miRNAs (e.g., miR-127-3p or miR-21) bind the *SKP2* 3' UTR, and subsequently trigger mRNA degradation or translational repression. **(Bottom)** Post-Translational Modifications (PTMs) and Protein Fate: SKP2 protein function is modulated by phosphorylation, ubiquitination, and acetylation. Phosphorylation by Akt and CDK2/mTORC1 dictates subcellular localization and protein stability, respectively. Whereas the APC/Cdh1 E3 ligase complex targets SKP2 for proteasomal degradation during the G1 phase, deubiquitinases (DUBs) counteract this process and consequently maintain Skp2 protein levels. Additionally, p300-mediated acetylation enhances SKP2 stability and oncogenic activity. Figure created with BioRender.com.

retention, thereby augmenting its oncogenic functions [144].

5.4 Splicing regulation of SKP2

Alternative splicing is an additional layer of regulation that expands the functional diversity of SKP2. The splice variant SKP2B bears a unique C-terminal domain produced through truncation of the distal LRR region at the C-terminus, owing to alternative exon usage at the 3' end of the transcript [148]. This structural modification is associated with predominantly cytoplasmic localization and confers altered substrate specificity. In contrast to full-length SKP2, which localizes primarily to the nucleus and promotes degradation of the CDK inhibitor p27, SKP2B does not measurably affect p27 protein abundance [149, 150]. Instead, SKP2B interacts with and regulates distinct substrates, including the repressor of estrogen receptor activity [151] and prohibitin [152]. Notably, SKP2B-mediated degradation of prohibitin has been associated with attenuation of p53 transcriptional activity and diminished expression of the p53-responsive gene PIG3, thereby decreasing apoptotic signaling,

at least partly through p53-independent mechanisms [152]. Together, these observations support that SKP2B is a functionally distinct SKP2 isoform with non-redundant regulatory roles.

6. THE CANONICAL ROLE OF SKP2: ORCHESTRATING THE CELL CYCLE

Originally identified as the S-phase kinase-associated protein, SKP2 is best known for its role in promoting the cell cycle transition from G1 to S phase [5]. This critical transition is orchestrated primarily through the timely recognition and elimination of Cyclin-dependent kinase inhibitors (CKIs) [2].

6.1 p27^{Kip1} degradation and the G1/S switch

p27^{Kip1} functions as the primary molecular brake on the cell cycle, by physically restraining the kinase activity of Cyclin E-CDK2 and Cyclin A-CDK2 complexes and consequently impeding DNA replication [153]. During G0/G1 quiescence, SKP2 levels are kept low via APC/Cdh1-mediated turnover [154]. Consequently, p27

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accumulates and maintains cells in a resting state. Notably, CDK2 phosphorylates p27 at Thr187. This specific phosphorylation event is thermodynamically required for the high-affinity binding of CKS1 to the p27 peptide, as confirmed by structural energetics [155]. Concurrently, SKP2 accumulates through E2F-mediated transcriptional activation and APC/C E3 ligase complex inactivation. The SCF-SKP2 complex specifically recognizes this phosphodegron within p27 and tags p27 with K48-linked ubiquitin chains for subsequent proteasomal execution, thereby ensuring timely G1/S transition [5, 156]. Consequently, p27 degradation activates CDK2. In a positive feedback loop, active CDK2 further phosphorylates p27, and additionally phosphorylates and inactivates Cdh1 (thereby stabilizing SKP2 as a positive feedback loop). This steep, irreversible bistable switch commits cells to DNA replication [157, 158].

6.2 Targeting other CKIs

Analogously to p27, SKP2 targets other members of the Cip/Kip family and dismantles cell cycle checkpoints. Specifically, SKP2 promotes ubiquitination-mediated degradation of p21^{Cip1} (CDKN1A), a downstream effector of p53 that mediates G1 arrest after DNA damage [159]. SKP2-mediated degradation of p21 allows cells to either bypass this DNA damage checkpoint or progress through a normal cycle unhindered [159, 160]. Degradation of p21 occurs specifically during the S phase and aids in DNA replication [159]. Whereas p57^{Kip2} (CDKN1C) is associated predominantly with stem cell maintenance and embryogenesis, its SKP2-mediated turnover remains a prerequisite for proliferation in specific tissue contexts [161].

Paradoxically, whereas E2F1 induces SKP2, SKP2 also targets E2F1 for degradation in the late S/G2 phase, thus establishing a negative feedback loop restricting the E2F1 activity window [162]. Moreover, SKP2 targets the tumor suppressor RASSF1A for ubiquitination, thus preventing it from inhibiting the APC-Cdc20 complex and promoting mitotic progression [163]. In addition, SKP2 prevents DNA re-replication by targeting the replication licensing factor Cdt1 for degradation during S-phase [164, 165]. Furthermore, SKP2 targets viral Cyclins for destruction. Kaposi's Sarcoma-associated herpesvirus encodes a viral cyclin that binds CDK6 and phosphorylates p27, thereby mimicking the physiological signal, and hijacking SCF-SKP2 to degrade p27 and force viral latency exit [166, 167].

6.3 The FOXO axis: a dual safeguard for survival (FOXO1 and FOXO3a)

The FOXO family of transcription factors (specifically FOXO1 and FOXO3a) acts as the cellular "custodian" of quiescence and apoptosis [168, 169]. In the absence of growth signals, these unphosphorylated factors reside in the nucleus, where they actively transcribe growth-arrest genes (e.g., *p27*) and pro-apoptotic effectors (e.g., *Bim* and *FasL*). Under growth factor stimulation (e.g., insulin

or EGF), the PI3K-Akt pathway is triggered. Activated Akt phosphorylates FOXO1 (at Ser256) and FOXO3a (at Ser253) [170, 171]. This phosphorylation induces binding of 14-3-3 proteins, which mask the nuclear localization signal, thereby inhibiting FOXO transcriptional activity through nuclear exclusion [172, 173]. However, nuclear exclusion offers only "functional" sequestration. The complete physical clearance of these tumor suppressors relies on SKP2. Cytoplasmic SKP2 specifically recognizes the Akt-phosphorylated species of both FOXO1 and FOXO3a. Acting as an E3 ligase, the SCF-SKP2 complex conjugates K48-linked ubiquitin chains to them and marks them for proteasomal destruction [174], thus establishing the Akt-SKP2-FOXO signaling axis. The simultaneous elimination of FOXO1 and FOXO3a provides a robust safeguard for cell proliferation [130, 174]. By degrading these factors, SKP2 disrupts the *de novo* transcriptional supply of p27 (complementing its direct protein degradation) and blocks the induction of Bim-mediated apoptosis. This irreversible clearance confers a potent survival advantage and therapeutic resistance in oncogenic contexts [175].

6.4 The expanded degradome: beyond the canonical gatekeepers

Beyond the canonical G1/S regulators, SKP2 orchestrates K48-linked ubiquitination and proteasomal clearance of a vast "degradome" and exerts pleiotropic effects on cellular homeostasis. This expanded substrate repertoire can be categorized into several functional modules. To ensure robust proliferation, SKP2 targets a broad spectrum of cell cycle mediators, including the elimination of pocket proteins (p130) [176] and the turnover of key transcriptional drivers and cyclins, such as E2F-1 [162], c-Myc [177], Cyclin D [160], and Cyclin E [178]. Furthermore, SKP2 suppresses apoptosis by targeting RhoE [179] for degradation. SKP2 plays a critical role in coordinating DNA replication licensing by degrading Orc1 [180] and Cdt1 [181]. Concurrently, it modulates the DDR and recombination by regulating RAG2 stability [182]. SKP2 further modulates multiple critical signaling pathways: it dampens the TGF- β and ERK pathways by targeting Smad4 and the phosphatase MKP1, respectively [183, 184], and limits the interferon response via UBP43 degradation [185]. In the context of viral pathogenesis, SKP2 is hijacked to mediate the turnover of viral oncoproteins, including HPV-18 E2 and HPV-E7, thereby facilitating viral life cycles [186, 187].

Although these substrates have been biochemically validated, further investigations are warranted to dissect the precise physiological contexts and clinical relevance of these interactions within specific tumor microenvironments.

6.5 Compensatory networks and miRNAs

Notably, *Skp2*-knockout mice, despite exhibiting dwarfism and polyploidy, are viable [188]. This finding implies the existence of intricate compensatory networks and

indicates that, if on target, the SKP2 inhibitor should cause minimal toxicity at the organismal level. Further research has underscored that the miR-221/222 cluster functions as a critical backup mechanism. In the absence of functional SKP2, these miRNAs are upregulated and translationally repress p27, thereby maintaining cell cycle progression to some extent [189]. Furthermore, the finding that the related E3 ligase Pirh2 partially compensates for p27 degradation in the absence of SKP2 has revealed redundancy in CKI turnover [190]. Additionally, the KIP1 ubiquitination-promoting complex acts as a cytoplasmic backup E3 ligase for p27 degradation during the G1 phase [191, 192]. This complementarity between non-coding RNAs and the UPS reveals the multidimensional robustness inherent in cell-cycle control.

7. BEYOND THE CELL CYCLE: SKP2 AS AN ARCHITECT OF METABOLISM AND SIGNALING

The proteomic revolution has vastly broadened the functional repertoire of SKP2. According to the consensus as of 2025, SKP2 operates not only as a proteolytic executioner via K48-linked ubiquitination but also as a potent signal transducer through the assembly of K63-linked ubiquitin chains (Table 4, Figure 4).

7.1 The K63-Akt axis: an engine for metabolic reprogramming

The regulation of Akt (also known as Protein Kinase B) by SKP2 challenges the conventional view that ubiquitination necessarily leads to proteasomal degradation. SKP2 has been found to catalyze the formation of K63-linked polyubiquitin chains on Akt. These K63 chains, in contrast to the K48 destruction tag, function as molecular scaffolds [7, 193]. Mechanistically, this specific polyubiquitination topology facilitates Akt translocation to the plasma membrane. Only after this membrane

recruitment can Akt be phosphorylated and activated by PDK1 and mTORC2 [66]. Moreover, in a feed-forward mechanism, activated Akt stabilizes SKP2, either via direct phosphorylation (e.g., at Ser72) or by driving E2F/ Myc-mediated transcription. This mutual activation loop is a primary mediator of the Warburg effect and the progression of CRPC [198, 199]. Biologically, the SKP2-driven activation of Akt promotes the surface localization of Glucose Transporter 1 (Glut1) and the mitochondrial association of Hexokinase 2 (HK2), thereby maximizing the glycolytic flux essential for tumor growth [200, 201].

7.2 Nutrient sensing: the unexpected “brake” on mTORC1

In the context of nutrient sensing, SKP2 has unexpectedly been revealed to function as a metabolic attenuator. Notably, under amino acid stimulation, SKP2 conjugates K63-linked ubiquitin chains to the RagA GTPase [14]. This modification serves as a docking site for the GAP for RagA (GATOR1) complex and subsequently accelerates the hydrolysis of RagA-GTP. This action effectively terminates the signal and therefore suppresses lysosomal recruitment of mTORC1. Consequently, a critical negative feedback loop is established that prevents hyperactivation of mTORC1 under conditions of sustained nutrient availability. Hence, loss of SKP2 results in constitutive mTORC1 signaling, and leads to cellular hypertrophy and defective autophagy [14].

7.3 Coupling cell cycle to metabolism: the SKP2-IDH1/2 axis

Whether glucose is metabolized predominantly via oxidative phosphorylation or glycolysis differs between quiescent and proliferating cells. Mammalian cells are now understood to exhibit periodic metabolic fluctuations: they predominantly use the tricarboxylic acid (TCA) cycle during G1 phase but switch to aerobic glycolysis

Table 4 | The dichotomy of SKP2-mediated ubiquitination events: canonical degradation vs. non-canonical signaling.

Target substrate	Ubiquitin topology	Molecular consequence	Pathophysiological effects	Refs.
p27 ^{Kip1} (CDKN1B)	K48-linked	Proteasomal turnover	G1/S acceleration; oncogenesis	[153, 154, 157, 158]
Akt (PKB)	K63-linked	Plasma membrane recruitment; kinase activation	Glycolysis; chemoresistance; survival	[7, 193]
RagA	K63-linked	GTPase stimulation (via GATOR1)	mTORC1 negative feedback	[14]
YAP	K63-linked	Nuclear entry; transcriptional activation	Hippo dysregulation; organ hypertrophy	[194]
FOXO1/FOXO3a	K48-linked	Proteolysis	Apoptosis evasion; cell survival	[130, 174]
LKB1	K63-linked	Stability/localization; AMPK modulation	Metabolic adaptation; starvation survival	[195]
IDH1/2	K48-linked	S-phase degradation	Warburg effect; metabolic–cell cycle coordination	[8]
MTH1	K63-linked	Protein stabilization	ROS defense; senescence prevention	[196]
NBS1	K63-linked	Promotes HR	Genomic stability; DDR; drug resistance	[197]

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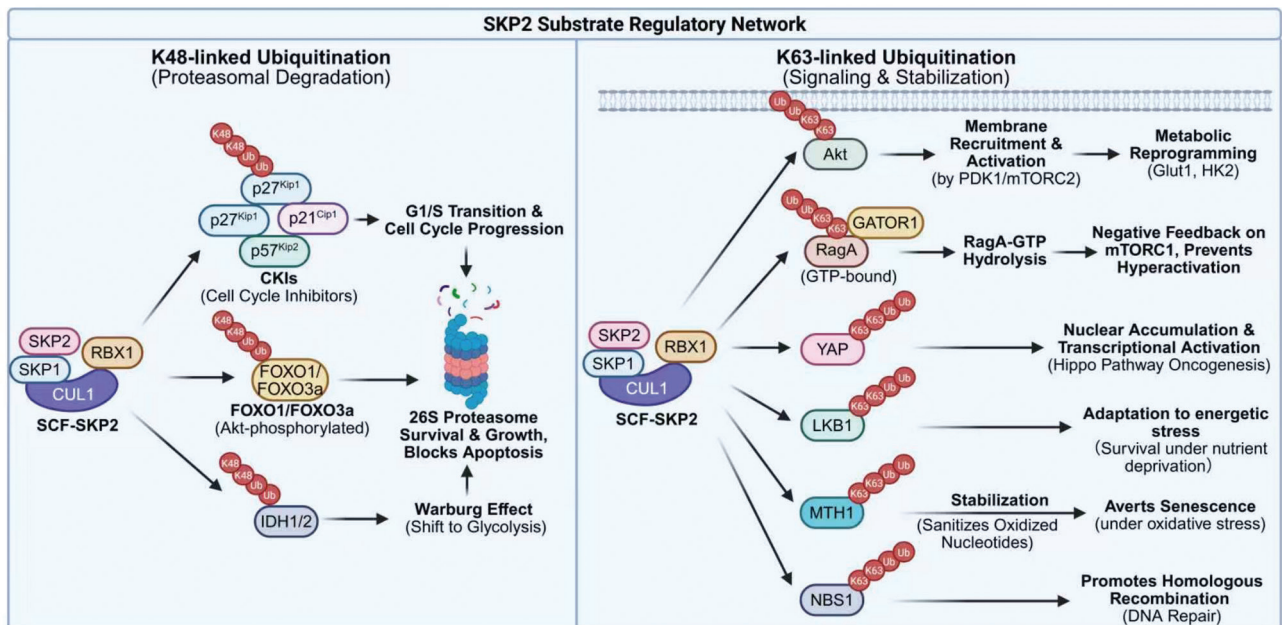


Figure 4 | The SKP2 substrate regulatory network: a dual arbiter of protein fate.

(Left) K48-linked Ubiquitination: In this canonical proteasomal degradation pathway, SKP2 mediates the polyubiquitination and subsequent 26S proteasome-dependent degradation of cell-cycle inhibitors (CKIs: p27, p21, and p57), the transcription factor FOXO1/FOXO3a, and the metabolic enzymes IDH1/2. This process primarily drives the G1/S transition, promotes cell survival, and induces glycolysis. **(Right)** SKP2 promotes K63-linked ubiquitination of signaling molecules (Akt and YAP) and stress response factors (LKB1, MTH1, and NBS1). This non-proteolytic modification enhances their stability, subcellular localization, or activity, thereby facilitating signal transduction, DNA repair, and adaptation to oxidative or metabolic stress. Notably, K63-linked ubiquitination of RagA exerts negative feedback regulation on mTORC1 activity. Figure created with [BioRender.com](#).

during S phase to support DNA replication [8, 202]. This temporal synchronization is orchestrated by SKP2. SKP2 has recently been revealed to target isocitrate dehydrogenases 1 and 2 (IDH1/2), key rate-limiting enzymes in the TCA cycle, for timely ubiquitination and proteasomal destruction. Crucially, this SKP2-mediated degradation of IDH1/2 occurs specifically during S phase. The depletion of these TCA cycle enzymes shifts metabolic flux away from oxidative phosphorylation toward glycolysis [203]. Consequently, SKP2 depletion abolishes this cell-cycle-dependent fluctuation of IDH1/2 and prevents the S-phase-specific surge in glycolysis. In prostate cancer, aberrant overexpression of SKP2 leads to the constitutive destabilization of IDH1. The enforced glycolytic phenotype (Warburg effect) facilitates tumorigenesis. Therefore, the SKP2-IDH1/2 axis is a direct mechanistic bridge linking two hallmarks of cancer: aberrant cell cycle progression and dependence on glycolysis [8, 203].

7.4 The expanded interactome: a network of diverse substrates

Notably, SKP2 enhances the nuclear accumulation and transcriptional output of YAP via K63-linked ubiquitination and consequently fuels the oncogenic potential of the Hippo pathway [194, 204]. Beyond regulating Hippo signaling, SKP2 modulates c-Myc oncogenic functions.

