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Review Article

Epithelial Proliferation and Remodeling Mechanisms Associated with Skin Repair: A Comprehensive Review

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Abstract

The reconstruction and proliferation of epithelial cells after skin injury are crucial steps in the process of skin repair and regeneration. Many growth factors are involved in this process, including epidermal growth factor, platelet-derived growth factor, keratinocyte growth factor, and transforming growth factor beta. These growth factors activate signal pathways by binding to receptors on epithelial cells, thereby affecting cell apoptosis, proliferation, and differentiation. CDK4/6-Cyclin D, ERK-MAPK, PI3K-AKT-mTOR, Wnt/β-catenin, and other signaling pathways are activated during epithelial cell proliferation. The activation of these signaling pathways not only directly stimulates epithelial cell proliferation, but also regulates the cell cycle and induces differentiation of epithelial cells after proliferation. In addition, cytokines also play an important role, such as the release of inflammatory factors, collagen, and elastic fibers, which attract endothelial cells and monocytes to the wound site, causing an inflammatory response and inducing matrix rebuilding. This article explores the mechanism of epithelial proliferation and reconstruction, which provides guidance for developing effective treatment strategies for skin injury and promoting skin regeneration.

Keywords: Skin wounds and injuries; Epithelial cells; Growth factor; Cytokines; Signal pathway

Background

The skin is one of the largest organs in the human body, with primary functions including protection, maintenance of body temperature, regulation of water balance, prevention of external pathogens from entering, and transmission of sensory information [1,2]. The skin consists of three layers: the epidermis, dermis, and subcutaneous tissue. The epidermis is the outermost layer, composed of multiple layers of different types of epithelial cells (such as keratinocytes and melanocytes). The main function of the epidermis is to act as a barrier, preventing external substances from entering the body and maintaining the balance of water and nutrients inside. The dermis is located below the epidermis and consists of connective tissue, elastic fibers, and capillaries. The dermis provides support and elasticity, as well as serving as a source of blood and nutrients. The subcutaneous tissue is the deepest layer, composed of fat and connective tissue. The subcutaneous tissue plays an important role in maintaining body temperature and energy reserves. In addition to these structures and functions, the skin can also transmit sensory information and produce sweat through sweat glands and hair follicles [3-5].

However, the skin is often subjected to various traumatic injuries, such as cuts, burns, chemical burns, infections, etc. Severe cases may even lead to tissue necrosis, hemorrhagic shock, and other serious diseases [6]. According to statistics, skin injuries are a common public health problem faced by countries around the world, and the disease burden is constantly increasing due to its high incidence and diversity [7]. In the face of this situation, skin repair is obviously necessary [4]. Skin repair refers to the process of restoring the structure and function of damaged skin through various biological processes after trauma. As the outermost layer of the skin, when the skin is damaged, the damaged area of the epithelial cells will release a series of signaling molecules to attract surrounding epithelial cells and other types of cells to form a new layer of cells to replace the damaged tissue. In this process, epithelial cells undergo a series of biological processes such as proliferation, migration, and differentiation, ultimately completing the repair of damaged skin. Skin epithelial cells are mainly divided into epidermal cells, hair follicle epithelial cells, and sweat gland epithelial cells. These types of epithelial cells directly participate in the repair of skin after injury [8,9].

After skin injury, these epithelial cells exert their effects through proliferation, differentiation, and migration. Specifically, when the skin is damaged, the surrounding epithelial cells begin to proliferate and migrate towards the wound [9,10]. At the same time, cells involved in the healing process differenti-

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ate into different types of epithelial cells to complete the task of sealing and repairing the damaged area [11]. Epithelial cells from hair follicles and sweat glands also participate in the healing process, and they can repair the structure of hair follicles and sweat glands through similar mechanisms of proliferation and differentiation [12]. In addition to proliferation, differentiation, and migration, these epithelial cells can also secrete growth factors, extracellular matrix proteins, and other molecules to coordinate skin healing [13]. For example, epithelial cells can produce platelet-derived growth factor and epidermal growth factor, which can stimulate epithelial cell proliferation and migration, promoting regeneration of the epidermal layer [14].

