ISSN 2706-6819 Vol.6, Issue 12: 9-13, DOI: 10.25236/IJFM.2024.061202

The Role of Mitochondria in Wound Repair

Jie Huang[1], Yiwen Xu[1], Zhen Lin[1,*]

[1]Department of Orthopedics, First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510632, China
1982558628@qq.com
[*]Corresponding author

Abstract: *Mitochondria possess their own genetic material and genetic system, and are semi-autonomous organelles. In addition to providing energy to the cell, mitochondria are involved in processes such as cell differentiation, cellular information transfer, and apoptosis. They also have the ability to regulate cell growth and the cell cycle. The application of mitochondria in various fields is currently a hot topic of research. In addition, mitochondria can coordinate effector cells such as macrophages through effectors, thereby affecting the four phases of haemostasis, inflammation, proliferation and skin remodelling in wound repair. This article briefly reviews the role of mitochondria in wound repair.*

Keywords: *Mitochondria; Structural Function; Wound Repair; Inflammatory Response; Energy*

1. Introduction

Wound repair has been a major challenge in human medical endeavours since ancient times. Although ordinary wounds can be repaired by the organism itself, some chronic wounds or large skin wounds are difficult to repair on their own, which requires clinical interventions. Additionally, multiple peptide growth factors have also been used more frequently in the treatment of common soft tissue injuries, with excellent results[1]. As the mechanism of trauma research becomes more in-depth, we still need to explore and expand new therapeutic directions. Mitochondria, as a kind of semi-autonomous organelles, have gradually come into people's view. They can not only provide ATP energy for the organism, which plays an indispensable role in the organism's activities, but also undergo structural and functional changes during the process of traumatic wound repair as the repair process progresses. These changes enable mitochondria to regulate their own functions and thereby promote wound repair. The role of mitochondria in traumatic wound repair and the progress of related research is summarized as follows[2].

2. Basic structure of mitochondria

Under light microscopy, mitochondria appear as short rods, and under electron microscopy, their double-layered membrane is visible. The outer membrane is smooth, while some parts of the inner membrane fold inward to form cristae, which significantly increase the surface area of the inner membrane. Between the inner and outer membranes lies the intermembrane space (or outer compartment) of the mitochondrion, which is connected to the inner gaps of the cristae. The inner compartment, also known as the stromal compartment, is located inside the inner boundary membrane. In addition, the type and number of proteins on the inner membrane are greater than those on the outer membrane. The inner membrane contains DNA related to cytoplasmic genetics, and there are a variety of enzymes related to aerobic respiration present in the mitochondria, which serve as the main site of aerobic respiration for the cell, providing it with the energy required for life activities.In 2000, T. G. Frey et al. found that the inner membrane of the mitochondrion, observed under electron microscope (EM) tomography, was a dynamic structure capable of responding to changes in osmotic or metabolic conditions by rapidly changing shape. The hypothesis that cristae morphology can in fact regulate the rate of chemical osmosis was put forward, suggesting that such structural changes may be part of the feedback mechanism by which mitochondria respond to environmental changes[3]. The mitochondrial outer membrane regulates its own fusion and division through two molecules, the mitochondrial fusion proteins Mfn1 and Mfn2, which precisely regulate cellular life activities[4, 5] , and is also closely related to the mitochondria-endoplasmic reticulum structural couplings (MAMs) that regulate lipid metabolism,

ISSN 2706-6819 Vol.6, Issue 12: 9-13, DOI: 10.25236/IJFM.2024.061202

calcium signalling, mitochondrial morphology, etc[6].

