·REVIEWS· ·综 述·

泛素化修饰调控T细胞稳态与自身免疫病

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[摘 要] 泛素化是一种高度动态且可逆的翻译后修饰，广泛参与真核细胞内蛋白质降解、信号转导及细胞功能调控。泛素化修饰通过泛素活化酶(ubiquitin-activating enzyme，E1)-泛素缀合酶(ubiquitin-conjugating enzyme，E2)-泛素-蛋白质连接酶(ubiquitin-protein ligase，E3)三级酶系协同作用，将泛素以不同链型连接于底物蛋白，从而决定底物蛋白的蛋白酶体降解、亚细胞转运及非降解性支架功能。在免疫系统中，E3与去泛素化酶(deubiquitinases，DUB)通过调控底物选择和泛素链编辑，精细控制T细胞抗原识别、受体信号转导、活化增殖和效应分化。通过调节T细胞受体、共刺激与细胞因子信号，以及关键转录因子和代谢调控分子的稳定性，E3与DUBs可影响T细胞活化阈值、无反应状态、存活及分化方向，共同构成维持T细胞稳态和外周免疫耐受的重要调控网络。该网络失衡可导致致炎性T细胞应答增强和调节性T细胞功能受损，削弱外周免疫耐受，并参与系统性红斑狼疮、类风湿关节炎和1型糖尿病等多种自身免疫病的发生和发展。系统归纳E3与DUBs调控T细胞命运的分子机制和关键信号通路，解析不同T细胞亚群中的底物谱、泛素链型偏好及其与代谢调控的交叉机制，有助于深化对泛素化维持T细胞稳态及参与自身免疫病发生和发展的认识，并为链型特异性和细胞类型选择性靶向策略的开发提供理论依据和转化方向。

[关键词] 泛素化；去泛素化；T细胞稳态；T细胞分化；自身免疫病

Ubiquitination-mediated regulation of T cell homeostasis and autoimmune diseases

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ABSTRACT Ubiquitination is a highly dynamic and reversible post-translational modification that is

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extensively involved in protein degradation, signal transduction, and functional regulation in eukaryotic cells. Through the coordinated action of the ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3) cascade, ubiquitin molecules are conjugated to substrate proteins through distinct ubiquitin chain linkages, thereby determining proteasomal degradation, subcellular trafficking, or non-degradative scaffold functions of target proteins. In the immune system, E3 ligases and deubiquitinases (DUBs) precisely regulate T cell antigen recognition, receptor signaling, activation, proliferation, and effector differentiation by controlling substrate selection and ubiquitin chain editing. By modulating the stability of T cell receptors, co-stimulatory and cytokine signaling molecules, as well as key transcription factors and metabolic regulators, E3 ligases and DUBs influence T cell activation thresholds, anergic states, survival, and differentiation programs. Together, they constitute an essential regulatory network responsible for maintaining T cell homeostasis and peripheral immune tolerance. Dysregulation of this network can enhance pro-inflammatory T cell responses and impaired regulatory T cell function, thereby weakening peripheral immune tolerance and contributing to the development and progression of various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes mellitus. Systematic summarization of the molecular mechanisms and key signaling pathways through which E3 ligases and DUBs regulate T cell fate, together with elucidation of substrate landscapes, ubiquitin chain preferences, and their metabolic crosstalk among different T cell subsets, will deepen our understanding of how ubiquitination maintains T cell homeostasis and contributes to autoimmune disease pathogenesis. Furthermore, such insights may provide a theoretical foundation and translational directions for the development of chain-specific and cell-type-selective therapeutic strategies.

KEY WORDS ubiquitination; deubiquitination; T cell homeostasis; T cell differentiation; autoimmune diseases

蛋白质翻译后修饰是细胞整合外界刺激并调控功能状态的重要机制。其中，泛素化因具有可逆性强、链型多样和底物选择性高等特点，在免疫调控中发挥关键作用[1-2]。T细胞在激活、分化和效应功能执行过程中，对抗原信号的强度、持续时间及空间分布高度敏感，因此其命运依赖精确而动态的分子调控网络[3]。

泛素-蛋白酶体系统(ubiquitin-proteasome system，UPS)广泛参与T细胞介导的免疫应答。该系统可通过调控T细胞受体(T cell receptor，TCR)信号复合体组装、关键转录因子稳定性及代谢适配过程，精细设定信号强度和持续时间，并为T细胞功能状态的形成提供重要分子基础[3-12]。基于此，本文系统综述UPS中的核心成分泛素-蛋白质连接酶(ubiquitin-protein ligase，E3)与去泛素化酶(deubiquitinases，DUB)在T细胞功能调控中的关键机制，并探讨其在自身免疫病中的作用与靶向干预潜力。

1 UPS在免疫调控中的功能定位

UPS是维持蛋白质稳态与信号精确性的核心调控网络[6-8, 10-11]。该系统以泛素为修饰单元，通过泛素活化酶(ubiquitin-activating enzyme，E1)、泛素缀合酶(ubiquitin-conjugating enzyme，E2)和E3的级联反应，将泛素共价连接至底物蛋白的赖氨酸残基，形成单泛素化或不同链型的多聚泛素链[13-16]；DUBs则可去除或重塑这些泛素链，从而调控靶蛋白的降解周转、功能活性及亚细胞定位。E3与DUBs分别参与泛素信号的写入和去除/编辑，共同决定底物选择性、链型特征和信号输出，是泛素信号特异性的关键来源[17]。在T细胞免疫调控中，UPS的作用并不局限于蛋白质降解，还可通过不同泛素链型传递特定信号[15]。例如，K48连接型泛素链多介导蛋白酶体降解，用于终止或重置信号；K63连接型及其他非降解型泛素链则常作为信号支架，促进信号复合体装配和级联放大[15, 18-22]。

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E3是泛素信号特异性的主要决定因素。其通过识别特定底物并催化不同链型的泛素化修饰，将TCR、共刺激和细胞因子信号转化为相对稳定的通路活化状态及细胞分化程序[13, 16]。在T细胞中，免疫相关E3的功能大致可归纳为2类。第1类作用于TCR近端信号平台，通过调控信号复合体的组装、维持和拆解，设定T细胞激活阈值及信号持续时间。第2类直接调控谱系决定因子、共刺激分子及免疫突触相关组分的蛋白质周转，从而影响转录程序的维持或重置[17, 23-29]。因此，Casitas B系淋巴瘤蛋白b(Casitas B-lineage lymphoma-b，Cbl-b)、Itchy E3泛素蛋白连接酶(Itchy E3 ubiquitin protein ligase，Itch)、Roquin蛋白家族等E3在多种自身免疫病模型中反复被鉴定为关键调控节点。它们位于T细胞激活阈值和谱系分化程序的交汇处，其功能改变可削弱外周免疫耐受，并推动异常炎症反应发生。

DUBs通过去除、修剪或重塑泛素链，使泛素信号不再只是简单的“开启”或“关闭”，而是呈现出更精细的强度和时程调控[1, 30-31]。与E3相比，DUBs的功能特异性往往更依赖细胞类型、亚细胞定位、底物可及性及泛素链型偏好，因此在T细胞这种高度动态的信号环境中具有重要意义[31-32]。目前已鉴定的DUBs超过百种，常见家族包括泛素特异性蛋白酶(ubiquitin-specific protease，USP)家族与卵巢肿瘤相关蛋白酶(ovarian tumor domain-containing protease，OTU)家族等；但在免疫系统中，已经完成体内底物识别、链型解析和功能表型验证的DUBs仍然有限。从转化角度看，DUBs具有明确的催化结构域，理论上更适合小分子靶向干预。然而，许多DUBs同时参与多条信号通路，系统性抑制可能引起广泛的蛋白质稳态扰动和免疫不良反应。因此，开发链型或底物偏好性更强的DUB抑制剂，并结合细胞类型选择性递送或短程干预，以提高疗效并扩大安全窗，是未来更可行的方向。

T细胞命运由抗原信号强度与下游转录程序的精确偶联所决定。当TCR识别抗原并接收充分共刺激信号时，T细胞启动克隆扩增与谱系分化[33]；反之，在共刺激缺失、抑制性信号主导或调节性T(regulatory T，Treg)细胞介导的免疫抑制环境下，T细胞倾向于分化为无能或耗竭等低功能状态[3, 12, 34-35]。多数自身免疫病最终表现为促炎性辅助性T细胞(T helper，Th)1和Th17应答增强和Treg细胞功能不足。因此，阐明UPS如何调控TCR及细胞因子信号，以及如何影响谱系关键转录因子的稳定性，是连接基础调控机制与自身免疫病进程的重要环节[35-37]。