In summary, epithelial cells in the skin participate in the healing process of skin injuries through a series of mechanisms, including proliferation, differentiation, migration, and secretion of growth factors. Their synergistic action is crucial for maintaining skin integrity and function, and studying the relevant mechanisms and pathways is essential for skin injury repair.

The Healing Process of Skin

After injury the healing process of skin can be divided into four stages: inflammation, proliferation, remodeling, and maturation [9]. In the inflammation stage, blood vessels at the site of injury will contract, and clotting and thrombosis will occur. Inflammatory cells and mediators will also gather at the site of injury to clear pathogens and necrotic tissue. In the proliferation stage, new blood vessels begin to grow towards the site of injury, and fibroblasts move from the surrounding tissue to the site of injury to produce collagen and other matrix molecules to fill the injury site. In the remodeling stage, new blood vessels and fibroblasts continue to proliferate and repair at the site of injury, while keratinocytes begin to move upwards to restore the skin's barrier function. In the maturation stage, collagen is rearranged to make the wound more robust, and cells and matrix molecules gradually shrink to restore the skin's original structure and function [15-17].

The regulatory mechanisms involved in the process of skin healing include the participation of various molecules and cytokines [18-20]. In the inflammation stage, inflammatory mediators such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6 promote the occurrence and maintenance of inflammation to clear pathogens and necrotic tissue [21]. In the proliferation and remodeling stages, growth factors secreted by fibroblasts and keratinocytes, such as epidermal growth factor, fibroblast growth factor, and transforming growth factor-beta, promote cell proliferation and matrix synthesis to fill the injury site [22]. In addition, endothelial cells and macrophages secrete angiogenic factors and vascular endothelial growth factor to promote the generation and growth of new blood vessels. In the maturation stage, molecules such as metalloproteinases and tissue inhibitors participate in the degradation and rearrangement of cells and matrix molecules to restore the skin's original structure and function [23]. The healing process of skin after injury is a complex biological process, and its regulatory mechanisms involve the participation of various molecules and cytokines. The following will provide a detailed discussion of the regulatory mechanisms of epithelial proliferation in the process of skin healing.

Proliferation of Epithelial Cells

In the process of skin repair and regeneration, the proliferation of epithelial cells is a crucial step, as they need to form a new layer of cells to cover the damaged area and restore the normal skin structure [24-27].

Cell proliferation can be roughly divided into three stages: G1 phase, S phase, and G2 phase.

G1 phase: Cells in this phase prepare to enter the S phase of DNA replication. Prior to this, they need to increase the content of their internal proteins and enzymes to help complete the various tasks required for DNA replication and division. The length of the G1 phase can vary depending on the cell type and environmental conditions, and is regulated by external signaling molecules.

S phase: In the S phase, cells begin DNA replication and produce two identical chromosomes. This process is called DNA synthesis or replication. Many enzymes and auxiliary proteins, including DNA polymerase, are involved in this stage.

G2 phase: In the G2 phase, cells must make final preparations to help complete cell division. At this stage, cells synthesize many necessary proteins and enzymes to help with division and generate two new cells.

Epithelial Proliferation Rebuilding Related Growth Factors and Their Receptors

Growth factors are a class of protein molecules with biological functions that promote cell growth, proliferation, and differentiation [28,29]. They include various types of molecules such as Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), and Nerve Growth Factor (NGF). Growth factors play an important role in regulating organ development, tissue repair and regeneration, immune responses, and other physiological processes in the body [30].

Epidermal Growth Factor (EGF) is a small peptide composed of 53 amino acids. It can regulate the proliferation and differentiation of epithelial cells, promote angiogenesis, matrix synthesis, and immune regulation. The biological effects of EGF are mainly achieved by binding to its receptor, Epidermal Ggrowth Factor Receptor (EGFR). EGFR belongs to the tyrosine kinase receptor family and has the ability to activate multiple signaling pathways, playing an important role in skin wound healing. EGF can promote the migration and proliferation of epithelial cells, allowing them to quickly cover the damaged area, and enhance the self-renewal ability of epidermal cells. In addition, EGF can also stimulate matrix synthesis and angiogenesis. Recent studies have also found that EGF can promote the healing process by regulating the inflammatory response. In addition to EGFR, EGF also interacts with several other receptors, including Herc4, Cripto-1, and ADAM17 [31,33]. The presence of these receptors may regulate the EGFR signaling pathway and affect the biological process of skin wound healing. In summary, the EGF/EGFR signaling pathway plays a crucial role in skin wound healing, and its mechanism has been widely studied and recognized [34,35].