The relationship between SKP2 and c-Myc is multifaceted. SKP2 enhances Myc transcriptional activity (in coordination with HectH9-mediated K63 chains) while simultaneously governing its turnover via the SCF complex. This “turnover-as-activation” model suggests that controlled instability is a prerequisite for the cyclic functionality of transcription factors [205, 206]. More recently, in non-small cell lung cancer (NSCLC), SKP2 has been identified as a critical stabilizer of PD-L1 downstream of LKB1. Mechanistically, SKP2 promotes K63-linked ubiquitination of PD-L1 (at residues K136 and K280) and therefore antagonizes proteasomal degradation. This stabilization maintains PD-L1 expression and fosters an inflamed, “hot” tumor microenvironment rich in cytotoxic T cells. Consequently, disruption of this axis, as seen in LKB1-mutant tumors, results in PD-L1 instability and an immune-excluded “cold” phenotype [207].

More recently, SKP2 has been shown to regulate oxidative stress through stabilizing MTH1 by promoting K63-linked polyubiquitination. Because MTH1 is responsible for sanitizing the oxidized nucleotide pool, this interaction protects tumor cells against the incorporation of damaged bases into DNA, thus averting senescence under high oxidative stress [196]. Additionally, SKP2 interacts with LKB1, a master metabolic and stress-sensing kinase, and subsequently modulates its

stability and subcellular localization. Through this regulation, SKP2 fine-tunes LKB1-mediated AMPK activation and downstream metabolic checkpoints, and enables tumor cells to adapt to energetic and oxidative stress [195]. By controlling LKB1 activity, SKP2 indirectly supports cell survival under nutrient deprivation or high metabolic demand; these findings highlight a broader role in integrating cell-cycle progression with stress-response pathways [195].

7.5 Interplay between SKP2 and the PARP-mediated DNA damage response

SKP2 is likely to exert dual effects on genomic stability through regulating various key DNA repair factors such as NBS1 or BRCA2. Specifically, SKP2 promotes homologous recombination (HR) by targeting NBS1 for K63-linked ubiquitination [197]. Several studies have suggested that SKP2 promotes ubiquitin-dependent degradation of BRCA2, potentially via K48-linked chains, thereby undermining BRCA2 stability and HR function in specific cellular contexts [208]. This bidirectional regulation is dictated by the specific cellular context and the nature of the DNA lesion, but additional in-depth mechanistic studies are required [209].

Although SKP2 is widely recognized for supporting HR and alleviating replication stress, it functionally intersects with the poly(ADP-ribose) polymerase (PARP)-mediated DDR. PARP1 acts as an early detector of single-strand breaks and stalled replication forks by catalyzing poly(ADP-ribose) chain formation, thereby orchestrating the recruitment of DDR factors [210, 211]. PARP1 activity rapidly recruits the MRE11–RAD50–NBS1 (MRN) complex, which is essential for initiating double-strand break (DSB) processing [212]. Emerging evidence indicates that SKP2 contributes to efficient MRN function: SKP2-dependent ubiquitination of NBS1 supports optimal MRN assembly and ATM activation at DSBs, and therefore promotes end resection and productive HR [197].

Under replication stress, PARP1 also protects stalled forks against nuclease-mediated degradation and preserves structural integrity until fork restart mechanisms can operate [213]. To this end, SKP2 indirectly supports replication-fork resilience by modulating factors that influence fork remodeling and restart. For example, by facilitating degradation of the cyclin-dependent kinase inhibitor p27, SKP2 promotes CDK kinase activity, which in turn enables efficient engagement of HR-associated fork restart processes [188]. Additionally, SKP2 has been implicated in maintaining RAD51 function and chromosomal stability, processes central to the stabilization of recombination intermediates at perturbed forks [214].

The convergence of these pathways provides a mechanistic rationale for the reported therapeutic synergy between PARP inhibitors and SKP2 suppression. Because SKP2 contributes to HR competence, its inhibition induces features of HR deficiency and sensitizes tumor

cells to PARP inhibition [215]. This functional interplay supports the potential value of co-targeting SKP2 and PARP to enhance antitumor efficacy.

8. A PATHOLOGICAL ATLAS: SKP2 IN ONCOLOGY AND NEURODEGENERATION

Aberrant SKP2 expression is a pervasive feature across human pathologies as diverse as aggressive malignancies and neurodegenerative disorders. Its dysregulation is highly context-dependent: it serves as a broad-spectrum proto-oncogene in cancer and is emerging as a critical regulator of neuronal survival and function (Table 5, Figure 5).

8.1 The oncogenic landscape of SKP2 in human malignancies: tumorigenesis, progression, and therapeutic resistance

In oncology, SKP2 functions as a broad-spectrum proto-oncogene; it is frequently overexpressed in most solid tumors, including prostate [242], breast [150], lung [243], and colorectal carcinomas [244], as well as hematological malignancies, in which its abundance strongly correlates with poor prognosis [245].

Cancer cell dormancy is a reversible state in which malignant cells remain viable yet temporarily exit the cell cycle [246]. This quiescent condition allows tumor cells to tolerate cytotoxic stress and can ultimately give rise to metastatic relapse [246]. Among the regulators of this process, the cyclin-dependent kinase inhibitor p27 (CDKN1B) plays a central role [247]. Nuclear accumulation of p27 restrains Cyclin-CDK activity and enforces G0/G1 arrest, thereby sustaining the dormant phenotype [248]. In this context, the dynamic balance between SKP2-mediated degradation vs. stabilization of p27 has been proposed to act as a regulatory switch governing dormancy transitions [249].

Notably, maintenance of quiescence requires sustained inhibition of CDK activity, which is typically accompanied by increased nuclear p27 levels [247]. Diminished SKP2 expression or E3 ligase activity limits proteasomal turnover of p27 and favors cell cycle exit. Experimental models of disseminated tumor cells have shown that attenuation of β 1-integrin signaling lowers SKP2 protein abundance, and leads to p27 stabilization and induction of a dormant state [249, 250]. In contrast, metastatic reactivation is frequently associated with renewed SKP2 expression, which in turn facilitates phosphorylation-dependent ubiquitination of p27 and promotes cell-cycle re-entry.

Therapeutic stress might further modulate this signaling axis. Certain cytotoxic regimens have been associated with enrichment of quiescent, p27-high subpopulations that evade cell death; therefore, alterations in SKP2 activity might contribute to therapy-induced dormancy and subsequent relapse [251, 252]. Hence, understanding how cell cycle regulators such as SKP2 and p27 interact with dormancy-associated signaling pathways

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Table 5 | SKP2-mediated pathogenic mechanisms and therapeutic resistance in major malignancies.

Malignancy	Key pathogenic mechanism	Downstream effectors/ pathways	Clinical consequence and drug resistance	Refs.
Prostate cancer (CRPC)	AR paradox and epithelial-mesenchymal transition: SKP2 stabilizes Twist; drives androgen-independent growth	Akt, Twist, p27	CRPC transition: Resistance to androgen deprivation therapy (ADT); high Gleason scores	[216-222]
Breast cancer (TNBC and HER2+)	PI3K inhibition triggers SKP2 → K63-Akt activation	Akt, FOXO1, HER2	Resistance to PI3K inhibitors and suppression of apoptosis signaling	[7, 223-225]
Lung cancer (NSCLC)	Immune evasion: K63-Ub stabilizes PD-L1; prevents degradation	PD-L1, LKB1, AMPK	Immunotherapy resistance: “cold” tumors; T-cell suppression	[226-229]
Hematological (MM and CML)	Survival synergy: supports c-Myc/c-Maf stability	c-Myc, c-Maf, BCR-ABL	Bortezomib/imatinib resistance: SKP2 inhibition restores UPR stress	[230-233]
Colorectal cancer (CRC)	Metabolic rewiring: HK2 mitochondrial localization; Mcl-1 stability	Akt/HK2 axis, Mcl-1	Chemo/rad resistance: 5-FU and IR evasion	[234]
Hepatocellular Carcinoma	Oncogenic amplifier: explosive growth via N-Ras/Akt synergy	N-Ras, AKT	Activation of AKT/mTOR and Ras/MAPK pathways	[235, 236]
Glioblastoma	SKP2-mediated degradation of p27	p27	Temozolomide resistance: Glioma stem cell maintenance	[237]
Ovarian cancer	Checkpoint failure: continual p27 degradation	p27	Enhanced cell proliferation and poor clinical prognosis	[238, 239]
Melanoma	Stabilizes MTH1 for purging oxidized nucleotides	MTH1	Oxidative survival: gene amplification	[240, 241]

will be critical for devising strategies to prevent relapse from dormant residual disease.

8.1.1 Prostate cancer: the driver of castration resistance. In the lethal transition to CRPC, SKP2 has emerged as a central architect. However, the relationship between SKP2 and the androgen receptor (AR) is complex and distinct. Whereas SKP2 mediates AR turnover, its loss in CRPC paradoxically restores AR protein levels; therefore, SKP2 might subvert AR signaling and force cells into an androgen-independent growth mode [242]. Crucially, SKP2 provides an alternative survival signal under androgen-deprived conditions by activating the non-canonical Akt pathway [253]. Notably, in the TRAMP transgenic model, *Skp2* ablation completely abrogates tumorigenesis and distant metastasis [19]. Mechanistically, SKP2 stabilizes the transcription factor Twist, via either K63-linked ubiquitination or competitive binding, thereby orchestrating epithelial-mesenchymal transition and sustaining cancer stem cell properties [19, 66]. Importantly, high SKP2 titers significantly correlate with elevated Gleason scores, biochemical recurrence, and diminished survival, and are therefore a potent prognostic indicator in prostate cancer [254, 255].

8.1.2 Breast cancer: a mechanism of therapeutic escape. In TNBC, therapeutic resistance to PI3K/mTOR inhibitors often arises rapidly. Excitingly, recent studies have indicated that this resistance is likely to be driven by a vicious feedback loop: PI3K inhibition triggers

compensatory upregulation of SKP2. This surge in SKP2 subsequently reactivates Akt via K63-linked ubiquitination (independently of PIP₃ generation) and renders the initial drug ineffective [20]. In contrast, in HER2-positive subtypes, SKP2-mediated ubiquitination of Akt is essential for transducing HER2 signaling. Consequently, silencing *SKP2* has been shown to re-sensitize resistant cells to trastuzumab (Herceptin) and tamoxifen [7, 253]. Moreover, in agreement with the oncogenic role of SKP2 in breast cancer, natural compounds such as curcumin exert anti-metastatic effects in TNBC, specifically by disrupting the SKP2–Bim signaling axis [256].

8.1.3 Non-small cell lung cancer: an oncogenic driver and mediator of chemoresistance. SKP2 is frequently overexpressed in both NSCLC and small cell lung cancer, and its upregulation is closely associated with tumor progression, lymph node metastasis, and poor prognosis [257, 258]. Clinical samples and *in vitro* functional studies have indicated that elevated SKP2 correlates with aggressive NSCLC phenotypes, decreased p27 levels, and diminished patient survival [258]. RNA interference or genetic silencing of *SKP2* suppresses lung cancer cell proliferation, induces cell cycle arrest, and promotes apoptosis, thus underscoring its oncogenic role in lung tumorigenesis [259]. Moreover, SKP2-mediated ubiquitination of its substrates might contribute to chemoresistance, for example, by targeting necroptosis regulator MLKL and facilitating cisplatin resistance [260]. Collectively, these findings position SKP2 as a key

The Pathological Atlas of SKP2: A Multifaceted Hub Driving Cancer Progression and Therapeutic Resistance

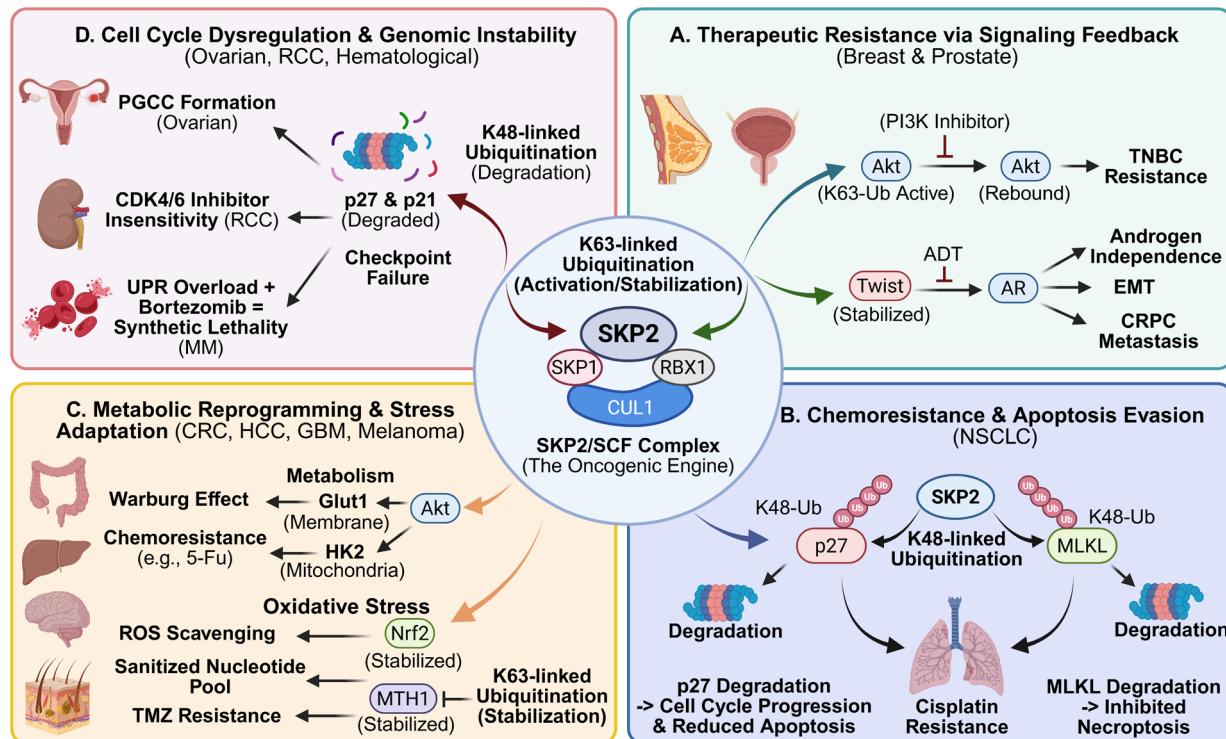


Figure 5 | The pathological atlas of SKP2: a multifaceted hub driving cancer progression and therapeutic resistance centered on the SCF-SKP2 E3 ligase complex.

(A) Therapeutic Resistance via Signaling Feedback: In breast and prostate cancers, SKP2 confers resistance to PI3K inhibitors and androgen deprivation therapy (ADT), partly by mediating K63-linked ubiquitination and subsequent activation of Akt or by stabilizing Twist, respectively. **(B) Chemoresistance and Apoptosis Evasion:** In Non-Small Cell Lung Cancer (NSCLC), SKP2 mediates K48-linked ubiquitination and degradation of p27 and MLKL, and leads to cisplatin resistance by promoting cell cycle progression and preventing apoptosis, while simultaneously inhibiting necroptosis. **(C) Metabolic Reprogramming and Stress Adaptation:** SKP2 promotes the Akt-dependent activation of glycolytic enzymes (Glut1 and HK2). Furthermore, by stabilizing Nrf2 and MTH1, SKP2 enhances tumor cell tolerance to oxidative stress and chemotherapeutics (e.g., 5-Fu or TMZ). **(D) Cell Cycle Dysregulation and Genomic Instability:** Through canonical K48-linked ubiquitination and degradation of p27 and p21, SKP2 causes cell cycle checkpoint failure and results in the formation of polyploid giant cancer cells (PGCCs) and insensitivity to CDK4/6 inhibitors (e.g., in renal cell carcinoma). In contrast, in multiple myeloma (MM), this mechanism creates a vulnerability that can be exploited for synthetic lethality. Figure created with [BioRender.com](#).

oncogenic driver in lung cancer, as well as a potential diagnostic, prognostic, and therapeutic target.

8.1.4 Hematological malignancies: a target for synthetic lethality. Although bortezomib is a frontline therapy, resistance is common. SKP2 inhibitors (e.g., SKPin C1, or DT204) have powerful synergistic lethality when combined with bortezomib [261, 262]. Mechanistically, this combination overloads the unfolded protein response (UPR) and downregulates key survival factors, such as c-Myc and c-Maf. In contrast, the BCR-ABL fusion protein, which is frequently observed in CML, drives SKP2 upregulation [263]. In agreement with the crucial oncogenic role of SKP2 in driving CML pathogenesis, *Skp2* deletion significantly enhances the sensitivity of CML cells to imatinib [264]; SKP2 might therefore be an important drug target for treating CML.

8.1.5 Colorectal and hepatocellular carcinoma: metabolic reprogramming. SKP2 overexpression confers resistance to 5-fluorouracil (5-Fu) in colorectal cancer (CRC). Mechanistically, this resistance is probably achieved through the Akt-Hexokinase 2 (HK2) axis, which sustains high rates of aerobic glycolysis [265]. Similarly, SKP2 acts as an oncogenic amplifier in hepatocellular carcinoma. Although SKP2 overexpression alone is insufficient to initiate hepatocarcinogenesis, it markedly accelerates tumor formation when it is co-expressed with N-Ras or Akt mutants [266]. Mechanistically, SKP2 maintains the Warburg phenotype by regulating Glut1 and HK2, and consequently facilitates tumorigenesis [7, 253].

