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Review

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Review

Mitochondrial dysfunction and mitophagy: crucial players in burn trauma and wound healing

Harshini Sheeja Prabhakaran[1,†], Dongxue Hu[1,†], Weifeng He[2,3], Gaoxing Luo[2,3,*] and Yih-Cherng Liou[1,*]

[1]Department of Biological Sciences, Faculty of Science, National University of Singapore, 14 Science drive 4, 117543 Singapore, Singapore, [2]State Key Laboratory of Trauma, Burn and Combined Injury, Institute of Burn Research, Southwest Hospital, Third Military Medical University (Army Medical University), Gao Tan Yan Zheng Street, Sha Ping Ba District, Chongqing, 400038, People's Republic of China and [3]Chongqing Key Laboratory for Disease Proteomics, Gao Tan Yan Zheng Street, Sha Ping Ba District, Chongqing, 400038, People's Republic of China

*Correspondence. Gaoxing Luo, Email: logxw@yahoo.com; Yih-Cherng Liou, Email: dbslyc@nus.edu.sg

[†]These authors contributed equally to this work.

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Abstract

Burn injuries are a significant cause of death worldwide, leading to systemic inflammation, multiple organ failure and sepsis. The progression of burn injury is explicitly correlated with mitochondrial homeostasis, which is disrupted by the hyperinflammation induced by burn injury, leading to mitochondrial dysfunction and cell death. Mitophagy plays a crucial role in maintaining cellular homeostasis by selectively removing damaged mitochondria. A growing body of evidence from various disease models suggest that pharmacological interventions targeting mitophagy could be a promising therapeutic strategy. Recent studies have shown that mitophagy plays a crucial role in wound healing and burn injury. Furthermore, chemicals targeting mitophagy have also been shown to improve wound recovery, highlighting the potential for novel therapeutic strategies based on an in-depth exploration of the molecular mechanisms regulating mitophagy and its association with skin wound healing.

Key words: Mitophagy, Mitochondria, Wound healing, Burn trauma, Macroautophagy

Highlights

- Burn injury disrupts mitochondrial homeostasis, leading to morphological alterations, impaired ATP synthesis and excessive ROS generation.
- Fine-tuned mitophagy is essential for the recovery of burn trauma, regulating several important steps of wound healing.
- Mitochondria and mitophagy have the potential to be therapeutic targets for burn and wound therapy.

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Review

Roles of mitochondria in normal skin heath

Mitochondria are essential organelles that serve as the primary source of energy in eukaryotes and are crucial for maintaining cellular homeostasis [1]. Along with ATP production, mitochondria also act as signalling hubs to regulate various cellular functions [2, 3]. A major population of mitochondria exists as an interconnected network that undergoes constant fission and fusion, allowing for rapid changes in morphology in response to cellular stresses while maintaining mitochondrial functions [4]. Mitochondrial integrity is essential for cellular homeostasis and survival. Disruption of mitochondrial function reduces the energy supply concurrent with the release of mitochondrial contents, such as cytochrome c, acetyl CoA, ATP, formyl peptides and mitochondrial DNA (mtDNA), which can trigger inflammatory responses and cell death [5–11]. Additionally, reactive oxygen species (ROS) produced during mitochondrial oxidative phosphorylation (OXPHOS) have been implicated in many physiological and pathological responses [12]. Cellular mechanisms that regulate mitochondrial integrity are crucial for maintaining cellular homeostasis and ultimately determining the fate of a cell [14, 15]. In normal skin, mitochondria play essential roles in maintaining cellular functions such as cell proliferation, differentiation, migration and cell–cell communication, which contribute to overall skin health and homeostasis.

The skin, being the largest organ in the body, provides a crucial barrier against various environmental stressors [13]. Mitochondria have emerged an important players in maintaining skin health, as supported by increasing evidence [14]. Notably, the constant regeneration of skin epidermis is dependent on ATP generated by mitochondria [15]. In addition, mitochondrial respiration and ROS generation also play a vital role in the differentiation of keratinocytes, with mitochondrial ROS activating the Notch and β-catenin signalling pathways to enhance epidermal differentiation [16]. Furthermore, mitochondria also activate the mitochondria-dependent apoptotic pathway, which enables the terminal differentiation of keratinocytes [20]. Collectively, these findings highlight the significant contributions of mitochondria in maintaining skin homeostasis.

Mitochondrial dysfunction in burn injury

Mitochondrial morphological changes Mitochondria are highly dynamic organelles that undergo constant morphological changes through fission and fusion processes [17]. Mitochondrial fission allows the segregation of damaged mitochondria, whereas mitochondrial fusion facilitates the exchange of intra-mitochondrial components to enhance metabolism. A fine balance between fission and fusion is important for mitochondrial homoeostasis and integrity [18–20], which can be significantly perturbed upon burn injury, as summarized in Figure 1. It has been reported that in rat hearts, burn injury can reduce the size, area and number of cardiac mitochondria, affecting mitochondrial replication [21].

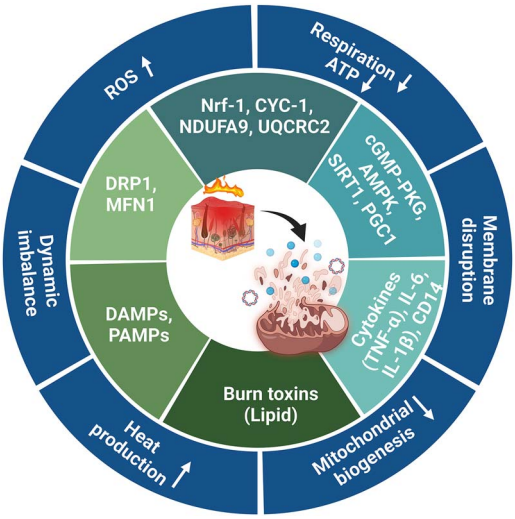

Figure 1. Burn-induced mitochondrial damage. Mitochondrial damage is commonly observed following burn injuries, which can manifest as impaired mitochondrial integrity, dynamics, biogenesis, metabolism and respiration, and increased production of reactive oxygen species (ROS) and oxidative stress. Mitochondrial dysfunction following a burn injury is influenced by multiple factors associated with ATP production like nuclear respiratory factor 1 (Nrf-1), cytochrome C1 (CYC-1), NADH ubiquinone oxidoreductase subunit A9 (NDUFA9), and ubiquinol-cytochrome C reductase core protein 2 (UQCRC2), cyclic guanosine monophosphate (cGMP), AMP-activated protein kinase (AMPK), Sirtuin 1 (SIRT1), peroxisomal proliferator activator receptor γ coactivator-1 (PGC-1) and cluster of differentiation 14 (CD14), cytokines like tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interlekin-1 beta (IL-1β), burn toxins, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular pattern molecules (PAMPs) and dynamin-related protein 1 (DRP1) and mitofusin 1, implying that mitochondria play a critical role in determining the severity and progression of burn injuries

Similarly, the number of mitochondrial cristae is reduced in mouse skeletal muscle due to metabolic aberration after burn injury [22]. Burn injury-induced cytokine interleukin-6 (IL-6) has been demonstrated to promote mitochondrial fragmentation, although the exact mechanism is not yet clearly understood [23]. Mitofusin 1 (MFN1) may play roles downstream of IL-6, as its level was reduced after burn serum stimulation [23]. In the case of alkali injury, the fission protein dynamin related protein 1 (DRP1) was upregulated, while the expression level of fusion protein MFN2 was downregulated, indicating an imbalance in mitochondrial fission/fusion cycles that impairs mitochondrial function after exposure to alkali [24]. In the late stage of burn injury, mitochondria appear longer and branched [25], which is usually associated with increased OXPHOS activity. The appearance of elongated mitochondria in the later stage might be an adaptive response to stress [26]. However, increased fission activity in the early stages of burn trauma can subsequently impair normal mitochondrial function and increase ROS levels. Increasing studies emphasize the role of mitochondrial dynamic proteins in the progression of burn injury and regulating them can bring beneficial effects to the recovery from burn injury. Nonetheless, the precise mechanisms of burn-induced mitochondrial morphological changes and cell death by mitochondrial dynamic proteins still require intensive investigation.