Platelet-Derived Growth Factor (PDGF) is a protein secreted by various cells such as platelets, macrophages, endothelial cells, and smooth muscle cells [36]. It binds to cell surface receptors and activates downstream signaling pathways, regulating processes such as cell proliferation, migration, and differentiation. In skin wound repair, PDGF is involved in multiple stages of biological processes, including platelet aggregation: when the skin is damaged, platelets rapidly aggregate at the site of injury and release a large amount of PDGF, promoting proliferation

of fibroblasts and collagen synthesis [37,39]. After binding to PDGFR-α and PDGFR-β receptors, PDGF activates downstream signaling pathways such as Ras-MAPK and PI3K-AKT, promoting fibroblast proliferation and collagen synthesis, thus generating new matrix and forming scar tissue at the wound site; inflammation stage: in the early stage of wound healing, accompanied by the occurrence of inflammation, various inflammatory cells and epidermal cells secrete PDGF, promoting proliferation and migration of various cells, thus forming lymphatic vessels and neovascularization; epidermal regeneration stage: in the middle stage of wound healing, epidermal regeneration becomes more important. PDGF can stimulate epithelial cell proliferation and migration, and promote epithelial cell differentiation and keratinization [40]. At the same time, PDGF also participates in the proliferation of endothelial cells and the formation of lumens, accelerating vascular regeneration at the wound site; scar formation stage: in the late stage of wound healing, scar tissue begins to form. PDGF can promote fibroblast proliferation and collagen synthesis, thus promoting scar formation.

The Fibroblast Growth Factor (FGF) family of proteins is an important group of cell growth factors, with FGF-2 being one of the most representative members. FGF plays a crucial role in skin wound healing by binding to its receptor on the cell surface, activating downstream signaling pathways, and regulating multiple biological processes involved in skin repair. FGF-2 is a potent inducer of fibroblast proliferation that binds to FGF receptors on the cell membrane, leading to an increase in intracellular cAMP levels and activation of Ras-MAPK and PI3K-AKT downstream signaling pathways to promote fibroblast proliferation. FGF-2 also plays a significant role in the formation and maintenance of the vascular system. It stimulates endothelial cell proliferation and migration, guides directional growth and differentiation of new blood vessels, and promotes vascular regeneration at the site of skin wounds. FGF-2 also promotes the synthesis of extracellular matrix components such as collagen, elastin fibers, and proteoglycans, increasing the strength and stability of newly formed skin tissue. In addition, studies have shown that FGF-2 can stimulate the production of Matrix Metalloproteinases (MMPs) during scar formation, aiding in the removal of old tissue and better adaptation of new tissue to the surrounding environment. FGF-2 can also stimulate the proliferation and migration of keratinocytes, stem cells, and ciliated cells. Furthermore, FGF-2 acts on epithelial cell FGF receptors to enhance the secretion of substances such as collagen and hyaluronic acid, aiding in the repair and regeneration of extracellular matrix.

