ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

Specific Mechanism and Application of Exosomes for Promoting Skin Tissue Repair after Injury

Jian Wang [1,2,*], Naishuo Zhu [1,2]

[1]*Anling (Shanghai) Biotechnology Co., Ltd, Shanghai, 201500, China*
[2]*Oriental Beauty Valley Institute of Regenerative Medicine, Shanghai, 201500, China*
**Corresponding author: wj@anextcell.com*

Abstract: *Skin has important physiological functions, such as protecting the body, sweating, feeling body temperature regulation, etc. Skin is very important for the health of the body. It can not only maintain the stability of the internal environment, but also directly or indirectly participate in various functional activities of the body. Because the skin is in direct contact with the outside world, it is vulnerable to external pressure or diseases and other factors, resulting in damage to epidermis, mucosa or tissue. In order to accelerate the healing of skin wounds, mesenchymal stem cells can be selected to repair skin injuries. Using the paracrine of mesenchymal stem cells, exosomes, the main component of mesenchymal stem cells, can regulate the formation of new blood vessels and promote cell proliferation, thus playing a role in repairing skin damage. The specific mechanism and application of exosomes in promoting skin repair and healing are still improving, and exosomes play a key role in skin tissue repair.*

Keywords: *skin tissue; Repair after injury; Exocrine body; Specific mechanism; Application*

1. Introduction

Skin is the largest organ of the body, accounting for about 70% of the body's surface area. As the outermost layer of the body structure, skin is in direct contact with the outside world, so it is vulnerable to skin damage and so on. Skin is very important to our health and participates in important physiological functions such as immune response. Common skin injuries include trauma, scald, burn, etc. These injuries will lead to the decrease of physiological functions of related tissues or organs of the body, bring great physical and mental torture to patients, and also cause huge economic burden to us. The process of skin tissue repair after injury will also be affected by many factors, and any link needs to be handled carefully to prevent secondary injury. These problems make the repair of skin tissue damage an urgent problem for scientific research and clinical workers. The exosomes are illustrated in Fig.1 below.

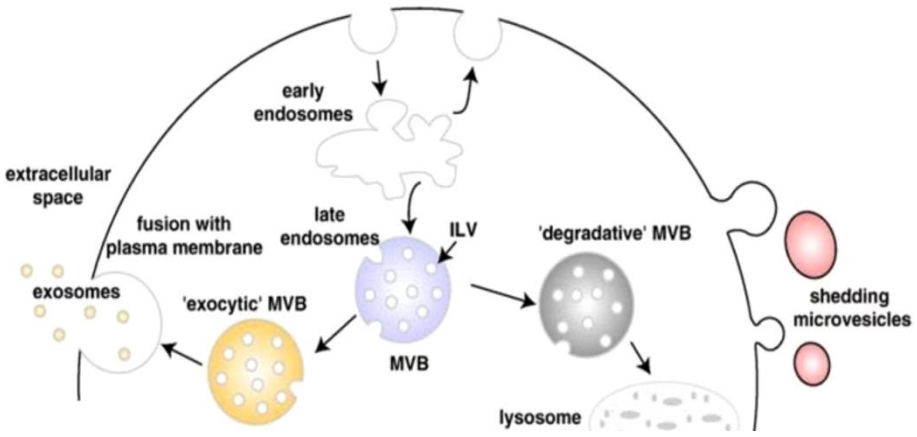

Fig.1: Exosome.

Exosomes refer to disk vesicles with a diameter of 40-100nm, or small membrane vesicles with a diameter of 30-150nm containing complex RNA and protein. Exosomes were first found in sheep reticulocytes, and later it was found that exosomes can be secreted in various cells under normal and pathological conditions. Exosomes mainly come from polycapsules formed by intracellular lysosomal particles invagination, which are released into extracellular matrix after fusion with cell membrane.

ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

Exosomes naturally exist in body fluids, including blood, saliva, urine, cerebrospinal fluid and milk. Exosomes are regarded as specific secretory vesicles, which participate in intercellular communication, and their research interests are increasing, whether to study their functions or to understand how to use them in the development of minimally invasive diagnosis.

Ultracentrifugation is the most commonly used method to extract exosomes. The exosomes obtained by this method are abundant, but the purity is insufficient.

When the skin tissue is damaged, we can repair the damage by supplementing collagen, but we need to overcome the related problems such as introducing high dose collagen and epidermal growth factor into the wound skin and maintaining high efficiency.

