

# Therapeutic potential of umbilical cord mesenchymal stem cells with Wnt/ $\beta$ -catenin signaling pathway pre-activated for the treatment of diabetic wounds

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**Abstract.** – The pathogenesis of diabetes mellitus wounds is complicate, and there lacks effective treatment strategies. Mesenchymal stem cells can promote wound healing. Compared with bone marrow mesenchymal stem cells, umbilical cord mesenchymal stem cells have obvious advantages in biological property. Wnts are potent regulatory molecules for stem cell turnover and skin regeneration, while Wnt signaling is not well activated in diabetic wounds. Umbilical cord mesenchymal stem cells with Wnt/ $\beta$ -catenin signaling pathway pre-activated have some potential in the treatment of diabetic wounds. In this paper, we review the research status as well as problems in this field.

*Key Words:*

Mesenchymal stem cell, Diabetes mellitus, Wnt signaling pathway, Wound healing, Application.

payed to the treatment of wounds caused by chronic diseases<sup>1</sup>. Studies in some developed countries and regions in Europe and America showed that the outcome of chronic skin ulcers caused by diabetes is poor and the amputation rate reaches 27%<sup>2</sup>. Therefore, there is a trend to develop wound therapeutics into an independent discipline.

The skin of diabetic patient can be easily injured, and the wound is often recurrent and hardly healed, which may lead to stubborn refractory ulcer. The diabetic wound is difficult to heal, high susceptible to infections and with high amputation rate, which not only causes great pain but also increases the burden of the family and society. Therefore, it is an urgent issue in clinical to find the way to promote diabetic wound healing.

## Introduction

With the social and economic development as well as the improvement of people's living standards in developing countries, the main causes of diseases have also been significantly changed, and the therapeutic problems of acute and chronic wounds become more prominent. The recent epidemiological study in 2009 showed that the main causes of chronic wounds in Chinese people have been changed from trauma and burns to chronic diseases (36%) such as diabetes mellitus. Due to the complex pathogenic factors, and difficulties in treatment, great attention has been

## Research Status and Problems in the Field

Wounds caused by diabetes and other chronic diseases are often called refractory wounds. The pathogenetic mechanism is complex. Generally, the wound can hardly be healed via normal healing process due to a variety of internal or external factors, and which, thus, lead to refractory recurrence<sup>3</sup>. One possible mechanism may be related to many factors, for instance, abnormal inflammation, abnormal expression of matrix metalloproteinases, proliferation deficiency and excessive apoptosis of fibroblasts in granulation tissue, proliferation disorder of epidermal cells, low

expression level of vascular endothelial growth factor, etc. A recent study<sup>4</sup> revealed that Wnt/ $\beta$ -catenin signaling pathway plays a role in diabetic wound healing in rats. Currently, the treatment of diabetic wounds is mainly based on the control of diabetes and mostly concentrated in wound protection and infection prevention, and in addition, external cell growth factors are applied to create healing conditions for the wound to achieve natural healing. However, the wounds can hardly be healed via conventional symptomatic treatment and application of cell growth factors, including angiogenic factors<sup>5,6</sup>. With the deepening understanding of wound healing, the ideas in wound healing have been changed from passive waiting for to active regulation and from surgical procedures to regeneration and perfect repair, where stem cells are considered to be the foundation of tissue regeneration<sup>7</sup>. Nowadays, studies have preliminarily revealed the therapeutic potential of adult or fetal stem or progenitor cells in the treatment of skin ulcers<sup>8</sup>. Mesenchymal stem cells (MSCs) can promote the repair and regeneration of skin wounds through not only the secretion of growth factors but also differentiation into vascular and non-vascular cell components<sup>9</sup>. So far, in the field of MSCs for the treatment of diabetic wounds, apart from successes for wound healing in experiment, little has been reported about the clinical application of

autologous stem cell, and the clinical efficacy is not stable and the transplantation way also needs to be further developed. In addition, a study revealed that the micro-environment in diabetic wound is not conducive to the survival, proliferation and differentiation of stem cells, and the survival time of exogenous bone marrow mesenchymal stem cells (BMMSCs) in diabetic wound is relatively short<sup>10</sup>, which may be related to the Wnt/ $\beta$ -catenin signaling pathway dysfunction in diabetic wound healing in rats<sup>4</sup>. Wnts are potent regulatory proteins of stem cells turnover and skin homeostasis and regeneration<sup>11</sup>, and it can promote stem cells proliferation and differentiation. Wnt signaling pathway is divided into the canonical and other noncanonical signaling pathways, and the canonical signaling pathway is an important signal transduction pathway to control animal embryonic development and tissue and organ morphogenesis<sup>12</sup>. Within the currently known family members, Wnt-1, Wnt-3a and Wnt-8 are able to activate the canonical pathway.  $\beta$ -catenin is a key factor in Wnt signaling pathway, and cyclin D (Cyclin-D1) and the proto-oncogene c-myc are the important target genes of Wnt/ $\beta$ -catenin signaling pathway. The canonical Wnt signaling pathway is shown in Figure 1.