3. Basic process of wound repair

Wound healing usually denotes the process of repairing the skin and other body tissues that appear to be injured after the body has been subjected to an external force, and wound healing can generally be divided into haemostasis, inflammation, proliferation, and skin remodelling, which are both differentiated from each other and interconnected with each other in the four stages.**1)** Haemostasis**:** after the formation of a wound, the body's first response is to turn on the coagulation mechanism to carry out its own haemostatic process. Platelets on the wound surface aggregate and appear as clots, platelet plugs prevent blood loss, and an initial fibrin matrix is formed; **2)** Inflammation: This stage is focused on destroying bacteria and removing necrotic tissue. Neutrophils influx, and monocytes arrive later, differentiating into tissue macrophages to remove the remaining cellular debris. This stage may initially be accompanied by redness, swelling, heat, and pain;**3)** Proliferation: The main manifestations of this stage are tissue hyperplasia and granuloma formation. Keratinocytes migrate to close the wound gap, blood vessels are reconstructed through angiogenesis, and fibroblasts replace the initial fibrin clot with granulation tissue;**4)** Skin remodelling**:** Mainly, the deposited matrix is further remodeled by fibroblasts, blood vessels undergo degeneration, and myofibroblasts cause overall wound contraction. After the proliferative phase, the wound has initially healed. Over time, the scar tissue and scabs that repair the wound gradually adapt, restoring the tissue to accommodate physiological function and ultimately resulting in improved appearance and function of the injured area[1].

4. Influence of mitochondria on the process of wound repair

4.1 Effect of mitochondria on haemostatic phase

The haemostatic stage refers to the period after the formation of the wound, during which the organism activates the coagulation mechanism and carries out its own haemostatic processes. It is specifically manifested by the aggregation of platelets on the wound surface and the formation of clots, which can effectively stop wound bleeding. From a microscopic observation, during the process of platelet activation, mitochondrial microparticles (mtMPs) exhibit procoagulant activity and play an indispensable role through the ROS pathway. At the same time, mtMPs (2×10^4 /μl) also stimulate a decrease in CD31 expression and an increase in VWF expression in endothelial cells, which in turn activates the endothelial cells and disrupts the interendothelial barrier, synergizing with platelets to increase endothelial cell leakage[7]. During platelet aggregation, the outer membrane of the mitochondria fuses with the lipid membrane of the endoplasmic reticulum, thereby renewing the mitochondrial phospholipid membrane and regulating the intracellular calcium ion concentration[9]. Mitochondria also act as mediators of several agonists (including collagen, ADP, thrombin, yeast glycans and others) to activate and recruit circulating platelets to growing haemostatic plugs[8]. Finally, mitochondria are also involved in the regulation of platelet apoptosis. The mitochondrial permeability transition (MPT) is a key mechanism in this process, leading to the exposure of platelet phosphatidylserine (PS). This, combined with a homeostatic imbalance mediated by mitochondrial calcium, further generates reactive oxygen species (ROS) and triggers PS ectopia. Additionally, the Bcl-2 family of apoptotic precursor proteins and anti-apoptotic proteins plays a crucial role in mediating apoptosis in a coordinated fashion with mitochondria. These mitochondrial activation pathways accelerate platelet apoptosis[8、 9、 10].

4.2 Effect of mitochondria on inflammatory stages

The inflammatory phase focuses on destroying bacteria and removing necrotic tissue to lay the foundation for tissue regeneration and repair. Inflammatory vesicles play an important role in this phase, Inflammatory vesicles are multiprotein complexes containing ASC, procystinase 1 and NLRP3 are an important component of the natural immune system. After sensing an external pathogen or injury, it transmits a signal to the immune system to initiate inflammation[11].

In addition, the predominant cell type in the early stages of trauma is the pro-inflammatory macrophage, and this cell subset is characterized by mitochondrial ROS (mtROS) production and HIF-1α stabilization. This is because early trauma-induced macrophages (MFs) require glycolysis and the reuse of mitochondrial activity, specifically mitochondrial ROS (mtROS) production, to generate