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Inefficient respiration and ATP synthesis Mitochondria are responsible for producing ATP molecules through the electron transport chain (ETC), which includes complexes I, II, III and IV, coenzyme Q and cytochrome C. These components generate a proton gradient across the mitochondrial inner membrane, which is utilized to synthesize ATP at complex V [27]. Disruption of the ETC can result in decreased ATP production and exacerbated cell metabolism [28]. After burn injury, an increase in the uncoupled state 4_o has frequently been observed, suggesting ETC damage [29]. A decrease in coupled complex I respiration with an increase in the uncoupled state 4_o may lead to increasing unmet energy demands [30]. Perturbation of the ETC could be attributed to the downregulation of several genes, including nuclear respiratory factor 1 (Nrf-1), cytochrome C1 (CYC-1) and NADH ubiquinone oxidoreductase subunit A9 (NDUFA9), which are observed after burn injury [31]. Nrf-1 is a transcriptional factor that regulates the expression of genes involved in oxidative phosphorylation [32]. CYC-1 is a soluble protein that enables rapid complex formation to maintain electron flow in the ETC [33]. NDUFA9 is a constituent of mitochondrial respiratory chain complex I and is essential for its stability [34]. The downregulation of these genes may lead to impaired ETC function and reduced ATP production, which can increase the energy demands of cells.

The critical factors that regulate ATP synthesis, such as cyclic guanosine monophosphate (cGMP), AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1) and peroxisomal proliferator activator receptor γ coactivator-1 (PGC-1), are altered after burn injury [35, 36]. The phosphodiesterase-5A (PDE5A)–cGMP–protein kinase G (PKG) pathway plays a crucial role in preserving cardiac function [37], while cGMP acts as a second messenger in many signalling pathways that regulate the cardiovascular system [38]. The cGMP–PKG axis attenuates stress responses and increases cell survival in conditions of ischaemic injury. The axis can be enhanced by inhibiting the degradation of cGMP using phosphodiesterase-5 (PDE5), as the inhibitor of the PDE5A–cGMP–PKG pathway rescued mitochondrial respiration after burn injury [21]. Wen *et al*. reported that after burn injury, the expression of AMPK, SIRT1 and PGC1 in proliferating human cardiomyocyte AC16 cells decreases, which impedes mitochondrial respiration capacity [35]. AMPK is a major cell metabolic sensor in cells [39], while SIRT1 regulates energy metabolism and amplifies energy production [40]. Both AMPK and SIRT1 can modulate PGC-1, a key player in energy metabolism and mitochondrial biogenesis [39]. An activator of AMPK1 and the PGC1α agonist rescued the mitochondrial respiration rate and improved dysfunction after burn injury, whereas an AMPK1 inhibitor worsened the mitochondrial energy profile [35]. Han *et al*. suggested that that SIRT1 is overexpressed in burned tissues and can abolish the inflammatory response caused by burn injury [36]. However, the exact role of SIRT1 in different stages of burn progression requires detailed investigation. Burn injury can also trigger inflammatory responses, and the pro-inflammatory cytokine IL-1β has been shown to regulate mitochondrial respiration after burn injury [41]. IL-1β expression increased after burn trauma and stimulated NO production, which significantly impaired mitochondrial efficiency in synthesizing ATP [42]. Thus, many key factors regulate burn-induced mitochondrial damage by impairing mitochondrial respiration and ATP synthesis, thereby producing excessive ROS (Figure 1).

Increased ROS and oxidative stress In the burn injury model, a burst of ROS causes oxidative stress and initiates tissue damage [43]. Prolonged activation of β-adrenergic receptors [44] can increase mitochondrial ROS production *via* cAMP and protein kinase A (PKA). Upregulated tumor necrosis factor alpha (TNF-α) has also been reported to induce ROS production and cause mitochondrial damage [45]. IL-6 restrains PGC-1α expression, which can upregulate the expression of many antioxidants. As a result, mitochondrial ROS (mtROS) production might increase with downregulated PGC-1α in burn trauma [46]. Thus, IL-6 increases ROS via PGC-1α downregulation. Cluster of differentiation 14 (CD14), one of the members of the toll-like receptor 4 (TLR4) signalosome, is reported to increase in the pathogenesis of burn [47], and blocking CD14 prevented an increase in mtROS, suggesting that the CD14 signalling pathway might participate in burn-induced oxidative stress [48].

Zhao *et al*. reported the downregulation of the mitochondrial injury-related gene ubiquinol-cytochrome C reductase core protein 2 (UQCRC2), a subunit of respiratory complex III, in burn injury [31]. The decline in UQCRC2 can induce excessive ROS generation by directing the electron flow into the intermembrane space [49]. Thus, several critical factors are involved in regulating the pathological response to burn trauma by modulating ROS production. The accumulation of excessive ROS might trigger Ca^{2+} reflux and cytochrome C release into the cytoplasm and trigger cell death [50]. Moreover, excessive ROS release can lead to oxidative stress and induce mtDNA mutations, altering membrane permeability [51]. Therefore, burn injury-induced oxidative stress contributes to mitochondrial dysfunction, and targeting ROS can serve as a potential therapeutic approach for aiding burn injury recovery.

Burn-induced mitochondrial damage via burn toxins and damage-associated molecular patterns Burn injury can cause significant tissue damage and releases harmful substances such as burn toxins, which can negatively impact mitochondrial function. Additionally, mitochondrial damage-associated molecular patterns (DAMPs) and pathogen-associated molecular pattern molecules (PAMPs) can also contribute to mitochondrial dysfunction [52, 53]. DAMPs are biomolecules derived from damaged mitochondria that are released into the extracellular space and include proteins, DNA and lipids [54]. Skin extracts collected from burn patients have been found to contain mitochondria-toxic substances that affect mitochondrial function [52]. A study by Zhang *et al*. demonstrated that injured cells release DAMPs

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and activate innate immunity via TLR9, leading to non-specific tissue attack [55]. Fibrinogen, a DAMP, has been found to increase in the plasma of burn patients, indicating a poor prognosis.

