



# The research advancement of fibroblast on diabetic non-healing skin wound

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## Abstract

The delayed wound healing especially non-healing skin wound is one of the problem in clinical practice and hot research in basic medicine. The common therapies' effects were not confirm. The induced Pluripotent Stem Cell (iPSC) technology is one of de novo approaches in regeneration medicine these years. The original iPSC was reprogrammed from rat tail fibroblast. So the concept of direct cellular reprogramming was reported versus the iPSC-based reprogramming. Thus we review the fibroblast potential "stem" characteristics and its promotion to the wound healing.

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## Introduction

The delayed wound healing especially non-healing skin wound is one of the problem in clinical practice and hot research in basic medicine. The common therapies included adequate surgical debridement, effective antibiotic therapy, correction of metabolic abnormalities, proper moist dressings and so on. But these therapy effects were not stable.

The induced Pluripotent Stem Cell (iPSC) technology is one of *de novo* approaches in regeneration medicine these years. The original iPSC was reprogrammed from rat tail fibroblast by the Japanese scientists in 2006 [1]. So the fibroblasts were the most commonly used primary somatic cell for the generation of iPSC. From this view point, the fibroblasts attracted wide attention in the regeneration medicine once more. The fibroblasts could be differentiated directly into many types of cell including neuron, chondrocytes, myoblast, cardiac cell and pancreatic beta cells etc. So the concept of direct cellular reprogramming

was reported versus the iPSC-based reprogramming.

When a new method was applied in basic or clinical medicine disciplinary, the surgeons in traumatology often think if it can be used in themselves' studies. Thus we review the fibroblast potential "stem" characteristics and its promotion to the wound healing.

## The features and mechanism of diabetic chronic wound

Wound healing is a complex biological process to restore the integrity of skin after injury. The Holy Grail of wound healing is the high function with mini scar. Normal cutaneous wound repair is characterized by four overlapping phases of healing termed the coagulation or hemostasis, inflammation, proliferation or re-epithelialization, and remodeling phases. Hopeful wound healing should include the re-establishment of both skin anatomic structure and physiological function.

As to the non healing wound, the typical diabetic skin wound



had its special characteristics: (1) The original structure of diabetic skin is in pathological state. The gross skin specimen of diabetic rat was thinner than that of normal rat in our observation. The skin of diabetic mouse was also thinner than that of normal one under microscope. In addition, capillary density, collagen fibers and collagen content in the diabetes were significantly reduced compared with the normal ones [2,3]. So the diabetic skin is abnormal in fact even before wound. (2) The diabetic subjects anti-infection were poor and infection adversely affected blood glucose control. This repetitive cycle leads to uncontrolled hyperglycemia, further affecting the host's response to infection. The inflammatory mediators, cytokines, and chemokines [4] can be changed in the hyperglycemia environment, too. All these factors can affect the diabetic wound proliferation phase. (3) The impaired neuron and vascular tissue of diabetes often caused malnutrition of the local wound skin. Especially high glucose related neuropathology often induced nervous sensory defect. This can lead to second trauma on lower limbs as a result of sensory impairment. It is the usually reason of diabetic foot ulcer. Diabetes also causes structural and functional variations within the artery and capillary systems, notably with thickening of the basement membrane. This thickened membrane impairs leukocytes migration and hampers the normal hyperemic or vasodilatory response to injury and following anti-inflammatory responses, thus simultaneously increasing the susceptibility to injury while also blunting the typical manifestations of such an injury. (4) The re-epidermal function of diabetic skin was defect. The high level of glucose could affect keratinocytes in epidermis and fibroblasts in dermis directly. In addition, the stem cells including epidermal stem cell, mesenchymal stem cell, adipose-derived stem cell, endothelial progenitor cells and any other stem cells also affected in both structure and biological functions followed by abnormal proliferation phase and remodeling process during wound healing. (5) Furthermore, fasting hyperglycemia and the presence of an open wound created a catabolic state. Negative nitrogen balance lead to metabolic dysfunction could impair the synthesis of proteins, fibroblasts and collagen. The further systemic deficiencies were propagated and induced to nutritional compromise. All these reasons lead to the difficult healing of diabetic skin wound.