ISSN 2706-6819 Vol.6, Issue 12: 9-13, DOI: 10.25236/IJFM.2024.061202

the appropriate early pro-inflammatory and vascular responses, ensuring timely healing[1]. Uncontrolled excessive inflammation promotes tissue damage and delays healing, as suggested by a recent study conducted in mice (e.g., diabetic mice). However, inadequate inflammatory cell recruitment, such as in TLR3 knockout mice, also hinders repair. Therefore, the inflammatory cell response must be contextualized[6]. When foreign substances stimulate macrophages, activation of the IKKβ/NF-κB pathway generates mitochondrial autophagy thereby removing damaged mitochondria. When these damaged mitochondria are removed, NLRP3 inflammatory vesicles are inactivated, inhibiting IL-1β production and preventing excessive inflammation. Macrophages maintain homeostasis and tissue repair through the regulation of the "NF-κB-p62-autophagy" pathway. It has also been suggested that the PINK1/Parkin pathway can mediate the regulation of mitochondrial autophagy, and that the activation of NLRP3 inflammatory somates (or 'inflammasomes,' depending on the context) may be related to the inactivation of mitochondrial autophagy through its negative regulatory mechanism[12] .

In addition to the production of mtROS and mtDNA, mitochondrial molecules (including mitochondrial antiviral signalling protein (MAVS), mitochondrial fusion protein 2 and cardiolipin) have been associated with NLRP3. It has also been suggested that NLRP3 stimulation induces mitochondrial translocation to the endoplasmic reticulum and that ASC on mitochondria is very close to NLRP3 on the endoplasmic reticulum, findings that suggest that mitochondria may act as a scaffold for the assembly of NLRP3 inflammatory vesicles[13] . In summary, we believe that mitochondria play a central role in organismal trauma inflammation and that improving mitochondrial function is important for the treatment of traumatic hyperinflammation.

4.3 Effect of mitochondria on the proliferation phase

The proliferative phase is dominated by tissue proliferation and granulation tissue formation. Shortly after the onset of inflammation, there is the appearance of neoplastic cells (although typically in wound healing it is more common to see the proliferation and differentiation of fibroblasts, endothelial cells, etc.), along with the formation of new capillaries. These components together form granulation tissue, which fills and covers the wound, ultimately leading to the formation of a scar. Mitochondria play an important role in this process, as glycolysis and mitochondrial respiration are crucial for tip cell and non-tip cell differentiation, as well as non-tip cell proliferation (tip cells, on the other hand, do not proliferate). During cell proliferation and differentiation, tip cells require glucose depletion to produce mitochondrial ATP for their survival[14]. Mitochondrial ROS (mtROS) enter the cytoplasm to facilitate redox signalling and mediate a variety of biological responses, including processes such as cell proliferation, differentiation and migration[15] . During neocapillary formation, mitochondria contain a variety of mitochondrial proteins and mitochondrial signalling agents that control angiogenesis by regulating endothelial cell migration, proliferation and apoptosis[16]. The mitochondrial fusion protein of the inner mitochondrial membrane, optic nerve atrophy 1 (OPA1), has been proposed to be required for angiogenesis in the research tumour related literature. In response to angiogenic stimuli, OPA1 levels increase rapidly, regulating the generation of nuclear factor-κB (NF-κB) light chain enhancers by affecting Ca2+ signaling to limit NF-κB signaling. Ultimately, this permits angiogenic gene expression and angiogenesis. Additionally, OPA1 regulates apoptosis by participating in the formation and maintenance of cristae junctions, independently of its role in mitochondrial fusion. And it also stabilises the respiratory chain supercomplex, controlling mitochondrial respiratory activity and mitochondria-dependent cell proliferation[15、17].In mitochondria, there is also FUN14 domain-containing protein 1 (FUNC1), an integral mitochondrial outer membrane protein, which mediates the formation of mitochondria-associated endoplasmic reticulum membranes (MAMs) and upregulates VEGFR2 expression[18]. In mouse studies, mitochondrial reactive oxygen species (mtROS) induces vascular endothelial growth factor (VEGF) expression and enhances angiogenesis and skin wound healing in mice through complex pathways in vascular smooth muscle cells and endothelial cells[15].