Elevated fibrinogen can contribute to various inflammatory responses and decrease mitochondrial membrane potential. Interestingly, the use of glycyrrhizin, a DAMPs inhibitor, has been shown to reverse the adverse effects of elevated plasma fibrinogen in burn injury [56]. Furthermore, mtDNA, also a DAMP, can cause inflammatory responses and lung damage after burn injury [57]. Overall, these findings suggest that burn toxins and DAMPs may significantly contribute to mitochondrial dysfunction after burn injury. Therapeutic interventions that target burn toxins and DAMPs to promote anti-inflammatory effects may be a promising approach to preventing burn-induced mitochondrial damage and metabolic changes.

Involvement of mitochondria in burn-induced hypermetabolism, sepsis and cell death Burn trauma can elicit a hypermetabolic response and muscle wasting, which are recognized as hallmarks of severe injury. The hypermetabolic response maximizes energy expenditure by increasing mitochondrial uncoupling [58]. Accordingly, Ogunbileje *et al.* have demonstrated that mitochondrial hypermetabolism damages and degrades mitochondrial proteins by activating mitochondrial unfolded protein response (mtUPR) and increasing the demand for mitochondrial proteins [59]. Furthermore, Porter *et al*. have also demonstrated that an increase in mitochondrial membrane proton conductance elevates heat production, which contributes to hypermetabolism [29]. Therefore, hypermetabolism-induced mitochondrial uncoupling further increases hypermetabolic stress, which in turn raises the demand for mitochondrial functioning and leads to uncoupling. The occurrence of hypermetabolic stress can additionally affect the mitochondrial quality control system [59, 60]. These studies suggest that maintaining mitochondrial function is crucial for alleviating burn-induced hypermetabolic stress. Strategies that target mitochondria and mitochondrial proton leak can mitigate the stress response of burn injury [29].

Sepsis is one of the most common consequences of burn injury, and mitochondrial damage is a critical factor in the pathogenesis of sepsis [61]. During sepsis, bacterial components such as lipopolysaccharide (LPS) bind to the immune receptors and trigger an inflammatory response [62]. The systemic inflammatory response generates NO, carbon monoxide, hydrogen sulfide (H_2S) and ROS, which directly impair several components of the mitochondrial ETC complexes and respiration. As the ETC is impaired, mitochondria produce excessive ROS, which in turn affects its integrity and ETC function [62–65]. Sepsis can significantly alter mitochondrial morphology causing loss of cristae and swelling [66]. Moreover, sepsis disrupts the balance in the oxidant/antioxidant system, resulting in excess ROS generation [67]. Zhu *et al*. demonstrated that treatment with mitochondrial fission inhibitor Mdivi-1 can alleviate sepsis-induced organ damage. Mdivi-1 treatment after sepsis improves mitochondrial ATP production and decreases ROS generation [68]. However, the exact role of mitochondrial fission and the mechanism by which fission dampens mitochondrial function in sepsis has not yet been fully elucidated, making it challenging to determine whether mitochondrial dysfunction is the inducer or consequence in the pathogenesis of sepsis after burn injury, as also stated by Zhang *et al.* in their review [69]. Nevertheless, mitochondrial damage is a critical factor involved in the aggravation of sepsis associated with burn injury.

Apoptosis denotes the programmed cell death that can occur via either the death-receptor pathway or the mitochondrial pathway [70]. Apoptosis plays a crucial role in regulating the progression of various illnesses [71], including burn injury, which can also trigger apoptosis [72]. In keratinocytes, burn injury disrupts mitochondrial membrane integrity, leading to the induction of apoptosis [73]. In animal studies, excessive ROS have been shown to activate apoptotic stimuli [74], which may be implicated in burn injury. Duan *et al.* found that burn injury increases the expression of apoptotic genes such as Bcl-2-associated X protein (Bax) and BH3-interacting domain death agonist (Bid) in the Bcl-2 family and activates caspase-3 and caspase-6 in the caspase family, inducing apoptosis [75]. Moreover, experimental evidence suggests that monocyte chemoattractant protein 1 (MCP-1), a chemokine, is upregulated after burn injury [76] and can induce apoptosis by caspase-9 activation [77].

Intriguingly, heat shock protein 70 (Hsp70) has been shown to inhibit burn-induced apoptosis by attenuating the activation of caspase-3, -8 and -9 and inhibiting the burn-induced cleavage of Bid into truncated Bid (tBid) [78]. In addition, Yasuhara *et al.* demonstrated that DNA fragmentation occurs after burn injury, triggering apoptosis, and hypothesized that apoptosis may be a mechanism involved in burn-induced muscle wasting [79]. Increased apoptosis may contribute to the delayed recovery following injury. Notably, there is growing evidence suggesting that burn injury induces mitochondrial dysfunction and subsequent apoptosis. Therefore, elucidating the underlying mechanisms relating to burn-induced apoptosis may be important in formulating therapeutic strategies. Mitophagy, which clears damaged mitochondria, can protect cells from apoptosis and aid in the smooth recovery from burn injury.

Mitophagy in burns and wound healing

Overview of mitophagy Autophagy is a cellular process that delivers damaged cellular contents to lysosomes for degradation. Three main autophagic forms have been described: (1) macroautophagy, which involves the formation of autophagosomes that sequester damaged organelles and protein aggregates with a double-membrane; (2) microautophagy, which involves direct engulfment of the cytoplasmic cargo by lysosomes or endosomes for degradation [80]; and (3) chaperone-mediated autophagy (CMA), which involves the recognition of cytosolic proteins with specific recognition

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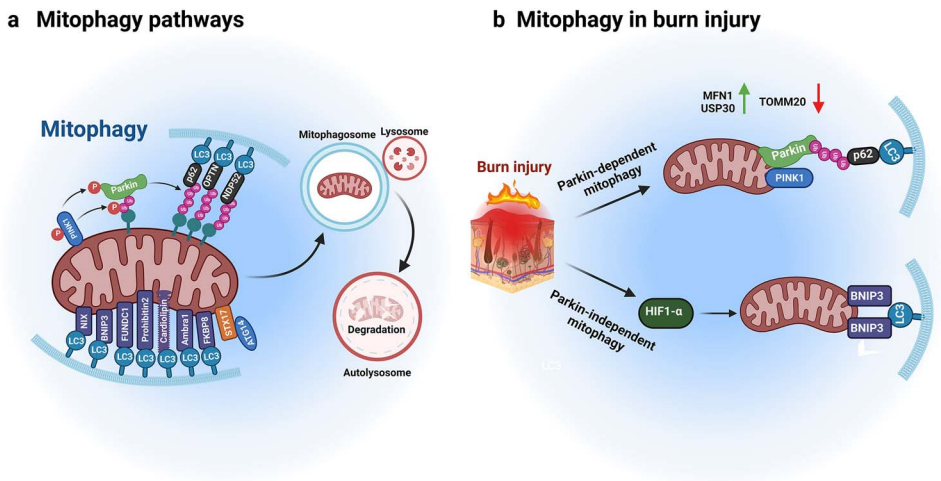

