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 controlled; for instance, an individual’s response to vascular injury or implantation of foreign materials. Extrinsic factors may also influence the process of gene expression, indicating that associations exist between the intrinsic and extrinsic factors. Previous studies have demonstrated significant associations between gene polymorphisms and susceptibility to restenosis after PCI. Furthermore, a bimodal distribution in angiographic restenosis after stent implantation was observed, suggesting the existence of 2 patient populations with different susceptibilities to restenosis.

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 mouse strains and identified differences among the strains in response to different arterial injuries. Kuhel et al examined the susceptibility of 5 mouse 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, Sindermann 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.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Langerwieser et al compared the susceptibility of major histocompatibility complex (MHC)-compatible stains 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-compatability 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...
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 al. 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

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