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**Vascular Precursors: Origin, Regulation and Function**

Karen K. Hirschi

In this miniseries, we discuss the phenotype, origin, and specialized microenvironment (niche) of distinct populations of stem and progenitor cells that exhibit vascular potential. Their usefulness and effectiveness for clinical therapies are also described. We have learned a great deal about postnatal vascular precursors since their discovery more than 10 years ago, and there is much hope in the field that the potential of such cell populations can be harnessed for cardiovascular tissue repair and regeneration. However, further studies are needed in cell culture systems, translational animal models, and human clinical trials to thoroughly explore and optimize the use of stem and progenitor cells with vascular potential for the treatment of cardiovascular diseases.

In addition to human embryonic and induced pluripotent stem cells, the cell populations presented exist as progenitors within postnatal tissues. They can be isolated based on cellular behavior (ie, adherence, proliferation, and colony formation) in culture and/or cell surface protein expression. They can also participate in revascularization in vivo. These populations of vascular precursors are thought to predominantly originate from, and/or reside within, the hematopoietic (bone marrow and peripheral blood) and vascular (endothelium and periendothelial compartment) systems. Although we discuss vascular and hematopoietic sources of endothelial progenitor cells as separate entities, based on existing literature, it is entirely possible that some, or all, of the identified cell populations are interrelated in a continuous and systemic cycle: circulation, tissue deposition, and mobilization. If this is the case, then “niches” within blood vessel structures in various somatic tissues, including bone marrow, may merely be a stop (resting or permanent) along the way. Cells may be deposited within and around blood vessels via systemic circulation, and their phenotype may be slightly adjusted to meet the demands and needs of their new microenvironment.

Although this theory is far from proven, previous studies conducted to understand the relationship between bone marrow–and muscle-derived progenitor cells demonstrated that vascular precursors residing within muscle are derived from bone marrow via blood circulation. This cellular compartment within muscle tissue is also continuously replenished throughout postnatal life by cells originating from bone marrow. Furthermore, once in the muscle environment, the marrow-derived cells exhibit a slightly different phenotype. Perhaps the same is true for vascular precursor populations in general: progenitor cells (with vascular potential) circulate all over the body via peripheral blood, randomly (or selectively) taking up residence within and/or around blood vessel structures in various tissues, and are either stored and turned over or mobilized in response to injury to function as vascular progenitor/precurser cells. It is equally plausible that distinct cell populations, with various degrees of vascular potential, arise independently within different tissue sites and are not biologically related. Thus, further studies are needed to definitely prove either hypothesis.

Another issue that remains to be determined is the lineage relationship between postnatal and embryonic vascular precursor cells, especially because the embryonic developmental program appears to be recapitulated in the differentiation of vascular cells from human pluripotent stem cells (embryonic and induced pluripotent stem cells) that can be used for adult clinical studies. In the embryo (and pluripotent stem cell) models, hematopoietic stem/progenitor cells are derived from specialized endothelium, referred to as hemogenic endothelium. In the adult, the origin of the hematopoietic stem cell is...
unclear and the existence of hemogenic endothelium is not proven. In contrast, it is thought that hematopoietic stem cells, or their progeny, can generate vascular progenitor cells and endothelial cells in vivo. Therefore, in the adult system, do hematopoietic stem/progenitor cells generate vascular cells, do vascular cells generate hematopoietic stem/progenitor cells, or both? Alternatively, neither would be true if vascular precursor cells are predominantly derived from the vasculature, independent of a hematopoietic lineage intermediate.

Clearly, important questions remain to be answered regarding the plasticity and interdependence of cells within the vascular and hematopoietic lineages during embryonic development and in postnatal tissues. Thus, as we move forward toward a better understanding of vascular precursor cell phenotype and origin, we must also move forward toward a better understanding of the in vivo vascular potential of distinct (and/or overlapping) cell populations. Advances in both basic and translational sciences are needed to realize and harness the full potential of vascular stem and progenitor cell types that we have identified and that we will further define in the future.

Reference
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