Genetic Susceptibility to Restenosis
Role of Bone Marrow Cells and Inflammatory Response
Masafumi Takahashi

Cardiovascular diseases such as ischemic heart disease are predicted to be the leading cause of death worldwide in the near future. Despite recent advances in percutaneous coronary intervention (PCI), including balloon angioplasty and stent implantation, restenosis is still the major limitation to long-term success of PCI. Restenosis is considered to be a wound healing response to trauma attributable to vascular injury; it is a multifactorial biological process resulting from interactions between extrinsic and intrinsic factors that predispose an individual to this condition. Extrinsic factors include anatomic lesion features (small vessel size, long lesions, and total occlusion), technical factors (dilatation pressure and the use of stents and medication), and humoral factors (blood glucose and cholesterol). The intrinsic factors predisposing to restenosis are most probably genetically determined. Other factors (blood pressure and the use of stents and medication), and humoral factors (blood glucose and cholesterol). The intrinsic factors predisposing to restenosis are most probably genetically determined.

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The genetic susceptibility of inbred mice strains to restenosis has previously been demonstrated. Harmon and colleagues examined arterial remodeling and neointimal formation after ligation of the left carotid artery in 11 different inbred mice strains and identified differences among the strains in response to different arterial injuries. Kuhel et al. examined the susceptibility of 5 mice strains to neointimal formation after catheter probe–mediated endothelial cell denudation and demonstrated that C57BL/6 mice were resistant to neointimal formation after injury, whereas C57L/J mice were susceptible to it. They further showed that multiple genes are involved in genetic susceptibility to neointimal formation by backcross experiments between C57L/J and C57BL/6 mice. Moreover, Sindersmann et al. demonstrated that electric vascular injury induced marked neointimal formation with infiltration of CD3+ lymphocytes in the mouse strain 129 and revealed the importance of the enhanced vascular inflammatory response in genetic susceptibility to restenosis.

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In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Langerwieser et al. compared the susceptibility of major histocompatibility complex (MHC)-compatible strains of inbred mice to intimal formation after wire-mediated vascular injury. They used 129X1/SvJ mice, which are reported to form extensive neointima after injury, and MHC-compatible strain C57BL/6 mice, which are reported to be less prone to neointimal formation. Gene expression analysis of neointimal tissue revealed differences in expressed genes associated with hematopoietic stem and progenitor cells (HSPCs) and inflammation. It is interesting to note that mobilization of CXCR4+ HSPCs after injury was remarkably increased in 129X1/SvJ mice, but not in C57BL/6 mice. Successful bone marrow transplantation between 129X1/SvJ and C57BL/6 mice was performed without immunosuppression because of MHC-compatibility in these 2 strains. The extent of neointimal formation and adventitial inflammatory response (CD45 infiltration) after injury was strictly associated with the genetic background of the bone marrow cells. Therefore, the authors propose that this differential response to injury is the mechanism underlying the difference in genetic susceptibility to restenosis in the 2 mouse strains (Figure).

Bone marrow–derived CXCR4+ cells play an important role in vascular homeostasis; however, the precise role of CXCR4+ cells in vascular diseases is still controversial. Several investigations showed that bone marrow–derived CXCR4+ cells function as smooth muscle progenitor cells (SMPCs) and contribute to neointimal formation after injury. In contrast, other investigations suggested that bone marrow–derived CXCR4 cells function as endothelial progenitor cells (EPCs) and promote neovascularization in ischemic tissue. From these findings, it is postulated that CXCR4+ cells have the potential to function as both EPCs and SMPCs and contribute to neointimal formation and neovascularization, depending on the circumstances. Another issue to be discussed is the inflammatory response to vascular injury. In general, the intensity of the inflammatory response in the vascular wall is thought to be dependent on the intensity of the injury. However, Langerwieser et al. suggested that mobilization and recruitment of CXCR4+ cells are the determinant factors for vascular wall inflammation. In this regard, the expression levels of CXCR4 in bone marrow cells paralleled the secretion of inflammatory cytokines, including IL-1β. Thus, it is likely that bone marrow–derived...
CXCR4+ cells play a role not only by differentiating into vascular cells but also in the inflammatory response.

Although it is assumed that a difference in pathophysiological mechanism(s) exists between restenosis and atherosclerosis, research in genetic susceptibility to atherosclerosis might provide useful information. In contrast to the study by Langerwieser et al,6 the C57BL/6 mice and 129/SvJ mice were reported to be susceptible and resistant, respectively, to atherosclerosis. Thus, susceptibilities to restenosis and atherosclerosis are currently considered to be independent of genetic control.11

Langerwieser et al10 used wire-mediated endothelial denudation to assess vascular response to injury. As mentioned above, several surgical procedures have been reported for the induction of injury.3–5 Tanaka et al12 reported that contribution of bone marrow–derived cells to neointimal formation considerably differs depending on the procedures used for vascular injury induction; therefore, these procedures might influence the contribution of bone marrow–derived cells.

In summary, although further research in the genetic control of susceptibility to restenosis is required, the findings obtained in mice can probably be extrapolated to human restenosis. Langerwieser et al10 have provided major inputs confirming that bone marrow–derived CXCR4+ cells could be new targets of genetic susceptibility to restenosis. A further understanding of the genetic factors underlying restenosis will help us to develop tailored therapies on the basis of an individual’s genetic predisposition.

Disclosures

None.

References

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doi: 10.1161/ATVBAHA.109.194928
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

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