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Review

Progress in stem cell therapy for the diabetic foot

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ABSTRACT

The diabetic foot is a common and severe complication of diabetes comprising a group of lesions including vasculopathy, neuropathy, tissue damage and infection. Vasculopathy due to ischemia is a major contributor to the pathogenesis, natural history and outcome of the diabetic foot. Despite conventional revascularization interventions including angioplasty, stenting, atherectomy and bypass grafts to vessels, a high incidence of amputation persists. The need to develop alternative therapeutic options is compelling; stem cell therapy aims to increase revascularization and alleviate limb ischemia or improve wound healing by stimulating new blood vessel formation, and brings new hope for the treatment of the diabetic foot.

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Contents

1. Introduction

The incidence of diabetes mellitus is increasing globally and diabetic foot disease represents one of the most common and severe complications, affecting 15% of those with diabetes. Based on the World Health Organization definition, the diabetic foot (DF) includes infection, ulceration, and/or destruction of deep tissue associated with various degrees of peripheral vascular disease, neurologic abnormalities, and/or metabolic complications in the lower limb. Diabetic vasculopathy is typically a multi-segmental diffuse lesion and many blood vessels may be affected. Complications associated with diabetic

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vasculopathy are commonly grouped into two categories: macrovascular and microvascular lesions, and are the major causes of morbidity and mortality in patients with DF.

Those with diabetes have a 12–25% lifetime risk of developing a foot ulcer [1,2], with 5–8% requiring major amputation within 1 year [3–5]. Foot ulceration precedes approximately 85% of lower extremity amputations [6,7].

Numerous factors such as repeated trauma, ischemia and infection, and intrinsic factors that lead to impairment of wound healing may result in the development of diabetic foot ulceration. It is estimated that ischemia may contribute to 30–40% of diabetic foot ulcers (DFUs). Diabetic patients with ischemic foot ulcers have the worst prognosis of all chronic skin wound patients. Consequently, improvement of blood supply to the ischemic limb is a treatment for DFUs.

General surgical procedures to improve lower-extremity ischemia in diabetics have been extensively practiced; however, has limitations. This is because of the widespread and distal location of vascular obstruction, in addition to the presence of multiple comorbidities. Bypass surgery and endovascular interventions are complementary techniques for revascularization in diabetic patients with non-healing ulcers [8]. By-pass graft surgery is used for long occlusions and is performed on distal arteries, such as the dorsalis pedis artery, since atherosclerosis mainly affects the infra-popliteal arteries [9,10]. According to a national vascular registry-based survey with more than 5000 patients, patency rates after crural and pedal bypass are similar for diabetic and non-diabetic individuals, whereas leg salvage rates are worse in those with diabetes [11]. Many patients with DFUs experience amputation more than once in their lifetime due to lack of effective interventions. Therefore, there has been an increased interest in novel therapies for the treatment of DFUs that have been refractory to standard treatment.

The potential use of stem cell-based therapies represents a promising therapeutic approach for DF. The DF is ischemic, and poor arterial flow reduces the blood supply to the ulcerated area resulting in reduced oxygenation, nutrition and healing. Autologous stem cell transplantation is a mechanism whereby stem cells can preferentially locate at damaged tissue sites to induce angiogenesis, and regenerate the epidermis. Healing of DFUs will be enhanced and the pain induced by tissue ischemia may be relieved. In the short-term, patients can avoid amputation or reduce the extent of amputation. Long-term effects may include a decrease in recurrence of ulceration and improvement in quality of life.

Here, we review the potential role of stem cells as new therapeutic agents in the treatment of DF.

2. The theory of stem cell therapy in DF

Stem cells and progenitor cells have a potential therapeutic role to induce angiogenesis and improve vascularisation of the ischemic limb so that perfusion increases sufficiently for wound healing to occur, relieving pain, and ultimately saving the limb.

2.1. *Characteristics of stem cells*

Self-renewal and multi-differentiation potential are two main characteristics of stem cells. In vitro, stem cells and progenitor cells possess the ability to self-renew and differentiate into organ-specific cell types; in vivo, transplantation of these cells may reconstitute an organ system. These two functional characteristics of stem cells show great promise for use in a variety of cell-based therapies, including diabetic foot disease. The self-renewal of stem cells means that they can maintain their characteristics after generating daughter cells through mitosis. Their plasticity means that stem cells could differentiate into various functional cells in a different microenvironment or regulatory system, and can repair damaged or dysfunctional tissues. Theoretically, vascular regeneration based on stem cell implantation could be an effective strategy to treat diabetic foot disease. This possibility is being evaluated through experimentation and medical practice.

2.2. *Types of stem cells*

There are two types of stem cell: embryonic stem cells (ES cell) and post-natal (or adult) stem cells. ES cells, as their name suggests, are derived from the embryo, more specifically, from the blastocyst's inner cell mass. ES cells are totipotent stem cells with the ability to differentiate into all types of cells, making them more suitable for the treatment of the complicated pathological changes that occur in DF. In addition, these cells tend to have a strong proliferative capacity and a low differentiation maturity. However, tumor cell lines are also easily created, having the characteristics of rapid proliferation and low differentiation. Further, immune rejection and ethical issues are real obstacles facing clinical application of these techniques. Therefore, embryonic stem cell therapy for DF is rarely carried out at present.

Adult stem cells thus are the preferred candidates for therapeutic approaches, particularly as there is no ethical controversy and the cells can be isolated in appropriate amounts from several sources. According to their tissue origin, adult stem cells can be divided into hematopoietic stem cells (HSCs), mesenchymal stromal stem cells (MSCs), neural stem cells, muscle stem cells and so on [12]. Adult stem cells exist in many tissues and vary in their potential to differentiate, thus representing an important therapeutic opportunity in regenerative medicine.

2.3. *Sources of stem cells*

The source of stem cells should be considered according to their intended purpose, that is, for experimental or therapeutic use. Currently, bone marrow is considered to be the most accessible and enriched source of stem cells for widespread medical treatments. It has previously been shown that a combination of bone marrow stroma-derived hematopoietic (HSC) and mesenchymal (MSC), stem cells can accelerate chronic wound healing in patients with DF [13].

2.4. *Stem cells and the DF*

Promising results in the treatment of DF have been achieved by administering stem cells either via intramuscular or intra-arterial injection into the diseased lower limb or by direct application over the wound [14]. Many human trials have shown intramuscular injection to be the preferred mode of

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