ATHERSCLEROSIS AND ENDOTHELIAL PROGENITOR CELLS: A NEW THERAPEUTIC APPROACH

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During the last few decades, it has become evident that the vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and maintenance of vascular homeostasis. Moreover, recent insights into the basic mechanisms involved in atherosclerosis indicate that deleterious alterations of endothelial dysfunction, represent a key early step in the development of atherosclerosis and are also involved in plaque progression and the occurrence of atherosclerotic complications [1-3]. In fact, activated endothelium recruits monocytes, which differentiate into macrophages. Elevated permeability of the endothelium is believed to allow entry of lipoproteins into the vessel wall, which become oxidized and propagates endothelial dysfunction [4]. Macrophages engulf low-density lipoproteins (LDL) and become foam cells, which can be visualized as fatty streaks in the vessel wall. In the continued presence of high LDL cholesterol and oxidant stress, fatty streaks progress to advanced atherosclerotic plaques. Effective drugs for lowering cholesterol and high blood pressure have been developed. In particular, the statins lower levels of atherogenic lipoproteins and dramatically decrease clinical events and mortality from atherosclerosis [5]. Nevertheless, heart disease and stroke remain by far the most common causes of death in westernized societies and new weapons, particularly new therapies translating into an improvement in endothelial health, are needed. The following is an overview of the endothelial progenitor cell (EPC) therapeutic potential in the endothelium improvement of cardiovascular diseases.

Endothelial Progenitor Cells (EPCs)

The discovery of EPCs by Asahara et al. in 1997 [6] resulted in a new paradigm for endothelial regeneration and introduced a potential new approach to the treatment of cardiovascular diseases. They isolated EPCs using magnetic bead selection of cell surface antigens such as CD34 an Flk1 from human peripheral blood. They have demonstrated that this cell population is found in areas of ischemia [7]. Prior to the discovery of this cell type, endothelial repair and new vessel formation were believed to occur due to proliferation of existing endothelial cells. These findings have overturned the previous dogma that vasculogenesis can only occur during embryogenesis. On the other hand, vasculogenesis is a process whereby new vessels are formed by EPCs or angioblasts, which home, differentiate, proliferate and incorporate into resident endothelial cells in response to various stimuli such as ischemia. On the other hand, angiogenesis is a process whereby new vessels are formed by the migration and differentiation of the existing endothelial cells. Since the original discovery of this cell type, multiple studies have shown derangement in EPC function and number in a wide variety of disease states and thus EPCs may serve as a surrogate marker of endothelial dysfunction. In addition, there have been an increasing number of elegant studies on the role of EPCs as a potential therapeutic agent for vascular disorders. For instance, the use of EPCs as a tool for therapeutic angiogenesis/vasculogenesis represents a new approach to the treatment of patients with ischemic disease not curable with conventional treatment.
Nevertheless, the role of EPCs in atherosclerosis/vascular diseases is currently an area of active investigation; not surprisingly, available findings appear to be incomplete and preliminary. Several reports have dealt with atherosclerosis [8]. It was demonstrated in animal model that EPCs was found in denuded vessel walls and atherosclerosis lesions. These functions contributed to the preservation of an intact endothelial layer in animal models. For example, Griese et al., in 2003 [9] reported that \textit{ex vivo} expanded CD34$^+$ mononuclear cells derived from peripheral blood led to rapid re-endothelialization of denuded vessels and graft segments in rabbits. As reported by Rauscher et al. in 2003 [10], transplantation of wild-type bone marrow to ApoE$^{-/-}$ mice reduced the formation of atherosclerotic lesions. The latter study pointed the role of aging and progenitor cells from young animals had preventive effects in terms of atherosclerosis.

**Therapeutic Strategies to Improve Endothelial Dysfunction by EPCs**

A potential of EPCs in vascular protection in humans was also suggested by the association between EPCs and risk factors for atherosclerosis [8]. Thus, the numbers of EPCs were found to be low in patients with a high degree of coronary artery disease [11]. Age, smoking, diabetes mellitus type 1 and 2, and hypercholesterolemia were characterized as states of impaired EPC numbers and/or function. At the same time, these conditions are associated with a high risk of atherosclerosis. Treatment with statins and PPAR$\gamma$ agonists result in increased numbers of circulating EPCs and an improved function of EPCs. Release of EPCs \textit{in vivo} has been also stimulated after application of growth factors such as GM-CSF or VEGF [12]. Physical activity has been also shown to enhance EPC numbers and migratory activity in healthy individuals.

Although the preclinical and clinical studies generally lend support to the therapeutic potential of autologous EPCs in the repair of injured blood vessels, many questions remain. Little is known, in fact, about the signals that direct circulating EPCs to sites of injured vessels (see Figure 1). Recent studies addressing the integration of EPCs into the mature endothelium found that a small fraction of these cells can also transdifferentiate into smooth muscle cells \textit{in vitro} [13]. This process seems to be dependent on the presence of transforming growth factor-$\beta 1$ and cell-cell contact. If this were the case, strategically located EPCs within the vascular endothelium could be an emerging standby tool for the regeneration of surrounding endothelial cells or smooth muscle cells subsequent to an injury. Furthermore, EPCs may be involved in the regeneration of ischemic myocardium by modulation of angiogenesis and myogenesis, cardiomyocyte apoptosis and remodeling in the ischemic cardiac tissues. Thus, EPCs derived from the haemopoietic tissues of postnatal bone marrow may possess highly regenerative potential and some characteristics of embryonic stem cells.

**References**

Figure 1 EPCs and the contribution of the injured vessel repair. However, the intercellular signaling between damaged endothelial cells and EPCs remains unclear. Some of the EPCs possibly integrate into the endothelial layer and may transdifferentiate into smooth muscle cells.