Re-endothelialization Via Bone Marrow-Derived Progenitor Cells
Still Another Target of Statins in Vascular Disease

Johan Thyberg

According to the response to injury hypothesis presented by Ross and Glomset more than 25 years ago, the formation of atherosclerotic plaques is the result of damage to the endothelium. The key steps in this process are: (1) a physical or chemical disruption of the endothelial cell (EC) barrier; (2) platelet adhesion to exposed subendothelial matrix and platelet degranulation; (3) movement of leukocytes (primarily monocytes and T lymphocytes) and plasma constituents into the arterial intima; (4) migration of smooth muscle cells (SMCs) from the media to the intima; and (5) growth in size of the intimal lesions by cell proliferation, deposition of extracellular matrix components, and lipid accumulation (Figure 1). The original model has later been modified continually, among other reasons, to stress that the endothelial damage may have the nature of a functional disturbance rather than a real detachment. This also implies that the relative importance of the above-mentioned steps may differ in different situations. Nevertheless, the basic concept is still largely the same, and as long as the injurious influence remains, the process will continue and lead to formation of complicated lesions, eventually causing complications such as heart and brain infarction. If, on the other hand, the factors causing a harmful effect on the inner lining of the arteries are removed (eg, hypertension, hyperlipidemia, and smoking), the physical and/or functional integrity of the endothelial cell layer may be restored and the disease halted. An important object in the treatment and prevention of atherosclerosis and other related conditions, such as restenosis after balloon angioplasty, graft stenosis, and transplant vasculopathy, is therefore to promote healing of the endothelium.

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It was long believed that endothelial regeneration is a local process achieved by proliferation and immigration of ECs from adjacent, intact parts of the intima. More recently, it has become evident that bone marrow–derived endothelial progenitor cells (EPCs) exist in the blood. This is in agreement with the notion that ECs and blood cells share a common origin in both the embryo and adult. In a series of articles from the laboratory of Takayuki Asahara and Jeffrey Isner, it has further been shown that bone marrow–derived EPCs take part in neovascularization, for instance in connection with wound healing and in response to ischemia. A subsequent finding of considerable therapeutic interest is that treatment with statins (HMG-CoA reductase inhibitors) brings about an increase in the number of circulating EPCs. This effect appeared to be unrelated to the reduction in serum cholesterol levels, and a more direct role was assigned to activation of the protein kinase Akt (PKB) and stimulation of EPC proliferation, migration, and survival.

An important confirmation and extension of these findings has now been provided by two reports, one by Walter et al in a recent issue of Circulation, and one by Werner et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology. These articles demonstrate that statins accelerate re-endothelialization and reduce neointimal thickening in rat and mouse models of vascular injury. The first study used nude rats and mice transplanted with bone marrow from mice that expressed lacZ (β-galactosidase) under transcriptional control of the endothelium-specific promotor Tie 2. Carotid arteries were injured by using a balloon catheter or a flexible wire and removed after 2 to 4 weeks for microscopic and cytochemical analysis. During the time after the operation, the animals were given daily IP injections of simvastatin (0.2 or 1 mg/kg) or saline. The second study used mice transplanted with bone marrow cells propagated in vitro and labeled by retroviral transfer of the gene for EGFP (enhanced green fluorescent protein). The animals received daily subcutaneous injections of rosvustatin (20 mg/kg) or saline for 10 days before carotid injury with a flexible wire and then until the vessels were harvested after 14 days.

The results of both reports indicate that statins: (1) increase the number of circulating EPCs; (2) stimulate the incorporation of bone marrow–derived cells in injured arteries; (3) speed up the re-endothelialization of the vessels; and (4) limit the growth in size of the neointimal lesions. The work of Walter et al further reveals that cultured human EPCs exposed to simvastatin show an increased expression of integrin αvβ3 (the main fibronectin receptor) and αvβ5, as well as an increased adhesiveness to dishes coated with fibronectin (a plasma and tissue protein that accumulates at sites of vascular injury) and an increased incorporation into a monolayer of human umbilical vein ECs. The in vivo significance of these findings was verified by experiments in which bone marrow–transplanted nude rats were cojected with simvastatin and a cyclic RGD peptide that interferes with the function of integrins αvβ3 and αvβ5. This peptide decreased
that promote EPC mobilization from the bone marrow and re-endothelialization of injured arteries are sufficiently low to allow normal rates of cell proliferation in different tissues and to lack apoptotic effect. In any case, it seems safe to conclude that the list of beneficial effects of statins in vascular disease continues to lengthen.

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References


Schematic model of the involvement of local tissue (yellow and blue colors) and blood cells (rose and red colors) in the formation of atherosclerotic plaques via a modified response to injury model including endothelial and smooth muscle progenitors of bone marrow origin. Arrows indicate migration of cells into a region where the integrity of the endothelium has been interrupted. For further details, see the text. EEL indicates external elastic lamina; FBLs, fibroblasts; IEL, internal elastic lamina; PCs, bone marrow-derived progenitor cells.


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