In order to promote the healing of skin wounds, mesenchymal stem cells can be selected to repair skin injuries. This is because mesenchymal stem cells can not only directly differentiate into permanent skin cells, but also secrete exosomes, the main component, by virtue of its paracrine function, and its therapeutic methods for promoting tissue regeneration have been widely studied at present. The research on exosomes promoting skin wound healing is still improving, which lays the foundation for realizing cell-free therapy.

2. Exosomes repairing skin tissue injury

Exosomes are lipid bilayer vesicles secreted by various tissues and cells, which contain bioactive components such as protein, lipid, mRNA, etc., and have the functions of mediating substance transfer and information exchange between cells, thus regulating the biological functions of cells. Mesenchymal stem cell exosomes from different sources can promote wound healing and inhibit scar formation by regulating inflammatory reaction, cell proliferation and migration, angiogenesis, collagen deposition and other stages in the process of skin wound healing, which has a good application prospect in skin injury repair.[1]

The repair and healing of skin wound is composed of many dynamic and complex stages of tissue recovery, which generally requires the joint participation of immune cells, hematopoietic cells and skin resident cells. The repair and healing of skin wounds includes four stages: hemostasis stage, inflammation stage, proliferation stage and remodeling stage[2]. The biological processes of these four stages are closely coordinated to ensure that the skin can normally exercise its barrier function and that exosomes can play an important role in all stages of skin regeneration.

The first stage in the healing process of skin injury is hemostasis, which is the main physiological mechanism to restore skin barrier function through vasoconstriction and platelet aggregation in blood clots. Mesenchymal stem cell exosomes need further research and analysis to prove their specific functions, which may have potential functions in the hemostasis stage of skin injury repair and healing. The two stages in the healing process of skin injury are inflammation stage, which is the beginning of wound healing and tissue regeneration. At this stage, immune cells can proliferate and inflammatory cytokines and chemokines can be secreted. Mesenchymal stem cell exosomes can promote the proliferation and differentiation of B lymphocytes and inhibit the proliferation of T lymphocytes, thus exerting immunosuppression, reducing the damage of immune response to skin and promoting wound healing. The proliferation stage is the key step in the process of normal skin injury repair and healing. Exosomes of mesenchymal stem cells can activate the angiogenesis activity of endothelial cells and play a positive role in cell formation, thus accelerating the healing of skin wounds. The last stage in the process of skin injury repair and healing is the remodeling stage, in which cells and blood vessels are gradually reduced and granulation tissue is gradually fibrosed.[3]

The whole repair process needs a series of processes such as cell arrangement, integration, differentiation, migration, proliferation and apoptosis to restore the regeneration of skin structure. One of the important steps is the formation of new blood vessels, which will directly affect the repair effect.

3. Mechanism of exosomes repairing skin injury

After skin injury, fibroblasts began to proliferate and produce extracellular matrix (including fibronectin, type I and type III collagen, etc.). Epithelial cells began to proliferate and migrate to the edge of the injured area, accelerating wound closure and reducing skin infection. Therefore, cell proliferation and skin re-epithelization are very important for skin regeneration.[4]

ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

3.1. Exosomes of mesenchymal stem cells promote the proliferation of fibroblasts

Fibroblast is the main cell component of dermis, which can produce collagen and other extracellular matrix components. Fibroblasts hardly proliferate in vivo, and their function damage and changes of extracellular matrix are closely related to exogenous skin aging. Exosomes mainly gather around the nucleus after entering fibroblasts. MSC-exo can activate MAPK signaling pathway, and promote fibroblast proliferation and collagen synthesis by up-regulating the gene expression of N-cadherin, cyclin-1, PCNA, collagen type I and collagen type III.

3.2. Exosomes of mesenchymal stem cells promote angiogenesis

The promote angiogenesis are illustrated in Fig.2 below.

