Novel Faces to Old Friends

A Central Role of Inducible NO Synthase for Progenitor Cell Recruitment and a New Antiinflammatory Mechanisms of Statins

Ralf P. Brandes

Coronary artery bypass grafting (CABG) is performed using autologous vein and arterial grafts. Patency rates of arterial grafts are significantly higher than those of vein grafts. Early vein graft occlusion occurs in up to 12%, potentially attributable to graft thrombosis. The subsequent occlusion rate is 2% to 4% per year, and this problem has been attributed to accelerated vein graft atherosclerosis, a process preceded by intimal hyperplasia that occurs in the first year after implantation. The neointima that forms consists largely of cells expressing smooth muscle markers which are derived in part from circulating progenitor cells (CPC).

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(Circ Res. 2006;98:303-305.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/01.RES.0000208078.53239.53

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The expression of smooth muscle markers. Certainly of relevance to the work by Mayr et al is the fact that interaction between iNOS and the TGF-β1 and PDGF cascades have been demonstrated. Although both growth factors prevent the induction of iNOS in smooth muscle cells, NO inhibits the synthesis and the actions of the two growth factors on smooth muscle cells. Therefore, it is attractive to speculate that NO, generated from iNOS in the vein graft model is a central fate-determining switch for vasculogenic CPC. Consequently, it might be that the enhanced neointima formation observed in iNOS−/− mice is a consequence of a fate change of the CPC. The observation of Mayr et al that exogenous VEGF prevented the effect of iNOS gene deletion on neointima formation, however, argues that VEGF, and not inhibitory effects of NO on the smooth muscle differentiating system, is the predominant fate-determining factor. Most importantly, the data obtained with VEGF suggest that the inhibitory effect of NO on neointima formation is not a consequence of a direct effect of NO on CPC or smooth muscle cell function (Figure). VEGF, however, has effects above and beyond those on CPCs and endothelial cells; such as the recruitment of “inflammatory cells” to the vascular wall. The contribution of the latter cells in angiogenesis, for example, is so central, that a role for inflammatory cells should also be considered in the vein graft model.

If NO acts primarily to promote reendothelialization, it seems obvious to ask about the role of reendothelialization in the prevention of neointima formation. Given that the neointima largely comprises differentiated CPC, it could be speculated that the restoration of endothelial integrity prevents CPCs homing to tissues. Currently there are more open than solved questions regarding the mechanisms, factors, and conditions that control CPC homing. However, integrins are thought to be central to this process, and this class of adhesion molecules mediates the attachment of CPC to the matrix.
Consequently, reendothelialization would prevent CPC-integrin interactions and should therefore block the process of CPC recruitment to the neointima.

What can be done to accelerate the reendothelialization process by CPC? HMG-CoA–reductase inhibitors (statins) mobilize CPC from the bone marrow,13,14 increase the number of CPCs in blood,15 promote CPC differentiation,16 and accelerate reendothelialization.17 Indeed, pravastatin (albeit at high concentrations) suppresses intima hyperplasia in a rabbit vein graft model.18 HMG-CoA–reductase inhibitors also improve vein graft patency rates in humans, although it is unclear whether this effect is a consequence of the lipid lowering action of the statins, of their pleiotropic effects on CPC, or of the antiinflammatory actions of this class of compounds.19

It is only recently that the antiinflammatory effects of statins have gained more attention.20 Most of these pleiotropic effects are attributed to the inhibition of protein isoprenylation. Consequently, statins affect a very broad range of signaling molecules, in particular small GTPases. In this issue of Circulation Research, Paumelle et al report that in mouse macrophages and neutrophils the antiinflammatory effects of statins are operative in man, and are of clinical and pathophysiological importance.

Acknowledgments
This manuscript was supported by a grant from the Deutsche Forschungsgemeinschaft (BR1839/2–3).

References

standing of the mechanisms underlying neointima formation and the antiinflammatory action of statins. The next challenge will be to determine whether or not the mechanisms described are operative in man, and are of clinical and pathophysiological importance.


Key Words: progenitor cells PPAR statins
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Circ Res. 2006;98:303-305
doi: 10.1161/01.RES.0000208078.53239.53
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/3/303

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