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Clinical perspectives on mesenchymal stem cells promoting wound healing in diabetes mellitus patients by inducing autophagy

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Abstract. – BACKGROUND: The pathogenesis of wound healing in diabetes mellitus is complicated, and results in less effective healing. Mesenchymal stem cells (MSCs) have been thought to promote wound healing in diabetes. However, the underlying mechanisms are not well understood. Autophagy plays an important role in wound healing. It has been speculated that the mesenchymal stem cells derived from the umbilical cord can improve wound healing in diabetes mellitus by inducing autophagy. Hence, we reviewed the research progress in this field to identify new strategies of clinical treatment for wound healing in diabetes mellitus.

Key Words:
Mesenchymal stem cells, Diabetes mellitus, Autophagy, Wound healing, Application.

Introduction

The incidence of diabetes has been increasing with the development of social economy and improvement of people's living standards. Difficulty in wound healing is one common complication of diabetes mellitus, it is characterized by easy infection and high rates of amputation. It brings great pain to patients and increases economic burden on society and family. Therefore, diabetic wound healing is an urgent clinical problem. A refractory wound is defined as the wound caused by chronic diseases such as diabetes mellitus. Its pathogenesis is very complicated. The lack of proper wound healing is in part caused by ineffective and improper wound healing process in the intrinsic or environmental conditions[1]. Cellular apoptosis plays an important role in skin damage and healing in diabetic patients[2]. It has been reported that diabetic ulcers are related to unbalanced cellular apoptosis[3]. However, cellular apoptosis is not the only mechanism leading to cell death. Autophagy is known as type II programmed cell death, regulating cell death altogether with apoptosis. However, in some cases, the inhibition of cell apoptosis due to autophagy is a survival approach. Autophagy is considered as a key regulatory factor in disease recovery[4]. The effect and mechanism of autophagy in diabetic wound healing needs to be elucidated to provide a new strategy for clinical treatment in diabetes.

The pathogenesis of diabetic wound healing is characterized by less effective treatment. The main factors that cause the diabetic ulcer wound hard to heal are considered to be angiogenesis disorder and loss of function of microvessel[5-7], which are different in other chronic wounds, such as venous ulcer, pressure ulcer, denervated ulcer and radiation wound. Thus, to repair wound of diabetic ulcer, it is very important to restore the function and structure of microvessel[8]. The current research results have suggested that mesenchymal stem cells enhance wound healing through differentiation, angiogenesis and ameliorating impaired glucose metabolism in diabetic mice[9,10]. Therefore, restoration of diabetic wound healing by transplantation of mesenchymal stem cells is a potential clinical application. However, its underlying mechanism is unknown. Hence, uncovering the molecular mechanism of wound healing induced by mesenchymal stem cells is of great clinical value.

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Research Status and Existing Problems

Recently, effect of autophagy in wound healing has gained as much attention as necrosis and apoptosis[11,12]. Autophagy is a common intracellular degradation process in eukaryotes that has an important role in protecting eukaryotic cells and maintaining intracellular homoeostasis. Cell organelles and proteins are first enclosed within double-membrane vacuoles resulting in the formation of autophagosome. Autophagosomes subsequently fuse with lysosomes to become autolysosomes, resulting in the degradation of the content. The degraded products are then transported to the cytosol for recycling by the cell. Autophagy functions at a low level under physiological conditions to eradicate damaged cell organelles (like mitochondria) and macromolecules (like proteins) for maintaining normal physiological cell functions[13]. In some cases, nutrient depletion, growth factor deprivation, and ischemia-hypoxia can upregulate autophagy. Cells can degrade some components to release free amino acids and fatty acids for maintaining cellular ATP production and macromolecular synthesis. Due to the important role of autophagy in eradicating damaged cell organelles such as mitochondria, attenuation of autophagy activity can cause an accumulation of damaged organelles and molecules in the cell, thus resulting in cell death[14]. It has been demonstrated that autophagy plays an important role in diabetes mellitus and nephrosis. Autophagy inducer, rapamycin, can prevent the development of diabetes and kidney diseases in mouse models of type 1 and type 2 diabetes mellitus[15].