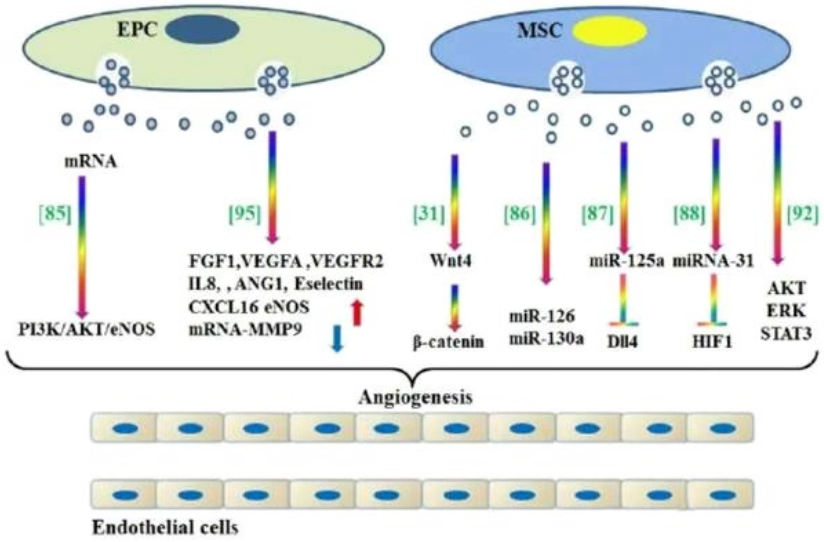

Fig.2: Promote angiogenesis.

Vascular regeneration is one of the main mechanisms by which exosomes promote the repair of skin injury. The exosomes of mesenchymal stem cells are rich in a variety of proteins and RNA (including mRNA and miRNA) related to angiogenesis, and MSC-exo can induce the expression of many nutritional factors. Microcapsules derived from endothelial progenitor cells promote angiogenesis through the horizontal transfer of mRNA related to PI3K/AKT and eNOS signaling pathways.

3.3. Exosomes of mesenchymal stem cells inhibit scar formation

The early stage of wound healing is illustrated in Fig.3 below.

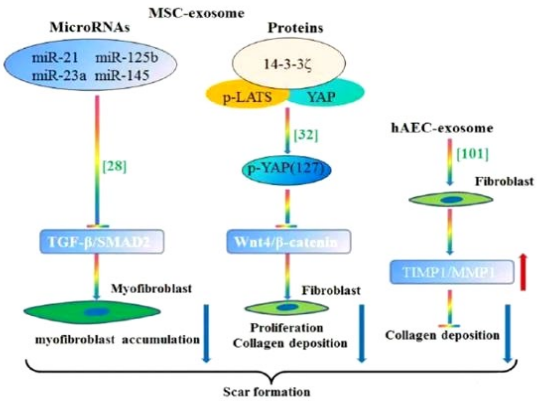

Fig.3: Early stage of wound healing.

Severe trauma and extensive burns usually lead to scar formation. Scar formation not only affects

ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

beauty but also hinders skin function. Studies have shown that exocrine can inhibit scar formation. UCMSC-exo can promote the production of type I and type III collagen in the early stage of wound healing and accelerate wound healing. However, in the later stage, it can inhibit the expression of collagen and reduce the formation of scars.

3.4. Immunoregulatory mechanism of exosomes of mesenchymal stem cells on damaged skin

Inflammation is an important step in skin regeneration. Inflammation is the body's self-defense response to harmful stimuli, thus restoring the body's steady state. After skin injury, neutrophils are initially recruited to the injured site. Subsequently, neutrophils eliminate foreign particles, pathogens or damaged tissues and cells through phagocytosis. After skin injury, macrophages are attracted to the wound site and continue to play a phagocytic role. Mesenchymal stem cell exosomes can promote the transformation of recipient macrophages to anti-inflammatory M2 phenotype. B cells and T cells in wound tissue play a key role in wound healing. Activated Treg cells can promote the accumulation of inflammatory M1 phenotype macrophages by reducing the production of IFN-γ, thus promoting wound healing. MSC-exo can promote the activation, differentiation and proliferation of B cells and inhibit the proliferation of T cells. MSC-exo can transform activated T cells into Treg cells, thus playing an immunosuppressive role.

4. Culture of exosomes derived from mesenchymal stem cells

Mesenchymal stem cells belong to pluripotent stem cells, and there are many kinds of mesenchymal stem cells. Nowadays, mesenchymal stem cells can be isolated and extracted from bone marrow, fat, amniotic fluid, umbilical cord blood and other tissues. [5] Mesenchymal stem cells are pluripotent adult stem cells with self-renewal and multi-directional differentiation potential, and are widely used as cell sources in medical research. Mesenchymal stem cells have great potential in the field of skin tissue repair and healing because of their anti-inflammatory, anti-apoptosis, promoting angiogenesis and regulating cell proliferation, differentiation and migration. Mesenchymal stem cells have been paid close attention to by medical researchers because of their self-renewal and multi-directional differentiation potential, immune regulation and secretion ability, and can be used as good materials for skin tissue repair and healing.