Transforming Growth Factor-beta (TGF-β) is an important growth factor that plays a crucial role in skin wound repair. It mainly acts through binding to cell surface receptors and activating downstream signaling pathways to regulate various biological processes, thereby participating in skin wound healing [41]. TGF-β mainly acts on fibroblasts and can induce fibroblast migration and proliferation in the early stage of the initial inflammatory response, as well as promote fibroblast differentiation into mature fiber-bundle cells in the late stage of scar formation. TGF-β can promote fibroblast proliferation and differentiation by inducing the Smad signaling pathway, PI3K, MAPK, and other signaling pathways. In the process of skin wound healing, TGF-β can also promote collagen synthesis and deposition, providing sufficient strength to support wound growth [42]. TGF-β can promote collagen synthesis and tight connections through Smad signaling pathways and non-Smad signaling pathways, while inhibiting the release of Matrix Metalloproteinases (MMPs) to maintain a good matrix environment. In addition to its action on fibroblasts, TGF-β can also stimulate epithelial cell proliferation and migration. By activating signaling pathways such as Smad2/3 and PI3K-AKT, TGF-β can induce the expression of transcription factor Snail in epithelial cells, thereby regulating epithelial-mesenchymal transition, promoting the transformation and migration of epidermal cells to mesenchymal cells to support the formation of new tissue. TGF-β can also regulate inflammation and participate in apoptosis and autophagy during the repair process. TGF-β can inhibit the production of inflammatory mediators by regulating signaling pathways such as NF-κB and MAPK, limiting excessive inflammatory responses. At the same time, it can also induce cell apoptosis and autophagy, clear damaged cells, and provide a better growth environment for new tissue formation. TGF-β participates in skin wound healing by regulating various biological processes, including promoting cell proliferation and differentiation, regulating matrix synthesis and deposition, promoting epithelial cell proliferation and migration, and regulating inflammatory responses [43]. These actions work together to promote skin wound repair and healing.

EGFR/HER1 is one of the receptors for EGF, and the most widely expressed tyrosine kinase receptor on the surface of epithelial cells. Activation of EGFR/HER1 can promote epithelial cell proliferation and migration, and participate in biological processes such as apoptosis and cell cycle regulation. After activation, EGFR/HER1 participates in epithelial cell proliferation and migration through multiple downstream signaling pathways, such as PI3K/Akt, MEK/ERK, and others [44].

The PDGF receptor family includes two members: PDGFαR and PDGFβR. PDGFαR is mainly expressed in basal cells, hair follicle stem cells, and glial cells, while PDGFβR is distributed in hair follicle progenitor cells, mesenchymal cells, and others. Activation of PDGF receptors can induce cell proliferation and migration through signaling pathways such as PI3K-Akt, MEK-ERK, etc [45].

The FGFR family includes four members, of which FGFR1 and FGFR2 are receptors that play important roles in skin wound healing. Activation of FGFR1 and FGFR2 can promote epithelial cell proliferation, migration, and induce extracellular matrix protein synthesis. The FGFR signaling pathway includes multiple downstream pathways, such as RAF/MEK/ERK and PI3K/Akt [46].

The TGF-β receptor family includes TGF-βR1 and TGF-βR2. TGF-βR1 is the main member of the TGF-β receptor and its activation can inhibit epithelial cell proliferation and promote the formation of fibroblasts through the Smad-dependent pathway. Additionally, the TGF-β receptor can also regulate multiple downstream signaling pathways, including PI3K/Akt, JNK, etc [47].

In summary, the molecular mechanism of epithelial cell proliferation during skin wound healing involves the synergistic action of multiple growth factors and their receptors.

Epithelial Proliferation-Related Cytokines

Cytokines are a class of small molecule proteins produced by various cells that participate in regulating and coordinating interactions between multiple cells. They transmit signals by binding to specific receptors, affecting cellular processes such as proliferation, differentiation, survival, and death [48]. Chemokines are a class of small molecule proteins that func-

tion similarly to cytokines and can attract different types of cells such as white blood cells and lymphocytes to move in specific directions. In skin wound healing, chemokines play a crucial role by attracting and activating various cell types such as epithelial cells, macrophages, and fibroblasts, to participate in tissue repair and regeneration. Cytokines and chemokines related to epithelial proliferation and reconstruction mainly include [49]:

Matrix Metalloproteinases (MMPs) are a class of enzymes that can hydrolyze matrix molecules and play an important role in skin wound healing. MMPs are mainly distributed in Extracellular Matrix (ECM) and can cleave and clear components of the ECM and some bridging molecules, thereby creating an environment favorable for epithelial cell proliferation, migration, and repositioning. In skin wound healing, the role of MMPs involves the following aspects [50]:

Epithelial cell migration and proliferation: MMPs can hydrolyze ECM molecules, including fibronectin and collagen, which are the structural components of the extracellular matrix. If not degraded, these matrix molecules can hinder the migration and proliferation of epithelial cells. Therefore, MMPs cleave the ECM, providing a pathway for epithelial cells to migrate and proliferate towards the wound [51].