#### The role of fibroblast in promotion the wound healing

We observed previously that the fibroblasts could become into myofibroblast by the silver nanoparticles (AgNPs) in wound mouse model. The results showed that AgNPs could increase the rate of wound closure. On one hand, this was achieved through the promotion of proliferation and migration of keratinocytes. On the other hand, AgNPs can drive the differentiation of fibroblasts into myofibroblasts, thereby promoting wound contraction [5]. Furthermore, we observed the AgNPs could promote the fibroblast differentiated into osteogenic in vitro in our preliminary experiment (Figure 1).

The other research group also published the similar results. As we known, the epidermal-dermal interactions were the key modulators for keratinocyte proliferation and differentiation. And the re-epidermal stage was the first step in wound healing. The research group found that fibroblast differentiated into myofibroblast at early and later stages of wound healing was regulated by the balance of endogenous TGF-beta and IL-1 activity [6]. The future results demonstrated that the hypoxia circumstance could affect the wound healing in vitro study. That maybe the mechanism of the chronic wound especially the non healing wound [7].

Sometimes the skin ulcer were deep to the subcutaneous and muscle layer. So if the fibroblast around the deep wound have the multi potential differentiation to both epidermal and dermal even subcutaneous tissue. It would be the ideal "stem" cell for wound healing.

#### The advantage of fibroblast v.s. the other stem cells

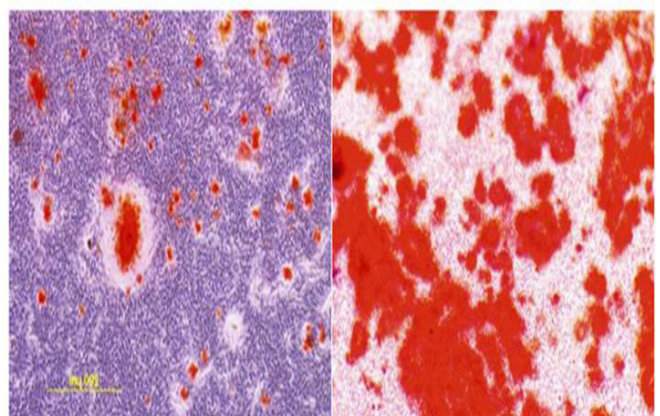
The fibroblasts are original from mesenchymal cell of mesoderm during the development. It is the main cell type of loose connective tissue particularly in the dermal tissue. The fibroblasts are easy to be acquired and without immune as well as ethics problems. So the fibroblasts play the key role in the non healing wound.

The others researchers reported that mesenchymal stem cells could enhance diabetic rat wound healing through recruitment of tissue regeneration [8]. So we can union the fibroblasts, the others stem cells and cytokines, as well as combine the prior technique, for example the 3D bio-printing [9,10] or 3D tissue culture technique [11] to repair the non healing wound in dimensions.

#### Outlook and research in the future

The technology of gene transfer to fibroblasts has been reviewed already. The gene therapy and tissue engineering for treatment chronic wound and systemic disorders such as diabetes are also discussed. But the gene therapy focus on non healing wound is not researched deeply enough. This is the direction of researching non healing wound furthermore. Due to the superficial location, the skin is so easy to access and fibroblasts can be expanded in culture acutely. Compare with the other stem cells including embryonic stem cell, hematopoietic stem cell, mesenchymal stem cell and induced pluripotent stem cell, fibroblasts have limited tumor formation and less immune rejection response, especially no ethics arguments. So we hope that future studies can lead to a better understanding of the nature and growth regulation of fibroblasts. This exciting laboratory research on nonhealing wound care will be successfully translated to the enhancing management in clinical practice. And we look forward to the translation medicine can take the fibroblast from bench to bed to take care of the chronic wound patients as early as possible.

Figure



**Figure 1:** Our preliminary experiment results showed the AgNPs could promote the mouse fibroblast differentiated into osteogenic in vitro. The red particles stand for the osteogenic node. Left: Day 10 of Fibroblast culture. Right: Day 17 of Fibroblast culture. ARS, 100×

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