4.4 Effect of mitochondria on skin remodelling stages

During this phase, the granulation tissue is gradually replaced by scar tissue as fibroblasts synthesize more and more collagen fibers, which are also modified by various enzymes and external forces to meet their physiological requirements. Myofibroblasts are involved in coordinating the synthesis and remodelling of ECM components, and the contraction of granulation tissue can lead to wound closure. During physiological wound healing, once the wound is closed, myofibroblasts are no longer required and are eliminated mainly through mitochondrial apoptosis, controlled by the BCL-2

ISSN 2706-6819 Vol.6, Issue 12: 9-13, DOI: 10.25236/IJFM.2024.061202

protein family. This process involves the release of mitochondrial cytochrome c into the cytoplasm via mitochondrial outer membrane permeabilization (MOMP), which promotes the activation of the effector caspase, ultimately leading to cell death[19]. Proliferative scarring occurs as a result of collagen overproduction and extracellular matrix (ECM) overdeposition, often due to severe injuries. This pathological scarring can be treated through pharmacological modulation of the mitochondrial apoptotic pathway[20].

5. Summary

Wound healing is a very complex biological process with the involvement of a variety of important biomolecules. At the same time, it is regulated by a variety of regulatory factors, and the co-regulation of the various factors allows it to proceed programmatically. Although the authors of this article discuss the role of mitochondria on the various stages of the healing process separately, the stages are inseparable from each other. With the in-depth study of the mechanisms of trauma healing, diverse therapeutic tools are now gradually being developed in various fields of research. For example, mesenchymal stem cell mitochondrial transfer therapeutic approach utilises mitochondrial structure and function to repair damaged tissues in a variety of diseases[21]. Oleanolic acid (OA) regulates the expression of Bcl-2 family proteins for the treatment of hyperplastic scarring[20]. In conclusion, with the further exploration of wound healing and mechanisms, it will have far-reaching impacts on many fields such as basic research, improvement of skin wound repair and clinical applications.

References

[1] Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. Open Biol. 2020 Sep; 10(9):200223. doi: 10.1098/rsob.200223. Epub 2020 Sep 30. PMID: 32993416; PMCID: PMC7536089.

[2] Willenborg S, Sanin DE, Jais A, Ding X, Ulas T, Nüchel J, Popović M, MacVicar T, Langer T, Schultze JL, Gerbaulet A, Roers A, Pearce EJ, Brüning JC, Trifunovic A, Eming SA. Mitochondrial metabolism coordinates stage-specific repair processes in macrophages during wound healing. Cell Metab. 2021 Dec 7; 33(12):2398-2414.e9.doi:10.1016/j.cmet.2021.10.004. Epub 2021 Oct 28. PMID: 34715039.

[3] Frey TG, Mannella CA. The internal structure of mitochondria. Trends Biochem Sci. 2000 Jul; 25(7):319-24. doi: 10.1016/s0968-0004(00)01609-1. PMID: 10871882.

[4] Xu Yue, Qin Shuangli.The Relationship Between Mitofusin and Mitochondrial Morphology[J]. Shandong Chemical Industry,2017,46(18):133+138.DOI:10.19319/j.cnki.issn.1008-021x.2017.18.051.

[5] Li Yujie, Gao song.Toward the Mechanism of Mitochondrial Outer Membrane Fusion[J].China Basic Science,2020,22(03):1-5+48.

[6] Qin Jiahong, Huang Zitong.Advances in structural coupling of mitochondria-associated endoplasmic reticulum membrane[J].Chin J Emerg Med,2017,26(09):1095-1098.

[7] Zhao Zilong.Investigation of the mechanism of brain-derived mitochondrial microparticles in traumatic brain injury-associated coagulopathy[D].Tianjin Medical University,2016.

[8] Garcia-Souza LF, Oliveira MF. Mitochondria: biological roles in platelet physiology and pathology. Int J Biochem Cell Biol. 2014 May;50:156-60. doi: 10.1016/j.biocel.2014.02.015. Epub 2014 Feb 22. PMID: 24569121.

[9] Zhao Xiaoxia. Research progress of mitochondria in platelets[J].Laboratory Medicine, 2021, 36(12): 1283-1286.

[10] Yuan Yuan, Zhang Feng.Advancement of Studies on Mitochondria-mediated Platelet Apoptosis[J]. Medical Recapitulate,2014,20(22):4066-4068.