Figure 2. Mitophagy pathways in normal physiology and in burn injury. (**a**) Mitophagy is an important mechanism for mitochondrial quality control and involves the selective removal of damaged mitochondria via autophagy. The PTEN-induced kinase (PINK1)-Parkin pathway is the most extensively studied pathway for mitophagy. Upon mitochondrial damage, PINK1 accumulates on the outer mitochondrial membrane (OMM), leading to the recruitment of Parkin via its phosphorylation function. Parkin subsequently establishes polyubiquitin chains on the OMM, which act as bridges with receptors such as sequestosome 1 (p62/SQSTM1), optineurin (OPTN) and **n**uclear domain 10 protein 52 **(**NDP52) to connect the phagophore membrane for mitochondrial sequestration (mitophagosome). The mitophagosome then fuses with lysosome for the degradation of damaged mitochondria. Additionally, several Parkin-independent mitophagy pathways have been identified, which involve mitochondrial membrane receptors such as BCL2-interacting protein 3-like (BNIP3L/NIX), FUN14 domain containing 1(FUNDC1), BCL2-interacting protein 3 (BNIP3), autophagy and Beclin 1 regulator 1 (Ambra1), FK506-binding protein 8 (FKBP8), cardiolipin (CL) and prohibitin 2 (PHB2). These receptors directly interact with microtubule-associated proteins 1A/1B light chain 3B (LC3) and recruit phagophore for mitophagy. The existence of different mitophagy pathways may enable cells to cope with various physiological or pathological situations, such as proliferation, differentiation, hypoxia and inflammation. (**b**) Burn injury can trigger both Parkin-dependent and Parkin-independent mitophagy. Activated Parkin interacts with Pink1 to initiate mitophagy, while levels of ubiquitin-specific protease 30 (USP30) and mitofusin 1 (MFN1) remain upregulated, and mitochondrial protein translocase of the outer mitochondrial membrane complex subunit 20 (TOMM20) levels are reduced. Additionally, Parkin-independent mitophagy can be induced by hypoxia-inducible factor 1-alpha (HIF1-α) and BNIP3, respectively. BNIP3 resides in the mitochondrial outer membrane and interacts directly with LC3, thereby initiating mitophagy. The activation of mitophagy can lower oxidative stress and restore homeostasis in cells affected by burn injury

sequences by chaperone protein HSP70 and their subsequent targeting to lysosomes via lysosomal-associated membrane protein 2A (LAMP2A) for degradation [81].

Mitophagy is a selective form of macroautophagy that eliminates damaged mitochondria and contributes to mitochondrial quality control [82, 83], as depicted in Figure 2. Impairment of mitophagy can cause mitochondrial dysfunction and cell death [84]. Mitophagy can be Phosphatase and tensin homolog (PTEN)-induced kinase (PINK1)-Parkin dependent or independent [85]. PINK1, a serine/threonine kinase, is imported into the inner mitochondrial membrane from cytosol and processed for degradation in normal conditions [86–88]. PINK1 acts as a sensor and constantly surveys for damaged mitochondria. When mitochondria are damaged, PINK1 activates the E3 ligase Parkin by phosphorylating at the Ser65 residue in the ubiquitin-like (UBL) domain, suppressing the interaction of the UBL and the R1 domain of Parkin [89] and thereby recruiting phosphorylated Parkin to the damaged mitochondria [90, 91].

After PINK1 activates Parkin, the key mitochondrial outer membrane proteins including MFN1, MFN2 and voltage dependent anion channel 1 (VDAC1) are ubiquitinated by Parkin. The ubiquitinated mitochondrial proteins are then phosphorylated by PINK1, which triggers further Parkin recruitment and activation of mitophagy [92–94]. The polyubiquitinated mitochondrial proteins are recognized by the autophagy cargo receptors sequestosome 1 (p62\SQSTM1), optineurin (OPTN) and nuclear domain 10 protein 52 (NDP52), leading to the sequestration of damaged mitochondria [95, 96]. The autophagy receptor NDP52 oligomerizes and facilitates the degradation of damaged mitochondria [97]. These autophagy receptors can directly interact with microtubule-associated proteins 1A/1B light chain 3B (LC3) and form a complex that is delivered to the lysosome for autophagic degradation [98].

Other proteins involved in mitophagy include BCL2-interacting protein 3-like/Nip3-like protein X (BNIP3L/NIX), FUN14 domain containing 1(FUNDC1) and BCL2-interacting protein 3 (BNIP3), which are localized on the outer mitochondrial membrane and interact with LC3 as shown in Figure 2a [99–101]. BNIP3L is involved in mitophagy under hypoxic conditions [102], while BNIP3 senses stress signals to induce cell death in response to stress conditions. Both BNIP3 and BNIP3L are important players in hypoxia-induced mitophagy [103, 104]. BNIP3 is a hypoxia-inducible protein that is phosphorylated under hypoxia by c-Jun N-terminal kinase 1/2 (JNK1/2), which facilitates its binding to LC3 to promote mitophagy [105]. FUNDC1 is another important mitochondrial membrane protein that is involved in mitochondrial uncoupling and mediates mitophagy in hypoxic conditions [106]. The phosphorylation states of FUNDC1 can be changed to alter its binding capacity to LC3

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and regulate mitophagy [101]. FUNDC1 is also implicated in tethering mitochondria-associated membrane (MAM)-specific proteins and can regulate mitochondrial dynamics [101, 107].

There are several non-canonical mitophagy receptors, include autophagy and beclin 1 regulator 1(Ambra1), FK506-binding protein 8 (FKBP8), cardiolipin (CL) and prohibitin 2 (PHB2) [108]. Ambra1 induces mitophagy *via* a Parkin-independent pathway by interacting with the E3 ubiquitin ligase, HUWE1 [109]. In addition, Ambra1 can also induce mitophagy *via* the canonical PINK1/Parkin pathway by interacting with LC3 [110]. FKBP8, localized on the outer mitochondrial membrane, can cause mitochondrial fission, and subsequently induce mitophagy when overexpressed [111]. CL, a phospholipid abundantly present in the inner mitochondrial membrane, can facilitate mitophagy by interacting with LC3, especially LC3A [112], under mitochondrial stress conditions [113, 114]. PHB2, an inner mitochondrial membrane receptor, can mediate mitophagy upon mitochondrial depolarization. PHB2 binds to Parkin, promoting its ubiquitination and enhances its interaction with LC3 to drive efficient mitophagy [115, 116].

Our group has made the exciting discovery that Syntaxin 17 (STX17), a protein belonging to the family of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), residing in the endoplasmic reticulum (ER), can induce mitophagy when the outer mitochondrial membrane protein mitochondrial fission 1 protein (Fis1) is depleted. Normally, Fis1 prevents STX17 from dynamically trafficking to mitochondria, resulting in minimal mitophagy induction under resting conditions. However, upon Fis1 loss, STX17 translocates from the ER to the MAM and the mitochondria, where it interacts with Autophagy Related 14 (ATG14) and recruits other autophagy proteins to form mitophagosome. Subsequently, Rab7 is recruited to facilitate mitophagosome-lysosome fusion and mitophagy [117]. Overall, mitophagy acts as a quality control mechanism for mitochondria through both autophagy receptors and mitochondrial dynamics. Enhancing mitophagy and promoting the recovery of damaged mitochondria could be a promising therapeutic strategy for various diseases [118].