MSCs are a class of tissue stem cells with multiple differentiation potential, which were first discovered in the bone marrow. In specific

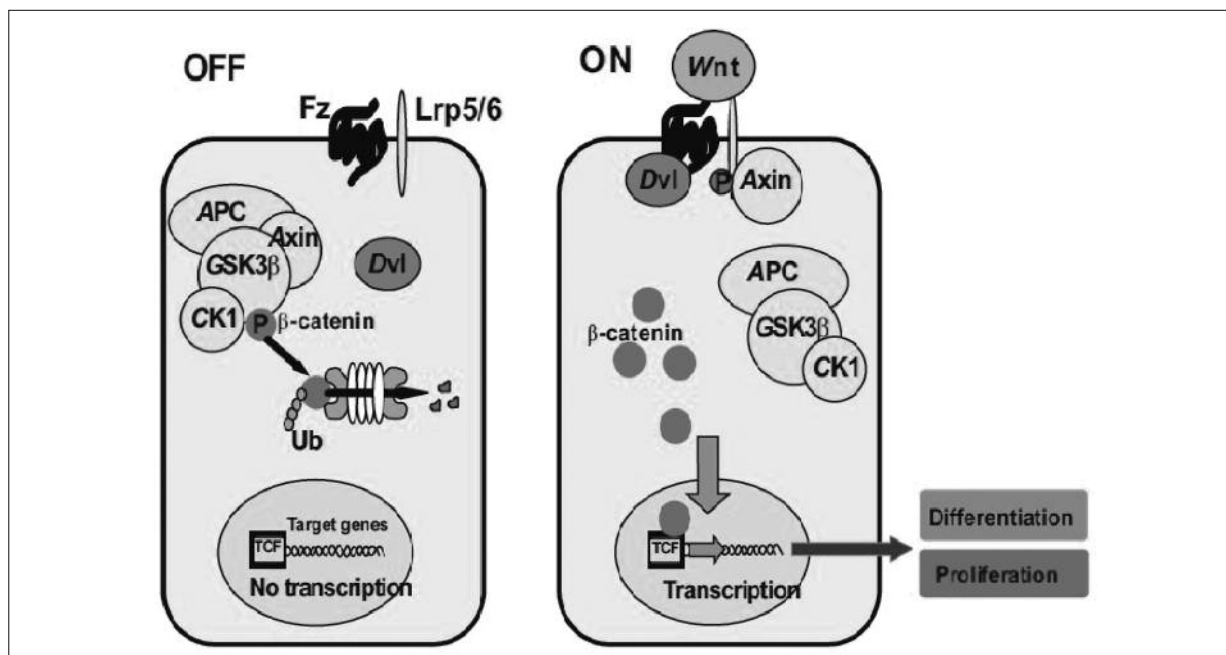


Figure 1. The schematic diagram of blocking and activation of Wnt/ $\beta$ -catenin signaling pathway. Reproduced from Chen et al<sup>13</sup>.

induction conditions *in vitro*, MSCs can differentiate into many kinds of cells such as bone, cartilage, fat, tendon, muscle and nerve cells. Present study suggests that BMMSCs can secrete several cytokines, invade into the wound area, differentiate into skin appendages such as epidermal cells, endothelial cells and sweat glands and, thus, promote wound healing<sup>14-16</sup>, while the exact molecular mechanism remains unclear. The Wnt/ $\beta$ -catenin signaling pathway is closely related to the proliferation and differentiation of MSCs<sup>17,18</sup>. Previous study has confirmed that CD133+ progenitor cells from human fetal aorta can promote healing of diabetic ischemia wounds through activation of Wnt signaling pathway<sup>19</sup>. It is speculated that transplantation of MSCs with activated Wnt signaling pathway in diabetic wounds can promote wound healing.