[11] Andrieux P, Chevillard C, Cunha-Neto E, Nunes JPS. Mitochondria as a Cellular Hub in Infection and Inflammation. Int J Mol Sci. 2021 Oct 20;22(21):11338. doi: 10.3390/ijms222111338. PMID: 34768767; PMCID: PMC8583510.

[12] Wang Meng.Study on the Mechanism of Xiaojianzhong Decoction inhibiting the NLRP3 Inflammasome Activation by Up-regulating Mitophagy in the Treatment of Depression[D].Chengdu University of Traditional Chinese Medicine,2020.DOI:10.26988/d.cnki.gcdzu.2020.000070.

[13] Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci. 2019 Jul 6;20(13):3328. doi: 10.3390/ijms20133328. PMID: 31284572; PMCID: PMC6651423.

[14] Yetkin-Arik B, Vogels IMC, Nowak-Sliwinska P, Weiss A, Houtkooper RH, Van Noorden CJF, Klaassen I, Schlingemann RO. The role of glycolysis and mitochondrial respiration in the formation

ISSN 2706-6819 Vol.6, Issue 12: 9-13, DOI: 10.25236/IJFM.2024.061202

and functioning of endothelial tip cells during angiogenesis. Sci Rep. 2019 Aug 30;9(1):12608. doi: 10.1038/s41598-019-48676-2. PMID: 31471554; PMCID: PMC6717205.

[15] Xu S, Li S, Bjorklund M, Xu S. Mitochondrial fragmentation and ROS signaling in wound response and repair. Cell Regen. 2022 Dec 1;11(1):38. doi: 10.1186/s13619-022-00141-8. PMID: 36451031; PMCID: PMC9712903.

[16] Marcu R, Zheng Y, Hawkins BJ. Mitochondria and Angiogenesis. Adv Exp Med Biol. 2017; 982:371-406. doi: 10.1007/978-3-319-55330-6_21. PMID: 28551799.

[17] Herkenne S, Ek O, Zamberlan M, Pellattiero A, Chergova M, Chivite I, Novotná E, Rigoni G, Fonseca TB, Samardzic D, Agnellini A, Bean C, Di Benedetto G, Tiso N, Argenton F, Viola A, Soriano ME, Giacomello M, Ziviani E, Sales G, Claret M, Graupera M, Scorrano L. Developmental and Tumor Angiogenesis Requires the Mitochondria-Shaping Protein Opa1. Cell Metab. 2020 May 5; 31(5):987-1003.e8. doi: 10.1016/j.cmet.2020.04.007. Epub 2020 Apr 20. PMID: 32315597.

[18] Wang C, Dai X, Wu S, Xu W, Song P, Huang K. FUNDC1-dependent mitochondria-associated endoplasmic reticulum membranes are involved in angiogenesis and neoangiogenesis. Nat Commun. 2021 May 10;12(1):2616. doi: 10.1038/s41467-021-22771-3. PMID: 33972548; PMCID: PMC8110587.

[19] Kuehl T, Lagares D. BH3 mimetics as anti-fibrotic therapy: Unleashing the mitochondrial pathway of apoptosis in myofibroblasts. Matrix Biol. 2018 Aug;68-69:94-105. doi: 10.1016/j.matbio.2018.01.020. Epub 2018 Jan 31. PMID: 29408011.

[20] Chen JY, Zhang L, Zhang H, Su L, Qin LP. Triggering of p38 MAPK and JNK signaling is important for oleanolic acid-induced apoptosis via the mitochondrial death pathway in hypertrophic scar fibroblasts. Phytother Res. 2014 Oct; 28(10):1468-78. doi: 10.1002/ptr.5150. Epub 2014 Apr 6. PMID: 24706573.

[21] Wang Zhangling, Yu Limei, Zhao Chunhua. Tissue repair using mesenchymal stem cells via mitochondrial transfer[J].Chinese Journal of Tissue Engineering Research,2020,24(07):1123-1129.