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Opportunities and Challenges for Repair of Macrovascular Disease using Circulating Blood-Derived Progenitor Cells

Mary R. Loeken

Section on Islet and Regenerative Cell Biology, Joslin Diabetes Center

Abstract

There are currently few solutions for diabetic vascular disease that involve repair of damaged tissues. The manuscript by Porat, et al., suggests a possible method to use a patient's own circulating blood cells to provide progenitors to repair damaged vascular tissues.

Keywords

stem cell therapy; diabetic vasculopathy; ischemic disease

It is well recognized that diabetic complications that result from micro- and macrovascular dysfunction, such as end-stage renal disease, retinopathy, and lower limb amputation, are among the most disabling. The cellular pathology of lower limb disease is complex, involving perfusion insufficiency, neuropathy, inflammation, and deficient repair of damaged tissues (1). With the increasing prevalence of diabetes in aging adults, lower limb pathology caused by vascular disease is likely to increase (2, 3). And yet, problems still remain in developing and implementing practical strategies to repair damaged vascular tissues.

Some approaches that have been studied in recent years in experimental animals or clinical investigations are antiplatelet therapy (4), fenofibrates to lower cholesterol and triglycerides (5), angiogenic peptide administration (6), or treatment of endothelial progenitor cells with osteopontin (7). Utilization of stem cells, derived from the circulation, bone marrow, residing in tissues, or induced pluripotent cells (8-13), or even derived from amniotic fluid (14) may hold promise. However, development of these approaches depends upon determining which progenitor cell type(s) and from which tissue source or niche cells should be obtained, and what *in vitro* treatments will provide optimum therapy. Also, it would be ideal for histocompatibility antigen matching if the donor cells were derived from the patient. However, diabetes might compromise regenerative capacity of progenitor cells (10). Additionally, it would be preferable if therapeutic progenitor cells could be derived using less invasive methods than bone marrow biopsy.

In this issue of *Diabetes Metabolism Research and Reviews*, Porat and colleagues report a method to treat vascular disease in diabetic patients with blood-derived stem or progenitor cells [15]. Using blood bank-donated samples from nondiabetic subjects, dendritic cells and stem/progenitor cells were enriched by antibody selection for cell surface markers. Immature dendritic cells were activated as described in the manuscript, and then cultured

with the stem/progenitor cells to form enriched endothelial precursor cells which they call, BGC101. However, optimal concentrations of activating and co-culture factors that will permit standardization of the protocol still need to be determined. Preliminary experiments using blood-derived cells from two donors with type 2 diabetes suggest that they show similar capacity to form BGC101 *in vitro* as do cells from nondiabetic subjects. The potential for autologous provision of therapeutic cells is advantageous, but it will be important to demonstrate that donor cells can be derived regardless of type, duration, or control of diabetes. The investigators performed limited animal studies that provide evidence that the blood-derived endothelial progenitor cells can repair hindlimb ischemia. While more investigation is needed using BGC101 cells derived from both nondiabetic and diabetic subjects to determine whether they can repair diabetes-induced limb ischemia in animal models, the procedure holds promise to solve a major disabling diabetic complication. Benefits of this approach are that autologous cells could be used for treatment, and that obtaining the stem/progenitor cells is minimally invasive. Thus, while still highly preliminary, these methods to derive endothelial progenitor cells hold promise.

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