It is worth noting that there are still many limitations in the application of mesenchymal stem cells today, such as significantly affecting the activity and curative effect of cells in many aspects. After the passage of mesenchymal stem cells, the proliferation and differentiation potential will decrease, and the survival rate of transplanted cells will be low, the cost will be high and the repeatability will be low. There may also be potential risks, such as tumorigenicity and immune rejection.[6]

Therefore, medical researchers need to actively look for alternative treatments. Although mesenchymal stem cells disappear quickly in our body in a short time after administration, the therapeutic effect of mesenchymal stem cells can last for a long time. The culture solution of mesenchymal stem cells has a considerable biological function with mesenchymal stem cells, which can play a vital role in promoting the repair and healing of skin tissue injury. The effect of mesenchymal stem cells is achieved through the paracrine mechanism of mesenchymal stem cells, so there are exosomes treatment methods based on mesenchymal stem cells.

The exosome culture derived from mesenchymal stem cells includes the following steps:

(1) construction of expression vectors of collagen gene or various growth factors related to skin injury repair; Obtain or construct exosome cytoplasmic transport auxiliary plasmid, exosome secretion promoting plasmid and target gene mRNA packaging plasmid.

(2) Co-transfecting mesenchymal stem cells with mixed plasmids consisting of target gene expression vectors, cytoplasmic exosomes transport auxiliary plasmids, exosomes secretion promoting plasmids and target gene mRNA packaging plasmids and culturing.

(3) promoting the separation of engineered exosomes for skin tissue repair after injury: collecting the culture solution of the transfected mesenchymal stem cells, and filtering to obtain exosomes in the culture solution.

Collagen mRNA or growth factor mRNA in exosomes extracted and separated will be delivered to skin fibroblasts and expressed as protein in them, which will be used for the repair and healing of skin tissue damage. The extracted exosomes can be added to skin care products and medical products as

ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

ingredients of cosmetics.[7]

5. Repair methods of exosomes

At present, there are two main ways to promote the repair and healing of skin tissue injury by using exosomes derived from mesenchymal stem cells, namely local injection and intravenous injection. Local injection of exosomes derived from mesenchymal stem cells does not directly distribute exosomes on the wound surface of skin tissue injury, but evenly injects exosomes around the wound surface of skin tissue injury. It is difficult to maintain a high concentration of exosomes derived from mesenchymal stem cells by intravenous injection, so it is necessary to use drugs repeatedly, which will waste exosomes to some extent. The reason why we need to use drugs repeatedly is that intravenous injection can not ensure that all exosomes participate in promoting the repair and healing of skin tissue damage, and exosomes will disappear quickly in our body in a short time, which will bring some difficulties to the repair and healing of skin tissue damage, and medical researchers need to carry out further research and improvement.[10]

At present, natural scaffolds and synthetic scaffolds are commonly used as biological scaffold materials to promote the repair and healing of skin tissue damage. Hydrogel scaffold is the most widely used scaffold for repairing and healing skin tissue injury, because hydrogel scaffold can ensure the stable concentration of exosomes derived from mesenchymal stem cells after application in damaged skin tissue, which can delay the release of exosomes and enhance the ability of repairing and healing skin tissue injury.

6. Conclusion

Skin is an important organ of our body, which has important physiological functions such as protecting the body, sweating, immunity, endocrine and so on. It can participate in a variety of functional activities and is very important for our health. Therefore, when skin tissue is damaged by external factors, it is necessary to do a good job in promoting the repair and healing of skin tissue injury, so as to avoid secondary injury caused by improper treatment of skin wound surface. In the case of skin tissue injury such as trauma, scald and burn, the physiological function of related tissues or organs of the body may be reduced, which should attract the attention of medical researchers and require them to develop treatment methods that can solve and promote the repair and healing of skin tissue injury.