Umbilical cord blood and umbilical cord tissue are major sources of MSCs, while richer content of MSCs is found in the umbilical cord tissue<sup>20</sup>. Compared with BMMSCs, umbilical cord MSCs (UCMSCs) have many advantages, i.e., wide variety of sources, low antigenicity, no bioethics issues, and in addition, UCMSCs are more similar to embryonic cells and are better than adult stem cells in promoting wound healing<sup>21</sup>. Umbilical cord tissue-derived MSCs are of weak immunogenicity, and they can also suppress allogeneic immune response and reduce the local inflammatory response by secreting anti-inflammatory cytokines<sup>22</sup>. Nowadays, the techniques for umbilical cord tissue-derived MSCs isolation & culture as well as differentiation have been well developed<sup>23,24</sup>, and the modified enzyme digestion method has been established<sup>25</sup>. Therefore, UCMSCs are expected to be the new source of seed cells for cell therapy and tissue engineering. It has been confirmed that UCMSCs are applicable in xenograft<sup>26,27</sup>. UCMSCs show good prospects in clinical application due to the fact that, in clinical xenotransplantation, no apparent transplant reaction occurred without a match<sup>28,29</sup>.

It is not safe for systemic use of MSCs by intravenous infusion. However, local direct application of MSCs cells cannot make the cells settled in local wound, and MSCs can rarely migrate to the wound when injected subcutaneously or intramuscularly around the wound, which is not conducive to cell survival and functioning. Suitable carrier materials are helpful in maintaining the cell activity and function and, thus, they can improve the therapeutic efficacy of

MSCs<sup>30,31</sup>. It has been proved that BMMSCs combined with collagen sponge can promote chronic ulcer healing<sup>32</sup>. Acellular dermal matrix can be used as the scaffold material for epidermal cell culture to construct the skin substitutes, while during the decellularization process, the cell anchors on the surface of scaffold are damaged and the attachment of the cells on the dermal matrix is thus affected. Laser micropore acellular dermal matrix has been proved to be a better kind of three-dimensional scaffolds in experiment, which can contribute to cell growth and vascularization<sup>33</sup>. Collagen and chitosan have good biocompatibility and support cell adhesion, thus in theory, collagen-chitosan modified micropore acellular dermal matrix is the ideal scaffold material, which can be used as scaffolds of tissue engineering skin containing MSCs.

In summary, the umbilical cord tissue-derived MSCs have many advantages, i.e., wide variety of sources, high purity, no ethical problems, low immunogenicity, multiple differentiation potential, ability to secrete growth factors and differentiate into skin cells for wound repair, immune regulation function and anti-inflammatory effects. The collagen-chitosan-laser micropore acellular dermal matrix is the ideal scaffold for tissue-engineered skin. Wnt signaling pathway is closely related to the proliferation and differentiation of MSCs as well as wound healing. Wnt3a is proved to be a key protein in Wnt protein family in activation of the Wnt/ $\beta$ -catenin signaling pathway, and it is typical representative in the canonical Wnt protein family. Exogenous Wnt3a can activate Wnt/ $\beta$ -catenin signaling pathway *in vitro*, and it plays an important regulatory role in the proliferation and differentiation of a variety of stem cells<sup>34</sup>. It is speculated that composite scaffolds containing UCMSCs with Wnt signaling pathway pre-activated can promote diabetic wound healing. Wnt signal regulation is helpful in the treatment of diabetic wounds with use of tissue-engineered skin containing stem cells, which can accelerate wound healing and improve the outcome.

### **Application and Prospect**

With the aged tendency of population and the change in life and diet, the incidences of chronic diseases such as diabetes also gradually increase. In the life of diabetes patients, they have a 25% chance of developing diabetic foot ulcers<sup>35</sup>. The chronic wounds caused by diabetes have brought to the society and family a huge economic bur-

den. However, the clinical treatment is very difficult, and it is difficult to achieve satisfactory outcome. Currently, there is still no ideal treatment protocol for chronic wounds caused by diabetes. In clinical, it is urgent to find less invasive, tolerable and effective therapeutic methods. The study about Wnt signal regulation in tissue engineering skin containing UCMSCs promoting diabetic wounds healing may yield new ideas and new strategies for the treatment of refractory chronic wounds such as diabetic wounds, which can be verified by clinical researches and is expected to increase the rate of wound healing, to reduce amputation rates, to shorten hospital stay and to lower hospital costs. Thereby, it is expected to improve patients' life quality, i.e., make patients capable of self-care and alleviate the patients' pain and the burdens on families and society.

### Conclusions

Tissue engineering skin containing UCMSCs with Wnt/ $\beta$ -catenin signaling pathway pre-activated may be widely applied in clinical and have significant economic and social benefits.

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### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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