2 泛素化对T细胞分化和自身免疫病的影响

2.1 T细胞活化：近端信号平台的泛素化动态平衡

TCR近端信号转导具有明显的平台依赖性。非降解型泛素链可作为信号支架，促进激酶复合体募集和信号平台组装；DUBs则通过拆解这些平台限制信号持续放大，防止T细胞发生低阈值异常激活[38-41]。以CBM复合体[胱天蛋白酶募集结构域家族成员11(caspase recruitment domain family member 11，CARD11)-B细胞淋巴瘤10(B cell lymphoma 10，BCL10)-黏膜相关淋巴组织淋巴瘤易位蛋白1(mucosa-associated lymphoid tissue lymphoma translocation protein 1，MALT1)]为核心，K63连接型泛素化可促进转化生长因子β活化激酶1(transforming growth factor-beta-activated kinase 1，TAK1)和IκB激酶(IκB kinase，IKK)募集与活化，进而驱动核因子κB(nuclear factor kappa B，NF-κB)/丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)信号转导[38, 42-44]；同时，MALT1的类胱天蛋白酶活性可切割A20等负调控因子，使抑制信号在T细胞初始激活阶段短暂解除，从而保障免疫应答启动[45]。TAK1/IKK信号平台中K63连接型泛素链的写入并不依赖单一E3。肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6，TRAF6)及其他TRAF家族成员均可能参与该过程，提示T细胞中E3存在功能冗余和情境依赖性[39, 46]。与之相对，A20、CYLD赖氨酸63去泛素化酶(CYLD lysine 63 deubiquitinase，CYLD)等DUBs与部分降解型E3共同构成负向调控模块，通过去除K63连接型泛素链、限制NF-κB必需调节蛋白(NF-κB essential modulator，NEMO)/TAK1激酶活性，或促进关键信号节点降解，将TCR信号维持在可控范围内[39, 47]。因此，TCR信号并非简单的线性级联，而是由信号平台组装与拆解共同维持的动态平衡。该平衡失控可降低T细胞对共刺激信号的依赖，增强炎症反应，并促进免疫耐受失衡。

除K63连接型泛素化外，线性泛素链组装复合物(linear ubiquitin chain assembly complex，LUBAC)介导的Met1线性泛素化也参与抗原受体触发的NF-κB信号平台稳定和激活阈值设定[22]。具有线性泛素链特异性的OTU结构域去泛素化酶(OTU deubiquitinase with linear linkage specificity，OTULIN)、CYLD等链型偏好性DUBs可选择性拆解该泛素化模块，从而调节信号持续时间和输出强度[48-49]。此外，部分DUBs还可在T细胞活化后发挥负向反馈作用。近期研究[50]显示，泛素特异性蛋白酶17样蛋白A(ubiquitin-specific peptidase 17-like A，USP17LA)在T细胞刺激后上调，并限制$CD4^+$ T细胞

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和CD8$^+$ T细胞的活化、增殖及效应功能，提示DUBs不仅参与近端信号平台拆解，也可在活化后阶段约束T细胞功能输出。

2.2 E3/DUBs对谱系转录程序的双向塑形

2.2.1 E3调控谱系分化

E3与DUB通过调控TCR信号、细胞因子通路、转录因子稳定性和代谢适配过程，共同参与T细胞分化命运的塑造。首先，在激活阈值设定方面，Cbl-b等E3可靶向CD3ζ/淋巴细胞特异性蛋白酪氨酸激酶(lymphocyte-specific protein tyrosine kinase，Lck)和磷脂酰肌醇3激酶-蛋白激酶B(phosphoinositide 3-kinase-protein kinase B，PI3K-Akt)等信号节点，限制T细胞在缺乏共刺激条件下的异常激活；其功能缺失常伴随白细胞介素-2(interleukin-2，IL-2)过量分泌、T细胞增殖增强及自身免疫病易感性升高[51-57]。其次，在分化程序维持方面，TRAF6/3等E3可调控TCR-NF-κB信号输出，并与转化生长因子β(transforming growth factor beta，TGF-β)/Sma和Mad相关蛋白(Sma- and Mad-related protein，SMAD)等通路交叉作用，从而影响Th/Treg细胞平衡[46, 58-62]；Itch、淋巴细胞无反应相关基因(gene related to anergy in lymphocytes，GRAIL)等通过促进免疫突触成分及JunB、c-Jun等转录因子的泛素化周转，限制Th2偏倚活化并维持Treg/诱导型Treg稳态[63-70]；STUB1、Pellino1与Roquin1/2则分别通过调控叉头框蛋白P3(forkhead box P3，FOXP3)稳定性、NF-κB家族成员活性或共刺激分子mRNA稳定性，限制滤泡辅助性T(T follicular helper，Tfh)细胞和Th17的异常扩增[71-76]。此外，在细胞因子-Janus激酶(Janus kinase，JAK)/信号转导及转录活化因子(signal transducer and activator of transcription，STAT)信号通路中，细胞因子信号转导抑制因子(suppressor of cytokine signaling，SOCS)等Cullin-RING复合体适配因子可限制JAK/STAT信号的强度和持续时间，并与TCR激活阈值共同决定T细胞极化方向[77-81]。除经典信号和转录调控外，E3介导的代谢适配也参与T细胞命运决定。冯·希佩尔-林道肿瘤抑制蛋白(von Hippel-Lindau tumor suppressor，VHL)作为E3复合体的底物识别组分，可促进缺氧诱导因子1α(hypoxia-inducible factor 1 alpha，HIF-1α)泛素化降解，从而限制低氧应答和糖酵解相关转录程序；Treg细胞中特异性缺失VHL可导致HIF-1α异常稳定，削弱FOXP3$^+$ Treg细胞稳定性和抑制功能，并诱导炎症性偏移[82]。Pellino E3泛素蛋白连接酶1(Pellino E3 ubiquitin protein ligase 1，Peli1)则可通过介导结节性硬化症复合体亚基1(tuberous sclerosis complex subunit 1，TSC1)泛素化负向调控哺乳动物雷帕霉素靶蛋白复合体1(mechanistic target of rapamycin complex 1，mTORC1)活性，进而限制T细胞糖酵解代谢和效应功能，提示UPS可通过氧感应、mTORC1活化和糖酵解代谢等代谢检查点，进一步塑造T细胞功能状态[83]。

2.2.2 DUBs调控信号持续性与谱系转录因子稳定性

相较于E3，DUBs参与Th和Treg细胞命运调控的研究相对分散，但其功能分工已逐渐清晰[84]。USP7可通过稳定FOXP3维持Treg细胞的免疫抑制功能[85]；USP18和OTUD5分别通过调节TAK1信号或促进视黄酸受体相关孤儿核受体γt(retinoic acid receptor-related orphan receptor gamma t，RORγt)周转，限制Th17细胞分化及炎症因子输出[86-87]；USP15和USP22可调控活化T细胞核因子(nuclear factor of activated T cells，NFAT)信号轴，进而影响IL-2分泌及Th1相关信号输出[88-89]；此外，USP10、USP21和USP17分别通过稳定Th1核心转录因子T盒转录因子21(T-box transcription factor 21，T-bet21)、Th2核心转录因子GATA结合蛋白3(GATA-binding protein 3，GATA3)及Th17核心转录因子RORγt，参与不同Th细胞谱系程序的维持[90-92]。

CYLD是具有K63连接型泛素链偏好性的DUB，既可负向调控NF-κB/MAPK信号通路，也参与Treg细胞功能成熟[41, 93-95]；OTUB1与USP8则可通过稳定GRAIL，间接支持Treg细胞功能[96-98]。这些研究提示，DUBs并非仅作为E3作用的反向调节因子，而是通过链型选择性、底物稳定性和信号持续时间控制，参与T细胞谱系命运的精细塑造。

总体而言，E3主要决定泛素信号的底物选择和链型写入，DUBs则通过去除或重塑泛素链，调节信号持续时间和输出强度。二者协同作用，使T细胞能够将抗原刺激和细胞因子信号转化为相对稳定的谱系分化结果。

2.3 T细胞失能中的泛素化调控网络

T细胞失能依赖于免疫突触近端信号的持续抑制。在持续Ca^{2+}-calcineurin信号驱动的失能模型中，Cbl-b、Itch和GRAIL等E3表达上调，并富集于免疫突触区域，促进磷脂酶Cγ1(phospholipase C gamma 1，PLCγ1)和蛋白激酶Cθ(protein kinase C theta，PKCθ)等信号分子的泛素化清除，从而削弱Ca^{2+}/NFAT和NF-κB信号输出，推动T细胞进入低反应状态[99-101]。这一过程具有明显的网络调控特征，单一E3缺失时可被其他成员部分补偿，而多个负调控节点共同激活时，则更容易维持稳定的失能表型。此外，FOXP3可通过诱导早期生长反应蛋白2/3(early growth response 2/3，Egr2/3)等转录程序上调Cbl-b、Itch和GRAIL，提示Treg细胞核心转录网络与E3介导的耐受程序之间存在正向偶联；这一机制也与

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GRAIL在Treg细胞中高表达及其与FOXP3共定位的现象相一致[102-103]。除E3外，DUBs还可通过稳定抑制性受体参与T细胞功能抑制。近期研究[104]显示，USP24可去除程序性细胞死亡蛋白1(programmed cell death protein 1，PD-1)的K48连接型泛素链并增强其蛋白质稳定性，从而促进T细胞耗竭样状态维持。因此，T细胞失能并非单一分子事件，而是由E3介导的近端信号削弱、DUBs介导的抑制性受体稳定及转录程序重塑共同构成的系统性调控结果。