8.1.6 Glioblastoma and melanoma: stress adaptation. In glioblastoma, a novel SelK-SKP2 axis drives poor prognosis; SelK upregulation mitigates ER stress

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and maintains the stability of SKP2, which in turn suppresses β -TrCP1, thereby preventing CDK4 degradation and fueling malignant proliferation [267]. In contrast, in *BRAF* V600E-mutant melanomas, SKP2 is not only a downstream effector but also a prerequisite for survival. Biologically, SKP2 stabilizes MTH1, an enzyme responsible for “sanitizing” the oxidized nucleotide pool [196]. Consequently, the prevention of the incorporation of damaged bases into DNA allows these highly metabolically active tumors to avert oxidative stress-induced cell death.

8.1.7 Renal and ovarian cancer: cell cycle and DNA repair. Continual SKP2-mediated degradation of p27 leads to checkpoint failure and the formation of polyploid giant cancer cells, a root cause of resistance to paclitaxel and cisplatin in ovarian cancer [268, 269]. Notably, high SKP2 levels render renal cell carcinoma cells insensitive to CDK4/6 inhibitors (e.g., palbociclib) partly by suppressing p21/p27. More importantly, downregulation of SKP2 restores therapeutic sensitivity [270]. SKP2 is therefore an attractive anti-cancer therapeutic for ccRCC.

8.1.8 The pan-cancer landscape: emerging oncogenic contexts. Beyond its roles in major malignancies, SKP2 is a universal driver of tumorigenesis across diverse tissues through distinct context-specific mechanisms. In gastric cancer, SKP2 overexpression is an independent prognostic factor for poor survival [271]. Similarly, in pancreatic cancer, SKP2 drives proliferation by promoting p27 degradation, a process often regulated by upstream cytokine signaling [272]. In contrast, recent studies have indicated that SKP2 confers radioresistance in nasopharyngeal carcinoma, whereas its inhibition breaks this resistance, partly by leading to p27 accumulation and apoptosis induction [273]. In oral squamous cell carcinoma and thyroid cancer, targeting SKP2 significantly suppresses metastasis and tumor growth [274, 275]. Moreover, relatively high SKP2 expression is strongly associated with mortality in soft tissue sarcomas [276]. However, the physiological contribution of SKP2 in the pathogenesis of these tumor types remains to be further explored.

8.2 Neurodegeneration: the lethal consequence of aberrant cell cycle re-entry

Although oncology dominates the current discourse on SKP2, its potential role in the central nervous system warrants attention in the context of AD. Terminally differentiated, post-mitotic neurons typically maintain permanent G0 arrest [277]. However, a pathological hallmark of the brain in AD is the abortive attempt of neurons to re-enter the cell cycle, a fatal error that results in mitotic catastrophe and apoptosis rather than successful division. Mechanistically, the maintenance of the G0 state heavily relies on CDK inhibitors such as

p27^{Kip1}. Dysregulation or loss of p27 has been implicated in the aberrant cell cycle activation in neurons, which in turn contributes to neuronal death in both AD patient samples and transgenic models [278]. Although SKP2 is a well-established regulator of p27 in proliferating cells, its specific role in post-mitotic neurons in AD remains largely unexplored [21]. Targeting the pathways controlling p27 protein stability and cell cycle re-entry might therefore be a potential strategy to prevent this specific mode of neuronal loss in AD.

Although SKP2 has not directly been implicated in Parkinson’s disease (PD), data suggest a role of a functionally linked protein, SKP1A. SKP1A and SKP2 are components of the same SCF complex. SKP1A is an adapter protein that bridges Cullin 1 to F-box proteins (including SKP2) within the SCF complex. Diminished SKP1A levels have been observed in the substantia nigra pars compacta in postmortem PD brains; moreover, knockdown of *SKP1* *in vitro* and *in vivo* leads to PD-associated changes in dopaminergic neurons [279]. SKP1A interacts with F-box only protein 7 (FBXO7), a component of the SCF E3 ubiquitin ligase complex; moreover, mutations in FBXO7 have been found to cause autosomal recessive early-onset PD [280]. FBXO7 also interacts with PINK1 and Parkin, two genes that are likewise associated with early-onset autosomal recessive PD [281].

8.3 SKP2’s dual roles and therapeutic potential

Although SKP2 is categorized predominantly as an oncogene, its functional output is strictly contingent on the genetic landscape. A striking paradox is observed in *Pten*-deficient mouse models, wherein SKP2 exhibits a complex relationship with tumor initiation.

In the context of *Pten* loss, SKP2 inactivation not only decreases proliferation but also induces a robust senescence response [282], and consequently abrogates prostate tumorigenesis. This phenomenon highlights the crucial role of SKP2 in enabling cells to breach the “oncogene-induced senescence” barrier. *Pten*-null cells are dependent on SKP2 to escape senescence and progress to malignancy [17]. This dependency has revealed a unique, genotype-specific therapeutic window: targeting SKP2 in *Pten*-mutant tumors might be synthetically lethal by trapping cancer cells in a permanent senescent state.

9. THERAPEUTIC EVOLUTION: FROM INTERFACE INHIBITION TO TARGETED DEGRADATION

Given the critical oncogenic status of SKP2, its pharmacological blockade has become a priority in drug discovery. However, unlike kinases that possess deep, druggable ATP-binding pockets, E3 ligases typically rely on expansive, featureless PPI surfaces. This structural characteristic has historically rendered SKP2 a challenging, if not “undruggable” target [283] (Table 6, Figure 6).

Table 6 | Pharmacological strategies and emerging therapeutic modalities targeting SKP2.

Therapeutic modality	Lead agent	Mechanism of action	Development stage and key insights	Refs.
Small-molecule inhibitor (F-box interface)	SZL-P1-41	Binds F-box pocket; blocks SKP1/SCF assembly	Preclinical: efficacious in CRPC; limited by poor oral bioavailability	[13]
Small-molecule inhibitor (CKS1 interface)	SKPin C1	Disrupts SKP2-CKS1 contact surface	Probe: restores p27; spares K63-linked functions	[23, 284]
Small-molecule inhibitor (p27-binding pocket)	NSC689857	Occludes p27 pocket in SKP2-CKS1 interface	Preclinical: stabilizes p27; induces G1 arrest; validates site druggability	[285]
Small-molecule inhibitor (Cullin-1 interface)	DT204	Disrupts SKP2-Cul1; destabilizes SCF	Preclinical: overcomes bortezomib resistance in myeloma	[286]
Expression modulator (stress inducer)	SMIP004	Elicits ROS/UPR; suppresses SKP2 TXN/TLN	Probe: triggers cytotoxic autophagy in prostate cancer	[262]
Induced-proximity degrader	SKPer1	Recruits STUB1 E3 for SKP2 ubiquitination	Preclinical: from DEFUSE screen; <i>in vivo</i> tumor suppression	[25]
Natural product	Flavokawain A	Promotes SKP2 auto-degradation	Nutraceutical: efficacy in CRPC patient organoids	[287]
Natural product	Tanshinone IIA	Inhibits USP2-SKP2; accelerates proteolysis	Preclinical: 5-FU chemosensitization in CRC	[265]

9.1 First-generation strategy: small molecule interface blockade

Early efforts leveraging computer-aided drug design and high-throughput screening focused on identifying small molecules capable of disrupting specific SKP2 interfaces via occupancy-based inhibition.

9.1.1 SZL-P1-41 (targeting the F-box). This compound, identified by the Lin group, specifically binds a hydrophobic pocket within the SKP2 F-box domain [13]. Mechanistically, it acts via steric hindrance and prevents the adaptor protein SKP1 from docking, thus triggering physical disassembly of the SCF-SKP2 E3 ligase complex, halting substrate recruitment, and suppressing Akt activity. SZL-P1-41 exhibits high specificity and efficacy in lung and prostate cancer models [13].

9.1.2 SKPin C1 (targeting the CKS1 interface). This agent specifically disrupts the SKP2-CKS1 contact surface. Consequently, it selectively impedes the ubiquitination of p27 (a process requiring CKS1) but might spare substrates that bind SKP2 independently of CKS1. It serves primarily as a chemical probe to restore p27 protein levels in metastatic models [23, 284].

9.1.3 NSC689857 (targeting the p27-binding pocket). NSC689857, identified as an inhibitor of the SKP2-Cks1 protein-protein interaction via a high-throughput AlphaScreen assay, inhibits p27^{Kip1} ubiquitination *in vitro*. This compound provides a tool to probe SKP2-mediated degradation of p27 rather than disassembling the core SCF-SKP2 E3 ligase complex [285].

9.1.4 SMIP004 (targeting upstream regulation). SMIP004 is a small molecule that downregulates SKP2 protein levels and stabilizes p27/p21 in cancer cells. According to mechanistic studies, it induces oxidative stress and activates the unfolded protein response, in a manner correlating with suppression of SKP2 expression and consequent cell-cycle arrest and apoptosis [286].

9.1.5 DT204 (disrupting SCF integrity). DT204, identified through chemical library screening, inhibits SCF-SKP2 activity by decreasing SKP2 binding Cullin-1 and Commd1, thus stabilizing the CDK inhibitor p27 and eliciting synergistic anti-myeloma effects that overcome bortezomib resistance in preclinical models [262].

9.1.6 Phytochemical modulators. Tanshinone IIA (Tan IIA) promotes SKP2 ubiquitination and degradation by attenuating its interaction with the DUB USP2, suppressing the SKP2/Akt/HK2 signaling axis, and inhibiting aerobic glycolysis in CRC cells [265]. Additionally, Flavokawain A has been shown to induce deneddylation-linked SKP2 degradation and to suppress tumorigenesis in prostate cancer models [287].

9.2 Second-generation strategy: the revolution of targeted protein degradation

Whereas traditional inhibitors struggle with the “undruggable” nature of PPIs, targeted protein degradation offers a revolutionary alternative. A recent breakthrough has successfully identified the first authentic small-molecule degrader for SKP2.

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Targeting Strategies for SKP2: From Interface Inhibitors to Targeted Degradation

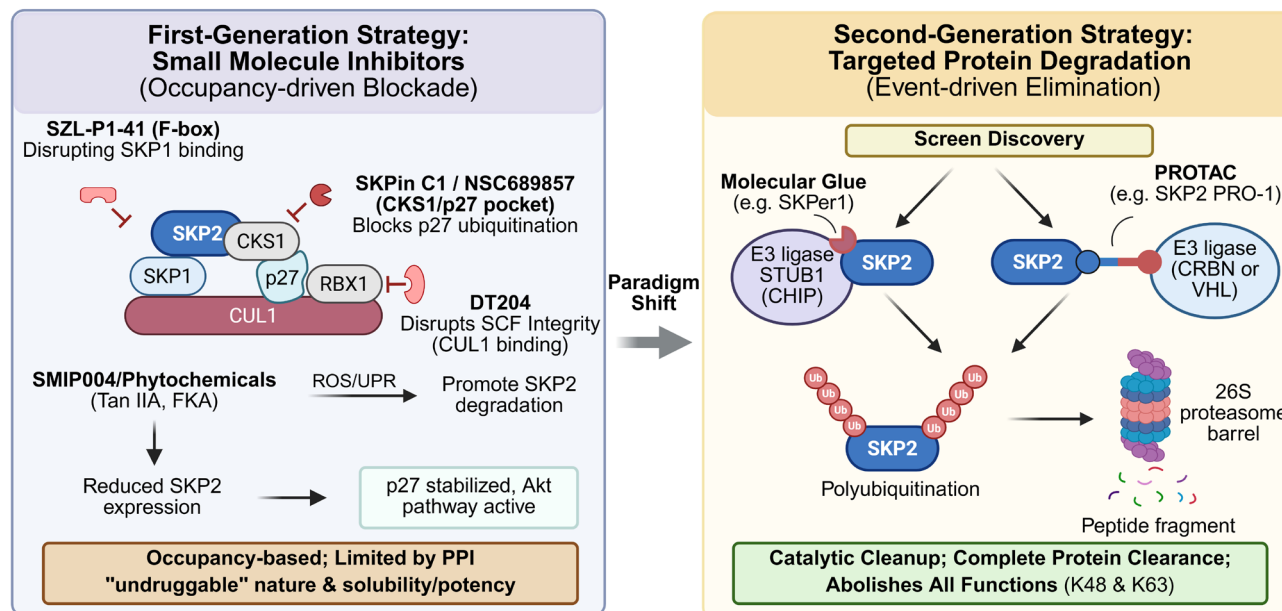


Figure 6 | Progress in SKP2-targeting strategies: from interface inhibitors to targeted protein degradation.

(Left) Small Molecule Inhibitors. This approach relies on occupancy-driven blockade to interfere with protein-protein interactions (PPIs) within the SCF complex. Specific inhibitors target distinct interfaces: SZL-P1-41 disrupts SKP1 binding; SKPin C1 and NSC689857 target the CKS1/p27 pocket and block p27 ubiquitination; and DT204 interferes with CUL1 binding and disrupts SCF integrity. Additionally, agents such as SMIP004 and phytochemicals (e.g., Tan IIA or Flavokawain A) indirectly promote SKP2 degradation via ROS/UPR stress pathways. However, this strategy is limited by the “undruggable” nature of PPIs, solubility issues, and potential compensatory signaling (e.g., activation of the Akt pathway). **(Right)** Targeted Protein Degradation (TPD). This approach uses an event-driven mechanism for the complete catalytic clearance of SKP2. Through the DEFUSE screen, novel degraders have been identified, including molecular glue-like degraders (e.g., SKPer1) that recruit the E3 ligase STUB1 (CHIP). Prototype PROTACs (e.g., SKP2 PRO-1, supported by grant No. 5R01CA277682-04) link SKP2 to ligases such as CRBN or VHL. Both methods induce polyubiquitination and subsequent proteasomal degradation of SKP2. This strategy enhances efficacy by broadly suppressing both proteolytic (K48-linked) and non-proteolytic (K63-linked) SKP2-dependent ubiquitination programs through complete protein removal. Figure created with [BioRender.com](https://www.biorender.com).

To overcome the limitations of rational design, researchers have developed a novel high-throughput screen termed DEath FUSion Escaper (DEFUSE). This approach ingeniously translates target protein degradation into a cell survival phenotype. Conjugation of the protein of interest to a fast-acting, triggerable death protein ensures that only cells that successfully degrade the target (and therefore the death protein) survive. With the DEFUSE method, the small molecule SKPer1 has been identified. Unlike traditional PROTACs, which are often designed to recruit Cereblon or VHL, SKPer1 functions as a “molecular glue” or induced-proximity degrader that specifically recruits the E3 ligase STUB1 (CHIP) to SKP2. This induced interaction triggers the ubiquitination and subsequent proteasomal degradation of SKP2. Mechanistically, SKPer1 specifically kills SKP2-expressing cancer cells and exhibits substantial tumor suppression with a good safety profile *in vivo*. Furthermore, a specific sequence of ten amino acids from SKP2 has been found to serve as a versatile degradation tag [25].

Although specific SKP2-targeting PROTACs have yet to be fully realized in clinical settings, the maturation of PROTAC technology offers a theoretical solution to the “undruggable” nature of SKP2’s PPI interfaces. Unlike inhibitors that must occupy a functional binding site with high affinity, PROTACs theoretically require only a transient binding event to recruit an E3 ligase (e.g., Cereblon or VHL) to SKP2, thereby triggering its polyubiquitination and subsequent proteasomal degradation. Ongoing research funded by the NIH (grant No. 5R01CA277682-04) is developing SKP2 PRO-1, a dedicated SKP2-targeting PROTAC. Emerging data indicating that SKP2 PRO-1 robustly induces SKP2 degradation have validated the feasibility of using PROTAC technology to eliminate this onco-protein. Because this event-driven mechanism might potentially abolish both the catalytic (p27 degradation) and non-canonical (Akt activation) functions of SKP2, it is a potential critical direction for future drug development.

9.3 Validated combination strategies

Given the plasticity of cancer cells, monotherapy often leads to resistance. The following combinatorial approaches are supported by specific mechanistic evidence.

9.3.1 Overcoming resistance to proteasome inhibitors. The SCF-SKP2 complex, by promoting cell-cycle progression, limits the efficacy of proteasome inhibitors. Combining DT204 with bortezomib synergistically induces apoptosis in bortezomib-resistant multiple myeloma cells. Mechanistically, DT204 prevents the counter-regulatory upregulation of SKP2 often observed in bortezomib monotherapy [262].

9.3.2 Overcoming 5-Fu resistance via metabolic modulation. 5-Fu resistance, a major hurdle in CRC, is often driven by metabolic reprogramming. Combining Tan IIA with the USP2 inhibitor ML364 exerts synergistic effects. Through dual inhibition of USP2 function, this combination significantly promotes Ub-mediated SKP2 degradation, suppresses aerobic glycolysis (via the Skp2/Akt/HK2 signaling axis), and overcomes 5-Fu resistance in both *in vitro* and xenograft mouse models [265].

9.3.3 SKP2 knockdown via siRNA nanoparticles enhances anti-tumor efficacy. Targeted knockdown of SKP2 with siRNA-loaded nanoparticles is a promising combinatorial approach for prostate cancer. When combined with the natural compound quercetin, siSKP2 nanoparticles significantly decrease SKP2 expression, inhibit cell proliferation and migration, and induce apoptosis more effectively than either treatment alone. *In vivo*, this dual strategy has been found to suppress tumor growth in xenograft models and to demonstrate favorable biocompatibility; therefore, gene silencing plus chemical modulation has potential as a synergistic SKP2-targeted therapy [288].