In conclusion, autophagy eliminates damaged cellular contents and has three main forms: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Mitophagy, a selective form of macroautophagy, eliminates damaged mitochondria through the activation of Parkin, the ubiquitination of mitochondrial outer membrane proteins, recognition of autophagy cargo receptors, and delivery to lysosomes for autophagic degradation. Other proteins involved in mitophagy include BNIP3L/NIX, FUNDC1 and BNIP3. Non-canonical mitophagy receptors, such as Ambra1, FKBP8, CL and PHB2, have also been identified. Additionally, STX17 induces mitophagy when Fis1 is depleted, resulting in STX17 translocation to the MAM and mitochondria, where it interacts with ATG14 and recruits autophagy machinery for mitophagy induction.

Mitophagy in burn injury Studies suggest that mitophagy plays a crucial role in attenuating burn pathogenesis by selectively targeting damaged mitochondria [31, 119, 120]. As enunciated in the previous sections, burn injury leads to increased ROS production, which is reported to trigger Parkin-mediated mitophagy [121]. In skin tissues, mitophagy is upregulated after burn injury, as evidenced by the increased expression of key genes including PINK1, Parkin, MFN1 and ubiquitin-specific protease 30 (USP30), as shown in Figure 2b. The interaction between PINK1 and Parkin further confirms the initiation of mitophagy, and these proteins are attractive targets for mitigating burn injury [31]. A recent report implied that deferiprone (DFP), a drug that stimulates mitophagy, has been shown to reduce oxidative stress by ~95% in a burn injury model, in a BNIP3L-dependent manner [120]. Guo *et al*. demonstrated a reduction in translocase of the outer mitochondrial membrane complex subunit 20 (TOMM20) levels and a change in autophagic flux with increased microtubule-associated protein 1 light chain 3 II (LC3II) levels, a typical indicator of mitophagy, after burn trauma, and established the role of hypoxia-inducible factor 1-alpha (HIF-1α)-mediated mitophagy occurring after burn trauma as illustrated in Figure 2b [122]. The role of hypoxia and HIF-1α is an interesting front in burn-wound progression. Although Guo *et al*. reported the upregulation of hypoxic-mitophagy receptors such as FUNDC1 and BNIP3, the exact mechanism underlying hypoxia-mediated mitophagy in burn injury remains elusive. The activated mitophagy helps to reduce oxidative stress by eliminating damaged mitochondria and further decreased any secondary ROS release [122, 123]. A better understanding of the exact mechanism governing mitophagy in burn progression is necessary to fully comprehend the role of mitophagy in burn injury.

In conclusion, mitophagy appears to be a critical process in attenuating burn pathogenesis by selectively removing damaged mitochondria. Burn injury increases ROS production, which can trigger Parkin-mediated mitophagy. Skin tissues upregulate mitophagy after burn injury, as evidenced by increased expression of several key genes, including PINK1, Parkin, MFN1, and USP30. Additionally, drugs that stimulate mitophagy, such as deferiprone, have shown promising results in reducing oxidative stress in burn injury models. The role of hypoxia and HIF-1α in burn-wound progression and their impact on mitophagy require further investigation. Nonetheless, activated mitophagy is shown to help reduce oxidative stress by eliminating damaged mitochondria and decreasing secondary ROS release. A better understanding of the precise mechanism governing mitophagy in burn progression is essential to fully comprehend its role in burn injury and develop targeted treatments for burn patients.

Mitophagy regulates burn wound healing After burn injury, the body initiates a wound-healing process to restore the tissue homeostasis, through a series of precisely controlled events by multiple types of cells [124]. Maintaining

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mitochondrial health is essential to ensure cell functions, as damaged mitochondria can trigger numerous cellular processes, including intrinsic cell death. Previous research has observed dysfunctional mitochondria following burn-induced injury, suggesting that mitochondrial dysfunction is a passive result of the injury. However, recent research suggests that mitochondria can also mediate adaptive responses to cope with the injury during the wound-healing process. A fine-tuned level of mitophagy is necessary for the recovery of burn-induced wounds.

Wound-healing processes Wound healing is a complex and dynamic process that consists of four continuous and overlapping phases: haemostasis, inflammation, proliferation and remodelling (Figure 3). These phases occur in a chronological sequence, with haemostasis occurring immediately after the injury and the subsequent phases occurring over a period of 1–3 days, 3–20 days, 7–40 days and 40 days to 2 years, respectively [125]. Platelets, macrophages, neutrophils, fibroblasts and endothelial cells are important participants of wound healing.

The first phase, haemostasis, takes place immediately after wound injury. During this stage, blood vessels constrict to prevent exsanguination, accompanied with the activation of platelets and the establishment of a fibrin network, leading to the formation of a clot in the wound area (also known as a provisional matrix) [126]. The inflammatory phase is characterized by the infiltration of immune cells, such as neutrophils, macrophages and lymphocytes, which eliminate pathogens and damaged cells in the wound area. Inflammation eliminates the infectious microbes and damaged cells in the wound area [127].

During the proliferative phase, epithelial cells migrate and proliferate over the provisional matrix in the injured site. The re-epithelialization process accounts for up to 80% of wound closure [128]. In this stage, fibroblasts and endothelial cells also play critical roles, promoting capillary formation, collagen synthesis and tissue granulation. Within the wound bed, collagen, glycosaminoglycans and proteoglycans produced by fibroblasts accumulate to form the new extracellular matrix (ECM) [129].

After vigorous cell proliferation and ECM generation, wound healing subsequently transits to the remodelling phase. The ECM is then reorganized to form the normal tissue, and the size of scar reduces with the progression of remodelling [124, 130]. Various cells, including platelets, macrophages, neutrophils, fibroblasts and endothelial cells, are sequentially involved in the wound-healing process. The coordinated activation, differentiation and proliferation of these cells are essential for efficient wound repair.

Mitophagy sustains platelet activation during the haemostatic stage Haemostasis is a crucial process that prevents exsanguination and provides a matrix for immune cells during the later phases [130]. Platelet activation is a key step in clot formation during haemostasis, and it relies on functionally active mitochondria [131]. To date, several mitophagic receptors have been reported to sustain the activation of platelets by maintaining mitochondrial health (Figure 3) [132–134]. NIX is known to be a master mediator of mitophagy during erythroid maturation [135]. Given that both platelets and erythrocytes are anuclear cells that originate from the same hematopoietic cell lineage, it is reasonable to speculate that mitophagy in platelets is also regulated *via* the NIX pathway [133]. Zhang *et al*. discovered that NIX-controlled mitophagy is a housekeeping process to maintain the quality of mitochondria in platelets. Genetic ablation of NIX compromises the clearance of defective mitochondria, significantly inhibiting platelet aggregation and haemostasis, suggesting that NIX sustains platelet activation by regulating mitophagy [133].