2.4 自身免疫病中的UPS失衡：从典型节点到转化靶点

现有证据表明，UPS功能异常主要通过2类机制推动自身免疫病进程。其一，降低外周T细胞激活阈值，放大致炎性效应T细胞应答；其二，破坏Treg细胞稳态，或使炎性T细胞谱系转录程序异常持续激活。在激活阈值调控层面，Cbl-b缺失可使T细胞在缺乏共刺激信号时仍保持高反应性，并伴随多器官免疫细胞浸润，提示Cbl-b是维持外周免疫耐受的重要负调控分子[52, 54, 105-108]。在1型糖尿病(type 1 diabetes，T1D)中，Cbl-b作为限制T细胞共刺激依赖性和外周耐受的重要E3，其遗传变异与疾病易感性相关；Cbl-b可限制胰岛反应性$CD4^+$ T细胞异常激活，从而影响糖尿病易感性[108-109]。Itch功能缺陷则常表现为Th2偏倚活化与组织炎症浸润，反映其对效应T细胞分化程序的约束作用[29, 64, 110-112]。在炎症性肠病(inflammatory bowel disease，IBD)中，Itch-Nedd4家族相互作用蛋白1(Nedd4 family-interacting protein 1，Ndfip1)轴参与限制肠道Th17炎症。Itch可通过促进RORγt泛素化抑制IL-17介导的结肠炎症，而Ndfip1作为Itch相关适配因子，可限制Th17细胞致病性和促炎性细胞因子产生[27, 113]。在谱系命运调控层面，Roquin突变(sanroque模型)可导致Tfh异常积累，增强自身反应性B细胞阳性选择，最终呈现系统性红斑狼疮(systemic lupus erythematosus，SLE)样病理表型，明确了共刺激分子表达调控与生发中心反应稳态在系统性自身免疫发生中的重要意义[114]；Pellino1、神经前体细胞表达发育下调蛋白4(neural precursor cell expressed, developmentally downregulated 4，NEDD4)等E3可通过调控NF-κB家族成员和RORγt等关键转录因子的泛素化修饰，放大致炎细胞因子表达，进而推动实验性自身免疫性脑脊髓炎(experimental autoimmune encephalomyelitis，EAE)等自身免疫模型的病程进展[73-74, 115]。其中，NEDD4介导的K27连接型RORγt泛素化可增强Th17相关炎症输出，提示非经典链型修饰在Th17介导的自身免疫反应中具有重要调控作用[115]。含三联基序蛋白11 (tripartite motif-containing protein 11，TRIM11)则可负向调控Treg细胞分化，并以黑色素瘤缺失蛋白2(absent in melanoma 2，AIM2)依赖方式促进EAE进展[116]。此外，SLE相关研究[117]进一步提示，E3还可通过调控核酸感知通路参与自身免疫炎症：TRIM21可与干扰素基因刺激蛋白(stimulator of interferon genes，STING)相互作用并促进其降解，从而限制I型干扰素(interferon，IFN)产生和狼疮样自身免疫。基于SLE队列T细胞转录组的机器学习分析还鉴定出UHRF1P为新的SLE相关生物标志物。UHRF1假基因衍生蛋白(UHRF1 pseudogene-derived protein，UHRF1P)在SLE外周T细胞中表达升高，并可能通过含PHD和RING指结构域的泛素样蛋白1(ubiquitin-like with PHD and RING finger domains 1，UHRF1)-丝裂原活化蛋白激酶激酶激酶激酶3(mitogen-activated protein kinase kinase kinase kinase 3，MAP4K3)轴促进IL-17A上调和自身免疫炎症[118]。

在DUBs层面，A20与CYLD是NF-κB轴上较为明确的负向调控分子，其遗传变异或表达失衡与IBD、银屑病和类风湿关节炎(rheumatoid arthritis，RA)等炎症表型密切相关[119-121]。USP7除可稳定FOXP3、支持Treg细胞功能外，还可在不同免疫细胞中调控IFN相关通路[85, 122-123]。既往研究表明，I型IFN通路参与SLE免疫异常[122]，而USP7可通过稳定IFNα受体增强IFN信号，并与SLE疾病活动度升高相关[123]。在T1D中，USP7参与STAT5B诱导的耐受性树突状细胞(dendritic cell，DC)功能维持。USP7阻断可削弱耐受性DC表型并增强其促炎特征，提示UPS不仅可直接作用于T细胞或Treg细胞，也可通过抗原呈递细胞(antigen-presenting cell，APC)-T细胞轴间接影响Th/Treg细胞平衡和自身免疫进程[124]。Th17/Treg细胞平衡是DUBs参与自身免疫调控的另一关键环节。USP1可通过去泛素化并稳定含PDZ结合基序的转录共激活因子(transcriptional coactivator with PDZ-binding motif，TAZ)，调节Th17和Treg细胞的相互分化[125]。USP4和USP17等DUBs可通过稳定RORγt增强Th17相关炎症输出，并与银屑病或RA相关炎症有关[92, 126-127]。相对地，USP18可通过限制TAK1相关信号抑制Th17生成，OTUD5则通过促进RORγt周转降低IL-17A输出[86-87]。此外，OTUD7B和USP9X等DUBs可通过调控ZAP70泛素化影响效应T细胞克隆扩增或胸腺选择阈值，从而间接造成自身免疫风险[128-129]。这些发现提示，UPS在自身免疫病中的作用不能简单归为促炎或抗炎，而应结合具体细胞类型、底物转录因子、泛素链型和组织微环境进行判断。

综上，E3与DUBs通过共同塑造TCR/细胞因子信号及转录调控网络的强度、时程和阈值，影响Th1/Th17-Treg细胞平衡、炎症因子表达及APC介导的T细胞启动过程，从而构成自身免疫病发生和发展的关键调控节点(图1)。

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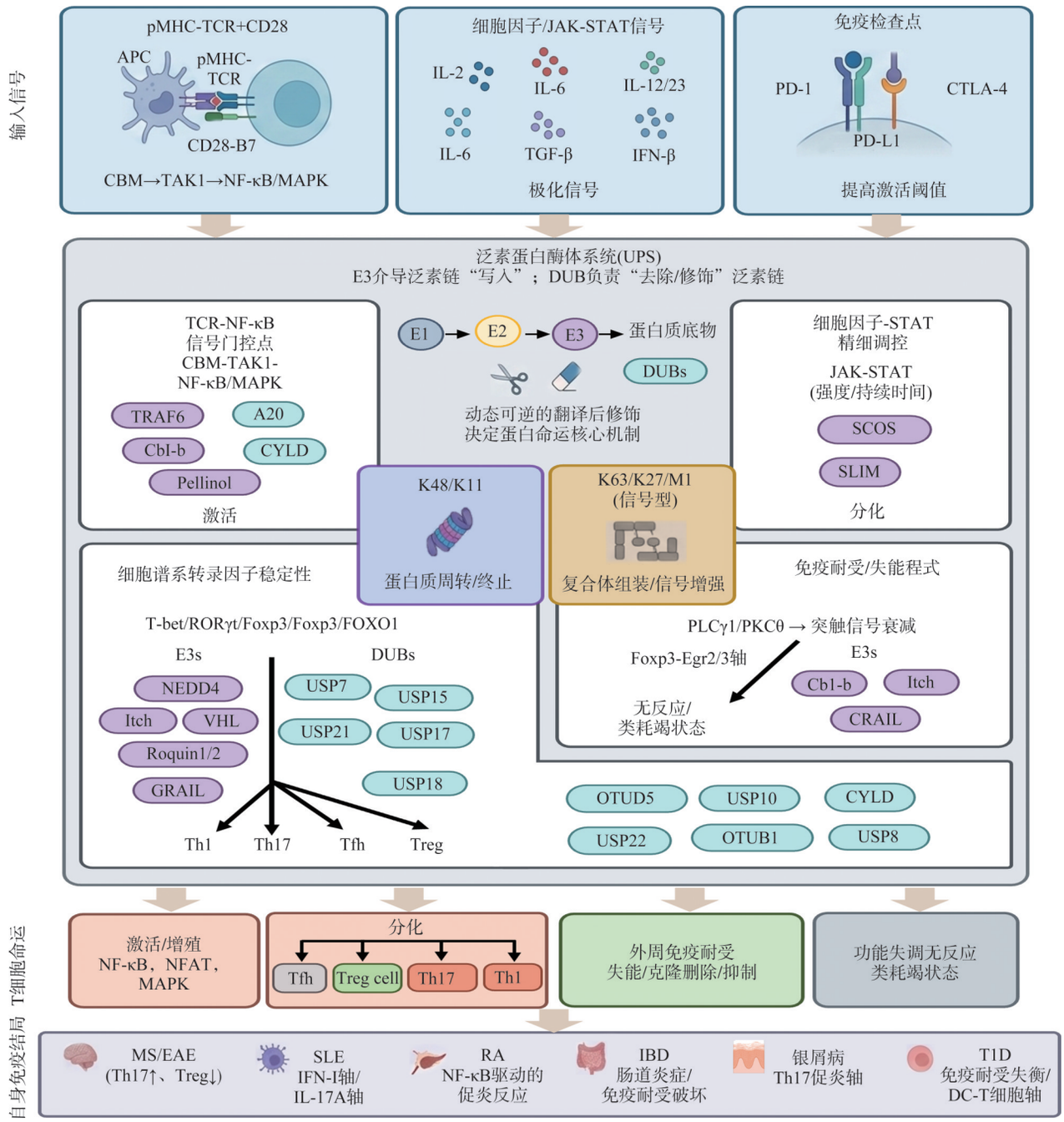


