Aging of Progenitor Cells: Limitation for Regenerative Capacity?*

Stefanie Dimmeler, PhD,† Mariuca Vasa-Nicotera, MD‡
Frankfurt, Germany; and Leicester, United Kingdom

It is becoming clear that postnatal neovascularization involves circulating endothelial progenitor cells (EPCs), which home to sites of neovascularization and differentiate into endothelial cells in a manner consistent with a process initially termed “vasculogenesis” (1). These circulating EPCs derive from hematopoietic stem cells and contribute to reparative processes, including neovascularization after ischemia (2,3). Ischemia, vascular trauma, and proangiogenic chemokines stimulate EPC mobilization from the bone marrow (4–6). In particular, ischemia was shown to enhance circulating EPC levels by vascular endothelial growth factor (VEGF)-mediated mobilization of bone marrow-derived EPCs (5). Mobilized EPCs are then attracted to ischemic areas by locally elevated VEGF or stromal cell-derived factor-1 levels (7). The functional regeneration of ischemic tissue by improved neovascularization and possibly tissue repair is critically dependent on the mobilization and integration of EPCs into the ischemic tissue. Moreover, infusions of EPCs expanded ex vivo can limit scar extension in the ischemic myocardium (8) and improve the recovery of contractility and thereby may be useful as a novel therapeutic approach (9). However, aging may constitute a potential limitation to the ability of progenitor cells to sustain ischemic tissue neovascularization and repair.

Aging is one of the major risk factors for coronary artery disease (CAD) and is associated with a reduction of the functional activity of the endothelium (10). In an animal model, aging also appeared to impair neovascularization after ischemia (11). Moreover, increasing age was shown to be associated with reduced levels of circulating EPCs in patients with CAD (12), thereby providing first evidence of dysfunctional regulation of EPCs in elderly individuals. Age may interfere with neovascularization at various steps (Fig. 1)

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of the American College of Cardiology

†Molecular Cardiology, Department of Internal Medicine IV, University of Frankfurt, Frankfurt, Germany; and the Department of Cardiovascular Science, Division of Cardiology, University of Leicester, Leicester, United Kingdom. Dr. Dimmeler is supported by a grant from the Deutsche Forschungsgemeinschaft (FOR 501).
pool can be revitalized in vivo or after ex vivo expansion by treatment with pharmacologic agents, cytokines, or even gene therapy. Previous studies have shown that VEGF gene transfer efficiently mobilizes EPCs in humans (18). Other possibilities to augment circulating EPC levels in elderly patients may include the use of statins, which have been shown to increase EPC levels in patients with CAD (19). One may also consider estrogen (20) or erythropoietin (21) as a possible strategy to increase EPCs. Clearly, the susceptibility to these treatments in elderly patients has not been tested.

Another option may be to more directly influence age-associated changes in telomere biology ex vivo. Age leads to telomere shortening and dysfunction, which are implicated in senescence and apoptotic signaling. Counteracting the reduction of telomere length by overexpression of the active subunit of the telomerase, TERT, increased the neovascularization capacity of EPCs from healthy volunteers (22). Likewise, one may consider the use of the telomere repeat binding factor, TRF2, which protects critically short telomeres from fusion and confers protection from oxidative stress in other cell types (23,24).

Taken together, although it may still be premature to rush to conclusions about the role of age-related phenomena on EPC-based therapies, the findings reported by Scheubel et al. (15) strengthen the idea that the EPC pool must be stimulated in vivo and most likely expanded ex vivo to enhance neovascularization and improve myocardial function. In light of the results of this study, these approaches would be even more important in elderly individuals.

REFERENCES