The involvement of mitophagy in platelet activation is also supported by a study on FUNDC1 [132]. Stimulated by a low oxygen level, FUNDC1-mediated mitophagy provides a defensive mechanism against ischemia/reperfusion-induced heart injury by regulating mitochondrial activity and platelet activation [132]. Although there is no direct evidence that FUNDC1 contributes to platelet activation during wound healing, it is possible that it can activate the platelets at wound sites after burn injury, where the hypoxic conditions disrupt the vasculature [119, 136]. PHB2 is another mitophagy mediator that has recently been found to regulate platelet activation, but its underlying functions and mechanisms are not yet clear [134]. Unlike NIX, FUNDC1 and PHB2, the deletion of PINK1 does not seem to affect platelet function, indicating that PINK1/Parkin-induced mitophagy may not be involved in platelet activation [137]. However, the role of other mitophagic pathways in platelet activation is still elusive. Although mitophagy is necessary for platelet activation, excessive elimination of mitochondria could be detrimental, as platelet activation is greatly reduced after hypoxia and carbonyl cyanide *m*-chlorophenyl hydrazone (CCCP) treatment, both of which cause robust mitophagy [132, 133]. This observation suggests that over-activated mitophagy leads to the massive loss of mitochondria and a subsequent reduction in ATP, which is necessary for platelet activation [131–133].

Mitophagy regulates the inflammatory stage via redox balance Severe burns can trigger a chronic and widespread inflammation response that can result in, in the initial stage, systemic inflammatory response syndrome, multiple organ failure and long-term sequalae [138, 139]. Inflammation is an essential biological response to tissue injury infection, initiated by pattern recognition receptors (PRRs) like TLRs and Nod-like receptors (NLRs) that recognize PAMPs or DAMPs signals [140]. This recognition of PAMPs or DAMPs can stimulate chemical signalling cascades that activate leukocyte chemotaxis from the general circulation to the wound site. The recruited leukocytes then secrete cytokines to further enhance the inflammatory responses [141]. During wound healing, proper inflammatory responses are essential to create a favourable environment for tissue regeneration in the later

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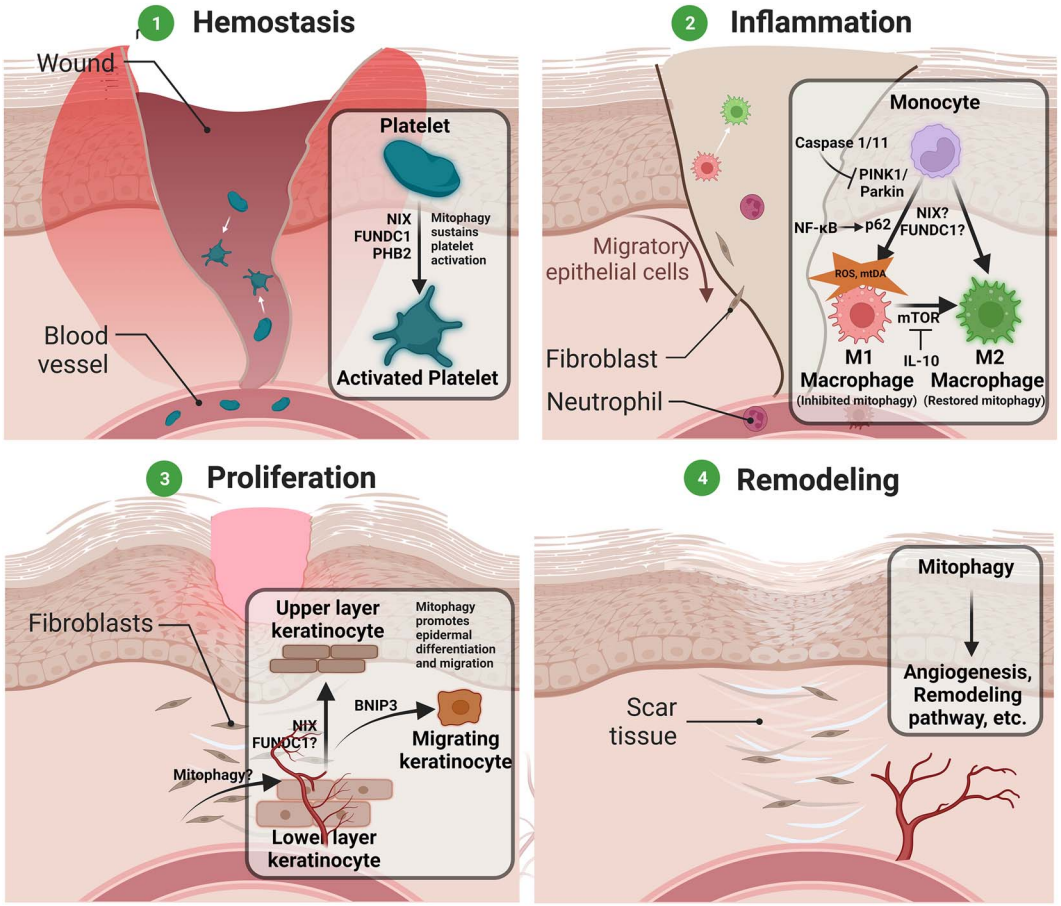

Figure 3. Roles of mitophagy in wound healing stages. Wound healing is a complex and dynamic process that involves four overlapping stages: haemostasis, inflammation, proliferation and remodelling. Mitophagy, the selective degradation of damaged mitochondria, has been found to play important roles in each of these stages. (1) During the hemostasis stage, mitophagy is critical for the maintenance of mitochondrial quality and the activation of platelets. Mitophagy is mediated by mitochondrial membrane receptors such as BCL2-interacting protein 3-like (BNIP3L/NIX), FUN14 domain-containing 1 (FUNDC1), and prohibitin 2 (PHB2). (**2**) In the inflammatory stage, mitophagy plays a fine-tuning regulatory role. In the beginning, caspase 1 and 11 degrade PTEN-induced kinase (PINK1)/Parkin and inhibit mitophagy to promote the production of mitochondrial ROS (mtROS), which promote the activation of macrophage. Meanwhile, nuclear factor kappa B (NF-kB) negatively controls the inflammation by upregulating the expression of mitophagic receptor p62, which enables NF-kB to prevent long-lasting tissue inflammation and damage. In the later inflammatory stage, interleukin-10 (IL-10) inhibits the mammalian target of rapamycin (mTOR) signal to promote mitophagy, priming the metabolic transition of macrophages from M1 state to M2 state. This transition marks the changes of macrophages to promote angiogenesis and tissue regeneration. (**3**) During the proliferative stage, NIX-mediated mitophagy is necessary for keratinocyte differentiation. In addition, BCL2-interacting protein 3 (BNIP3) can stimulate the migration of keratinocytes under hypoxia conditions. Recently, it has been reported that treatment with urolithin A (UA) significantly improves the restoration of skin wounds. Given the fact that UA can promote mitophagy, it will be interesting to investigate whether UA promotes wound healing in a mitophagy-dependent manner. (**4**) During the remodelling stage, the wound continues to contract, and fibres are reorganized. Mitophagy may continuously facilitate angiogenesis and activate 'wound healing' signalling pathways, promoting tissue regeneration. In summary, mitophagy plays a critical role in wound healing by regulating inflammation, maintaining mitochondrial quality, promoting differentiation and migration of keratinocytes, and facilitating tissue remodelling. The identification of mitophagy pathways may lead to the development of novel therapeutic strategies for promoting wound healing

stage, while excessive or persistent inflammation can induce disease and tissue damage [142]. Loss of inflammatory cells, such as macrophages, can lead to reduced tissue formation, haemorrhage and failure to progress to the next phase of wound repair [143].