图1 泛素化调控广泛参与T细胞稳态和自身免疫病

Figure 1 Ubiquitination regulation is broadly involved in T cell homeostasis and autoimmune diseases

The ubiquitin-proteasome system (UPS), coordinated by E3 ubiquitin ligases and deubiquitinases (DUBs), regulates T cell receptor, costimulatory, cytokine, and immune checkpoint signaling, thereby shaping T cell activation, differentiation, peripheral tolerance, and autoimmune outcomes. pMHC: Peptide-major histocompatibility complex; TCR: T cell receptor; APC: Antigen-presenting cell; CBM: CARD11-BCL10-MALT1 complex; CARD11: Caspase recruitment domain family member 11; BCL10: B cell lymphoma 10; MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1; NF-κB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; JAK-STAT: Janus kinase-signal transducer and activator of transcription pathway; IL: Interleukin; IFN: Interferon; TGF-β: Transforming growth factor beta; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PTM: Post-translational modification; Tfh: T follicular helper cell; Treg: Regulatory T; Th: T helper cell; VHL: Von Hippel-Lindau tumor suppressor; OTUD: OTU deubiquitinase; USP: Ubiquitin-specific protease; OTU: Ovarian tumor domain-containing protease; MS: Multiple sclerosis; EAE: Experimental autoimmune encephalomyelitis; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; IBD: Inflammatory bowel disease; T1D: Type 1 diabetes.

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3 展　望

近年来，E3与DUBs在T细胞活化阈值设定、谱系分化和外周免疫耐受维持中的作用逐渐清晰。作为UPS的关键调控模块，E3/DUBs通过底物识别和泛素链型编辑，调节TCR、共刺激信号及细胞因子通路的强度、时程和空间组织，并进一步影响FOXP3、RORγt、T-bet等谱系转录因子及炎症信号平台的稳定性。由此，UPS不仅参与蛋白质稳态维持，也深度调控效应T细胞与Treg细胞之间的功能平衡。该调控网络一旦失衡，可降低T细胞激活阈值、放大炎症性分化反应或削弱免疫耐受，进而推动SLE、RA、T1D等自身免疫病的发生和发展。

尽管该研究方向已取得重要进展，但仍有多个关键问题尚待厘清。多数免疫相关E3与DUBs的体内直接底物、泛素链型偏好及功能发挥的环境依赖性仍缺乏系统解析；E3与DUBs是否在特定信号通路中形成相对稳定的“写入-擦除”功能配对，以及这类配对如何随组织微环境和疾病阶段动态变化，也尚未明确。与此同时，UPS核心分子在稳态与炎症条件下的时空表达特征，以及其与磷酸化、SUMO化、乙酰化和乳酸化等翻译后修饰之间的交叉调控机制，仍需进一步研究[37, 130]。未来依托条件性基因编辑模型、定量泛素组学、E3/DUBs底物互作筛选和链型特异性检测，这些问题有望在体内功能层面得到更精准的解析。

在转化研究层面，UPS靶向干预的研发思路也需要进一步拓展。当前DUB抑制剂、蛋白质降解靶向嵌合体(proteolysis targeting chimeras，PROTACs)和分子胶等策略主要作用于催化活性或蛋白质降解过程，但可能受到底物谱广、细胞靶向性不足和全局蛋白质稳态扰动等限制[2, 104, 131-133]。相比之下，靶向泛素链识别环节可能提供更精细的干预方式[20-21]。K63链、M1线性链及部分分支链常作为信号支架，依赖泛素结合结构域或相关识别蛋白质促进NF-κB、MAPK等炎症信号复合体组装。若能开发阻断特定泛素链与其阅读蛋白质互作的小分子、肽模拟物或变构调节剂，理论上可在不全面抑制E3/DUBs活性的情况下，选择性削弱自身免疫病中的病理性炎症信号，推动UPS靶向干预由“泛素酶活性抑制”转向“泛素信号输出重塑”[134]。

在此基础上，解析不同T细胞亚群中的UPS调控规律将是另一重要方向。初始T细胞、Th1、Th17、Tfh、Treg细胞、组织驻留记忆T细胞及耗竭样T细胞处于不同的信号、代谢和分化状态，其E3/DUBs表达模式和泛素链型使用偏好可能并不相同。因此，单纯比较某一E3或DUB的总体表达水平，难以解释其在不同疾病模型或免疫细胞中呈现的相反效应。未来可进一步整合单细胞转录组、细胞索引转录组和表位测序(cellular indexing of transcriptomes and epitopes by sequencing，CITE-seq)、T细胞受体测序(T cell receptor sequencing，TCR-seq)、空间转录组与定量泛素组学，在细胞状态和组织位置层面解析UPS节点的表达特征、底物互作及功能输出[135-142]。这将有助于识别维持特定T细胞状态的关键调控轴，并为自身免疫病的机制分层、细胞类型选择性靶点筛选和药效学标志物开发提供依据。

此外，UPS与代谢重编程及新型翻译后修饰之间的交叉，正在成为理解T细胞命运调控的重要切入点[143-145]。研究[146]表明，泛素化可通过控制氧感应因子的稳定性，将组织缺氧、糖酵解增强与T细胞谱系偏向相连接。在慢性炎症微环境中，乳酸积累、脂质代谢重塑和线粒体应激不仅改变T细胞代谢状态，也可能影响E3/DUBs活性、底物构象、亚细胞定位和蛋白质降解阈值[147]。乳酸化、乙酰化、SUMO化和磷酸化等修饰可与泛素化形成竞争、协同或级联调控，共同决定转录因子、代谢酶和信号复合体的稳定性与功能输出[145, 148]。因此，UPS不应被简单视为蛋白质降解系统，而应置于代谢状态、多重翻译后修饰和免疫命运决定相互偶联的框架下重新审视。

总体来看，UPS通过调控TCR信号、细胞因子通路、转录因子稳定性和代谢适配，深度参与T细胞稳态维持与免疫耐受建立。其功能失衡可重塑T细胞活化阈值、效应/调节性平衡、失能状态及APC介导的免疫启动，从而推动自身免疫病发生和发展。未来研究若能在细胞状态、组织微环境和疾病阶段中明确关键UPS节点的真实功能，将有助于推动自身免疫病治疗从广谱免疫抑制走向更精准、更具细胞选择性的靶向调控。

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参考文献

[1] Yu H, Yang W, Cao M, et al. Mechanism study of ubiquitination in T cell development and autoimmune disease[J]. Front Immunol, 2024, 15: 1359933. https://doi.org/10.3389/fimmu.2024.1359933.

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[2] Ebadi P, Stratton CM, Olsen SK. E3 ubiquitin ligases in signaling, disease, and therapeutics[J]. Trends Biochem Sci, 2025, 50(11): 960-976. https://doi.org/10.1016/j.tibs.2025.07.009.

[3] Sumida TS, Cheru NT, Hafler DA. The regulation and differentiation of regulatory T cells and their dysfunction in autoimmune diseases[J]. Nat Rev Immunol, 2024, 24(7): 503-517. https://doi.org/10.1038/s41577-024-00994-x.

[4] Le Menn G, Jabłońska A, Chen Z. The effects of post-translational modifications on Th17/Treg cell differentiation[J]. Biochim Biophys Acta BBA Mol Cell Res, 2022, 1869(6): 119223. https://doi.org/10.1016/j.bbamcr.2022.119223.

[5] Pisetsky DS. Pathogenesis of autoimmune disease[J]. Nat Rev Nephrol, 2023, 19(8): 509-524. https://doi.org/10.1038/s41581-023-00720-1.

[6] Liu J, Cheng Y, Zheng M, et al. Targeting the ubiquitination/deubiquitination process to regulate immune checkpoint pathways[J]. Signal Transduct Target Ther, 2021, 6: 28. https://doi.org/10.1038/s41392-020-00418-x.

[7] Deng L, Meng T, Chen L, et al. The role of ubiquitination in tumorigenesis and targeted drug discovery[J]. Signal Transduct Target Ther, 2020, 5: 11. https://doi.org/10.1038/s41392-020-0107-0.

[8] Sun T, Liu Z, Yang Q. The role of ubiquitination and deubiquitination in cancer metabolism[J]. Mol Cancer, 2020, 19 (1): 146. https://doi.org/10.1186/s12943-020-01262-x.

[9] Liu F, Chen J, Li K, et al. Ubiquitination and deubiquitination in cancer: from mechanisms to novel therapeutic approaches [J]. Mol Cancer, 2024, 23(1): 148. https://doi.org/10.1186/s12943-024-02046-3.

[10] Cockram PE, Kist M, Prakash S, et al. Ubiquitination in the regulation of inflammatory cell death and cancer[J]. Cell Death Differ, 2021, 28(2): 591-605. https://doi.org/10.1038/s41418-020-00708-5.

[11] Roberts JZ, Crawford N, Longley DB. The role of ubiquitination in apoptosis and necroptosis[J]. Cell Death Differ, 2022, 29(2): 272-284. https://doi.org/10.1038/s41418-021-00922-9.