9.3.4 SKP2 inhibition combined with Aurora-A kinase inhibition. In ccRCC models, the Aurora-A kinase inhibitor MLN8237 combined with the SKP2 inhibitor SZL P1-41 exhibits significantly greater anti-proliferative effects than either agent alone. Mechanistically, this combination synergistically induces cell death *in vitro*, thus highlighting the potential of dual targeting of SKP2 and Aurora-A as an effective therapeutic strategy in ccRCC [131].

9.3.5 Functional convergence of SKP2 and PARP-mediated repair: a synthetic lethality perspective. Although no definitive biochemical evidence has yet demonstrated that SKP2 directly ubiquitinates PARP1 or modulates its catalytic activity, accumulating data support a functional crosstalk between SKP2 signaling and PARP-dependent DNA repair pathways. This connection stems primarily from the established role of SKP2 in maintaining HR competence, a pathway essential for accurate DSB repair [210, 289].

Mechanistically, SKP2 contributes to early DNA damage signaling events required for HR. Under genotoxic stress, SKP2 mediates K63-linked ubiquitination of NBS1, thereby enhancing the interaction between NBS1 and ATM, and facilitating efficient activation of the DDR cascade necessary for end resection and HR initiation [197]. Recent studies and reviews of DDR signaling networks further support the importance of ubiquitin-dependent regulation of MRN-ATM signaling in coordinating HR activation [290]. In addition, SKP2 depletion has been associated with impaired formation of RAD51 foci and diminished HR efficiency in cancer cells, thus indicating compromised assembly of HR repair complexes [197]. Collectively, these findings suggest that loss of SKP2 function creates an HR-defective state resembling “BRCAness,” characterized by diminished ability to repair DSBs through canonical HR mechanisms [210].

Cells with impaired HR become increasingly reliant on PARP-mediated repair pathways, including single-strand-break repair and alternative end-joining mechanisms [291]. This compensatory dependency provides a mechanistic basis for synthetic lethality. Indeed, pre-clinical studies have shown that SKP2 deficiency sensitizes tumor cells to PARP inhibition, in agreement with an HR-deficient phenotype. In this framework, SKP2 suppression functionally shifts reliance on DNA repair toward PARP activity; simultaneously, inhibition of PARP results in unrepaired DNA lesions, genomic instability, and cell death [210, 291].

Importantly, available evidence supports a functional interdependence between SKP2 and PARP pathways rather than a direct enzyme-substrate relationship. Accordingly, future investigations should examine whether SKP2 indirectly influences PARP pathway dynamics, either by modulating HR factor availability or through ubiquitin-dependent regulation of DDR scaffolding proteins. Establishing such biochemical connections would substantially refine the mechanistic understanding of how SKP2 integrates into PARP-centered DNA repair networks.

9.4 Limitations and future challenges

Despite the therapeutic promise of targeting SKP2, several barriers to clinical translation persist; notably, the “undruggable” nature of SKP2 remains a central challenge. The shallow, hydrophobic PPI interfaces require inhibitors with high surface-area coverage, which often leads to high molecular weight and poor physicochemical properties (e.g., low solubility of SZL-P1-41) and hinders oral bioavailability [292]. SKP2 drives the cell cycle in normal proliferating tissues (e.g., the bone marrow or gut epithelium). Consequently, systemic inhibition poses theoretical risks of adverse effects such as cytopenia or gastrointestinal toxicity [127]. However, the biological viability of *Skp2*-knockout mice provides a strong rationale for a therapeutic window; these mice are viable and fertile despite growth retardation;

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therefore, normal tissues appear to tolerate SKP2 loss better than cancer cells [188, 293]. The development of SKPer1 highlights the potential of small-molecule degraders to selectively target SKP2 [25]. Building on this foundation, future research should focus on optimizing chemical scaffolds and PROTAC designs to enhance SKP2 degradation efficiency, improve pharmacokinetic properties, and achieve robust anti-tumor activity in preclinical models. These efforts are aimed at translating the proof of concept provided by SKPer1 into next-generation SKP2-targeted therapeutics with higher potency and broader applicability.

9.5 Translational challenges and clinical prospects: from bench to bedside

Despite the compelling preclinical evidence validating SKP2 as an oncogenic driver, no SKP2-targeted therapies have yet entered clinical trials. This translational gap stems from several inherent challenges associated with targeting the UPS. Unlike kinases with deep, hydrophobic ATP-binding pockets, E3 ligases such as SCF-SKP2 function through large, flat protein-protein interfaces (e.g., the SKP2-SKP1 or SKP2-Cks1 interface). Developing small molecules with high affinity and specificity for these surface interactions remains a formidable challenge in medicinal chemistry [294]. Although first-generation inhibitors such as compound #25 and SZL-P1-41 have shown proof-of-concept efficacy, frequent suboptimal potency and off-target effects limit their clinical development [23, 295].

Novel modalities such as peptides and PROTACs offer higher specificity but face substantial pharmacokinetic hurdles. Peptides that disrupt the SKP2-substrate interface generally exhibit poor membrane permeability and rapid *in vivo* degradation [292]. Similarly, although SKP2-targeting PROTACs can catalytically degrade the protein, their high molecular weight often results in poor oral bioavailability and cellular uptake, and restricts their utility to intravenous administration or use of complex delivery systems [296, 297]. A major concern regarding systemic SKP2 inhibition is the potential toxicity to normal proliferating tissues (e.g., bone marrow or gut epithelium), given SKP2's essential role in cell-cycle progression [298]. However, genetic studies provide a rationale for a therapeutic window: *skp2*-knockout mice are viable and healthy, albeit small; these findings suggest that normal cells possess redundant mechanisms (e.g., other F-box proteins) to regulate p27, whereas cancer cells often exhibit "oncogene addiction" to SKP2 [66]. Nevertheless, comprehensive toxicology studies are required to rule out adverse effects on stem cell maintenance and gametogenesis [13].

To improve the success rate of future clinical trials, patient stratification will be critical. Given that not all tumors are driven by SKP2, predictive biomarkers must be established to ensure clinical success. To this end, a high SKP2/p27 ratio (detected via immunohistochemistry) is the most logical candidate [245, 299]. Additional

strategies may include replication-stress signatures (HR-defective tumor contexts), rational combination regimens with PARP inhibitors or replication-stress-inducing agents, and the development of next-generation modalities that selectively modulate SCF-SKP2 E3 ligase activity in tumor cells while sparing normal proliferating tissues [300, 301]. Future trials should prioritize these molecularly defined subgroups to maximize the therapeutic index.

10. CONCLUSION AND FUTURE PERSPECTIVES

In the research landscape, the conceptual framework for SKP2 has substantially evolved. No longer viewed merely as a single cell-cycle modulator, SKP2 is now recognized as an integrative nexus that couples cellular proliferation with metabolic reprogramming and genomic integrity [66]. Whereas the crystallographic elucidation of the SKP2-CKS1 interface provided the initial blueprint for rational drug design [23], the field is currently witnessing a paradigm shift from occupancy-based inhibition to targeted protein degradation.

In the future, several key trends will define the trajectory of SKP2 research. The validation of the DEFUSE screening platform and the discovery of SKPer1 marked a turning point [25]. These findings provided the first proof of concept that SKP2, traditionally considered "undruggable" because of its featureless PPI interfaces, can be effectively targeted for destruction via induced proximity to E3 ligases such as STUB1 [25]. Future medicinal chemistry efforts are likely to focus on optimizing the physicochemical properties of such degraders to enhance their oral bioavailability and stability. Refinement of predictive biomarkers will be crucial for establishing precise patient stratification criteria. Genetic contexts, such as *PTEN* loss [17] and the interplay between SKP2 and oncogenic drivers, such as MYC, suggest potential stratification criteria for future biomarker development [66]. Consequently, SKP2-directed therapies might yield the highest therapeutic index in these defined molecular subgroups rather than in unselected patient populations [203]. The therapeutic horizon extends beyond simple cell cycle arrest. The recent elucidation of the Tan IIA-USP2-SKP2 axis highlights the potential of targeting SKP2 to reverse metabolic reprogramming (aerobic glycolysis) and overcome chemotherapy resistance (e.g., to 5-Fu) in CRC [265]. In immunotherapy, targeting the SKP2-PD-L1 axis is supported by pan-cancer evidence showing that SKP2 overexpression correlates with an immune-cold tumor microenvironment and might limit T-cell infiltration; these findings suggest that SKP2 inhibition might enhance responsiveness to immune checkpoint blockade by promoting anti-tumor immunity [207, 274]. Given that aberrant neuronal cell cycle re-entry is a recognized pathological feature of neurodegenerative conditions such as AD, cell cycle regulators have been implicated in disease mechanisms, although direct evidence of SKP2-specific intervention to prevent

this process is currently lacking [302]. Achieving any CNS therapeutic effect will require agents capable of effectively crossing the blood–brain barrier.

Despite its well-documented pro-tumorigenic activity through degradation of the CDK inhibitor p27, SKP2's physiological role in cancer is not universally oncogenic and can vary according to genetic context. In some experimental systems, loss of *Skp2* does not uniformly suppress tumor development but paradoxically engages tumor-suppressive processes in specific settings. For example, in compound mouse models combining *Pten* loss with *Skp2* deficiency, inactivation of *Skp2* enhances p27 accumulation and induces robust cellular senescence, thereby inhibiting tumor progression in prostate and other tissues that are otherwise prone to oncogenic growth [282, 303]. Therefore, under certain tumor suppressor-deficient backgrounds, SKP2 might restrain aberrant proliferation by preventing senescence or other fail-safe mechanisms; these findings underscore the need to delineate the molecular switches governing whether SKP2 functions predominantly as a proliferative driver or as a context-dependent check on tumorigenesis [304].

A related concern in translating SKP2 inhibition into therapy is the risk of selecting therapy-resistant cell states. As discussed in Section 8.1, downregulation of SKP2 is associated with entry into a dormant, quiescent (G0) state marked by high p27, which can enable residual tumor cells to survive initial cytotoxic therapy and contribute to later relapse [253, 305]. Therefore, prolonged systemic inhibition of SKP2 might possibly drive a subpopulation of tumor cells into quiescence rather than eliminating them. Hence, determining whether intermittent versus continuous dosing regimens can mitigate such adaptive resistance will be important for future clinical development [246].

Although SKP2 has traditionally been considered a nuclear ubiquitin ligase, its regulation outside the nucleus and non-canonical cytoplasmic functions remain underexplored. SKP2-mediated K63-linked ubiquitination of cytoplasmic substrates such as Akt has been implicated in promoting oncogenic signaling and chemoresistance, thus challenging a strictly nuclear-centric view of SCF complexes [193, 292]. The mechanisms governing nuclear-cytoplasmic shuttling of SKP2 and the relative contributions of its cytoplasmic activities to tumor progression, distinct from its canonical cell-cycle roles, are important areas for future research, particularly because they might offer opportunities to selectively target oncogenic functions while sparing essential nuclear processes [245, 306].

In summary, targeting SKP2 is a potent strategy to disrupt a core mechanism required by cancer cells [13]. With the emergence of authentic degraders such as SKPer1 and validated combination strategies involving metabolic and immune modulators, SKP2-directed therapies are increasingly maturing. The focus must now shift toward rigorous pharmacological optimization and

biomarker-driven clinical validation to translate these biological insights into tangible patient benefits.

DATA AVAILABILITY STATEMENT

No data were used for the research described in the article.

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CONFLICT OF INTEREST

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REFERENCES

- [1] Popovic D, Vucic D, Dikic I: Ubiquitination in Disease Pathogenesis and Treatment. *Nature Medicine* 2014, 20:1242–1253.
- [2] Nakayama KI, Nakayama K: Ubiquitin Ligases: Cell-Cycle Control and Cancer. *Nature Reviews Cancer* 2006, 6:369–381.
- [3] Hershko A, Ciechanover A: The Ubiquitin System. *Annual Review of Biochemistry* 1998, 67:425–479.
- [4] Petroski MD, Deshaies RJ: Function and Regulation of Cullin-RING Ubiquitin Ligases. *Nature Reviews Molecular Cell Biology* 2005, 6:9–20.
- [5] Carrano AC, Eytan E, Hershko A, Pagano M: SKP2 is Required for Ubiquitin-Mediated Degradation of the CDK Inhibitor p27. *Nature Cell Biology* 1999, 1:193–199.
- [6] Tsvetkov LM, Yeh KH, Lee SJ, Sun H, Zhang H: p27^{Kip1} Ubiquitination and Degradation is Regulated by the SCF^{Skp2} Complex through Phosphorylated Thr187 in p27. *Current Biology* 1999, 9:661–664.
- [7] Chan CH, Li CF, Yang WL, Gao Y, Lee SW, Feng Z, et al.: The Skp2-SCF E3 Ligase Regulates Akt Ubiquitination, Glycolysis, Herceptin Sensitivity, and Tumorigenesis. *Cell* 2012, 149:1098–1111.
- [8] Liu J, Peng Y, Shi L, Wan L, Inuzuka H, Long J, et al.: Skp2 Dictates Cell Cycle-Dependent Metabolic Oscillation between Glycolysis and TCA Cycle. *Cell Research* 2021, 31:80–93.
- [9] Jia J, Yan D, Wang Y, Liu M, Jia Z, Luo L, et al.: Skp2 Regulates DNA Damage Repair and Apoptosis via Interaction with Ku70. *Experimental Cell Research* 2020, 397:112335.
- [10] Wang J, Han F, Wu J, Lee SW, Chan CH, Wu CY, et al.: The Role of Skp2 in Hematopoietic Stem Cell Quiescence, Pool Size, and Self-Renewal. *Blood* 2011, 118:5429–5438.
- [11] Wang J, Han F, Lee SW, Wu J, Chan CH, Zhang X, et al.: E3-Ligase Skp2 Regulates β -Catenin Expression and Maintains Hematopoietic Stem Cell Homing. *Biochemical and Biophysical Research Communications* 2014, 445:566–571.
- [12] Gassen NC, Niemeyer D, Muth D, Corman VM, Martinelli S, Gassen A, et al.: SKP2 Attenuates Autophagy through Beclin1-Ubiquitination and its Inhibition Reduces