Studies in recent years can prove that exosomes secreted by mesenchymal stem cells play a vital role in promoting the repair and healing of skin tissue injury. Mesenchymal stem cells can differentiate in many directions, regulate the body's immunity, and secrete a variety of bioactive substances. For example, mesenchymal stem cells can control angiogenesis by paracrine exosomes, which plays a key role in promoting the repair and healing of skin tissue damage, because exosomes can promote cell proliferation, and then repair and heal skin tissue damage.[8]

Mesenchymal stem cells can provide new ideas for regenerative medicine by paracrine exosomes, which can play an important role in the repair of skin tissue injury, reduce immune rejection and make the treatment more effective and secure. Many medical researchers have proved that exosomes derived from mesenchymal stem cells can repair skin tissue injury, and exosomes can be used as medical products, which provides a new idea for stem cell therapy of skin injury and has broad application prospects.[11]

Clinically, exosomes of mesenchymal stem cells are mainly used to treat burns, scalds and skin ulcers and regenerate healthy skin. Used in skin care, it is mainly used to repair the injured, aging and poisoned skin, comprehensively regulate the skin, improve the skin quality and restore the skin to a young and healthy state. In the future, exosomes derived from stem cells can be combined with organic biomaterials to enhance the healing process. Or through the co-culture of stem cells and other types of cells, and using different chemicals or cell culture media for gene modification or pretreatment to improve the potential of stem cell exosomes to promote healing. In addition, by clarifying the regulatory mechanism of stem cell exosomes in tissue regeneration, customized exosomes with specific targets can be prepared for efficient and precise medical treatment.[9]

Medical researchers also need to overcome the limitations of the application of mesenchymal stem cells through paracrine exosomes, such as acceptable operating standards in cell culture conditions and procedures, exosomes separation and storage, drug efficacy, etc. In addition, the optimal route of administration of exosomes also needs further research and evaluation. At present, the mechanism and application of exosomes derived from mesenchymal stem cells in the repair and healing of skin tissue

ISSN 2706-6819 Vol.5, Issue 8: 34-39, DOI: 10.25236/IJFM.2023.050804

injury wounds are not perfect. These problems deserve our attention and solution, and provide a basis for better clinical application.

References

[1] Liu Ziwei, Shi Quan, Wang Situo, Xu Juan. Research progress of exosomes derived from mesenchymal stem cells in skin injury repair [J]. Journal of PLA Medical College, 2022,43 (8): 896-900.
[2] Cheng Yansiwei, Song Guanbin. Mesenchymal stem cells and skin repair [J]. Journal of Biomedical Engineering, 2021,(38): 387-392.
[3] Li Man, Zhu Wei, Zhang Haiping. Research progress of exosomes of mesenchymal stem cells from different sources in skin injury repair [J]. Chinese Journal of Injury and Repair (Electronic Edition), 2021, Vol.16 (6): 515-519.
[4] Zhang Guowei, Wang Long, Deng Zhifeng. Research progress on the mechanism of repairing tissue injury by exosomes derived from MSCs [J]. China Journal of Repair and Reconstruction Surgery, 2016,30(04):499-503.
[5] Sun Xuan, Mao Nianyu, Liu Mingzhu, Dong Chuanming. Research progress of exosomes derived from mesenchymal stem cells in skin injury repair [J]. Systematic Medicine, 2019,4(16): 196-198.
[6] Han Rui, lin li, Wang Runqing, Hou Zongliu.Role and application prospect of exosomes derived from mesenchymal stem cells in regulating immune function[J]. China Tissue Engineering Research, 2019,23(17): 2762-2769.
[7] Li Shuangshuang and Du Chunyang.Characteristics and functions of exosomes from different cells[J]. International Journal of Pharmaceutical Research, 2019,46(6): 411-417.
[8] Shen Zhiming, Yuan Lei, Lu Yi, Shi Hongcan.Research progress on the role of exosomes of mesenchymal stem cells in wound repair and regeneration[J]. Chinese Journal of Trauma, 2022, 38(2):182-186.
[9] Guo Jia, Ding Qionghua, Liu Ze, Lv Siyi, Zhou Quancheng, Gao Yuhua, Bai Chunyu.Biological characteristics and immune regulation of exosomes derived from mesenchymal stem cells[J]. China Tissue Engineering Research, 2022,26(7):1141-1150.
[10] Poltavtseva RA,Poltavtsev AV,Lutsenko GV,et al. Myths reality and future of mesenchymal stem cell therapy[J].Cell Tissue Res,2019,375(3):563-574.
[11]Medhat D，Rodríguez CI，Infante A.Immunomodulatory effects of MSCs in bone healing[J].Int J Mol Sci,2019,20(21):5467.