[12] Wang L, Liang Y, Zhao C, et al. Regulatory T cells in homeostasis and disease: molecular mechanisms and therapeutic potential[J]. Signal Transduct Target Ther, 2025, 10: 345. https://doi.org/10.1038/s41392-025-02326-4.

[13] Cruz Walma DA, Chen Z, Bullock AN, et al. Ubiquitin ligases: guardians of mammalian development[J]. Nat Rev Mol Cell Biol, 2022, 23(5): 350-367. https://doi.org/10.1038/s41580-021-00448-5.

[14] Martínez-Férriz A, Ferrando A, Fathinajafabadi A, et al. Ubiquitin-mediated mechanisms of translational control[J]. Semin Cell Dev Biol, 2022, 132: 146-154. https://doi.org/10.1016/j.semcdb.2021.12.009.

[15] Dikic I, Schulman BA. An expanded lexicon for the ubiquitin code[J]. Nat Rev Mol Cell Biol, 2023, 24(4): 273-287. https://doi.org/10.1038/s41580-022-00543-1.

[16] Yang Q, Zhao JY, Chen D, et al. E3 ubiquitin ligases: styles, structures and functions[J]. Mol Biomed, 2021, 2(1): 23. https://doi.org/10.1186/s43556-021-00043-2.

[17] Liao Y, Zhang W, Liu Y, et al. The role of ubiquitination in health and disease[J/OL]. MedComm, 2024, 5(10): e736[2026-01-23]. https://doi.org/10.1002/mco2.736.

[18] Nakasone MA, Majorek KA, Gabrielsen M, et al. Structure of UBE2K-Ub/E3/polyUb reveals mechanisms of K48-linked Ub chain extension[J]. Nat Chem Biol, 2022, 18(4): 422-431. https://doi.org/10.1038/s41589-021-00952-x.

[19] Tracz M, Bialek W. Beyond K48 and K63: non-canonical protein ubiquitination[J]. Cell Mol Biol Lett, 2021, 26(1): 1. https://doi.org/10.1186/s11658-020-00245-6.

[20] Kolla S, Ye MC, Mark KG, et al. Assembly and function of branched ubiquitin chains[J]. Trends Biochem Sci, 2022, 47(9): 759-771. https://doi.org/10.1016/j.tibs.2022.04.003.

[21] French ME, Koehler CF, Hunter T. Emerging functions of branched ubiquitin chains[J]. Cell Discov, 2021, 7: 6. https://doi.org/10.1038/s41421-020-00237-y.

[22] Fiil BK, Gyrd-Hansen M. The Met1-linked ubiquitin machinery in inflammation and infection[J]. Cell Death Differ, 2021, 28(2): 557-569. https://doi.org/10.1038/s41418-020-00702-x.

[23] Belizaire R, Koochaki SHJ, Udeshi ND, et al. CBL mutations drive PI3K/AKT signaling via increased interaction with LYN and PIK3R1[J]. Blood, 2021, 137(16): 2209-2220. https://doi.org/10.1182/blood.2020006528.

[24] Wang HY, Altman Y, Fang DY, et al. Cbl promotes ubiquitination of the T cell receptor ζ through an adaptor function of zap-70[J]. J Biol Chem, 2001, 276(28): 26004-26011. https://doi.org/10.1074/jbc.m010738200.

[25] Meng W, Sawasdikosol S, Burakoff S, et al. Structure of the amino-terminal domain of Cbl complexed to its binding site on ZAP-70 kinase[J]. Nature, 1999, 398(6722): 84-90. https://doi.org/10.1038/18050.

[26] Zhou Q, Yang T, Yu XX, et al. Lanatoside C activates the E3 ligase STUB1 to inhibit FOXP3 transcriptional activity and promote antitumor immunity[J]. EMBO Mol Med, 2025, 17(3): 563-588. https://doi.org/10.1038/s44321-025-00200-y.

[27] Kathania M, Khare P, Zeng MH, et al. Itch inhibits IL-17-mediated colon inflammation and tumorigenesis by ROR-γt ubiquitination[J]. Nat Immunol, 2016, 17(8): 997-1004. https://doi.org/10.1038/ni.3488.

[28] Janssen E, Peters Z, Alosaimi MF, et al. Immune dysregulation caused by homozygous mutations in CBLB[J/OL]. J Clin Investig, 2022, 132(20): e154487[2026-01-23]. https://doi.org/10.1172/jci154487.

[29] Kathania M, Tsakem EL, Theiss AL, et al. Gut microbiota contributes to spontaneous colitis in E3 ligase itch-deficient mice[J]. J Immunol, 2020, 204(8): 2277-2284. https://doi.org/10.4049/jimmunol.1701478.

[30] Choi HS, Baek KH. Pro-apoptotic and anti-apoptotic regulation mediated by deubiquitinating enzymes[J]. Cell Mol Life Sci, 2022, 79(2): 117. https://doi.org/10.1007/s00018-022-04132-5.

[31] Lange SM, Armstrong LA, Kulathu Y. Deubiquitinases: From

©Journal of Central South University (Medical Science). All rights reserved.

mechanisms to their inhibition by small molecules[J]. Mol Cell, 2022, 82(1): 15-29. https://doi.org/10.1016/j.molcel.2021.10.027.

[32] Squair DR, Virdee S. A new dawn beyond lysine ubiquitination [J]. Nat Chem Biol, 2022, 18(8): 802-811. https://doi.org/10.1038/s41589-022-01088-2.

[33] Shah K, Al-Haidari A, Sun JM, et al. T cell receptor (TCR) signaling in health and disease[J]. Signal Transduct Target Ther, 2021, 6: 412. https://doi.org/10.1038/s41392-021-00823-w.

[34] ElTanbouly MA, Noelle RJ. Rethinking peripheral T cell tolerance: checkpoints across a T cell's journey[J]. Nat Rev Immunol, 2021, 21(4): 257-267. https://doi.org/10.1038/s41577-020-00454-2.

[35] Carbone F, Russo C, Colamatteo A, et al. Cellular and molecular signaling towards T cell immunological self-tolerance[J]. J Biol Chem, 2024, 300(4): 107134. https://doi.org/10.1016/j.jbc.2024.107134.

[36] Sun L, Su Y, Jiao A, et al. T cells in health and disease[J]. Sig Transduct Target Ther, 2023, 8: 235. https://doi.org/10.1038/s41392-023-01471-y.

[37] Gavali S, Liu J, Li X, et al. Ubiquitination in T-cell activation and checkpoint inhibition: new avenues for targeted cancer immunotherapy[J]. Int J Mol Sci, 2021, 22(19): 10800. https://doi.org/10.3390/ijms221910800.

[38] Chen ZJ. Ubiquitination in signaling to and activation of IKK [J]. Immunol Rev, 2012, 246(1): 95-106. https://doi.org/10.1111/j.1600-065x.2012.01108.x.

[39] Reiley WW, Jin W, Lee AJ, et al. Deubiquitinating enzyme CYLD negatively regulates the ubiquitin-dependent kinase Tak1 and prevents abnormal T cell responses[J]. J Exp Med, 2007, 204 (6): 1475-1485. https://doi.org/10.1084/jem.20062694.

[40] Endo A, Takahashi C, Ishibashi N, et al. Ubiquitination-activated TAB-*TAK1*-*IKK*-NF-κB axis modulates gene expression for cell survival in the lysosomal damage response[J]. eLife, 2025, 14: RP106901. https://doi.org/10.7554/elife.106901.

[41] Guo Q, Jin Y, Chen X, et al. NF-κB in biology and targeted therapy: new insights and translational implications[J]. Signal Transduct Target Ther, 2024, 9: 53. https://doi.org/10.1038/s41392-024-01757-9.

[42] Hamilton KS, Phong B, Corey C, et al. T cell receptor-dependent activation of mTOR signaling in T cells is mediated by Carma1 and MALT1, but not Bcl10[J/OL]. Sci Signal, 2014, 7(329): e2005169[2026-01-23]. https://doi.org/10.1126/scisignal.2005169.

[43] Shi JH, Sun SC. TCR signaling to NF-κB and mTORC1: Expanding roles of the CARMA1 complex[J]. Mol Immunol, 2015, 68(2): 546-557. https://doi.org/10.1016/j.molimm.2015.07.024.

[44] Sun L, Deng L, Ea C, et al. The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes[J]. Mol Cell, 2004, 14(3): 289-301. https://doi.org/10.1016/S1097-2765(04)00236-9.

[45] Coornaert B, Baens M, Heyninck K, et al. T cell antigen receptor stimulation induces MALT1 paracaspase-mediated cleavage of the NF-κB inhibitor A20[J]. Nat Immunol, 2008, 9 (3): 263-271. https://doi.org/10.1038/ni1561.

[46] King CG, Kobayashi T, Cejas PJ, et al. TRAF6 is a T cell-intrinsic negative regulator required for the maintenance of immune homeostasis[J]. Nat Med, 2006, 12(9): 1088-1092. https://doi.org/10.1038/nm1449.

[47] Marín-Rubio JL, Raote I, Inns J, et al. CYLD in health and disease[J]. Dis Models Mech, 2023, 16(6): dmm050093. https://doi.org/10.1242/dmm.050093.

[48] Staal J, Driege Y, Bekaert T, et al. T-cell receptor-induced JNK activation requires proteolytic inactivation of CYLD by MALT1[J]. EMBO J, 2011, 30(9): 1742-1752. https://doi.org/10.1038/emboj.2011.85.

