PERSPECTIVE

Endothelial Progenitor Cells

Anthony Rosenzweig, M.D.

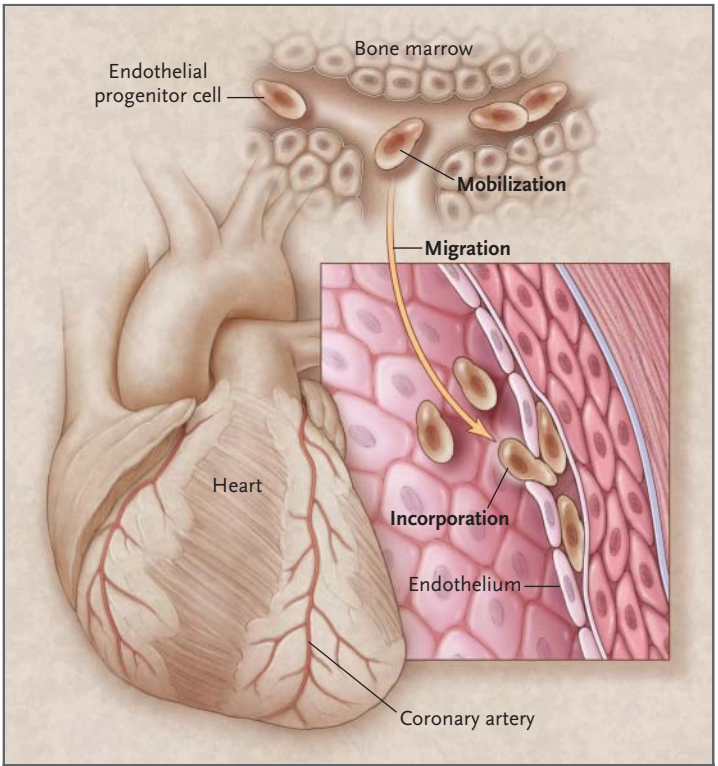
Vascular endothelial cells form a lining — one cell thick — for all the blood vessels in the body, providing a critical interface between the vessel itself and blood-borne elements. From this location, the endothelium regulates a host of essential processes on both sides, by means of molecular signals expressed on its surface or released into the environment. In the normal state, vascular endothelium presents a nonadhesive surface to circulating leukocytes and platelets while helping to prevent the clotting of blood. In response to specific stimuli, however, the endothelium changes rapidly, providing signals that effectively orchestrate the recruitment of these same blood cells to sites of injury or infection. The normal endothelium also plays an important part in the regulation of vascular tone through the production and release of nitric oxide, leading to the relaxation of smooth-muscle cells in the vessel wall. However, in a variety of disease states, including atherosclerosis, dysfunctional vascular endothelium can lead to increased leukocyte adhesion as well as impaired nitric oxide production and vascular relaxation.

Endothelial cells are also crucial participants in the formation of new blood vessels. These new vessels have a beneficial role in the healing response to wounds or tissue ischemia and infarction. However, they also appear to be important in tumor progression and metastasis, as well as in the neovascularization seen in diabetic retinopathy. Until recently, it was generally thought that the formation of new vessels in adults occurred exclusively through the extension of mature existing blood vessels and the associated vascular endothelium. A growing body of evidence now suggests that bone marrow–derived endothelial progenitor cells circulate in the blood and, at least in animal models, can play an important part in the formation of new blood vessels in these pathologic conditions. The extent to which endothelial progenitor cells are incorporated into normal or minimally dysfunctional vessels and the functional consequences of this incorporation, if it occurs, remain to be established.

The odyssey from bone marrow to vascular endothelium can be divided into three stages (see Figure). First, endothelial progenitor cells are mobilized or released from the marrow. A number of cytokines and growth factors appear to promote this step. Subsequently, the cells move through the circulation and appear to home preferentially to sites of tissue injury. Finally, some endothelial progenitor cells are incorporated into new blood vessels formed by the extension of existing vessels (angiogenesis) or possibly formed in situ (vasculogenesis).

These processes may have important clinical implications. First, genetic or acquired defects in any of these steps may undermine the formation of new blood vessels and could therefore contribute to an impaired healing response in some patients. Second, endothelial progenitor cells may provide an opportunity for therapeutic intervention either through enhancement of the mobilization, migration, or incorporation of endogenous endothelial progenitor cells or through transplantation of exogenous cell populations that have been expanded ex vivo. In animal models, both these approaches have shown great promise. In addition, clinical studies have demonstrated that the number of circulating endothelial progenitor cells can be significantly increased by treatment with drugs such as statins.

In a study described in this issue of the *Journal* (pages 593–600), Hill et al. examined endothelial progenitor cells in 45 men without known cardiovascular disease. As in studies of patients with known cardiovascular disease, the authors found an inverse correlation between the number of circulating endothelial progenitor cells and risk factors for cardiovascular disease. The number of endothelial progenitor cells was also associated with brachial-artery reactivity, an index of endothelial function (nitric oxide release) that can be measured by non-



Three Stages in the Movement of Endothelial Progenitor Cells from Bone Marrow to Vascular Endothelium.

invasive means. It is entirely possible that this association reflects a common underlying pathophysiological process, rather than a causal connection between the observations. However, the explanation favored by the authors is the intriguing possibility that endothelial progenitor cells maintain endothelial function in mature blood vessels and that the failure of this function may lead to abnormal vasoreactivity. Further studies are needed to test this hypothesis rigorously. Nevertheless, at the very least, endothelial progenitor cells appear to provide a useful index of cumulative cardiovascular risk and vascular function.

These studies reflect the growing realization that adult cells and tissues have far more plasticity and potential for regeneration than previously realized. We have much to learn about the function of endothelial progenitor cells, not only in the context of disease but also in the more subtle yet equally important context of vascular homeostasis. The identification of specific markers for endothelial progenitor cells would greatly facilitate ongoing studies and might highlight functionally important heterogeneity in populations of these cells. It remains to be seen whether it will be possible to use endothelial progenitor cells to augment the formation of new vessels in wound healing or ischemia without the adverse consequences of neovascularization. Little is known about the traffic signals that direct circulating endothelial progenitor cells to sites of tissue injury or the stimuli that induce their incorporation into new vessels. An understanding of these processes, which will require an ongoing synthesis of data from clinical and basic studies, may provide important insights into the specificity of vessel formation. This knowledge, in turn, may help us learn how to harness the regenerative potential of endothelial progenitor cells.

From the Program in Cardiovascular Gene Therapy, Massachusetts General Hospital, Charlestown, Mass.