It has been said that one is as old as one's arteries. In view of the supreme importance of endothelium in arterial function, I should like to modify . . . this statement by saying that one is as old as one's endothelium.1

R. Altschul, 1954

Just a few years ago, the rules of blood vessel formation seemed simple. Endothelial cells emerged from the blood islands of the embryo to form primitive tubes, the precursors of the vasculature. Smooth muscle cells, recruited locally from various germ layers, invested the endothelial tubes, forming the sandwich structure of mature arteries and veins. Mechanical or metabolic injury supposedly stimulated smooth muscle cells, normally resident in the arterial tunica media, to migrate into the intima, proliferate, and form the lesions of the hyperplastic arterial diseases such as atherosclerosis, restenosis, in-stent stenosis, and transplantation arteriopathy.2–4 Such endothelial progenitor cells (EPCs) bear characteristic markers such as CD133, CD34, and vascular endothelial growth factor receptor-2.5

Smooth muscle cells in the artery may also derive from bone marrow precursors. Our laboratory stumbled on this finding in pursuit of the pathogenesis of transplantation-associated arteriosclerosis. We have long posited an allogeneic response directed against donor vascular cells as an essential element in the pathogenesis of this disease. This hypothesis required that vascular endothelial cells can not only arise postnatally from primitive precursors, but can originate also from the adult bone marrow or peripheral blood and take up residence on mature blood vessels.2–4 Such endothelial progenitor cells (EPCs) bear characteristic markers such as CD133, CD34, and vascular endothelial growth factor receptor-2.5

The clinical implications of this “new biology” of the origin of arterial cells abound. The nascent field of regenerative medicine has spawned great interest in myocardial repair using bone marrow-derived and other stem cells. This concept may apply to the blood vessel as well as the myocardium. In the current issue of Circulation, imaginative and provocative experiments by Rauscher et al6 show that transfer of cells propagated from the bone marrow of youthful donor mice can limit the evolution of experimental atherosclerosis in mice lacking apolipoprotein E. These investigators found signs of senescence in the endothelial cells that line atherosclerotic arteries. They hypothesize that the cells derived from the youthful bone marrow help to repair a deficit in endothelial longevity associated with atherosclerosis. Their results raise the possibility that the bone marrow might provide a “fountain of youth” that could modify the natural history of atherosclerosis.

As the authors acknowledge, many questions remain unanswered regarding their striking findings. Their studies do not definitively identify a mechanism of the modulatory effect on atherogenesis. Do the “youthful” cells or the products that they may elaborate alter the biology of host cells at a distance or by actually taking up residence in the arterial lesion and acting locally? The recipients of the bone marrow cells did not undergo irradiation to limit the growth of endogenous bone marrow or vascular cells, thereby complicating the mechanistic interpretation of their experiments.

The protocols used included a period of culture of the bone marrow-derived cells to expand the population before it was transferred to the recipients. The different ages of the donors might favor selection in vitro that could contribute to the differences they observed between cells derived from young and old animals. The transferred cell populations lacked homogeneity. Often, the authors6 used a mixture of stromal and hematopoietic cells. It is not clear whether the effects they observed resulted from transfer of bona fide stem cells or transplantation of cells with limited replicative capacity. Indeed, some evidence suggests that cells of the mononuclear phagocytic lineage serve as the source of circulating endothelial progenitor cells.7

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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The authors propose in their title “progenitor cell exhaustion” as a mechanism for enhanced atherogenesis with aging. They interpret their data as “rejuvenation” of the vasculature by the transferred cells. Considerable future research will be required to define exhaustion and rejuvenation in more rigorous and precise molecular terms.

Curiously, the authors found a striking suppression of circulating interleukin-6 (IL-6) in the animals that received youthful bone marrow-derived cells, suggesting that the transfer of these cells has antiinflammatory effects. As vascular cells can elaborate copious quantities of IL-6, the observations presented by Rauscher et al suggest an interesting link between aging, atherogenesis, and inflammation. Because IL-6 drives production of C-reactive protein, the authors’ observations on this “messenger cytokine” may link to the pathobiology of elevated C-reactive protein as a marker of heightened risk of atherosclerotic complications.

Although the mouse offers an incredibly valuable tool for the study of disease in the laboratory, we must bear in mind that the results obtained in this experimental animal may not translate directly to humans. Indeed, atherogenesis in humans usually occurs at lower lipid levels and over a much more prolonged time scale than generally used in experiments on mice genetically altered to enhance their susceptibility to atherosclerosis. The biology of endothelial cell senescence and of bone marrow may differ between these species, limiting the clinical extrapolation of their results, but not detracting from their potential pathobiological significance.

Certainly, age is a major risk factor for atherosclerosis. However, the tempo of vascular degeneration may not follow a predetermined program, as inevitable as the march of time. Many modifiable factors contribute to the epidemic of atherosclerosis that besets contemporary societies. While gazing ahead toward future “high-technology” strategies for the modification of this disease, we must not lose sight of the urgent present need to stem the burden of atherosclerosis that we confront today with simpler but less glamorous measures: lifestyle modification and application of existing therapies according to current guidelines.

Although far from definitive or conclusive, the provocative report of Rauscher et al will doubtless inspire important further research. Their findings raise the possibility that the application of regenerative biology to the blood vessel may someday enable us to alter the course of atherosclerosis.

References

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Bone Marrow: A Fountain of Vascular Youth?
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