[49] Oikawa D, Hatanaka N, Suzuki T, et al. Cellular and mathematical analyses of LUBAC involvement in T cell receptor-mediated NF-κB activation pathway[J]. Front Immunol, 2020, 11: 601926. https://doi.org/10.3389/fimmu.2020.601926.

[50] Zhang H, Guo Z, Wei G, et al. The deubiquitinase USP17LA negatively regulates T-cell activation and attenuates anti-tumor immunity[J]. EMBO Rep, 2025, 26(21): 5300-5325. https://doi.org/10.1038/s44319-025-00584-5.

[51] Yang B, Gay DL, MacLeod MKL, et al. Nedd4 augments the adaptive immune response by promoting ubiquitin-mediated degradation of Cbl-b in activated T cells[J]. Nat Immunol, 2008, 9(12): 1356-1363. https://doi.org/10.1038/ni.1670.

[52] Fang D, Liu YC. Proteolysis-independent regulation of PI3K by Cbl-b－mediated ubiquitination in T cells[J]. Nat Immunol, 2001, 2(9): 870-875. https://doi.org/10.1038/ni0901-870.

[53] Chiang YJ, Sommers CL, Jordan MS, et al. Inactivation of c-cbl reverses neonatal lethality and T cell developmental arrest of SLP-76-deficient mice[J]. J Exp Med, 2004, 200(1): 25-34. https://doi.org/10.1084/jem.20040262.

[54] Fang D, Wang HY, Fang N, et al. Cbl-b, a RING-type E3 ubiquitin ligase, targets phosphatidylinositol 3-kinase for ubiquitination in T cells[J]. J Biol Chem, 2001, 276(7): 4872-4878. https://doi.org/10.1074/jbc.M008901200.

[55] Qiao G, Ying H, Zhao Y, et al. E3 ubiquitin ligase cbl-b suppresses proallergic T cell development and allergic airway inflammation[J]. Cell Rep, 2014, 6(4): 709-723. https://doi.org/10.1016/j.celrep.2014.01.012.

[56] Huang H, Jeon MS, Liao L, et al. K33-linked polyubiquitination of T cell receptor-ζ regulates proteolysis-independent T cell signaling[J]. Immunity, 2010, 33(5): 830. https://doi.org/10.1016/j.immuni.2010.11.019.

[57] Harada Y, Harada Y, Elly C, et al. Transcription factors Foxo3a and Foxo1 couple the E3 ligase Cbl-b to the induction of Foxp3 expression in induced regulatory T cells[J]. J Exp Med, 2010, 207(7): 1381-1391. https://doi.org/10.1084/jem.20100004.

[58] Muto G, Kotani H, Kondo T, et al. TRAF6 is essential for maintenance of regulatory T cells that suppress Th2 type autoimmunity[J/OL]. PLoS One, 2013, 8(9): e74639[2026-01-23]. https://doi.org/10.1371/journal.pone.0074639.

[59] Cejas PJ, Walsh MC, Pearce EL, et al. TRAF6 inhibits Th17

©Journal of Central South University (Medical Science). All rights reserved.

differentiation and TGF-β-mediated suppression of IL-2[J]. Blood, 2010, 115(23): 4750-4757. https://doi.org/10.1182/blood-2009-09-242768.

[60] Chang JH, Xiao YC, Hu HB, et al. Ubc13 maintains the suppressive function of regulatory T cells and prevents their conversion into effector-like T cells[J]. Nat Immunol, 2012, 13 (5): 481-490. https://doi.org/10.1038/ni.2267.

[61] Levine AG, Arvey A, Jin W, et al. Continuous requirement for the TCR in regulatory T cell function[J]. Nat Immunol, 2014, 15(11): 1070-1078. https://doi.org/10.1038/ni.3004.

[62] Xie P, Kraus ZJ, Stunz LL, et al. TNF receptor-associated factor 3 is required for T cell-mediated immunity and TCR/CD28 signaling[J]. J Immunol, 2011, 186(1): 143-155. https://doi.org/10.4049/jimmunol.1000290.

[63] Nurieva RI, Zheng SL, Jin W, et al. The E3 ubiquitin ligase GRAIL regulates T cell tolerance and regulatory T cell function by mediating T cell receptor-CD3 degradation[J]. Immunity, 2010, 32(5): 670-680. https://doi.org/10.1016/j.immuni.2010.05.002.

[64] Fang D, Elly C, Gao B, et al. Dysregulation of T lymphocyte function in itchy mice: a role for Itch in TH2 differentiation[J]. Nat Immunol, 2002, 3(3): 281-287. https://doi.org/10.1038/ni763.

[65] Xiao N, Eto D, Elly C, et al. The E3 ubiquitin ligase Itch is required for the differentiation of follicular helper T cells[J]. Nat Immunol, 2014, 15(7): 657-666. https://doi.org/10.1038/ni.2912.

[66] Jin HS, Park Y, Elly C, et al. Itch expression by Treg cells controls Th2 inflammatory responses[J]. J Clin Invest, 2013, 123(11): 4923-4934. https://doi.org/10.1172/jci69355.

[67] Whiting CC, Su LL, Lin JT, et al. GRAIL: a unique mediator of CD4 T-lymphocyte unresponsiveness[J]. FEBS J, 2011, 278 (1): 47-58. https://doi.org/10.1111/j.1742-4658.2010.07922.x.

[68] Lineberry NB, Su LL, Lin JT, et al. Cutting edge: the transmembrane E3 ligase GRAIL ubiquitinates the costimulatory molecule CD40 ligand during the induction of T cell anergy[J]. J Immunol, 2008, 181(3): 1622-1626. https://doi.org/10.4049/jimmunol.181.3.1622.

[69] Taylor JJ, Krawczyk CM, Mohrs M, et al. Th2 cell hyporesponsiveness during chronic murine schistosomiasis is cell intrinsic and linked to GRAIL expression[J]. J Clin Invest, 2009, 119(4): 1019-1028. https://doi.org/10.1172/jci36534.

[70] Sahoo A, Alekseev A, Obertas L, et al. Grail controls Th2 cell development by targeting STAT6 for degradation[J]. Nat Commun, 2014, 5: 4732. https://doi.org/10.1038/ncomms5732.

[71] Pratama A, Ramiscal RR, Silva DG, et al. Roquin-2 shares functions with its paralog roquin-1 in the repression of mRNAs controlling T follicular helper cells and systemic inflammation [J]. Immunity, 2013, 38(4): 669-680. https://doi.org/10.1016/j.immuni.2013.01.011.

[72] Wang S, Li Y, Hu YH, et al. STUB1 is essential for T-cell activation by ubiquitinating CARMA1[J]. Eur J Immunol, 2013, 43(4): 1034-1041. https://doi.org/10.1002/eji.201242554.

[73] Xiao Y, Jin J, Chang M, et al. Peli1 promotes microglia-mediated CNS inflammation by regulating Traf3 degradation [J]. Nat Med, 2013, 19(5): 595-602. https://doi.org/10.1038/nm.3111.

[74] Chang M, Jin W, Chang JH, et al. The ubiquitin ligase Peli1 negatively regulates T cell activation and prevents autoimmunity[J]. Nat Immunol, 2011, 12(10): 1002-1009. https://doi.org/10.1038/ni.2090.

[75] Vogel KU, Edelmann SL, Jeltsch KM, et al. Roquin paralogs 1 and 2 redundantly repress the icos and Ox40 costimulator mRNAs and control follicular helper T cell differentiation[J]. Immunity, 2013, 38(4): 655-668. https://doi.org/10.1016/j.immuni.2012.12.004.

[76] Jeltsch KM, Hu DS, Brenner S, et al. Cleavage of roquin and regnase-1 by the paracaspase MALT1 releases their cooperatively repressed targets to promote TH17 differentiation [J]. Nat Immunol, 2014, 15(11): 1079-1089. https://doi.org/10.1038/ni.3008.

[77] Fujimoto M. A regulatory role for suppressor of cytokine signaling-1 in Th polarization in vivo[J]. Int Immunol, 2002, 14 (11): 1343-1350. https://doi.org/10.1093/intimm/dxf094.

[78] Yang XO, Zhang HY, Kim BS, et al. The signaling suppressor CIS controls proallergic T cell development and allergic airway inflammation[J]. Nat Immunol, 2013, 14(7): 732-740. https://doi.org/10.1038/ni.2633.

[79] Zhan Y, Davey GM, Graham KL, et al. SOCS1 negatively regulates the production of $Foxp3^+$ $CD4^+$ T cells in the thymus [J]. Immunol Cell Biol, 2009, 87(6): 473-480. https://doi.org/10.1038/icb.2009.23.

[80] Tanaka T, Soriano MA, Grusby MJ. SLIM is a nuclear ubiquitin E3 ligase that negatively regulates STAT signaling[J]. Immunity, 2005, 22(6): 729-736. https://doi.org/10.1016/j.immuni.2005.04.008.

[81] Tanaka T, Yamamoto Y, Muromoto R, et al. PDLIM2 inhibits T helper 17 cell development and granulomatous inflammation through degradation of STAT3[J/OL]. Sci Signal, 2011, 4(202): e2001637[2026-01-23]. https://doi.org/10.1126/scisignal.2001637.