The production of ROS by neutrophils and macrophages plays a central role in the destruction of microorganisms and the synthesis of growth factors during inflammation. [144]. Although the cell membrane protein NADPH oxidase (Nox) has been considered as the primary contributor of ROS during host defence against microbes [145], mounting evidence suggests that mitochondria also play a critical role in generating inflammation-related ROS [146]. Mitophagy is a potent mechanism that maintains cellular redox balance, and its inhibition can lead to the accumulation of unhealthy mitochondria and ROS [147]. The involvement of mitophagy in inflammation has been underscored by the finding that inhibition of mitophagy significantly exacerbates inflammation [148–150]. Therefore, manipulating mitophagy represents a promising strategy for controlling inflammation and enabling macrophage functional adaptation during the inflammatory response.

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Interestingly, PAMPs inhibit mitophagy *via* caspase 1- and 11-mediated degradation of PINK1/Parkin, leading to suppression of mitophagy that at the early stage of wound healing promotes the production of mtROS and macrophage activation, thereby exacerbating the severity of bacterial infections and septic situations *in vivo* [150, 151]. In addition to mtROS, released mtDNA from the damaged mitochondria also contributes to the inflammatory response of macrophages, further supporting the importance of mitophagy in macrophage activation [9]. However, unlike caspase 1 and 11, the activation of nuclear factor kappa B (NF-kB) by LPS negatively regulates the extent of inflammation by upregulating the expression of mitophagic receptor p62 [152]. This mechanism enables NF-kB to orchestrate the activation of NLRP3 inflammasome and the release of cytokines, thereby preventing long-lasting tissue inflammation and damage [152]. Interestingly, the recruitment of p62 to the mitochondria still requires the involvement of Parkin, suggesting that Parkin is the key regulator of balanced mitophagy during macrophage activation (Figure 3) [152].

In addition to its role in promoting inflammation, mitophagy also plays a crucial role in the metabolic transition of macrophages necessary for tissue repair [153]. During the early inflammatory stage, activated macrophages produce cytokines to recruit and activate additional leukocytes and eliminate cellular debris *via* phagocytosis. Whereas at the later stage, activated macrophages dampen inflammation, promote angiogenesis and facilitate tissue regeneration, representing a transition from the M1 state to the M2 state [124, 154, 155].

At the early stage, M1 macrophages produce mtROS and stabilize HIF1α, which drives pro-angiogenic signalling that is crucial for timely healing. In contrast, M2 macrophages at the late stage rely on mitohormesis with reduced mtROS production [156]. The transition from M1 to M2 macrophages is regulated by several anti-inflammatory cytokines, including IL-10, IL-4 and IL-13 [157]. Recently, Ip *et al*. demonstrated that IL-10 downregulates ROS by promoting the removal of the dysfunctional mitochondria in macrophage through inhibition of the mammalian target of rapamycin (mTOR) signalling pathway. The absence of IL-10 results in the aberrant activation of the NLRP3 inflammasome [153]. This study highlights the mechanisms by which mitophagy regulates the metabolic transition of macrophages.

To date, several studies have implicated the Parkin-mediated mitophagy pathway in the inflammatory response of macrophages [150–152]. However, the involvement of other pathways in macrophage activation remains ambiguous. Given that HIF1α is stabilized in M1 macrophages [156], it is worth considering whether NIX and FUNDC1, which are well-known transcriptional targets of HIF1α, play a role in macrophage activation. Interestingly, Esteban-Martínez *et al*. found that the gene expression level of NIX is upregulated in M1 macrophages and that deletion of NIX in macrophages impairs their polarization to the M1 stage. These findings suggest the NIX-mediated mitophagy is essential for sustaining macrophage activation, [158], although the underlying mechanism is still poorly understood. Additionally, recent studies have demonstrated that FUNDC1 inhibits NLRP3-mediated inflammation by promoting mitophagy during brain injury [159, 160]. This supports the idea that FUNDC1 may also be a potential regulator of immune-cell activation.

Although increased ROS levels are necessary to activate the inflammatory response at the early stage of wound healing, a high level of ROS may be harmful to macrophages, as it can cause cell death [161]. Inhibition of mitophagy can lead to excessive mitochondrial damage, which can contribute to an increase in pyroptotic cell death. This, in turn, can cause plasma membrane rupture and enhances the release of DAMPs [151]. These released danger molecules may further activate macrophage cells and amplify the inflammatory response in the tissue [162]. Therefore, ROS levels are generally considered as a double-edged sword, which need to be well-mitigated to prevent undesirable consequences.

In summary, mitophagy has a fine-tuned regulatory role during the inflammatory stage of wound healing, including a pro-inflammatory function that promotes microbe clearance at the early stage and an anti-inflammatory function that primes tissue repair at the later stages. The regulatory role of mitophagy is achieved by controlling the level of mitochondria-derived ROS. Apart from inflammation, redox signalling also plays a role in haemostasis, granulation, wound closure and many other processes of wound healing. However, whether mitophagy underpins these events *via* redox signalling requires further investigation.

Mitophagy is essential for the proliferative stage Cytokines and growth factors, such as PDGF, TGF-β and IL-6, which are secreted by platelets, and macrophages, plays crucial roles not only in regulating hemagglutination and inflammation, but also in the restoration of tissue during the proliferative phase of wound healing [163, 164]. Upon activation of the cell membrane receptors by these cytokines and growth factors, extracellular signals are transmitted into the cytosol, which regulates the synthesis of proteins involved in cell growth, proliferation and migration [165]. This stimulation leads to the synthesis, deposition and organization of a new ECM in the wound by fibroblasts, replacing the provisional fibrin clot. In addition, endothelial cells initiate angiogenesis, while epithelial cells proliferate and migrate, re-establishing the epidermal layers that cover the wound surface, representing a clinical hallmark of healing [166].

Very recently, the importance of mitophagy during the proliferative phase of wound healing has been substantiated (Figure 3). Using microscopic images of organotypic epidermal cultures, Simpson *et al*. revealed that keratinocytes undergo increased mitophagy during their final stage of differentiation by upregulating NIX. Deletion of NIX attenuates epidermal maturation, suggesting that mitophagy is critical for the development of epidermis [167]. Similarly,

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up-regulation of BNIP3, a mitophagic homologue of NIX, is also observed in epidermis during wound healing [168]. Further analysis has shown that the increased levels of BINP3 promote the migration of epidermal keratinocytes under hypoxia by inducing autophagy [168, 169]. In another study on dental pulp injury, Liu *et al.* demonstrated that hypoxia induces human dental pulp cell proliferation, migration and differentiation *via* FUNDC1-mediated mitophagy [170]. These findings indicate that FUNDC1 could be an alternative mitophagic regulator that contributes to the growth of granulation tissue and epithelialization.