Repairs scar tissue: In the process of skin wound healing, MMPs can also participate in the repair of scar tissue. After the wound heals, MMPs participate in the degradation and clearance of collagen, gradually causing the scar tissue to disappear, and promoting the formation of normal skin tissue [2].

Participates in epithelial cell differentiation: In addition to cleaving matrix molecules, MMPs can also directly or indirectly regulate the activity of cytokines such as Epidermal Growth Factor (EGF) and Transforming Growth Factor β (TGF-β), which play an important role in epithelial cell differentiation and proliferation. MMPs degrade these cytokines' structures, releasing their active components and participating in epithelial cell differentiation and proliferation [53].

During skin wound healing, MMPs promote epithelial cell proliferation and migration by hydrolyzing matrix molecules, participating in the repair of scar tissue, and regulating the activity of cytokines. Ultimately, MMPs promote wound healing and the regeneration of normal skin tissue. Fibronectin is a large extracellular matrix protein composed of multiple functional domains including the RGD (Arg-Gly-Asp) peptide sequence, type III repeat regions, and FN, FN modules. In skin wound healing, fibronectin plays a critical role in cell adhesion, migration, proliferation, and matrix remodeling [54].

Specific mechanisms of fibronectin in skin wound healing include promoting the adhesion and migration of epithelial cells and fibroblasts through binding to their specific receptors (integrins). The RGD sequence on fibronectin can bind to α5β1 integrin on cell surfaces, inducing cell proliferation and migration. Fibronectin can also regulate cell directionality and orientation, promoting cells to migrate towards the wound area, and work cooperatively with other chemotactic factors such as epidermal growth factor in tissue repair [5].

Additionally, fibronectin can promote matrix remodeling and fibroblast transformation by regulating the activity of Transforming Growth Factor-beta (TGF-β), Mmatrix Metalloproteinase (MMP), and other pathways. In extensive trauma, fibronectin can induce fibroblasts to transform into endothelial-like cells for repairing damaged vessel walls [56].

Fibronectin also participates in immune response and regeneration by regulating various cytokines and chemokines. As an adsorption molecule, fibronectin can also control the directional migration of immune cells and regulate inflammation and tissue repair in the wound area [57].

Overall, fibronectin plays a vital role in skin wound healing by coordinating and regulating multiple aspects including cell adhesion, migration, proliferation, and matrix remodeling.

Tumor Necrosis Factor (TNF) is an important cytokine that plays a critical role in skin wound healing. TNF is a protein synthesized and secreted by various cells, which exerts its effects by binding to two receptors, TNFR1 and TNFR2. In the process of skin wound healing, TNF mainly functions through activating NF-κB pathway, promoting immune cell infiltration, changing matrix metabolism, and promoting angiogenesis [58]. The following will elaborate on the mechanism of TNF in skin wound healing in detail from the following aspects:

Activation of NF-κB pathway: TNF can activate IκB kinase (IKK) by binding to TNFR1 receptor, leading to the degradation of IκB and resulting in the entry of NF-κB into the nucleus and regulation of relevant gene expression [59]. In wound healing, TNF participates in regulating multiple biological processes such as inflammatory response, cell proliferation, and extracellular matrix regeneration through activating NF-κB pathway. Furthermore, TNF can also promote the production of inflammatory cytokines and chemokines, guiding the body's immune troops to gather at the site of injury [60].

Promotion of immune cell infiltration: TNF not only directly affects immune cells in the skin area but also acts as a signaling molecule to promote the migration of immune cells to the site of injury by regulating other molecules such as chemokines released by other cells. TNF increases the infiltration of macrophages, neutrophils, and lymphocytes by inducing the expression of MCP-1 (monocyte chemoattractant protein-1) and IL-8, thus participating in the local immune response and cell repair of the wound [61].

Changes in matrix metabolism and cell migration: TNF can also change matrix metabolism and cell migration in skin wound healing. Specifically, TNF can regulate the activity of various matrix metabolism enzymes, such as MMPs (matrix metalloproteinases), PAs (plasminogen activators), and TIMPs (tissue inhibitors of metalloproteinases), thereby promoting matrix remodeling and directional migration of fibroblasts. In addition, TNF can promote the migration and proliferation of endothelial cells and participate in the process of angiogenesis.