[82] Lee JH, Elly C, Park Y, et al. E3 ubiquitin ligase VHL regulates hypoxia-inducible factor-1α to maintain regulatory T cell stability and suppressive capacity[J]. Immunity, 2015, 42(6): 1062-1074. https://doi.org/10.1016/j.immuni.2015.05.016.

[83] Ko CJ, Zhang LY, Jie ZL, et al. The E3 ubiquitin ligase Peli1 regulates the metabolic actions of mTORC1 to suppress antitumor T cell responses[J/OL]. EMBO J, 2020, 40(2): EMBJ2020104532[2026-01-23]. https://doi.org/10.15252/embj.2020104532.

[84] Raj D, Verma AK, Mathur R, et al. Fine-tuning immunity: ubiquitin-dependent regulation of interleukin-17A expression by Th17 cells[J]. Front Immunol, 2025, 16: 1614409. https://doi.org/10.3389/fimmu.2025.1614409.

[85] van Loosdregt J, Fleskens V, Fu J, et al. Stabilization of the transcription factor Foxp3 by the deubiquitinase USP7 increases treg-cell-suppressive capacity[J]. Immunity, 2013, 39 (2): 259-271. https://doi.org/10.1016/j.immuni.2013.05.018.

[86] Liu X, Li H, Zhong B, et al. USP18 inhibits NF-κB and NFAT

©Journal of Central South University (Medical Science). All rights reserved.

activation during Th17 differentiation by deubiquitinating the TAK1-TAB1 complex[J]. J Exp Med, 2013, 210(8): 1575-1590. https://doi.org/10.1084/jem.20122327.

[87] Rutz S, Kayagaki N, Phung QT, et al. Deubiquitinase DUBA is a post-translational brake on interleukin-17 production in T cells[J]. Nature, 2015, 518(7539): 417-421. https://doi.org/10.1038/nature13979.

[88] Zou Q, Jin J, Hu HB, et al. USP15 stabilizes MDM2 to mediate cancer-cell survival and inhibit antitumor T cell responses[J]. Nat Immunol, 2014, 15(6): 562-570. https://doi.org/10.1038/ni.2885.

[89] Gao Y, Lin F, Xu P, et al. USP22 is a positive regulator of NFATc2 on promoting IL2 expression[J]. FEBS Lett, 2014, 588(6): 878-883. https://doi.org/10.1016/j.febslet.2014.02.016.

[90] Zhang J, Chen C, Hou XX, et al. Identification of the E3 deubiquitinase ubiquitin-specific peptidase 21 (USP21) as a positive regulator of the transcription factor GATA3[J]. J Biol Chem, 2013, 288(13): 9373-9382. https://doi.org/10.1074/jbc.M112.374744.

[91] Pan L, Chen Z, Wang L, et al. Deubiquitination and stabilization of T-bet by USP10[J]. Biochem Biophys Res Commun, 2014, 449(3): 289-294. https://doi.org/10.1016/j.bbrc.2014.05.037.

[92] Han L, Yang J, Wang XW, et al. The E3 deubiquitinase USP17 is a positive regulator of retinoic acid-related orphan nuclear receptor γt (RORγt) in Th17 cells[J]. J Biol Chem, 2014, 289(37): 25546-25555. https://doi.org/10.1074/jbc.M114.565291.

[93] Reissig S, Hövelmeyer N, Weigmann B, et al. The tumor suppressor CYLD controls the function of murine regulatory T cells[J]. J Immunol, 2012, 189(10): 4770-4776. https://doi.org/10.4049/jimmunol.1201993.

[94] Zhao Y, Thornton AM, Kinney MC, et al. The deubiquitinase CYLD targets Smad7 protein to regulate transforming growth factor β (TGF-β) signaling and the development of regulatory T cells[J]. J Biol Chem, 2011, 286(47): 40520-40530. https://doi.org/10.1074/jbc.M111.292961.

[95] Lee AJ, Wu XF, Cheng HY, et al. CARMA1 regulation of regulatory T cell development involves modulation of interleukin-2 receptor signaling[J]. J Biol Chem, 2010, 285(21): 15696-15703. https://doi.org/10.1074/jbc.M109.095190.

[96] Dufner A, Kisser A, Niendorf S, et al. The ubiquitin-specific protease USP8 is critical for the development and homeostasis of T cells[J]. Nat Immunol, 2015, 16(9): 950-960. https://doi.org/10.1038/ni.3230.

[97] Zhang X, Han L, Hou J, et al. Stress granule-localized USP8 potentiates cGAS-mediated type I interferonopathies through deubiquitination of DDX3X[J]. Cell Rep, 2024, 43(6): 114248. https://doi.org/10.1016/j.celrep.2024.114248.

[98] Soares L, Seroogy C, Skrenta H, et al. Two isoforms of otubain 1 regulate T cell anergy via GRAIL[J]. Nat Immunol, 2004, 5(1): 45-54. https://doi.org/10.1038/ni1017.

[99] Heissmeyer V, Macián F, Im SH, et al. Calcineurin imposes T cell unresponsiveness through targeted proteolysis of signaling proteins[J]. Nat Immunol, 2004, 5(3): 255-265. https://doi.org/10.1038/ni1047.

[100] Heissmeyer V, Macián F, Varma R, et al. A molecular dissection of lymphocyte unresponsiveness induced by sustained calcium signalling[J]. Novartis Found Symp, 2005, 267: 165-174;discussion174-9.

[101] Berg-Brown NN, Gronski MA, Jones RG, et al. PKCθ signals activation versus tolerance in vivo[J]. J Exp Med, 2004, 199(6): 743-752. https://doi.org/10.1084/jem.20031022.

[102] Chang X, Chen L, Wen J, et al. Foxp3 controls autoreactive T cell activation through transcriptional regulation of early growth response genes and E3 ubiquitin ligase genes, independently of thymic selection[J]. Clin Immunol, 2006, 121(3): 274-285. https://doi.org/10.1016/j.clim.2006.07.004.

[103] MacKenzie DA, Schartner J, Lin J, et al. GRAIL is up-regulated in $CD4^+$ $CD25^+$ T regulatory cells and is sufficient for conversion of T cells to a regulatory phenotype[J]. J Biol Chem, 2007, 282(13): 9696-9702. https://doi.org/10.1074/jbc.M604192200.

[104] Hsieh HC, Young MJ, Chen KY, et al. Deubiquitinase USP24 activated by IL-6/STAT3 enhances PD-1 protein stability and suppresses T cell antitumor response[J/OL]. Sci Adv, 2025, 11(16): eadt4258[2026-01-23]. https://doi.org/10.1126/sciadv.adt4258.

[105] Anderson MS, Venanzi ES, Klein L, et al. Projection of an immunological self shadow within the thymus by the Aire protein[J]. Science, 2002, 298(5597): 1395-1401. https://doi.org/10.1126/science.1075958.

[106] Chiang YJ, Kole HK, Brown K, et al. Cbl-b regulates the CD28 dependence of T-cell activation[J]. Nature, 2000, 403(6766): 216-220. https://doi.org/10.1038/35003235.

[107] Bachmaier K, Krawczyk C, Kozieradzki I, et al. Negative regulation of lymphocyte activation and autoimmunity by the molecular adaptor Cbl-b[J]. Nature, 2000, 403(6766): 211-216. https://doi.org/10.1038/35003228.

[108] Bergholdt R, Taxvig C, Eising S, et al. *CBLB* variants in type 1 diabetes and their genetic interaction with *CTLA4*[J]. J Leukoc Biol, 2005, 77(4): 579-585. https://doi.org/10.1189/jlb.0904524.

[109] Hoyne GF, Flening E, Yabas M, et al. Visualizing the role of cbl-b in control of islet-reactive CD4 T cells and susceptibility to type 1 diabetes[J]. J Immunol, 2011, 186(4): 2024-2032. https://doi.org/10.4049/jimmunol.1002296.

[110] Perry WL, Hustad CM, Swing DA, et al. The itchy locus encodes a novel ubiquitin protein ligase that is disrupted in a18H mice[J]. Nat Genet, 1998, 18(2): 143-146. https://doi.org/10.1038/ng0298-143.

[111] Oliver PM, Cao X, Worthen GS, et al. Ndfip1 protein promotes the function of itch ubiquitin ligase to prevent T cell activation and T helper 2 cell-mediated inflammation[J]. Immunity, 2006, 25(6): 929-940. https://doi.org/10.1016/j.immuni.2006.10.012.

[112] Kobayashi T, Walsh PT, Walsh MC, et al. TRAF6 is a critical factor for dendritic cell maturation and development[J]. Immunity, 2003, 19(3): 353-363. https://doi.org/10.1016/S1074-7613(03)00230-9.

©Journal of Central South University (Medical Science). All rights reserved.

[113] Layman AAK, Sprout SL, Phillips D, et al. Ndfip1 restricts Th17 cell potency by limiting lineage stability and proinflammatory cytokine production[J]. Sci Rep, 2017, 7: 39649. https://doi.org/10.1038/srep39649.

[114] Vinuesa CG, Cook MC, Angelucci C, et al. A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity[J]. Nature, 2005, 435(7041): 452-458. https://doi.org/10.1038/nature03555.