Review Article

- MERS-Coronavirus Infection. *Nature Communications* 2019, 10:5770.
- [13] Chan CH, Morrow JK, Li CF, Gao Y, Jin G, Moten A, et al.: Pharmacological Inactivation of Skp2 SCF Ubiquitin Ligase Restricts Cancer Stem Cell Traits and Cancer Progression. *Cell* 2013, 154:556–568.
 - [14] Jin G, Lee SW, Zhang X, Cai Z, Gao Y, Chou PC, et al.: Skp2-Mediated RagA Ubiquitination Elicits a Negative Feedback to Prevent Amino-Acid-Dependent mTORC1 Hyperactivation by Recruiting GATOR1. *Molecular Cell* 2015, 58:989–1000.
 - [15] Shin HJ, Kim H, Oh S, Lee JG, Kee M, Ko HJ, et al.: AMPK-SKP2-CARM1 Signalling Cascade in Transcriptional Regulation of Autophagy. *Nature* 2016, 534:553–557.
 - [16] Shin HR, Kim H, Kim KI, Baek SH: Epigenetic and Transcriptional Regulation of Autophagy. *Autophagy* 2016, 12:2248–2249.
 - [17] Lu W, Liu S, Li B, Xie Y, Adhiambo C, Yang Q, et al.: SKP2 Inactivation Suppresses Prostate Tumorigenesis by Mediating JARID1B Ubiquitination. *Oncotarget* 2015, 6:771–788.
 - [18] Frescas D, Pagano M: Deregulated Proteolysis by the F-box Proteins SKP2 and β -TrCP: Tipping the Scales of Cancer. *Nature Reviews Cancer* 2008, 8:438–449.
 - [19] Ruan D, He J, Li CF, Lee HJ, Liu J, Lin HK, et al.: Skp2 Deficiency Restricts the Progression and Stem Cell Features of Castration-Resistant Prostate Cancer by Destabilizing Twist. *Oncogene* 2017, 36:4299–4310.
 - [20] Clement E, Inuzuka H, Nihira NT, Wei W, Toker A: Skp2-Dependent Reactivation of AKT Drives Resistance to PI3K Inhibitors. *Science Signaling* 2018, 11:eaa03810.
 - [21] Wang W, Gu XH, Li M, Cheng ZJ, Tian S, Liao Y, et al.: MicroRNA-155-5p Targets SKP2, Activates IKK β , Increases A β Aggregation, and Aggravates a Mouse Alzheimer Disease Model. *Journal of Neuro pathology and Experimental Neurology* 2022, 81:16–26.
 - [22] Jakhmola-Mani R, Islam A, Katare DP: Liver-Brain Axis in Sporadic Alzheimer's Disease: Role of Ten Signature Genes in a Mouse Model. *CNS & Neurological Disorders Drug Targets* 2021, 20:871–885.
 - [23] Kamel EM, Khadrawy SM, Allam AA, Ahmed NA, Aba Alkhayl FF, Lamsabhi AM: Targeting the Skp2–Cks1 Protein–Protein Interaction: Structures, Assays, and Preclinical Inhibitors. *European Journal of Pharmacology* 2025, 1006:178129.
 - [24] Sun X, Gao H, Yang Y, He M, Wu Y, Song Y, et al.: PROTACs: Great Opportunities for Academia and Industry. *Signal Transduction and Targeted Therapy* 2019, 4:64.
 - [25] Chu Y, Chen S, Yang M, Chen Y, Fang H, Huang P, et al.: A Rapid Imaging-Based Screen for Induced-Proximity Degraders Identifies a Potent Degradator of Oncoprotein SKP2. *Nature Biotechnology* 2025. doi: 10.1038/s41587-025-02793-8
 - [26] Ciechanover A: Proteolysis: From the Lysosome to Ubiquitin and the Proteasome. *Nature Reviews Molecular Cell Biology* 2005, 6:79–87.
 - [27] Dikic I, Elazar Z: Mechanism and Medical Implications of Mammalian Autophagy. *Nature Reviews Molecular Cell Biology* 2018, 19:349–364.
 - [28] Zheng N, Shabek N: Ubiquitin Ligases: Structure, Function, and Regulation. *Annual Review Biochemistry* 2017, 86:129–157.
 - [29] Pohl C, Dikic I: Cellular Quality Control by the Ubiquitin-Proteasome System and Autophagy. *Science* 2019, 366:818–822.
 - [30] Hershko A, Ciechanover A, Heller H, Haas AL, Rose IA: Proposed Role of ATP in Protein Breakdown: Conjugation of Protein with Multiple Chains of the Polypeptide of ATP-Dependent Proteolysis. *Proceedings of the National Academy of Sciences of the United States of America* 1980, 77:1783–1786.
 - [31] Ciechanover A: The Unravelling of the Ubiquitin System. *Nature Reviews Molecular Cell Biology* 2015, 16:322–324.
 - [32] Liu H, Bui Q, Hassenstab J, Gordon BA, Benzinger TLS, Timsina J, et al.: Ubiquitin-Proteasome System in the Different Stages of Dominantly Inherited Alzheimer's Disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2025, 21:e70243.
 - [33] Bard JAM, Goodall EA, Greene ER, Jonsson E, Dong KC, Martin A: Structure and Function of the 26S Proteasome. *Annual Review Biochemistry* 2018, 87:697–724.
 - [34] Schulman BA, Harper JW: Ubiquitin-Like Protein Activation by E1 Enzymes: The Apex for Downstream Signalling Pathways. *Nature Reviews Molecular Cell Biology* 2009, 10:319–331.
 - [35] Smalle J, Vierstra RD: The Ubiquitin 26S Proteasome Proteolytic Pathway. *Annual Review of Plant Biology* 2004, 55:555–590.
 - [36] Verma R, Aravind L, Oania R, McDonald WH, Yates JR 3rd, Koonin EV, et al.: Role of Rpn11 Metalloprotease in Deubiquitination and Degradation by the 26S Proteasome. *Science* 2002, 298:611–615.
 - [37] Chen S, Wu J, Lu Y, Ma YB, Lee BH, Yu Z, et al.: Structural Basis for Dynamic Regulation of the Human 26S Proteasome. *Proceedings of the National Academy of Sciences of the United States of America* 2016, 113:12991–12996.
 - [38] Harper JW, Schulman BA: Cullin-RING Ubiquitin Ligase Regulatory Circuits: A Quarter Century Beyond the F-Box Hypothesis. *Annual Review Biochemistry* 2021, 90:403–429.
 - [39] Hua Z, Vierstra RD: The Cullin-RING Ubiquitin-Protein Ligases. *Annual Review of Plant Biology* 2011, 62:299–334.
 - [40] Qi Y, Rezaeian AH, Wang J, Huang D, Chen H, Inuzuka H, et al.: Molecular Insights and Clinical Implications for the Tumor Suppressor Role of SCF^{FBXW7} E3 Ubiquitin Ligase. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* 2024, 1879:189140.
 - [41] Zhou W, Wei W, Sun Y: Genetically Engineered Mouse Models for Functional Studies of SKP1-CUL1-F-Box-Protein (SCF) E3 Ubiquitin Ligases. *Cell Research* 2013, 23:599–619.
 - [42] Asmamaw MD, Liu Y, Zheng YC, Shi XJ, Liu HM: Skp2 in the Ubiquitin-Proteasome System: A Comprehensive Review. *Medicinal Research Reviews* 2020, 40:1920–1949.
 - [43] Rotin D, Kumar S: Physiological Functions of the HECT Family of Ubiquitin Ligases. *Nature Reviews Molecular Cell Biology* 2009, 10:398–409.
 - [44] Song MS, Pandolfi PP: The HECT Family of E3 Ubiquitin Ligases and PTEN. *Seminars in Cancer Biology* 2022, 85:43–51.
 - [45] Goto J, Otaki Y, Watanabe T, Watanabe M: The Role of HECT-Type E3 Ligase in the Development of Cardiac Disease. *International Journal of Molecular Sciences* 2021, 22:6065.
 - [46] Walden H, Rittinger K: RBR Ligase-Mediated Ubiquitin Transfer: A Tale with many Twists and Turns. *Nature Structural & Molecular Biology* 2018, 25:440–445.

- [47] Wenzel DM, Lissounov A, Brzovic PS, Klevit RE: UBCH7 Reactivity Profile Reveals Parkin and HHARI to be RING/HECT Hybrids. *Nature* 2011, 474:105–108.
- [48] Wauer T, Komander D: Structure of the Human Parkin Ligase Domain in an Autoinhibited State. *EMBO Journal* 2013, 32:2099–2112.
- [49] Pickrell AM, Youle RJ: The Roles of PINK1, Parkin, and Mitochondrial Fidelity in Parkinson's Disease. *Neuron* 2015, 85:257–273.
- [50] Komander D, Rape M: The Ubiquitin Code. *Annual Review Biochemistry* 2012, 81:203–229.
- [51] Dikic I, Schulman BA: An Expanded Lexicon for the Ubiquitin Code. *Nature Reviews Molecular Cell Biology* 2023, 24:273–287.
- [52] Kolla S, Ye M, Mark KG, Rapé M: Assembly and Function of Branched Ubiquitin Chains. *Trends in Biochemical Sciences* 2022, 47:759–771.
- [53] Tracz M, Bialek W: Beyond K48 and K63: Non-Canonical Protein Ubiquitination. *Cellular & Molecular Biology Letters* 2021, 26:1.
- [54] Lim KL, Lim GG: K63-Linked Ubiquitination and Neurodegeneration. *Neurobiology of Disease* 2011, 43:9–16.
- [55] Wickliffe KE, Williamson A, Meyer HJ, Kelly A, Rape M: K11-Linked Ubiquitin Chains as Novel Regulators of Cell Division. *Trends in Cell Biology* 2011, 21:656–663.
- [56] Emmerich CH, Schmukle AC, Walczak H: The Emerging Role of Linear Ubiquitination in Cell Signaling. *Science Signaling* 2011, 4:re5.
- [57] van Huizen M, Kikkert M: The Role of Atypical Ubiquitin Chains in the Regulation of the Antiviral Innate Immune Response. *Frontiers in Cell and Developmental Biology* 2019, 7:392.
- [58] Lee YR, Chen M, Lee JD, Zhang J, Lin SY, Fu TM, et al.: Reactivation of PTEN Tumor Suppressor for Cancer Treatment through Inhibition of a MYC-WWP1 Inhibitory Pathway. *Science* 2019, 364:eaau0159.
- [59] Yau R, Rape M: The Increasing Complexity of the Ubiquitin Code. *Nature Cell Biology* 2016, 18:579–586.
- [60] Draczkowski P, Chen SN, Chen T, Wang YS, Shih HA, Huang JYC, et al.: Structural Basis of K11/K48-Branched Ubiquitin Chain Recognition by the Human 26S Proteasome. *Nature Communications* 2025, 16:9094.
- [61] Yau RG, Doerner K, Castellanos ER, Haakonsen DL, Werner A, Wang N, et al.: Assembly and Function of Heterotypic Ubiquitin Chains in Cell-Cycle and Protein Quality Control. *Cell* 2017, 171:918–933.e20.
- [62] Ohtake F, Saeki Y, Ishido S, Kanno J, Tanaka K: The K48-K63 Branched Ubiquitin Chain Regulates NF- κ B Signaling. *Molecular Cell* 2016, 64:251–266.
- [63] Ohtake F, Tsuchiya H, Saeki Y, Tanaka K: K63 Ubiquitylation Triggers Proteasomal Degradation by Seeding Branched Ubiquitin Chains. *Proceedings of the National Academy of Sciences of the United States of America* 2018, 115:E1401–E1408.
- [64] Nijman SM, Luna-Vargas MP, Velds A, Brummelkamp TR, Dirac AM, Sixma TK, et al.: A Genomic and Functional Inventory of Deubiquitinating Enzymes. *Cell* 2005, 123:773–786.
- [65] Liao Y, Liu N, Xia X, Guo Z, Li Y, Jiang L, et al.: USP10 Modulates the SKP2/Bcr-Abl Axis via Stabilizing SKP2 in Chronic Myeloid Leukemia. *Cell Discovery* 2019, 5:24.
- [66] Cai Z, Moten A, Peng D, Hsu CC, Pan BS, Manne R, et al.: The Skp2 Pathway: A Critical Target for Cancer Therapy. *Seminars in Cancer Biology* 2020, 67(Pt 2):16–33.
- [67] Sato Y: Advances in Enzymatic Reconstitution of Ubiquitin Chains and Substrate Ubiquitination. *The Journal of Biochemistry* 2026, 179:155–162.
- [68] Finley D, Ulrich HD, Sommer T, Kaiser P: The Ubiquitin-Proteasome System of *Saccharomyces Cerevisiae*. *Genetics* 2012, 192:319–360.
- [69] Stewart MD, Ritterhoff T, Klevit RE, Brzovic PS: E2 Enzymes: More than just Middle Men. *Cell Research* 2016, 26:423–440.
- [70] Sarikas A, Hartmann T, Pan ZQ: The Cullin Protein Family. *Genome Biology* 2011, 12:220.
- [71] Zheng N, Schulman BA, Song L, Miller JJ, Jeffrey PD, Wang P, et al.: Structure of the Cul1-Rbx1-Skp1-F Box^{Skp2} SCF Ubiquitin Ligase Complex. *Nature* 2002, 416:703–709.
- [72] Wang Z, Liu P, Inuzuka H, Wei W: Roles of F-box Proteins in Cancer. *Nature Reviews Cancer* 2014, 14:233–247.
- [73] Tekcham DS, Chen D, Liu Y, Ling T, Zhang Y, Chen H, et al.: F-box Proteins and Cancer: An Update from Functional and Regulatory Mechanism to Therapeutic Clinical Prospects. *Theranostics* 2020, 10:4150–4167.
- [74] Ho MS, Tsai PI, Chien CT: F-box Proteins: The Key to Protein Degradation. *Journal of Biomedical Science* 2006, 13:181–191.
- [75] Randle SJ, Laman H: F-box Protein Interactions with the Hallmark Pathways in Cancer. *Seminars in Cancer Biology* 2016, 36:3–17.
- [76] Wu G, Xu G, Schulman BA, Jeffrey PD, Harper JW, Pavletich NP: Structure of a β -TrCP1-Skp1- β -Catenin Complex: Destruction Motif Binding and Lysine Specificity of the SCF $^{\beta$ -TrCP1 Ubiquitin Ligase. *Molecular Cell* 2003, 11:1445–1456.
- [77] Davis RJ, Welcker M, Clurman BE: Tumor Suppression by the Fbw7 Ubiquitin Ligase: Mechanisms and Opportunities. *Cancer Cell* 2014, 26:455–464.
- [78] Yumimoto K, Nakayama KI: Recent Insight into the Role of FBXW7 as a Tumor Suppressor. *Seminars in Cancer Biology* 2020, 67:1–15.
- [79] Kamura T, Koepp DM, Conrad MN, Skowyra D, Moreland RJ, Iliopoulos O, et al.: Rbx1, a Component of the VHL Tumor Suppressor Complex and SCF Ubiquitin Ligase. *Science (New York, N.Y.)* 1999, 284:657–661.
- [80] Hon WC, Wilson MI, Harlos K, Claridge TD, Schofield CJ, Pugh CW, et al.: Structural Basis for the Recognition of Hydroxyproline in HIF-1 Alpha by pVHL. *Nature* 2002, 417:975–978.
- [81] Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, et al.: The Tumour Suppressor Protein VHL Targets Hypoxia-Inducible Factors for Oxygen-Dependent Proteolysis. *Nature* 1999, 399:271–275.
- [82] Liao C, Hu L, Zhang Q: Von Hippel-Lindau Protein Signalling in Clear Cell Renal Cell Carcinoma. *Nature Reviews Urology* 2024, 21:662–675.
- [83] Genschik P, Sumara I, Lechner E: The Emerging Family of CULLIN3-RING Ubiquitin Ligases (CRL3s): Cellular Functions and Disease Implications. *The EMBO Journal* 2013, 32:2307–2320.
- [84] Pintard L, Willis JH, Willems A, Johnson JL, Srayko M, Kurz T, et al.: The BTB Protein MEL-26 is a Substrate-Specific Adaptor of the CUL-3 Ubiquitin-Ligase. *Nature* 2003, 425:311–316.
- [85] Stogios PJ, Privé GG: The BACK Domain in BTB-kelch Proteins. *Trends in Biochemical Sciences* 2004, 29:634–637.

Review Article

- [86] Yamamoto M, Kensler TW, Motohashi H: The KEAP1-NRF2 System: A Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis. *Physiological Reviews* 2018, 98:1169–1203.
- [87] Canning P, Sorrell FJ, Bullock AN: Structural Basis of Keap1 Interactions with Nrf2. *Free Radical Biology & Medicine* 2015, 88:101–107.
- [88] An J, Wang C, Deng Y, Yu L, Huang H: Destruction of Full-Length Androgen Receptor by Wild-Type SPOP, but not Prostate-Cancer-Associated Mutants. *Cell Reports* 2014, 6:657–669.
- [89] Gan W, Dai X, Lunardi A, Li Z, Inuzuka H, Liu P, et al.: SPOP Promotes Ubiquitination and Degradation of the ERG Oncoprotein to Suppress Prostate Cancer Progression. *Molecular Cell* 2015, 59:917–930.
- [90] Dai X, Gan W, Li X, Wang S, Zhang W, Huang L, et al.: Prostate Cancer-Associated SPOP Mutations Confer Resistance to BET Inhibitors Through Stabilization of BRD4. *Nature Medicine* 2017, 23:1063–1071.
- [91] Wang Z, Song Y, Ye M, Dai X, Zhu X, Wei W: The Diverse Roles of SPOP in Prostate Cancer and Kidney Cancer. *Nature Reviews. Urology* 2020, 17:339–350.
- [92] Biedermann S, Hellmann H: WD40 and CUL4-Based E3 Ligases: Lubricating all Aspects of Life. *Trends in Plant Science* 2011, 16:38–46.
- [93] Angers S, Li T, Yi X, MacCoss MJ, Moon RT, Zheng N: Molecular Architecture and Assembly of the DDB1-CUL4A Ubiquitin Ligase Machinery. *Nature* 2006, 443:590–593.
- [94] Petzold G, Fischer ES, Thomä NH: Structural Basis of Lenalidomide-Induced CK1 α Degradation by the CRL4^{CRBN} Ubiquitin Ligase. *Nature* 2016, 532:127–130.
- [95] Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, et al.: Cereblon is a Direct Protein Target for Immunomodulatory and Antiproliferative Activities of Lenalidomide and Pomalidomide. *Leukemia* 2012, 26:2326–2335.
- [96] Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, et al.: Identification of a Primary Target of Thalidomide Teratogenicity. *Science (New York, N.Y.)* 2010, 327:1345–1350.
- [97] Krönke J, Fink EC, Hollenbach PW, MacBeth KJ, Hurst SN, Udeshi ND, et al.: Lenalidomide Induces Ubiquitination and Degradation of CK1 α in del(5q) MDS. *Nature* 2015, 523:183–188.
- [98] Fischer ES, Böhm K, Lydeard JR, Yang H, Stadler MB, Cavadini S, et al.: Structure of the DDB1-CRBN E3 Ubiquitin Ligase in Complex with Thalidomide. *Nature* 2014, 512:49–53.
- [99] Zhao Y, Xiong X, Sun Y: Cullin-RING Ligase 5: Functional Characterization and its Role in Human Cancers. *Seminars in Cancer Biology* 2020, 67:61–79.
- [100] Adachi Y, Terakura S, Osaki M, Okuno Y, Sato Y, Sagou K, et al.: Cullin-5 Deficiency Promotes Chimeric Antigen Receptor T Cell Effector Functions Potentially Via the Modulation of JAK/STAT Signaling Pathway. *Nature Communications* 2024, 15:10376.
- [101] Yu X, Yu Y, Liu B, Luo K, Kong W, Mao P, et al.: Induction of APOBEC3G Ubiquitination and Degradation by an HIV-1 Vif-Cul5-SCF Complex. *Science (New York, N.Y.)* 2003, 302:1056–1060.
- [102] Lumpkin RJ, Baker RW, Leschziner AE, Komives EA: Structure and Dynamics of the ASB9 CUL-RING E3 Ligase. *Nature Communications* 2020, 11:2866.
- [103] Stanley BJ, Ehrlich ES, Short L, Yu Y, Xiao Z, Yu XF, et al.: Structural Insight into the Human Immunodeficiency Virus Vif SOCS Box and its Role in Human E3 Ubiquitin Ligase Assembly. *Journal of Virology* 2008, 82:8656–8663.
- [104] Shi L, Du D, Peng Y, Liu J, Long J: The Functional Analysis of Cullin 7 E3 Ubiquitin Ligases in Cancer. *Oncogenesis* 2020, 9:98.
- [105] Hopf LVM, Baek K, Klügel M, von Gronau S, Xiong Y, Schulman BA: Structure of CRL7^{FBXW8} Reveals Coupling with CUL1-RBX1/ROC1 for Multi-Cullin-RING E3-Catalyzed Ubiquitin Ligation. *Nature Structural & Molecular Biology* 2022, 29:854–862.
- [106] Litterman N, Ikeuchi Y, Gallardo G, O'Connell BC, Sowa ME, Gygi SP, et al.: An OBSL1-Cul7^{FBXW8} Ubiquitin Ligase Signaling Mechanism Regulates Golgi Morphology and Dendrite Patterning. *PLoS Biology* 2011, 9:e1001060.
- [107] Huber C, Dias-Santagata D, Glaser A, O'Sullivan J, Brauner R, Wu K, et al.: Identification of Mutations in CUL7 in 3-M Syndrome. *Nature Genetics* 2005, 37:1119–1124.
- [108] Nikolaev AY, Li M, Puskas N, Qin J, Gu W: Parc: A Cytoplasmic Anchor for p53. *Cell* 2003, 112:29–40.
- [109] Ortolano NA, Romero-Morales AI, Rasmussen ML, Bodnya C, Kline LA, Joshi P, et al.: A Proteomics Approach for the Identification of Cullin-9 (CUL9) Related Signaling Pathways in Induced Pluripotent Stem Cell Models. *PLoS One* 2021, 16:e0248000.
- [110] Pei XH, Bai F, Li Z, Smith MD, Whitewolf G, Jin R, et al.: Cytoplasmic CUL9/PARC Ubiquitin Ligase is a Tumor Suppressor and Promotes p53-Dependent Apoptosis. *Cancer Research* 2011, 71:2969–2977.
- [111] Horn-Ghetko D, Hopf LVM, Tripathi-Giesgen I, Du J, Kostrhon S, Vu DT, et al.: Noncanonical Assembly, Neddylation and Chimeric Cullin-RING/RBR Ubiquitylation by the 1.8 MDa CUL9 E3 Ligase Complex. *Nature Structural & Molecular Biology* 2024, 31:1083–1094.
- [112] Mason B, Laman H: The FBXL Family of F-box Proteins: Variations on a Theme. *Open Biology* 2020, 10:200319.
- [113] Hotton SK, Callis J: Regulation of Cullin RING Ligases. *Annual Review of Plant Biology* 2008, 59:467–489.
- [114] Pan ZQ, Kentsis A, Dias DC, Yamoah K, Wu K: Nedd8 on Cullin: Building an Expressway to Protein Destruction. *Oncogene* 2004, 23:1985–1997.
- [115] Duda DM, Borg LA, Scott DC, Hunt HW, Hammel M, Schulman BA: Structural Insights into NEDD8 Activation of Cullin-RING Ligases: Conformational Control of Conjugation. *Cell* 2008, 134:995–1006.
- [116] Goldenberg SJ, Cascio TC, Shumway SD, Garbutt KC, Liu J, Xiong Y, et al.: Structure of the Cnd1-Cul1-Roc1 Complex Reveals Regulatory Mechanisms for the Assembly of the Multisubunit Cullin-Dependent Ubiquitin Ligases. *Cell* 2004, 119:517–528.
- [117] Pierce NW, Lee JE, Liu X, Sweredoski MJ, Graham RL, Larimore EA, et al.: Cnd1 Promotes Assembly of New SCF Complexes Through Dynamic Exchange of F Box Proteins. *Cell* 2013, 153:206–215.
- [118] Hao B, Zheng N, Schulman BA, Wu G, Miller JJ, Pagano M, et al.: Structural Basis of the Cks1-Dependent Recognition of p27(Kip1) by the SCF(Skp2) Ubiquitin Ligase. *Molecular Cell* 2005, 20:9–19.
- [119] Morgan DO: Regulation of the APC and the Exit from Mitosis. *Nature Cell Biology* 1999, 1:E47–E53.
- [120] Rowland RJ, Heath R, Maskell D, Thompson RF, Ranson NA, Blaza JN, et al.: Cryo-EM Structure of SKP1-SKP2-CKS1