TNF is a very important regulatory factor in skin wound healing, participating in regulating biological processes such as inflammatory response, immune cell infiltration, matrix remodeling, and cell migration through multiple ways, thus coordinating and promoting skin repair and regeneration [62].

The Signaling Pathways Related to Epithelial Proliferation and Reconstruction

Epithelial proliferation and reconstruction require the involvement of multiple cellular pathways, which are mechanisms of signal transduction that regulate cellular activities such as growth, differentiation, and the cell cycle [63,64]. The following are several main cellular pathways and their roles in skin repair.

After skin trauma, the Wnt/beta-catenin signaling pathway is gradually activated and participates in early and mid-stage

repair processes [65]. The mechanisms by which the Wnt/beta-catenin signaling pathway works in skin repair are complex and mainly include: Promoting stem cell proliferation: The Wnt/beta-catenin signaling pathway can activate stem cell proliferation, increasing the number of stem cells and providing the driving force for skin repair. A study [66] found that genes such as Wnt10b, LEF1, and beta-catenin in the Wnt/beta-catenin signaling pathway are activated after skin trauma and promote the proliferation of skin stem cells. Promoting epithelial cell migration: The Wnt/beta-catenin signaling pathway can promote epithelial cell migration, facilitating the diffusion and regeneration of epithelial cells on the wound surface. A study of a Wnt2b mutant mouse found that the migration speed of its skin surface epithelial cells significantly decreased, indicating the crucial role of the Wnt/beta-catenin signaling pathway in promoting epithelial cell migration. Promoting epithelial cell differentiation: The Wnt/beta-catenin signaling pathway can regulate epithelial cell differentiation, promoting differentiation into epidermal keratinocytes, sweat glands, and hair follicles, among others [67]. In skin repair, the Wnt/beta-catenin signaling pathway repairs damaged areas by regulating differentiation and proliferation. Promoting matrix synthesis: The Wnt/beta-catenin signaling pathway can promote matrix synthesis, providing support and a scaffold for skin repair. A study found that beta-catenin and Tcf/Lef transcription factors can promote intercellular signaling and matrix synthesis between epithelial cells and dermal cells.

The TGF-β/Smad signaling pathway plays a crucial role in skin epithelial repair after trauma. When skin experiences trauma or injury, the body activates the transcription factors Smad2/3 of epithelial cells through the TGF-β/Smad signaling pathway, which promote transcription of specific genes and thus promote cell proliferation, migration, and Epithelial-Mesenchymal Transformation (EMT) [6]. Specifically, after TGF-β activates Smad2/3, they form a complex with Smad4 that enters the nucleus and participates in the transcription of specific genes. In this process, Smad acts in concert with kinase regulatory proteins and co-activators to regulate not only cell proliferation and migration but also EMT-related gene expression, facilitating the transformation and relocation of epithelial cells below the wound surface [69]. Additionally, the TGF-β/Smad signaling pathway plays a positive role in promoting matrix cell proliferation, differentiation, and synthesis, further promoting skin epithelial repair and regeneration [70].

The Notch signaling pathway is a highly conserved transmembrane receptor-ligand signaling mechanism that is closely related to processes such as cell proliferation, differentiation, apoptosis, and migration [71]. The components of this pathway include transmembrane Notch receptors, one or more transmembrane ligands (such as Delta and Jagged), and downstream effect genes (such as Hes and Hey transcription factors) activated by the Notch signaling pathway. After skin trauma, the Notch signaling pathway can regulate epithelial cell proliferation and migration, promoting epithelial regeneration and wound healing. Specifically, trauma stimulation leads to the activation of the Notch signaling pathway in epithelial cells, causing damaged epithelial cells to proliferate and form primitive cells, enhancing cell survival and proliferation, and promoting the regeneration of damaged epithelial cells [72]. At the same time, the Notch signaling pathway can also affect epithelial cell migration to form new epithelial tissue in the wound area, promoting wound healing. Abnormal activation of the Notch signaling pathway is also associated with skin diseases and tumors. In addition, Notch signaling pathway may cause excessive epithelial cell proliferation and malignant transformation in skin cancer, making it a hotspot of related tumor research. In summary, the Notch signaling pathway plays a crucial role in skin trauma repair and is closely related to skin diseases and tumors. Understanding the mechanism of this signaling pathway can provide new research clues for the prevention and treatment of related diseases [73].