BECN1 gene is a mammalian ortholog of yeast autophagy-related gene 6 (Atg6). Beclin-1, encoded by BECN1 gene, is an important positive regulatory factor in mammalian autophagy. Beclin-1 regulates the autophagy activity by forming a complex with class III phosphatidylinositol 3-kinase (PI3K) and regulating the orientation of proteins in autophagosome. During the initiation of autophagosome formation, Beclin-1 binds to the phagocytized vacuole membranes surrounding the degraded products as further recruitment of other Atg proteins takes place. Beclin-1 plays an important role in autophagy through the interaction between Bcl-2 homology 3 (BH3) domain and Bcl-2 family proteins[16]. Under physiological conditions, Beclin-1 interacts with Bcl-XL and Bcl-2 through the BH3 domain. However, under hypoxic conditions, the active HIF-1α (hypoxia inducible factor 1α, HIF-1α) can trigger the dissociation of Bcl-2-Beclin1 complex by upregulating BNIP3, which releases Beclin-1 and results in activation of autophagy[17]. mTOR is a major regulatory axis for autophagy. mTOR can be activated to inhibit the autophagy pathway during nutrient sufficient conditions characterized by high content of amino acids and growth factors. However, nutrient deprivation and starvation induces inhibition of mTOR activity. Thus, the restriction of autophagy pathway is relieved. As per recent studies, Beclin-1 and mTOR have been demonstrated to represent two pivotal signaling pathways regulating in cellular autophagy, especially under hypoxic conditions[18]. The detailed mechanism of autophagy induced by hypoxia is depicted in Figure 1.

Studies in the field of autophagy and wound healing have revealed that Beclin-1 is overexpressed in burned skin to improve the level of autophagy signaling for wound healing[19]. Although cell apoptosis has been studied well in diabetic wound healing, the effect of autophagy on diabetic wound healing has not yet been reported. We hypothesized that reduction of autophagy in wounds leads to difficulty in treating diabetic wounds.

As of now, the mechanism by which MSCs promote diabetic wound healing is not very well understood. In a lot of previous studies, MSCs have been shown to differentiate into vascular and non-vascular components to promote wound healing. It was subsequently verified that wound healing is enhanced by secretion of HIF and its downstream growth factors such as VEGF[20]. So far, there are very few reports about MSCs promoting tissue repair and regeneration via autophagy. In recent years, transplantation of mesenchymal stem cells has been shown to promote liver regeneration damaged by CCl_4 by upregulating cell autophagy[21].

Tissue and organ repair involve multiple complicated processes including synergistic effect of inflammation and cell survival and/or cell death. Particularly, hypoxia is one common stress factor in the microenvironment of injured tissue. Hypoxia in damaged tissues is usually related to microvascular injury and leads to the formation of hypoxia inducible factor 1 (HIF-1). HIF-1 is a heterodimeric transcription factor consisting of two subunits, HIF-1α and HIF-1β. Its molecular function is achieved by the expression and transcriptional activity of HIF-1α subunit. HIF-1 participates in many pathophysiologies including

