1. INTRODUCTION

Retinal neovascular diseases such as diabetic retinopathy and retinopathy of prema­turity are among the leading causes of vision impairment throughout the world. Retinal neovascularization is thought to occur in response to a hypoxic insult, which leads to changes in the existing microvasculature such as pericyte death and subsequent endothelial cell proliferation. Compensatory neovascularization then results in the formation of aberrant and pathologic capillaries. An important question whose answer would have broad implications for potential therapeutic strategies is the origin of the cells responsible for compensatory neovascularization.

Postnatal neovascularization has been attributed to angiogenesis, a process characterized by sprouting of new capillaries from pre-existing blood vessels. Recent evidence by Asahara and coworkers has demonstrated the presence of circulating endothelial progenitor cells (EPC) that may be recruited to areas of neovascularization. EPCs that are capable of contributing to in vitro capillary formation can be derived from bone marrow cells. Angiogenic growth factors such as vascular endothelial growth factor (VEGF) and granulocyte/macrophage colony stimulating factor (GM-CSF) can promote the release of these cells from the bone marrow into the circulation, and promote new blood vessel formation.

Vasculogenesis is the process within the developing embryo whereby pluripotent progenitor cells are generated that are capable of contributing to the formation of blood and blood vessels. These pluripotent stem cells are termed hemangioblasts. Hemangioblasts can also be produced from embryonic stem cells during in vitro differentiation in response to vascular endothelial growth factor. However, definitive evidence for the existence of the hemangioblast within the adult bone marrow, and in particular for a functional role of such BM-derived cells in neovascularization, has been lacking until now.
2. ENDOTHELIAL CELL DERIVATION

Numerous studies support the contribution by EPC to blood vessel formation in the adult. However, since these studies are based on short-term transplant and acute injury models, it is not clear whether the cell type giving rise to circulating EPCs is a true hematopoietic stem cell (HSC) or some other progenitor such as the mesenchymal stem cell (MSC).

HSCs derived from adult bone marrow are classically defined by their ability to self renew while functionally repopulating the cells of the blood and lymph for the life of an individual, as shown in schematic form in Figure 1. These abilities make HSCs clinically useful in therapeutic bone marrow transplantation for a variety of bone marrow diseases, including leukemia and lymphoma. HSCs can be highly enriched and quantified. As with other tissue-derived stem cells, HSCs are thought to retain a high capacity for "plasticity" that would allow for the potential contribution of regenerative progenitors to non-hematopoietic tissues following injury or stress.

Circulating EPCs may be derived from MSCs or, potentially, from HSCs with hemangioblast properties. Current EPC enrichment procedures have failed to distinguish convincingly the origin of circulating EPC. Previous studies utilized acute injuries and described the incorporation of bone marrow-derived cells into newly formed vessels.

Figure 1. Schematic representation of potential endothelial cell lineage. Triangles represent surface antigens (as labeled) associated with each stage of differentiation. The proposed adult hemangioblast (HB) may give rise to the pluripotent hematopoietic stem cell (HSC), or may in fact be the same cell. HSCs give rise to common lymphocyte precursors (CLP), common monocyte/granulocyte precursors (CMGP), and megakaryocyte/erythrocyte precursors (MEP). One differentiation pathway results in endothelial progenitor cells (EPC), which may be recruited via the circulation to form mature endothelial cells (EC).