The growth of new blood vessels is a critical factor in many human diseases including cancer, ischemic injury and wound healing. De novo vessel formation or vasculogenesis was thought to take place solely in the embryo from mesodermal progenitor cells, whereas the vasculature in postnatal life was considered to undergo remodeling through expansion of pre-existing endothelial cells, or angiogenesis. Current evidence suggests that endothelial progenitor cells (EPCs) also exist in adult organisms as circulating cells originating in the bone marrow. They can be mobilized after vascular trauma, myocardial infarction, tissue injury, or during peripheral vascular disease, by a number of growth factors and chemokines like VEGF, GM-CSF, G-CSF and SDF-1. EPCs do not appear to represent a distinct or homogeneous cell population, but they are defined as cells that can give rise to endothelial progeny under certain circumstances in culture or in vivo. EPCs enhance tissue revascularization by contributing to new vessels and stimulating local angiogenesis, thus offering novel ways to regulate vascular growth. Results from the first clinical studies using mostly bone marrow stem cells as a source of EPCs have been encouraging, emphasizing the therapeutic potential of endothelial progenitor cells. This review summarizes the role of EPCs in the formation of new blood vessels and provides an outline of their biological characteristics and potential use in the clinical setting.

Keywords: endothelial progenitor cell, neovasculogenesis, cell therapy
1. THE ORIGIN OF ENDOTHELIAL PROGENITOR CELLS DURING EMBRYONIC DEVELOPMENT

The vascular system is one of the first organs to develop in the embryo arising primarily from cells of mesodermal origin. Blood vessels appear almost simultaneously during embryogenesis at different anatomical sites including the extraembryonic yolk sac membrane, the proximal lateral mesoderm and the allantois. The primary vascular layout starts as a primitive, homogeneous endothelial plexus, which is remodeled stepwise into a mature diverse network consisting of arteries, veins and capillaries [1].

The initial event of blood vessel formation during embryonic development is called vasculogenesis, which describes the in situ and de novo assembly of blood vessels from differentiating progenitor cells. Subsequent remodeling and expansion of the vascular network takes place by angiogenesis, which refers to the proliferation, sprouting and migration of pre-existing endothelial cells [2, 3]. Blood vessels can also grow without sprouting by intussusception, or the fusion of opposing capillary walls and subsequent reorganization of endothelial cells and pericytes in order to divide a single vessel in two [4].

Vasculogenesis begins during gastrulation when mesodermal cells migrating through the primitive streak begin to differentiate to endothelial progenitor cells in lateral and posterior areas. The extraembryonic blood vessels form first in the yolk sac where cells within the inner, mesodermal layer assemble in clusters called blood islands [5]. The Flk-1\(^{+}\)/Tal1\(^{+}\) cells in the blood islands differentiate into endothelial progenitors at the perimeter, whereas those in the center lose Flk-1 (or VEGFR-2) expression and give rise to extraembryonic Flk-1\(^{-}\)/Tal1\(^{+}\) hematopoietic precursors [6]. The close association of early blood and endothelial cells, and careful observation of morphogenetic movements led to the idea of a common precursor for both endothelial and hematopoietic progenitor cells in the yolk sac, called the hemangioblast [5, 7].

In parallel to the development of blood vessels in the yolk sac, Flk-1\(^{+}\)/Tal1\(^{+}\) endothelial progenitors inside the mouse embryo appear in a bilateral distribution along the midline and begin to form the pre-endocardial tubes [6]; these will later fuse and give rise to the endocardium of the embryonic heart and the major blood vessels. As development progresses, endothelial progenitor cells gradually appear in most areas of the intraembryonic mesoderm (except the notochord and the prechordal plate) in vascular “hot spots” where they assemble into primitive vascular networks [8].

The intraembryonic endothelial progenitor cells are called angioblasts, because they differentiate mainly to endothelium without producing blood cells. However, later on, subpopulations of endothelial cells, for example in the ventral wall of the dorsal aorta, produce blood cells (also called the “hemogenic endothelium”). In this process, Flk-1\(^{+}\)/VE-cadherin\(^{+}\) expressing endothelial cells yield CD34\(^{+}\)/CD45\(^{+}\) hematopoietic stem cells [HSCs; 9,10]. The relationship between hemogenic endothelium and hemangioblasts is unclear.