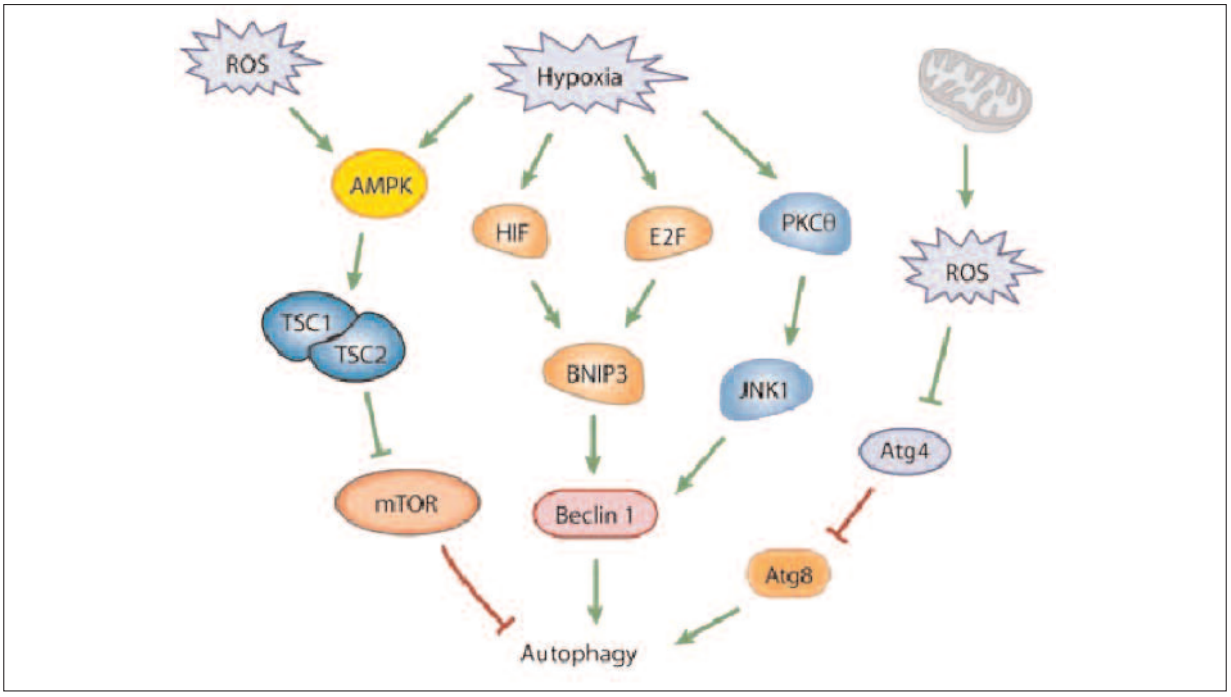

Figure 1. Hypoxia- and oxidative stress-induced autophagy is regulated by Beclin-1 and mTOR pathways under hypoxia and oxidative stress.

energy metabolism, vascularization, cell proliferation and migration, and cell apoptosis, thus, playing an important role in wound healing. Although hypoxia is one of the major factors regulating the level of HIF-1α, stability and function of HIF-1α are also affected by many other factors, including blood glucose concentration, growth factors, cytokines, reactive oxygen species, advanced glycation end products (AGES), and insulin. HIF-1 can regulate the expression of many genes directly or indirectly. It has been reported that hypoxia can induce autophagy in HIF-1 dependent manner to promote cell survival in normal and cancer cells[22]. HIF-1α/BNIP3/Beclin-1 pathway is an important signaling pathway for upregulating autophagy under hypoxia conditions[23]. Microvascular pathology often causes hypoxia in wounds during diabetic wound healing. In addition, high glucose concentration in the body can enhance oxidative stress. It has been demonstrated that hypoxia in tissues can increase the expression of HIF-1α and induce autophagy[24]. Thus, it indicates that MSCs promote diabetic wound healing via autophagy.

Applications and Prospects

MSCs transplantation can promote wound repair after skin injury in diabetic patients. The major proteins related to HIF-1α/BNIP3/Beclin-1 and PI3K/Akt/mTOR autophagy signaling pathways can be identified by determining the changes in expression levels during wound autophagy signaling, cell proliferation, and cell apoptosis. Unraveling the molecular mechanism by which MSCs induce autophagy signaling can lead to understanding the mechanism of diabetic wound healing. It is of great interest to demonstrate the role of autophagy in diabetic wound healing and explore whether MSCs promote wound healing via inducing autophagy in injured cells. Rapamycin is currently the most common used as autophagy inducer. However, rapamycin, an important regulatory protein in insulin signaling pathway, can influence multiple metabolic pathways[25]. In addition, the process of rapamycin inducing autophagy is slow and transient, and required for more indirect effect time. Also, it has been reported that rapamycin cannot induce autophagy in primary cultured neurons[26]. Due to the safety considerations and lack of any significant side effects of the application of MSCs in wound healing, MSCs may be an ideal autophagy inducer for promoting wound healing. This provides a new strategy for the difficult cases of wound healing, especially for diabetic wound healing. This strategy can improve the

rate of wound healing, reduce amputation rate, shorten hospital stay, and decrease the costs incurred at hospitals. Finally, it can improve the quality of life of diabetic patients, reduce the patients' pain, and decrease the burden on family and society. Thus, the research has a great potential for clinical application and for bringing about significant economic and social benefit.

Conclusions

Mesenchymal stem cells can promote diabetic wound healing by inducing autophagy. It will be a great breakthrough to improve autophagy activity to promote wound healing in diabetes mellitus patients. This provides a new strategy for diabetic wound healing.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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