- in Complex with CDK2-Cyclin A-p27KIP1. *Scientific Reports* 2023, 13:10718.
- [121] Wang W, Ungermannova D, Chen L, Liu X: Molecular and Biochemical Characterization of the Skp2-Cks1 Binding Interface. *The Journal of Biological Chemistry* 2004, 279:51362–51369.
- [122] Yao ZP, Zhou M, Kelly SE, Seeliger MA, Robinson CV, Itzhaki LS: Activation of Ubiquitin Ligase SCF^{Skp2} by Cks1: Insights from Hydrogen Exchange Mass Spectrometry. *Journal of Molecular Biology* 2006, 363:673–686.
- [123] Bulatov E, Ciulli A: Targeting Cullin-RING E3 Ubiquitin Ligases for Drug Discovery: Structure, Assembly and Small-Molecule Modulation. *The Biochemical Journal* 2015, 467:365–386.
- [124] Bretones G, Acosta JC, Caraballo JM, Ferrándiz N, Gómez-Casares MT, Albajar M, et al.: SKP2 Oncogene is a Direct MYC Target Gene and MYC Down-Regulates p27(KIP1) Through SKP2 in Human Leukemia Cells. *The Journal of Biological Chemistry* 2011, 286:9815–9825.
- [125] Chen L, Tweddle DA: p53, SKP2, and DKK3 as MYCN Target Genes and Their Potential Therapeutic Significance. *Frontiers in Oncology* 2012, 2:173.
- [126] Schneider G, Saur D, Siveke JT, Fritsch R, Greten FR, Schmid RM: IKK α Controls p52/RelB at the skp2 Gene Promoter to Regulate G1- to S-phase Progression. *The EMBO Journal* 2006, 25:3801–3812.
- [127] Rodriguez S, Abundis C, Boccalatte F, Mehrotra P, Chiang MY, Yui MA, et al.: Therapeutic Targeting of the E3 Ubiquitin Ligase SKP2 in T-ALL. *Leukemia* 2020, 34:1241–1252.
- [128] Sarmento LM, Huang H, Limon A, Gordon W, Fernandes J, Tavares MJ, et al.: Notch1 Modulates Timing of G1-S Progression by Inducing SKP2 Transcription and p27 Kip1 Degradation. *The Journal of Experimental Medicine* 2005, 202:157–168.
- [129] Wu J, Lee SW, Zhang X, Han F, Kwan SY, Yuan X, et al.: Foxo3a Transcription Factor is a Negative Regulator of Skp2 and Skp2 SCF Complex. *Oncogene* 2013, 32:78–85.
- [130] Wang F, Chan CH, Chen K, Guan X, Lin HK, Tong Q: Deacetylation of FOXO3 by SIRT1 or SIRT2 Leads to Skp2-Mediated FOXO3 Ubiquitination and Degradation. *Oncogene* 2012, 31:1546–1557.
- [131] Li P, Chen T, Kuang P, Liu F, Li Z, Liu F, et al.: Aurora-A/FOXO3A/SKP2 Axis Promotes Tumor Progression in Clear Cell Renal Cell Carcinoma and Dual-Targeting Aurora-A/SKP2 Shows Synthetic Lethality. *Cell Death & Disease* 2022, 13:606.
- [132] Lee SM, Kaye KM, Slack FJ: Cellular microRNA-127-3p Suppresses Oncogenic Herpesvirus-Induced Transformation and Tumorigenesis Via Down-Regulation of SKP2. *Proceedings of the National Academy of Sciences of the United States of America* 2021, 118:e2105428118.
- [133] Qi F, He T, Jia L, Song N, Guo L, Ma X, et al.: The miR-30 Family Inhibits Pulmonary Vascular Hyperpermeability in the Premetastatic Phase by Direct Targeting of Skp2. *Clinical Cancer Research* 2015, 21:3071–3080.
- [134] He Z, Chen L, Wang Q, Yin C, Hu J, Hu X, et al.: MicroRNA-186 Targets SKP2 to Induce p27^{Kip1}-Mediated Pituitary Tumor Cell Cycle Deregulation and Modulate Cell Proliferation. *The Korean Journal of Physiology & Pharmacology* 2019, 23:171–179.
- [135] Gao D, Inuzuka H, Tseng A, Chin RY, Toker A, Wei W: Phosphorylation by Akt1 Promotes Cytoplasmic Localization of Skp2 and Impairs APC^{Cdh1}-Mediated Skp2 Destruction. *Nature Cell Biology* 2009, 11:397–408.
- [136] Lin HK, Wang G, Chen Z, Teruya-Feldstein J, Liu Y, Chan CH, et al.: Phosphorylation-Dependent Regulation of Cytosolic Localization and Oncogenic Function of Skp2 by Akt/PKB. *Nature Cell Biology* 2009, 11:420–432.
- [137] Rodier G, Coulombe P, Tanguay PL, Boutonnet C, Meloche S: Phosphorylation of Skp2 Regulated by CDK2 and Cdc14B Protects it from Degradation by APC^{Cdh1} in G1 Phase. *The EMBO Journal* 2008, 27:679–691.
- [138] Geng Q, Liu J, Gong Z, Chen S, Chen S, Li X, et al.: Phosphorylation by mTORC1 Stabilizes Skp2 and Regulates its Oncogenic Function in Gastric Cancer. *Molecular Cancer* 2017, 16:83.
- [139] Wei W, Ayad NG, Wan Y, Zhang GJ, Kirschner MW, Kaelin WG Jr: Degradation of the SCF Component Skp2 in Cell-Cycle Phase G1 by the Anaphase-Promoting Complex. *Nature* 2004, 428:194–198.
- [140] Bashir T, Dorrello NV, Amador V, Guardavaccaro D, Pagano M: Control of the SCF^{Skp2-Cks1} Ubiquitin Ligase by the APC/C^{Cdh1} Ubiquitin Ligase. *Nature* 2004, 428:190–193.
- [141] Kona SV, Kalivendi SV: The USP10/13 Inhibitor, Spautin-1, Attenuates the Progression of Glioblastoma by Independently Regulating RAF-ERK Mediated Glycolysis and SKP2. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2024, 1870:167291.
- [142] Zhang F, Zhao Y, Sun Y: USP2 is an SKP2 Deubiquitylase that Stabilizes Both SKP2 and its Substrates. *The Journal of Biological Chemistry* 2021, 297:101109.
- [143] Cope GA, Deshaies RJ: Targeted Silencing of Jab1/Csn5 in Human Cells Downregulates SCF Activity Through Reduction of F-box Protein Levels. *BMC Biochemistry* 2006, 7:1.
- [144] Inuzuka H, Gao D, Finley LW, Yang W, Wan L, Fukushima H, et al.: Acetylation-Dependent Regulation of Skp2 Function. *Cell* 2012, 150:179–193.
- [145] Zhang L, Wang C: F-box Protein Skp2: A Novel Transcriptional Target of E2F. *Oncogene* 2006, 25:2615–2627.
- [146] Yung Y, Walker JL, Roberts JM, Assoian RK: A Skp2 Autoinduction Loop and Restriction Point Control. *The Journal of Cell Biology* 2007, 178:741–747.
- [147] Shao Y, Ren W, Dai H, Yang F, Li X, Zhang S, et al.: SKP2 Contributes to AKT Activation by Ubiquitination Degradation of PHLPP1, Impedes Autophagy, and Facilitates the Survival of Thyroid Carcinoma. *Molecules and Cells* 2023, 46:360–373.
- [148] Germain D: Skp2 and Skp2B Team up Against Rb and p53. *Cell Division* 2011, 6:1.
- [149] Radke S, Pirkmaier A, Germain D: Differential Expression of the F-box Proteins Skp2 and Skp2B in Breast Cancer. *Oncogene* 2005, 24:3448–3458.
- [150] Zhang W, Cao L, Sun Z, Xu J, Tang L, Chen W, et al.: Skp2 is Over-Expressed in Breast Cancer and Promotes Breast Cancer Cell Proliferation. *Cell Cycle* 2016, 15:1344–1351.
- [151] Umanskaya K, Radke S, Chander H, Monardo R, Xu X, Pan ZQ, et al.: Skp2B Stimulates Mammary Gland Development by Inhibiting REA, the Repressor of the Estrogen Receptor. *Molecular and Cellular Biology* 2007, 27:7615–7622.
- [152] Chander H, Halpern M, Resnick-Silverman L, Manfredi JJ, Germain D: Skp2B Attenuates p53 Function by Inhibiting Prohibitin. *The EMBO Reports* 2010, 11:220–225.

Review Article

- [153] Ullah Z, Lee CY, Depamphilis ML: Cip/Kip Cyclin-Dependent Protein Kinase Inhibitors and the Road to Polyploidy. *Cell Division* 2009, 4:10.
- [154] Liu W, Wu G, Li W, Lobur D, Wan Y: Cdh1-Anaphase-Promoting Complex Targets Skp2 for Destruction in Transforming Growth Factor Beta-Induced GROWTH Inhibition. *Molecular and Cellular Biology* 2007, 27:2967–2979.
- [155] Russo AA, Jeffrey PD, Patten AK, Massagué J, Pavletich NP: Crystal Structure of the p27^{Kip1} Cyclin-Dependent-Kinase Inhibitor Bound to the Cyclin A-Cdk2 Complex. *Nature* 1996, 382:325–331.
- [156] Montagnoli A, Fiore F, Eytan E, Carrano AC, Draetta GF, Herskho A, et al.: Ubiquitination of p27 is Regulated by Cdk-Dependent Phosphorylation and Trimeric Complex Formation. *Genes Development* 1999, 13:1181–1189.
- [157] Cappell SD, Chung M, Jaimovich A, Spencer SL, Meyer T: Irreversible APC^{Cdh1} Inactivation Underlies the Point of No Return for Cell-Cycle Entry. *Cell* 2016, 166:167–180.
- [158] Yuan X, Srividhya J, De Luca T, Lee JH, Pomerening JR: Uncovering the Role of APC-Cdh1 in Generating the Dynamics of S-phase Onset. *Molecular Biology of the Cell* 2014, 25:441–456.
- [159] Bornstein G, Bloom J, Sitry-Shevah D, Nakayama K, Pagano M, Herskho A: Role of the SCF^{Skp2} Ubiquitin Ligase in the Degradation of p21^{Cip1} in S Phase. *The Journal of Biological Chemistry* 2003, 278:25752–25757.
- [160] Yu ZK, Gervais JL, Zhang H: Human CUL-1 Associates with the SKP1/SKP2 Complex and Regulates p21^{CIP1}/WAF1 and Cyclin D Proteins. *Proceedings of the National Academy of Sciences of the United States of America* 1998, 95:11324–11329.
- [161] Kamura T, Hara T, Kotoshiba S, Yada M, Ishida N, Imaki H, et al.: Degradation of p57^{Kip2} Mediated by SCF^{Skp2}-Dependent Ubiquitylation. *Proceedings of the National Academy of Sciences of the United States of America* 2003, 100:10231–10236.
- [162] Marti A, Wirbelauer C, Scheffner M, Krek W: Interaction Between Ubiquitin-Protein Ligase SCF^{SKP2} and E2F-1 Underlies the Regulation of E2F-1 Degradation. *Nature Cell Biology* 1999, 1:14–19.
- [163] Song MS, Song SJ, Kim SY, Oh HJ, Lim DS: The Tumour Suppressor RASSF1A Promotes MDM2 Self-Ubiquitination by Disrupting the MDM2-DAXX-HAUSP Complex. *The Embo Journal* 2008, 27:1863–1874.
- [164] Li X, Zhao Q, Liao R, Sun P, Wu X: The SCF^{Skp2} Ubiquitin Ligase Complex Interacts with the Human Replication Licensing Factor Cdt1 and Regulates Cdt1 Degradation. *The Journal of Biological Chemistry* 2003, 278:30854–30858.
- [165] Nishitani H, Sugimoto N, Roukos V, Nakanishi Y, Saijo M, Obuse C, et al.: Two E3 Ubiquitin Ligases, SCF-Skp2 and DDB1-Cul4, Target Human Cdt1 for Proteolysis. *The Embo Journal* 2006, 25:1126–1136.
- [166] Ellis M, Chew YP, Fallis L, Freddersdorf S, Boshoff C, Weiss RA, et al.: Degradation of p27^{Kip} Cdk Inhibitor Triggered by Kaposi's Sarcoma Virus Cyclin-Cdk6 Complex. *The Embo Journal* 1999, 18:644–653.
- [167] Greene W, Zhang W, He M, Witt C, Ye F, Gao SJ: The Ubiquitin/Proteasome System Mediates Entry and Endosomal Trafficking of Kaposi's Sarcoma-Associated Herpesvirus in Endothelial Cells. *PLoS Pathogens* 2012, 8:e1002703.
- [168] Kops GJ, Dansen TB, Polderman PE, Saarloos I, Wirtz KW, Coffey PJ, et al.: Forkhead Transcription Factor FOXO3a Protects Quiescent Cells from Oxidative Stress. *Nature* 2002, 419:316–321.
- [169] Coomans de Brachène A, Demoulin JB: FOXO Transcription Factors in Cancer Development and Therapy. *Cellular and Molecular Life Sciences* 2016, 73:1159–1172.
- [170] Nho RS, Hergert P: FoxO3a and Disease Progression. *World Journal of Biological Chemistry* 2014, 5:346–354.
- [171] Stahl M, Dijkers PF, Kops GJ, Lens SM, Coffey PJ, Burgering BM, et al.: The Forkhead Transcription Factor FoxO Regulates Transcription of p27^{Kip1} and Bim in Response to IL-2. *The Journal of Immunology* 2002, 168:5024–5031.
- [172] Jiramongkol Y, Lam EW: FOXO Transcription Factor Family in Cancer and Metastasis. *Cancer and Metastasis Reviews* 2020, 39:681–709.
- [173] Kodani N, Nakae J: Tissue-Specific Metabolic Regulation of FOXO-Binding Protein: FOXO Does Not Act Alone. *Cells* 2020, 9:702.
- [174] Huang H, Regan KM, Wang F, Wang D, Smith DI, van Deursen JM, et al.: Skp2 Inhibits FOXO1 in Tumor Suppression Through Ubiquitin-Mediated Degradation. *Proceedings of the National Academy of Sciences of the United States of America* 2005, 102:1649–1654.
- [175] Huang H, Tindall DJ: Regulation of FOXO Protein Stability via Ubiquitination and Proteasome Degradation. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2011, 1813:1961–1964.
- [176] Tedesco D, Lukas J, Reed SI: The pRb-Related Protein p130 is Regulated by Phosphorylation-Dependent Proteolysis via the Protein-Ubiquitin Ligase SCF^{Skp2}. *Genes Development* 2002, 16:2946–2957.
- [177] Kim SY, Herbst A, Tworkowski KA, Salghetti SE, Tansey WP: Skp2 Regulates Myc Protein Stability and Activity. *Molecular Cell* 2003, 11:1177–1188.
- [178] Yeh KH, Kondo T, Zheng J, Tsvetkov LM, Blair J, Zhang H: The F-Box Protein SKP2 Binds to the Phosphorylated Threonine 380 in Cyclin E and Regulates Ubiquitin-Dependent Degradation of Cyclin E. *Biochemical and Biophysical Research Communications* 2001, 281:884–890.
- [179] Lonjedo M, Poch E, Mocholí E, Hernández-Sánchez M, Ivorra C, Franke TF, et al.: The Rho Family Member RhoE Interacts with Skp2 and is Degraded at the Proteasome During Cell Cycle Progression. *The Journal of Biological Chemistry* 2013, 288:30872–30882.
- [180] Méndez J, Zou-Yang XH, Kim SY, Hidaka M, Tansey WP, Stillman B: Human Origin Recognition Complex Large Subunit is Degraded by Ubiquitin-Mediated Proteolysis After Initiation of DNA Replication. *Molecular Cell* 2002, 9:481–491.
- [181] Kondo T, Kobayashi M, Tanaka J, Yokoyama A, Suzuki S, Kato N, et al.: Rapid Degradation of Cdt1 Upon UV-Induced DNA Damage is Mediated by SCF^{Skp2} Complex. *The Journal of Biological Chemistry* 2004, 279:27315–27319.
- [182] Jiang H, Chang FC, Ross AE, Lee J, Nakayama K, Nakayama K, et al.: Ubiquitylation of RAG-2 by Skp2-SCF Links Destruction of the V(D)J Recombinase to the Cell Cycle. *Molecular Cell* 2005, 18:699–709.
- [183] Liang M, Liang YY, Wrighton K, Ungermannova D, Wang XP, Brunicardi FC, et al.: Ubiquitination and Proteolysis of Cancer-Derived Smad4 Mutants by SCF^{Skp2}. *Molecular and Cellular Biology* 2004, 24:7524–7537.