Angiogenesis is an important event in wound healing, involving the formation of new capillaries to replace damaged ones and restore circulation [171]. Studies suggest that urolithin A (UA) positively impacts endothelial cell proliferation, migration and tube formation abilities. Furthermore, UA treatment significantly improves the recovery of skin wounds by facilitating angiogenesis [172]. Interestingly, UA has also been demonstrated to promote mitophagy and enhance cell quality by activating AMPK signalling, a well-known upstream regulator of autophagy and mitophagy [173, 174]. Thus, investigating whether UA treatment-dependent acceleration of angiogenesis is mitophagy-dependent would be an interesting area for further research.

Mitochondrial therapeutic agents for burn injury and wound healing Mitigating the negative effects of burn trauma can be achieved by regulating mitochondrial function and mitophagy using potential mitochondrial therapeutics. Farnesyltransferase (FTase) and protein farnesylation levels increases in response to burn, but using the Ftase inhibitor (FTI) can reduce the mitochondrial alteration and dysfunction caused by burn injury [22]. Additionally, mitochondrial-specific antioxidants such as Mito-TEMPO can reverse cardiac mitochondrial dysfunction caused by burn trauma, making mitochondria-targeted antioxidants an effective therapy for treating cardiac dysfunction resulting from burn trauma [175]. Elamipretide, a mitochondrial-targeted peptide, has the potential to reduce mitochondrial dysfunction and alleviate the inflammatory response [176]. Coenzyme Q10 (CoQ10), an essential cofactor for mitochondrial electron transport, has been shown by Nakazawa *et al.* to alleviate the mitochondrial integrity changes brought about by burn injury and is a potential target for treating burn patients [177].

Targeting PINK1 and Parkin, which play critical roles in mitochondria-related burn injury, can serve as a potential therapy for burn-induced mitochondrial damage [31]. HIF-1α is also suggested to mediate BNIP3 or Parkin-mediated mitophagy in burn injury, making it an effective target for burn-wound progression. Melatonin, a neurohormone, regulates mitophagy and improves the survival of skin flaps used for wound healing [178]. Furthermore, Sirt3 enhances Pink1/Parkin-mediated mitophagy and can be efficiently targeted as a potential candidate for facilitating wound healing [179]. Rh2, a ginsenoside, inhibits mitophagy and increases mitochondrial ATP production in UV-damaged human skin fibroblasts, making it a potential candidate for wound healing [180]. Miller *et al.*, have reviewed potential therapeutic agents for regulating mitophagy, including Pink1 and Parkin activators and USP30 inhibitors, which might serve as potential targets for burn and wound healing [181]. However, more elaborate investigations are necessary to validate the role of mitophagy in burn injury and wound healing to enable the design of potential therapeutic agents.

Conclusions

In conclusion, mitochondria play a critical role in maintaining skin homeostasis, and mitochondrial dysfunction imposes adverse effects on skin health. Burn injuries can lead to altered mitochondrial morphology, impaired ATP synthesis and mitochondrial respiration, and increased mitochondrial ROS production. This is associated with the changes in the expression of mitophagy-related genes such as Parkin and PINK1, HIF-1α and BNIP3L. During wound healing, mitophagy plays an important role in maintaining a healthy mitochondria pool, which supports the processes of haemostasis, granulation and epithelialization. The regulation of mitophagy is critical during this time, and upregulated mitophagy has been shown to promote tissue restoration. In contrast, downregulated mitophagy leads to the accumulation of dysfunctional mitochondria and ROS, which promotes inflammation and accumulation of unwanted pathogens and host-cell debris. The promising advances in elucidating the mechanism of mitophagy in burn injury and wound healing have led to it becoming a prospective target for burn therapy. By targeting mitophagy, it may be possible to improve mitochondrial function and reduce inflammation and promote tissue restoration. A deeper understanding of the mitochondrial dysfunction in burn trauma and the regulation of mitophagy in wound healing is crucial for the development of an effective therapeutic strategy for burn treatment. Further research into mitophagy and its role in burn injury and wound healing will enable us to develop more effective interventions, ultimately leading to better patient outcomes and a better quality of life for those affected by burn injuries. The potential for targeting mitophagy in burn therapies offers an exciting avenue for future research and development in this field.

Abbreviations

AMBRA1: Autophagy and beclin 1 regulator 1; AMPK: AMP-activated protein kinase; BH3-interacting domain death agonist; BNIP3: BCL2-interacting protein 3; BNIP3L: BCL2-interacting protein 3-like; BAX: Bcl-2-associated X protein; CCCP: Carbonyl cyanide *m*-chlorophenyl hydrazone; CD14: Cluster of differentiation 14; cGMP: Cyclic guanosine monophosphate; CL: Cardiolipin; CMA: Chaperone-mediated autophagy; CoQ10: Coenzyme Q10; CYC1: Cytochrome C1; DAMPS: Damage-associated molecular patterns; DFP: Deferiprone; DRP1: Dynamin-related protein 1;

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ECM: Extracellular matrix; ER: Endoplasmic reticulum; ETC: Clectron transport chain; Fis1: Mitochondrial fission 1 protein; FKBP8: FK506-binding protein 8; FTase: Farnesyltransferase; FUNDC1: FUN14 domain-containing 1; HIF-1 α: Hypoxia-inducible factor 1-alpha; HSP70: Heat shock protein 70; IL-1β: Interleukin-1 beta; LAMP2A: Lysosomal-associated membrane protein 2A; LC3: Microtubule-associated proteins 1A/1B light chain 3B; LC3II: microtubule-associated protein 1 light chain 3 II; LPS: lipopolysaccharide; MAM: Mitochondria-associated membrane; MCP-1: Monocyte chemoattractant protein 1; MFN1: Mitofusin 1 mtUPR: mitochondrial unfolded protein response NDP52: Nuclear domain 10 protein 52; NDUFA9: NADH ubiquinone oxidoreductase subunit A9; NLRs: Nod-like receptors; NOX: NADPH oxidase; NRF1: Nuclear respiratory factor 1;OPTN: Optineurin; OXPHOS: Oxidative phosphorylation; PAMPs: Pathogen-associated molecular pattern molecules; PDE5: Phosphodiesterase-5; PGC-1: Peroxisomal proliferator activator receptor γ coactivator-1; PHB2: Prohibitin 2; PINK1: PTEN-induced kinase; PKG: Protein kinase; PRRs: Pattern recognition receptors; ROS: Reactive oxygen species; SIRT1: Sirtuin 1; SNARES: Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors; SQSTM1: Sequestosome1; STX17: Syntaxin 17; TLR: Toll-like receptor; TOMM20: Translocase of the outer mitochondrial membrane complex subunit 20; UA: Urolithin A; UBL: Ubiquitin-like; UQCRC2: Ubiquinol-cytochrome C reductase core protein 2; VDAC1: Voltage-dependent anion channel 1.

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Authors' contributions

HSP and DH did relevant literature collection and drafted the manuscript. YCL was involved in designing the scope of the review and literature, critical analysis and revision of the manuscript. All authors critically reviewed the manuscript and have approved the publication of this final version.

Consent for publication

All authors agreed to the submission and publication of the study.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Not applicable.

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