[115] Zeng Q, Guo H, Tang N, et al. K27-linked RORγt ubiquitination by Nedd4 potentiates Th17-mediated autoimmunity[J]. J Biomed Sci, 2025, 32(1): 26. https://doi.org/10.1186/s12929-025-01120-2.

[116] Yu T, Yang X, Fu Q, et al. TRIM11 attenuates Treg cell differentiation by p62-selective autophagic degradation of AIM2[J]. Cell Rep, 2023, 42(10): 113231. https://doi.org/10.1016/j.celrep.2023.113231.

[117] Kim DS, Park Y, Tsokos GC, et al. The ubiquitin E3 ligase TRIM21 suppresses type I interferon signaling via STING degradation and ameliorates systemic autoimmunity[J]. Exp Mol Med, 2025, 57(7): 1555-1566. https://doi.org/10.1038/s12276-025-01490-5.

[118] Chuang H, Lan K, Hsu P, et al. UHRF1P contributes to IL-17A-mediated systemic lupus erythematosus via UHRF1-MAP4K3 axis[J]. J Autoimmun, 2024, 146: 103221. https://doi.org/10.1016/j.jaut.2024.103221.

[119] Wei J, Wei C, Wang M, et al. The GTPase-activating protein GIT2 protects against colitis by negatively regulating Toll-like receptor signaling[J]. Proc Natl Acad Sci U S A, 2014, 111(24): 8883-8888. https://doi.org/10.1073/pnas.1309218111.

[120] Bagyinszky E, An SSA. Genetic mutations associated with TNFAIP3 (A20) haploinsufficiency and their impact on inflammatory diseases[J]. Int J Mol Sci, 2024, 25(15): 8275. https://doi.org/10.3390/ijms25158275.

[121] Elhani I, Riller Q, Boursier G, et al. A20 haploinsufficiency: a systematic review of 177 cases[J]. J Investig Dermatol, 2024, 144(6): 1282-1294. https://doi.org/10.1016/j.jid.2023.12.007.

[122] Crow MK. Advances in understanding the role of type I interferons in systemic lupus erythematosus[J]. Curr Opin Rheumatol, 2014, 26(5): 467-474. https://doi.org/10.1097/BOR.0000000000000087.

[123] Yu Y, Su Z, Wang Z, et al. USP7 is associated with greater disease activity in systemic lupus erythematosus via stabilization of the IFNα receptor[J]. Mol Med Rep, 2017, 16 (2): 2274-2280. https://doi.org/10.3892/mmr.2017.6819.

[124] Khan FU, Khongorzul P, Gris D, et al. Role of USP7 in the regulation of tolerogenic dendritic cell function in type 1 diabetes[J]. Cell Mol Biol Lett, 2025, 30(1): 47. https://doi.org/10.1186/s11658-025-00727-5.

[125] Zhu X, Wang P, Zhan X, et al. USP1-regulated reciprocal differentiation of Th17 cells and Treg cells by deubiquitinating and stabilizing TAZ[J]. Cell Mol Immunol, 2023, 20(3): 252-263. https://doi.org/10.1038/s41423-022-00969-9.

[126] Fan YH, Yu Y, Mao RF, et al. USP4 targets TAK1 to downregulate TNFα-induced NF-κB activation[J]. Cell Death Differ, 2011, 18(10): 1547-1560. https://doi.org/10.1038/cdd.2011.11.

[127] Yang J, Xu P, Han L, et al. Cutting edge: ubiquitin-specific protease 4 promotes Th17 cell function under inflammation by deubiquitinating and stabilizing RORγt[J]. J Immunol, 2015, 194(9): 4094-4097. https://doi.org/10.4049/jimmunol.1401451.

[128] Naik E, Dixit VM. Usp9X is required for lymphocyte activation and homeostasis through its control of ZAP70 ubiquitination and PKCβ kinase activity[J]. J Immunol, 2016, 196(8): 3438-3451. https://doi.org/10.4049/jimmunol.1403165.

[129] Naik E, Webster JD, DeVoss J, et al. Regulation of proximal T cell receptor signaling and tolerance induction by deubiquitinase Usp9X[J]. J Exp Med, 2014, 211(10): 1947-1955. https://doi.org/10.1084/jem.20140860.

[130] Bhat SA, Vasi Z, Adhikari R, et al. Ubiquitin proteasome system in immune regulation and therapeutics[J]. Curr Opin Pharmacol, 2022, 67: 102310. https://doi.org/10.1016/j.coph.2022.102310.

[131] Kannt A, Đikić I. Expanding the arsenal of E3 ubiquitin ligases for proximity-induced protein degradation[J]. Cell Chem Biol, 2021, 28(7): 1014-1031. https://doi.org/10.1016/j.chembiol.2021.04.007.

[132] Xian Y, Ye J, Tang Y, et al. Deubiquitinases as novel therapeutic targets for diseases[J/OL]. MedComm, 2024, 5(12): e70036[2026-01-23]. https://doi.org/10.1002/mco2.70036.

[133] Yang X, Lan T, Zhang B, et al. Targeting ubiquitination in disease and therapy[J]. Signal Transduct Target Ther, 2025, 10: 424. https://doi.org/10.1038/s41392-025-02392-8.

[134] Song Y, Zhou B, Long J, et al. Targeted protein degradation in autoimmune diseases: from mechanisms to therapeutic breakthroughs[J]. J Autoimmun, 2025, 156: 103475. https://doi.org/10.1016/j.jaut.2025.103475.

[135] Yang A, Poholek AC. Systems immunology approaches to study T cells in health and disease[J]. npj Syst Biol Appl, 2024, 10: 117. https://doi.org/10.1038/s41540-024-00446-1.

[136] Yasumizu Y, Takeuchi D, Morimoto R, et al. Single-cell transcriptome landscape of circulating $CD4^+$ T cell populations in autoimmune diseases[J]. Cell Genom, 2024, 4(2): 100473. https://doi.org/10.1016/j.xgen.2023.100473.

[137] Miyamoto AT, Shimagami H, Kumanogoh A, et al. Spatial transcriptomics in autoimmune rheumatic disease: potential clinical applications and perspectives[J]. Inflamm Regen, 2025, 45(1): 6. https://doi.org/10.1186/s41232-025-00369-2.

[138] Liu S, Iorgulescu JB, Li SQ, et al. Spatial maps of T cell receptors and transcriptomes reveal distinct immune niches and interactions in the adaptive immune response[J]. Immunity, 2022, 55(10): 1940-1952. https://doi.org/10.1016/j.immuni.2022.09.002.

[139] Sahu I, Zhu H, Buhrlage SJ, et al. Proteomic approaches to study ubiquitinomics[J]. Biochim Biophys Acta BBA Gene Regul Mech, 2023, 1866(2): 194940. https://doi.org/10.1016/j.bbagrm.2023.194940.

[140] Steger M, Demichev V, Backman M, et al. Time-resolved in

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vivo ubiquitinome profiling by DIA-MS reveals USP7 targets on a proteome-wide scale[J]. Nat Commun, 2021, 12: 5399. https://doi.org/10.1038/s41467-021-25454-1.

[141] Yang H, Li N, Chen L, et al. Ubiquitinomics revealed disease- and stage-specific patterns relevant for the 3PM approach in human sigmoid colon cancers[J]. EPMA J, 2023, 14(3): 503-525. https://doi.org/10.1007/s13167-023-00328-2.

[142] Orsburn BC. Analyzing posttranslational modifications in single cells[C]//Mass Spectrometry Based Single Cell Proteomics. New York, NY: Springer US, 2024: 145-156. https://doi.org/10.1007/978-1-0716-3934-4_12.

[143] Ma S, Dahabieh MS, Mann TH, et al. Nutrient-driven histone code determines exhausted $CD8^+$ T cell fates[J/OL]. Science, 2025, 387(6734): eadj3020[2026-01-23]. https://doi.org/10.1126/science.adj3020.

[144] Lee B, Jeong H, Kim Y, et al. Ubiquitin-like proteins in autoimmune diseases: current evidence and therapeutic opportunities[J/OL]. Immune Netw, 2025, 25(3): e21[2026-01-23]. https://doi.org/10.4110/in.2025.25.e21.

[145] Barbour H, Nkwe NS, Estavoyer B, et al. An inventory of crosstalk between ubiquitination and other post-translational modifications in orchestrating cellular processes[J]. iScience, 2023, 26(5): 106276. https://doi.org/10.1016/j.isci.2023.106276.

[146] Huang B, Phelan JD, Preite S, et al. In vivo CRISPR screens reveal a HIF-1α-mTOR-network regulates T follicular helper versus Th1 cells[J]. Nat Commun, 2022, 13: 805. https://doi.org/10.1038/s41467-022-28378-6.

[147] Raychaudhuri D, Singh P, Chakraborty B, et al. Histone lactylation drives $CD8^+$ T cell metabolism and function[J]. Nat Immunol, 2024, 25(11): 2140-2151. https://doi.org/10.1038/s41590-024-01985-9.

[148] Lacoursiere RE, Hadi D, Shaw GS. Acetylation, phosphorylation, ubiquitination (oh my!): following post-translational modifications on the ubiquitin road[J]. Biomolecules, 2022, 12(3): 467. https://doi.org/10.3390/biom12030467.

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