- [184] Lin YW, Yang JL: Cooperation of ERK and SCF^{Skp2} for MKP-1 Destruction Provides a Positive Feedback Regulation of Proliferating Signaling. *The Journal of Biological Chemistry* 2006, 281:915–926.
- [185] Tokarz S, Berset C, La Rue J, Friedman K, Nakayama K, Nakayama K, et al.: The ISG15 Isopeptidase UBP43 is Regulated by Proteolysis via the SCF^{Skp2} Ubiquitin Ligase. *The Journal of Biological Chemistry* 2004, 279:46424–46430.
- [186] Bellanger S, Tan CL, Nei W, He PP, Thierry F: The Human Papillomavirus Type 18 E2 Protein is a Cell Cycle-Dependent Target of the SCF^{Skp2} Ubiquitin Ligase. *Journal of Virology* 2010, 84:437–444.
- [187] Oh KJ, Kalinina A, Wang J, Nakayama K, Nakayama KI, Bagchi S: The Papillomavirus E7 Oncoprotein is Ubiquitinated by UbcH7 and Cullin 1- and Skp2-Containing E3 Ligase. *Journal of Virology* 2004, 78:5338–5346.
- [188] Nakayama K, Nagahama H, Minamishima YA, Matsumoto M, Nakamichi I, Kitagawa K, et al.: Targeted Disruption of *Skp2* Results in Accumulation of Cyclin E and p27^{Kip1}, Polyploidy and Centrosome Overduplication. *The Embo Journal* 2000, 19:2069–2081.
- [189] Galardi S, Mercatelli N, Giorda E, Massalini S, Frajese GV, Ciafrè SA, et al.: miR-221 and miR-222 Expression Affects the Proliferation Potential of Human Prostate Carcinoma Cell Lines by Targeting p27^{Kip1}. *The Journal of Biological Chemistry* 2007, 282:23716–23724.
- [190] Hattori T, Isobe T, Abe K, Kikuchi H, Kitagawa K, Oda T, et al.: Pirh2 Promotes Ubiquitin-Dependent Degradation of the Cyclin-Dependent Kinase Inhibitor p27^{Kip1}. *Cancer Research* 2007, 67:10789–10795.
- [191] Kamura T, Hara T, Matsumoto M, Ishida N, Okumura F, Hatakeyama S, et al.: Cytoplasmic Ubiquitin Ligase KPC Regulates Proteolysis of p27^{Kip1} at G1 Phase. *Nature Cell Biology* 2004, 6:1229–1235.
- [192] Hara T, Kamura T, Kotoshiba S, Takahashi H, Fujiwara K, Onoyama I, et al.: Role of the UBL-UBA Protein KPC2 in Degradation of p27 at G1 Phase of the Cell Cycle. *Molecular and Cellular Biology* 2005, 25:9292–9303.
- [193] Yu X, Wang R, Zhang Y, Zhou L, Wang W, Liu H, et al.: Skp2-Mediated Ubiquitination and Mitochondrial Localization of Akt drive Tumor Growth and Chemoresistance to Cisplatin. *Oncogene* 2019, 38:7457–7472.
- [194] Yao F, Zhou Z, Kim J, Hang Q, Xiao Z, Ton BN, et al.: SKP2- and OTUD1-Regulated Non-Proteolytic Ubiquitination of YAP Promotes YAP Nuclear Localization and Activity. *Nature Communications* 2018, 9:2269.
- [195] Lee SW, Li CF, Jin G, Cai Z, Han F, Chan CH, et al.: Skp2-Dependent Ubiquitination and Activation of LKB1 is Essential for Cancer Cell Survival Under Energy Stress. *Molecular Cell* 2015, 57:1022–1033.
- [196] Wang JY, Liu GZ, Wilmott JS, La T, Feng YC, Yari H, et al.: Skp2-Mediated Stabilization of MTH1 Promotes Survival of Melanoma Cells upon Oxidative Stress. *Cancer Research* 2017, 77:6226–6239.
- [197] Wu J, Zhang X, Zhang L, Wu CY, Rezaeian AH, Chan CH, et al.: Skp2 E3 Ligase Integrates ATM Activation and Homologous Recombination Repair by Ubiquitinating NBS1. *Molecular Cell* 2012, 46:351–361.
- [198] Gao D, Inuzuka H, Tseng A, Wei W: Akt Finds its New Path to Regulate Cell Cycle Through Modulating Skp2 Activity and its Destruction by APC/Cdh1. *Cell Division* 2009, 4:11.
- [199] Rezaeian AH, Phan LM, Zhou X, Wei W, Inuzuka H: Pharmacological Inhibition of the SKP2/p300 Signaling Axis Restricts Castration-Resistant Prostate Cancer. *Neoplasia* 2023, 38:100890.
- [200] Neary CL, Pastorino JG: Akt Inhibition Promotes Hexokinase 2 Redistribution and Glucose Uptake in Cancer Cells. *Journal of Cellular Physiology* 2013, 228:1943–1948.
- [201] Wieman HL, Wofford JA, Rathmell JC: Cytokine Stimulation Promotes Glucose Uptake via Phosphatidylinositol-3 Kinase/Akt Regulation of Glut1 Activity and Trafficking. *Molecular Biology of the Cell* 2007, 18:1437–1446.
- [202] Ahn E, Kumar P, Mukha D, Tzur A, Shlomi T: Temporal Fluxomics Reveals Oscillations in TCA Cycle Flux Throughout the Mammalian Cell Cycle. *Molecular Systems Biology* 2017, 13:953.
- [203] Liu J, Peng Y, Wei W: Cell Cycle on the Crossroad of Tumorigenesis and Cancer Therapy. *Trends in Cell Biology* 2022, 32:30–44.
- [204] Zhang S, Chen Q, Liu Q, Li Y, Sun X, Hong L, et al.: Hippo Signaling Suppresses Cell Ploidy and Tumorigenesis Through Skp2. *Cancer Cell* 2017, 31:669–684.e7.
- [205] von der Lehr N, Johansson S, Wu S, Bahram F, Castell A, Cetinkaya C, et al.: The F-box Protein Skp2 Participates in c-Myc Proteasomal Degradation and Acts as a Cofactor for c-Myc-Regulated Transcription. *Molecular Cell* 2003, 11:1189–1200.
- [206] Chen Y, Sun XX, Sears RC, Dai MS: Writing and Erasing MYC Ubiquitination and SUMOylation. *Genes & Diseases* 2019, 6:359–371.
- [207] Lv L, Miao Q, Zhan S, Chen P, Liu W, Lv J, et al.: LKB1 Dictates Sensitivity to Immunotherapy Through Skp2-Mediated Ubiquitination of PD-L1 Protein in Non-Small Cell Lung Cancer. *Journal for Immunotherapy of Cancer* 2024, 12:e009444.
- [208] Li Z, Wan J, Li S, Tang Y, Lin YC, Ni J, et al.: Multi-Omics Characterization of E3 Regulatory Patterns in Different Cancer Types. *International Journal of Molecular Sciences* 2024; 25:7639.
- [209] Wang Z, Fukushima H, Inuzuka H, Wan L, Liu P, Gao D, et al.: Skp2 is a Promising Therapeutic Target in Breast Cancer. *Frontiers in Oncology* 2012, 1:57.
- [210] Lord CJ, Ashworth A: PARP Inhibitors: Synthetic Lethality in the Clinic. *Science* 2017, 355:1152–1158.
- [211] Ray Chaudhuri A, Nussenzweig A: The Multifaceted Roles of PARP1 in DNA Repair and Chromatin Remodelling. *Nature Reviews Molecular Cell Biology* 2017, 18:610–621.
- [212] Haince JF, McDonald D, Rodrigue A, Déry U, Masson JY, Hendzel MJ, et al.: PARP1-Dependent Kinetics of Recruitment of MRE11 and NBS1 Proteins to Multiple DNA Damage Sites. *Journal of Biological Chemistry* 2008, 283:1197–1208.
- [213] Ray Chaudhuri A, Callen E, Ding X, Gogola E, Duarte AA, Lee JE, et al.: Replication Fork Stability Confers Chemoresistance in BRCA-Deficient Cells. *Nature* 2016, 535:382–387.
- [214] Saini S, Hirata H, Majid S, Dahiya R: Functional Significance of Cytochrome P450 1B1 in Endometrial Carcinogenesis. *Cancer Research* 2009, 69:7038–7045.
- [215] Peng Y, Qi X, Ding L, Huang J, Liu Y, Zheng R, et al.: SKP2 Inhibition Activates Tumor Cell-Intrinsic Immunity by Inducing DNA Replication Stress and Genomic Instability. *British Journal of Cancer* 2025, 132:81–92.

Review Article

- [216] Wang Z, Zhang Y, Liu J, Wang D, Wang S, Xie Z: Skp2 Targets the Androgen Receptor for Degradation to Regulate Prostate Cancer Cell Survival and Proliferation. *Biochemical and Biophysical Research Communications* 2014, 450:1335–1341.
- [217] Wang X, Wang J, Jin F: Identification of Skp2 as a Novel Target of the Akt/mTOR Pathway in Prostate Cancer. *International Journal of Oncology* 2012, 41:1289–1296.
- [218] Shimura H, Shimura-Miura H, Kuwano M, Harper JW, Nakayama KI: Skp2 is Required for Skp2-Mediated Degradation of p27 and Prostate Cancer Development in the TRAMP Model. *Cancer Research* 2003, 63:186–190.
- [219] Shigemasa K, Gu L, Tanimoto H, Oue N, Yasui W, Hamura T: Skp2 Regulates Twist Expression and Promotes Epithelial-Mesenchymal Transition in Human Prostate Cancer Cells. *Molecular Carcinogenesis* 2013, 52:11–19.
- [220] Shi C, Zhang Z, Shi Z, Wang S, Furuya T, Lin H, et al.: Skp2 Stabilizes Twist to Promote Proliferation and Migration of Prostate Cancer Cells. *Molecular Cancer Research* 2014, 12:1178–1187.
- [221] Yang G, Ayala G, De Marzo A, Tian W, Frolov A, Wheeler TM, et al.: Elevated Skp2 Protein Expression in Human Prostate Cancer: Association with High Histologic Grade and Reduced Patient Survival. *Cancer Research* 2002, 62:2583–2589.
- [222] Wang Z, Zhang Y, Liu J, Wang D, Wang S, Xie Z: Skp2: A Novel Potential Therapeutic Target for Prostate Cancer. *Biochimica et Biophysica Acta* 2016, 1866:207–218.
- [223] Li B, Niu A, Wu Z: Down-Regulation of Skp2 Expression Inhibits Invasion and Induces Apoptosis in Human Breast Cancer Cells. *Pathology & Oncology Research* 2014, 20:67–73.
- [224] Ning N, Liu S, Liu X, Tian Z, Jiang Y, Yu N, et al.: Curcumin Suppresses Breast Cancer Cell Metastasis by Inhibiting Skp2-Mediated Bim Degradation. *Oncology Reports* 2016, 36:3505–3511.
- [225] Clement E, Inuzuka H, Nihira NT, Wei W, Toker A: Skp2 Dictates Cell Cycle Progression and Therapeutic Resistance in Triple-Negative Breast Cancer. *Cancer Research* 2018, 78:3165–3175.
- [226] Wang X, Yang L, Huang F, Zhang Q, Liu S, Li L: Targeting the Skp2-PD-L1 Axis for Cancer Immunotherapy. *Trends in Cancer* 2019, 5:12–15.
- [227] Zhang H, Sun L, Liang J, Yu Z, Jin Y: Skp2 Regulates Non-Small Cell Lung Cancer Cell Growth and Sensitivity to Gefitinib. *Oncology Reports* 2015, 34:2479–2486.
- [228] Lim SO, Li CW, Xia W, Cha JH, Chan LC, Tanaka T, et al.: Glycosylation-Dependent PD-L1 Accumulation for Poor Clinical Outcome in Lung Cancer. *Molecular Cell* 2016, 62:390–402.
- [229] Yu H, Zhao T, Liu Z: Prognostic Value of Skp2 Expression in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis. *World Journal of Surgical Oncology* 2015, 13:33.
- [230] Gu C, Wang D, Liu J, Chen Z: Targeting the Skp2-p27 Axis in Multiple Myeloma. *Blood* 2012, 119:535–536.
- [231] Li Z, Liu S, Sun J, Li X: A Novel Small-Molecule Inhibitor of Skp2-Mediated Ubiquitin-Proteasome System (UPS) Induces Apoptosis in Multiple Myeloma. *Leukemia & Lymphoma* 2014, 55:115–123.
- [232] Katagiri S, Tauchi T, Okabe S, Sashida G, Ohyashiki K: Mblockade of the Ubiquitin-Proteasome Pathway Inhibits the Expression of Maf and Myc and Induces Cell Death in Multiple Myeloma. *Annals of Hematology* 2015, 94:1545–1553.
- [233] Andreu EJ, Lledo E, Pocovi M: The BCR-ABL Inhibitor Imatinib Suppresses Skp2 Expression and Promotes p27^{Kip1} Accumulation in Chronic Myelogenous Leukemia Cells. *Cancer Research* 2005, 65:3264–3272.
- [234] Wei Z, Jiang X, Qiao H, Zhai B, Zhang L, Zhang Q, et al.: Skp2 Overexpression is Associated with Poor Prognosis and 5-Fluorouracil Resistance in Human Colorectal Carcinoma. *Journal of Clinical Pathology* 2015, 68:962–968.
- [235] Calvisi DF, Ladu S, Conner EA, Seo D, Heyer J, Factor VM, et al.: Skp2 Drives the Ubiquitylation and Degradation of LKB1 and Regulates Hepatocellular Carcinoma Progression. *Cancer Research* 2011, 71:3332–3343.
- [236] Calvisi DF, Ladu S, Pinna F, Frau M, Tomasi ML, Sini M, et al.: SKP2 and CKS1 promote degradation of cell cycle regulators and are associated with hepatocellular carcinoma prognosis. *Gastroenterology* 2009, 137:1816–1826.e1–10.
- [237] Kan G, Wang Z, Ma Q, Chen C, Li X: CD147 Promotes Src-Dependent Activation of Skp2 to Enhance Nrf2 Stability and Temozolomide Resistance in Glioblastoma. *Cell Death & Disease* 2015, 6:e1918.
- [238] Zhang S, Mercado-Urbe I, Liu J: Polyploid Giant Cancer Cells: The “Root” of Tumor Recurrence and Drug Resistance. *Seminars in Cancer Biology* 2022, 81:109–119.
- [239] Lv C, Hong Y, Miao L, Li C: Skp2 Regulates Polyploidy Formation in Ovarian Cancer Cells. *Oncology Letters* 2020, 19:1255–1262.
- [240] Gad H, Koolmeister T, Jemth AS, Eshtad S, Jacques SA, Strom CE, et al.: MTH1 Inhibition Kills Cancer by Preventing Sanitation of the dNTP Pool. *Nature* 2014, 508:215–221.
- [241] Tu Y, Chen C, Pan W, Xu M, Zhai Y: Epigenetic Silencing of MTH1 Promotes Cell Cycle Arrest and Apoptosis in Human Malignant Melanoma. *Carcinogenesis* 2012, 33:1480–1488.
- [242] Li B, Lu W, Yang Q, Yu X, Matusik RJ, Chen Z: Skp2 Regulates Androgen Receptor Through Ubiquitin-Mediated Degradation Independent of Akt/mTOR Pathways in Prostate Cancer. *The Prostate* 2014, 74:421–432.
- [243] Zhu CQ, Blackhall FH, Pintilie M, Iyengar P, Liu N, Ho J, et al.: Skp2 Gene Copy Number Aberrations are Common in Non-Small Cell Lung Carcinoma, and its Overexpression in Tumors with Ras Mutation is a Poor Prognostic Marker. *Clinical Cancer Research* 2004, 10:1984–1991.
- [244] Yu X, Zhou L, Liu W, Liu L, Gao F, Li W, et al.: Skp2 Stabilizes Mcl-1 and Confers Radioresistance in Colorectal Cancer. *Cell Death & Disease* 2022, 13:249.
- [245] William JNG, Dhar R, Gundamaraju R, Sahoo OS, Pethusamy K, Raj AFPAM, et al.: SKping Cell Cycle Regulation: Role of Ubiquitin Ligase SKP2 in Hematological Malignancies. *Frontiers in Oncology* 2024, 14:1288501.
- [246] Aguirre-Ghiso JA: Models, Mechanisms and Clinical Evidence for Cancer Dormancy. *Nature Reviews Cancer* 2007, 7:834–846.
- [247] Besson A, Dowdy SF, Roberts JM: CDK Inhibitors: Cell Cycle Regulators and Beyond. *Developmental Cell* 2008, 14:159–169.
- [248] Slingerland J, Pagano M: Regulation of the Cdk Inhibitor p27 and its Deregulation in Cancer. *Journal of Cellular Physiology* 2000, 183:10–17.

