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ccording 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.

Re-endothelialization Via Bone Marrow-Derived Progenitor Cells

Still Another Target of Statins in Vascular Disease

Johan Thyberg

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 promoter 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 rosuvastatin (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 α5β1 (the main fibronectin receptor) and α5β3, 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 coinjected with simva- statin and a cyclic RGD peptide that interferes with the function of integrins α5β1 and α5β3. This peptide decreased
Recent articles have indicated that progenitors are not confined to ECs but also affect SMCs and leukocytes. The effects of statins on complex processes like atherosclerosis will thus not be limited to ECs and SMCs, but also involve leukocytes. The inhibitory effect of simvastatin on neointima formation suggests that statins at least in part exert their effect by promoting the homing of EPCs to sites of endothelial damage.

Summing up, the articles discussed above add to recent data indicating a basic role of stem cells/progenitor cells in vascular biology and pathology (Figure 1). They also attract attention to a novel effect of statins not directly related to lowering of serum cholesterol. Actions of this type are often due to depletion of early metabolites in cholesterol synthesis implicated in posttranslational modification (isoprenylation) and activation of signaling molecules such as the GTP-binding proteins Ras and Rho/Rac. Interference with these reactions (farnesylation and geranylgeranylation, respectively) cause general disturbances in cell differentiation, proliferation, migration, and survival. The effects of statins on complex processes like atherosclerosis will thus not be confined to ECs but also affect SMCs and leukocytes.

An exciting step forward has been taken but many questions remain. Recent articles have indicated that progenitors of bone marrow origin give rise to neointimal SMCs during transplant arteriosclerosis, lipid-induced atherosclerosis, and vascular remodeling after injury. This may be either positive (lesion stabilization) or negative (lesion growth and obliteration of the vessel lumen). Hence, it will be essential to further clarify the relation between EC and SMC progenitors as well as the mechanisms for their mobilization from the bone marrow, homing to the vasculature, and differentiation. More detailed information about how statins influence these processes is likewise wanted. Cell culture experiments have demonstrated that statins inhibit growth and stimulate apoptosis of many cell types, including ECs and SMCs. However, these effects have often been noted at concentrations higher than those obtained in the blood during clinical treatment. It therefore needs to be made clear whether the statin levels 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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