The PI3K/Akt signaling pathway plays a crucial role in skin epithelial repair after trauma. This signaling pathway promotes biological activities such as cell proliferation, migration, survival and differentiation while inhibiting apoptosis and inflammation [74]. After skin trauma, the activation of the PI3K/Akt signaling pathway in epithelial cells increases cell movement through intercellular gaps, stimulates cell proliferation and differentiation, and inhibits inflammation and apoptosis, thereby promoting skin wound healing [75].

The MAPK signaling pathway also plays an important role in skin repair after trauma, particularly with regards to the regulation of epithelial cell proliferation and migration by ERK1/2 kinase. Studies have shown that the ERK1/2 signaling pathway is activated at the initial stage of skin damage, regulating epithelial cell proliferation and migration [76,77].

Summary

The important role of epithelial cells in skin repair Epithelial cells are one of the basic cell types that make up the surface of the skin and form the barrier of the skin through tight connections. When the skin is traumatized or pathologically stimulated, the epithelial cells quickly respond and promote the healing of the injured site. This process includes multiple processes such as rapid differentiation of epithelial cells, proliferation of endothelial cells, and reconstruction of extracellular matrix. Epithelial cells not only respond to external stimuli immediately but also regulate various biological processes such as inflammation, cell migration, and matrix degradation during the healing process to maintain skin integrity [8]. In recent years, people have paid more and more attention to the matrix and immune microenvironments governed by epithelial cells in their research. Stimuli such as radiation, hormones, aflatoxin, ultraviolet radiation, and environmental pollution can change the matrix and immune environment, thus affecting the function of epithelial cells. Therefore, further research on the microenvironment of skin pathology and its impact on epithelial cells can better understand the mechanism of epithelial cell participation in skin repair. Given the important role of epithelial cells in skin repair, we need to analyze the interactions between this cell type and other skin cell types to facilitate the fine-tuning of their function. It may be possible to accelerate the treatment of skin damage caused by disease or trauma by strengthening the role of epithelial cells or altering their biological function. Finally, researchers can conduct simultaneous experiments on human or animal epithelial cells to explore the differences between large-scale cell subdivisions at the theoretical level and form a comprehensive cell type atlas, with the ultimate goal of gradually developing more effective skin repair strategies..

There are several limitations to the study of epithelial proliferation and reconstruction mechanisms in skin repair. Cell signal regulatory pathways are too complex, and there are many aspects that need exploration. For example, we still do not fully understand how epithelial cells collectively proliferate and differentiate, and how they respond to environmental stimuli. Many studies are only in the in vitro or in vivo experimental stage and cannot be expanded to deeper clinical research. There

is still controversy over effective classification methods for derived cells, meaning that we have not found a method or standard that can clearly define derived cell identity. In the future, research directions on epithelial proliferation and reconstruction mechanisms in skin repair may still focus on: in-depth study of the signal pathways and transcriptional regulation mechanisms of epithelial cells to fully grasp the process of cell proliferation and differentiation. This requires modern techniques like single-cell RNA sequencing, and construction of subpopulation expression maps. Strengthening the research on in situ repair mechanisms of limb organs based on human cell reconstruction system. Due to the influence of in vivo matrix and other factors, it is difficult to directly explore in situ repair. We can construct simulation systems through off-body reconstruction to explore potential mechanisms in situ repair. Using mature animal models to construct skin models with different types and conditions, especially emphasizing the effect and physiological differences of epidermal cells playing a distinct role in inflammation in different models. While focusing on the identity of derived cells, finding effective methods for derived cell classification to improve the efficiency and reliability of cell therapy technology is also important. Overall, future research directions will focus more on answering cellular diversity and complexity from a cellular and molecular perspective. At the same time, researchers should be good at using innovative techniques and ideas, defining research problems and classification methods clearly, and making scientific research more comprehensive and effective.

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