- [249] Elfolyi M, Mirza JY, Alaiya A, Al-Hazzani AA, Tulbah A, Al-Alwan M, et al.: PD-L1 Intrinsically Promotes the Proliferation of Breast Cancer Cells Through the SKP2-p27/p21 Axis. *Cancer Cell International* 2024, 24:161.
- [250] Porcelli G, D'Accardo C, Angeloro F, Cucchiara M, Bianca P, Pantina VD, et al.: Decoding Cancer Dormancy: Integrative Genomic, Phenotypic and Live-Cell Imaging Analysis to Reveal the Hidden Cancer Cell Reservoir. *Molecular Cancer* 2025, 24:286.
- [251] Murata S, Zhang C, Finch N, Zhang K, Campo L, Breuer EK: Predictors and Modulators of Synthetic Lethality: An Update on PARP Inhibitors and Personalized Medicine. *BioMed Research International* 2016, 2016:2346585.
- [252] Agudo J, Aguirre-Ghiso JA, Bhatia M, Chodosh LA, Correia AL, Klein CA: Targeting Cancer Cell Dormancy. *Nature Reviews Cancer* 2024, 24:97–104.
- [253] Wu T, Gu X, Cui H: Emerging Roles of SKP2 in Cancer Drug Resistance. *Cells* 2021, 10:1147.
- [254] Yang G, Ayala G, De Marzo A, Tian W, Frolov A, Wheeler TM, et al.: Elevated Skp2 Protein Expression in Human Prostate Cancer: Association with Loss of the Cyclin-Dependent Kinase Inhibitor p27 and PTEN and with Reduced Recurrence-Free Survival. *Clinical Cancer Research* 2002, 8:3419–3426.
- [255] Šimečková Š, Kahounová Z, Fedr R, Remšík J, Slabáková E, Suchánková T, et al.: High Skp2 Expression is Associated with a Mesenchymal Phenotype and Increased Tumorigenic Potential of Prostate Cancer Cells. *Scientific Reports* 2019, 9:5695.
- [256] Li CL, Huang CW, Ko CJ, Fang SY, Ou-Yang FU, Pan MR, et al.: Curcumin Suppresses Triple-Negative Breast Cancer Metastasis by Attenuating Anoikis Resistance via Inhibition of Skp2-Mediated Transcriptional Addiction. *Anticancer Research* 2020, 40:5529–5538.
- [257] Zhong K, Yang F, Han Q, Chen J, Wang J: Skp2 Expression has Different Clinicopathological and Prognostic Implications in Lung Adenocarcinoma and Squamous Cell Carcinoma. *Oncology Letters* 2018, 16:2873–2880.
- [258] Yokoi S, Yasui K, Mori M, Iizasa T, Fujisawa T, Inazawa J: Amplification and Overexpression of SKP2 are Associated with Metastasis of Non-Small-Cell Lung Cancers to Lymph Nodes. *The American Journal of Pathology* 2004, 165:175–180.
- [259] Takanami I: The Prognostic Value of Overexpression of Skp2 mRNA in Non-Small Cell Lung Cancer. *Oncology Reports* 2005, 13:727–731.
- [260] Zhou H, Zhou L, Guan Q, Hou X, Wang C, Liu L, et al.: Skp2-Mediated MLKL Degradation Confers Cisplatin-Resistant in Non-Small Cell Lung Cancer Cells. *Communications Biology* 2023, 6:805.
- [261] Faruq O, Ngo J, Iyer D, Nesson J, Shrestha M, Chang H: Targeting of SKP2 to Combat Drug Resistance in Multiple Myeloma. *Scientific Reports* 2025, 15:37838.
- [262] Malek E, Abdel-Malek MA, Jagannathan S, Vad N, Karns R, Jegga AG, et al.: Pharmacogenomics and Chemical Library Screens Reveal a Novel SCF^{SKP2} Inhibitor that Overcomes Bortezomib Resistance in Multiple Myeloma. *Leukemia* 2017, 31:645–653.
- [263] Andreu EJ, Lledó E, Poch E, Ivorra C, Alberio MP, Martínez-Climent JA, et al.: BCR-ABL Induces the Expression of Skp2 through the PI3K Pathway to Promote p27^{Kip1} Degradation and Proliferation of Chronic Myelogenous Leukemia Cells. *Cancer Research* 2005, 65:3264–3272.
- [264] Chen X, Huang Z, Wu W, Xia R: Inhibition of Skp2 Sensitizes Chronic Myeloid Leukemia Cells to Imatinib. *Cancer Management and Research* 2020, 12:4777–4787.
- [265] Dong X, Li K, Wang R, Wei B, Li Y, Zhang Y, et al.: Targeting Skp2 by Tanshinone IIA Overcomes Chemoresistance in Colorectal Cancer. *Cell Biology and Toxicology* 2025, 41:135.
- [266] Delogu S, Wang C, Cigliano A, Utpatel K, Sini M, Longerich T, et al.: SKP2 Cooperates with N-Ras or AKT to Induce Liver Tumor Development in Mice. *Oncotarget* 2015, 6:2222–2234.
- [267] Li J, Zhao L, Wu Z, Huang S, Wang J, Chang Y, et al.: SelK Promotes Glioblastoma Cell Proliferation by Inhibiting β -TrCP1 Mediated Ubiquitin-Dependent Degradation of CDK4. *Journal of Experimental & Clinical Cancer Research* 2024, 43:231.
- [268] Lv H, Shi Y, Zhang L, Zhang D, Liu G, Yang Z, et al.: Polyploid Giant Cancer Cells with Budding and the Expression of Cyclin E, S-phase Kinase-Associated Protein 2, Stathmin Associated with the Grading and Metastasis in Serous Ovarian Tumor. *BMC Cancer* 2014, 14:576.
- [269] Zhang S, Mercado-Urbe I, Xing Z, Sun B, Kuang J, Liu J: Generation of Cancer Stem-Like Cells through the Formation of Polyploid Giant Cancer Cells. *Oncogene* 2014, 33:116–128.
- [270] Chen T, Liu L, Zou Y, Hu X, Zhang W, Zhou T, et al.: Nobiletin Downregulates the SKP2-p21/p27-CDK2 Axis to Inhibit Tumor Progression and Shows Synergistic Effects with Palbociclib on Renal Cell Carcinoma. *Cancer Biology & Medicine* 2021, 18:227–244.
- [271] Masuda TA, Inoue H, Sonoda H, Mine S, Yoshikawa Y, Nakayama K, et al.: Clinical and Biological Significance of S-phase Kinase-associated Protein 2 (Skp2) Gene Expression in Gastric Carcinoma: Modulation of Malignant Phenotype by Skp2 Overexpression, Possibly via p27 Proteolysis. *Cancer Research* 2002, 62:3819–3825.
- [272] Einama T, Kagata Y, Tsuda H, Morita D, Ogata S, Ueda S, et al.: High-Level Skp2 Expression in Pancreatic Ductal Adenocarcinoma: Correlation with the Extent of Lymph Node Metastasis, Higher Histological Grade, and Poorer Patient Outcome. *Pancreas* 2006, 32:376–381.
- [273] Wang J, Huang Y, Guan Z, Zhang JL, Su HK, Zhang W, et al.: E3-Ligase Skp2 Predicts Poor Prognosis and Maintains Cancer Stem Cell Pool in Nasopharyngeal Carcinoma. *Oncotarget* 2014, 5:5591–5601.
- [274] Liao X, Zhang Y, Yu X, Du W, Chen L, Zhao Z, et al.: A Pan-Cancer Analysis Revealed SKP2 as an Inhibitor of the Tumor Immune Microenvironment and a Promising Therapeutic Target for Immunotherapy. *Precision Clinical Medicine* 2025, 8:pbaf022.
- [275] Tan S, Wang R, Fang J, Yi M, Guo P, Han S, et al.: E3 Ligase Skp2-Mediated Stabilization of Survivin Contributes to Radioresistance. *Cell Death Discovery* 2025, 11:151.
- [276] Oliveira AM, Okuno SH, Nascimento AG, Lloyd RV: Skp2 Protein Expression in Soft Tissue Sarcomas. *Journal of Clinical Oncology* 2003, 21:722–727.
- [277] Bonda DJ, Lee HP, Kudo W, Zhu X, Smith MA, Lee HG: Lee. Pathological Implications of Cell Cycle Re-entry in Alzheimer Disease. *Expert Reviews in Molecular Medicine* 2010, 12:e19.
- [278] García-Osta A, Dong J, Moreno-Aliaga MJ, Ramirez MJ: p27, The Cell Cycle and Alzheimer's Disease. *International Journal of Molecular Sciences* 2022, 23:1211.

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- [279] Fishman-Jacob T, Youdim MBH: A Sporadic Parkinson's Disease Model via Silencing of the Ubiquitin-Proteasome/E3 Ligase Component, SKP1A. *Journal of Neural Transmission (Vienna, Austria: 1996)* 2024, 131:675–707.
- [280] Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia Guedes L, et al.: FBXO7 Mutations Cause Autosomal Recessive, Early-Onset Parkinsonian-Pyramidal Syndrome. *Neurology* 2009, 72:240–245.
- [281] Burchell VS, Nelson DE, Sanchez-Martinez A, Delgado-Camprubi M, Ivatt RM, Pogson JH, et al.: The Parkinson's Disease-Linked Proteins Fbxo7 and Parkin Interact to Mediate Mitophagy. *Nature Neuroscience* 2013, 16:1257–1265.
- [282] Lin HK, Chen Z, Wang G, Nardella C, Lee SW, Chan CH, et al.: Skp2 Targeting Suppresses Tumorigenesis by Arf-p53-Independent Cellular Senescence. *Nature* 2010, 464:374–379.
- [283] Galdeano C: Drugging the Undruggable: Targeting Challenging E3 Ligases for Personalized Medicine. *Future Medicinal Chemistry* 2017, 9:347–350.
- [284] Wu L, Grigoryan AV, Li Y, Hao B, Pagano M, Cardozo TJ: Specific Small Molecule Inhibitors of Skp2-Mediated p27 Degradation. *Chemistry & Biology* 2012, 19:1515–1524.
- [285] Ungermannova D, Lee J, Zhang G, Dallmann HG, McHenry CS, Liu X: High-Throughput Screening AlphaScreen Assay for Identification of Small-Molecule Inhibitors of Ubiquitin E3 Ligase SCF^{Skp2-Cks1}. *Journal of Biomolecular Screening* 2013, 18:910–920.
- [286] Rico-Bautista E, Zhu W, Kitada S, Ganapathy S, Lau E, Krajewski S, et al.: Small Molecule-Induced Mitochondrial Disruption Directs Prostate Cancer Inhibition via UPR Signaling. *Oncotarget* 2013, 4:1212–1229.
- [287] Li X, Yokoyama NN, Zhang S, Ding L, Liu HM, Lilly MB, et al.: Flavokawain A Induces deNEDDylation and Skp2 Degradation Leading to Inhibition of Tumorigenesis and Cancer Progression in the TRAMP Transgenic Mouse Model. *Oncotarget* 2015, 6:41809–41824.
- [288] Liang H, Zhang F, Hong Y, Wu Y, Xie H, Zhang C, et al.: Synergistic Silencing of Skp2 by siRNA Self-Assembled Nanoparticles as a Therapeutic Strategy for Advanced Prostate Cancer. *Small (Weinheim an der Bergstrasse, Germany)* 2022, 18:e2106046.
- [289] Bigdeli M, Tremblay E, Provencher D, Mes-Masson AM, Rodier F: Exploiting Synthetic Lethality in Epithelial Ovarian Cancer: Multi-Dimensional Approaches Beyond DNA Damage Repair. *Molecular Cancer* 2026. doi: 10.1186/s12943-025-02562-w
- [290] Blackford AN, Jackson SP: ATM, ATR, and DNA-PK: The Trinity at the Heart of the DNA Damage Response. *Molecular Cell* 2017, 66:801–817.
- [291] Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, et al.: A Decade of Clinical Development of PARP Inhibitors in Perspective. *Annals of Oncology* 2019, 30:1437–1447.
- [292] Jing J, Rui L, Junyuan S, Jinfeng Y, Zhihao H, Weiguo L, et al.: Small-Molecule Compounds Inhibiting S-phase Kinase-Associated Protein 2: A Review. *Frontiers in Pharmacology* 2023, 14:1122008.
- [293] Zhu L: Skp2 Knockout Reduces Cell Proliferation and Mouse Body Size: and Prevents Cancer? *Cell Research* 2010, 20:605–607.
- [294] Rodríguez-Gimeno A, Galdeano C: Drug Discovery Approaches to Target E3 Ligases. *Chembiochem* 2025, 26:e202400656.
- [295] Lough L, Sherman D, Ni E, Young LM, Hao B, Cardozo T: Chemical Probes of Skp2-Mediated p27 Ubiquitylation and Degradation. *Medchemcomm* 2018, 9:1093–1104.
- [296] Dong G, Huang A, Zhao Z, Lai B, Pan X, Yang H, et al.: Discovery of SKP2-Recruiting PROTACs for Target Protein Degradation. *Advanced Science (Weinh)* 2026:e15159.
- [297] Radhakrishnan S, Hoff O, Muellner MK: Current Challenges in Small Molecule Proximity-Inducing Compound Development for Targeted Protein Degradation Using the Ubiquitin Proteasomal System. *Molecules* 2022, 27:8119.
- [298] Feng T, Wang P, Zhang X: Skp2: A Critical Molecule for Ubiquitination and its Role in Cancer. *Life Sciences* 2024, 338:122409.
- [299] Gstaiger M, Jordan R, Lim M, Catzavelos C, Mestan J, Slingerland J, et al.: Skp2 is Oncogenic and Overexpressed in Human Cancers. *Proceedings of the National Academy of Sciences of the United States of America* 2001, 98:5043–5048.
- [300] Mi D, Huang A, Song J, Chen Y: A Long March for Targeted Protein Degradation in the New Era: Expanding E3 Ligases. *Future Medicinal Chemistry* 2024, 16:2189–2191.
- [301] Lee J, Lee Y, Jung YM, Park JH, Yoo HS, Park J: Discovery of E3 Ligase Ligands for Target Protein Degradation. *Molecules* 2022, 27:6515.
- [302] Koseoglu MM, Norambuena A, Sharlow ER, Lazo JS, Bloom GS: Aberrant Neuronal Cell Cycle Re-entry: The Pathological Confluence of Alzheimer's Disease and Brain Insulin Resistance, and Its Relation to Cancer. *Journal of Alzheimer's Disease: JAD* 2019, 67:1–11.
- [303] McCarthy. Without SKP2, *Nature Reviews Cancer* 2010, 10:314–314.
- [304] Neudorf NM, Thompson LL, Lichtensztejn Z, Razi T, McManus KJ: Reduced SKP2 Expression Adversely Impacts Genome Stability and Promotes Cellular Transformation in Colonic Epithelial Cells. *Cells* 2022, 11:3731.
- [305] Jiang X, Li Y, Feng JL, Nik Nabil WN, Wu R, Lu Y, et al.: Safrana I Prevents Prostate Cancer Recurrence by Blocking the Re-activation of Quiescent Cancer Cells via Downregulation of S-phase Kinase-Associated Protein 2. *Frontiers in Cell and Developmental Biology* 2020, 8:598620.
- [306] Chen X, Zhou J, Dong X, Xu Y, Chen B: Regulatory Role of E3 Ubiquitin Ligases in Multiple Myeloma: From Molecular Mechanisms to Therapeutic Strategies. *Frontiers in Cell and Developmental Biology* 2025, 13:1620097.