Comparative Genetics of Atherosclerosis and Restenosis: Exploration With Mouse Models

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schemic heart disease is a consequence of coronary atherosclerosis. In addition to coronary bypass surgery, a common and often successful treatment is angioplasty, expanding the internal lumen of the coronary artery with a balloon. However, 30% to 50% of angioplasty patients soon develop significant restenosis, a narrowing of the artery through migration and growth of smooth muscle cells. Stents introduced into the coronary artery to keep it open after angioplasty considerably reduce the incidence of restenosis, but 10% to 50% of patients receiving stents still develop restenosis.1 Recent clinical trials that use local radiation to the treated artery or drugs released by the stent, such as sirolimus and paclitaxel, are reported to improve the clinical outcomes2–5 but may only provide transient protection. Even after these efforts, restenosis remains a major clinical problem in light of the more than 800,000 angioplasty procedures in the United States each year and the generally disappointing results of efforts to prevent restenosis with systemically delivered drugs in humans.

An understanding of the genetic factors underlying restenosis will help identify those patients resistant to restenosis for whom treatment is most likely to be successful. More importantly, identifying the critical genes involved will clarify the molecular mechanisms controlling restenosis, providing possibilities for substantially more effective therapeutic control of this significant problem.

Exploring the genetics of restenosis has now begun in experimental animals with significant implications for the human condition. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Kuhel et al6 have compared the susceptibility of five inbred mouse strains to injury-induced neointimal hyperplasia, which is a model of restenosis, and demonstrated considerable variation among strains. Their results make it clear that susceptibility to restenosis and to atherosclerosis, which both narrow the coronary artery, are not correlated with each other, even though atherosclerosis7 and restenosis8 are both under genetic control. They found that inbred strain C57BL/6 was resistant to restenosis and strain C57L was susceptible despite the fact that both these strains are quite susceptible to atherosclerosis. This study has taken a major step forward by making it clear that atherosclerosis and restenosis are under independent genetic control. Although these biological processes may share some minor features, the major controlling features are unique to each. Further genetic analyses are likely to be highly informative.

It is not surprising that atherosclerosis and restenosis are controlled by different genes because they differ in many respects. In humans, atherosclerosis develops slowly over decades whereas restenosis occurs only three months after angioplasty.9,10 Atherosclerosis involves a complex interaction among lipids, endothelial cells, circulating and tissue inflammatory cells (especially macrophages), platelets, and vascular smooth muscle cells, eventually resulting in deposition of lipids, formation of fibrous plaques, and rupture of those plaques. In contrast, restenosis is the process of growth factor–dependent proliferation of smooth muscle cells, migration of those cells from media into the intima, synthesis of extracellular matrix, and adventitial scarring. Restenosis usually does not involve lipid accumulation.

At least two different processes are involved in restenosis. One is neointimal hyperplasia, which is the proliferation of smooth muscle cells inside the internal elastic lamina. The other is arterial remodeling, which is the enlargement (positive remodeling) or constriction (negative remodeling) of the entire artery. Both play a role in clinical restenosis; it is thought that the response to balloon angioplasty is mostly negative arterial remodeling and the response to a stent is mostly neointimal hyperplasia. These are measured in different ways. Clinically, restenosis is measured by the size of the lumen of the coronary artery. Neointimal hyperplasia is measured by the size of the smooth muscle and extracellular matrix proliferation from the internal elastic lamina to the lumen, and this is what Kuhel et al6 measured. Arterial remodeling is measured by the area circumscribed by the external elastic lamina or by the perimeter of the external elastic lamina. It has been proposed that one reason drug treatment in animal models of restenosis has failed to predict the outcome of drug treatment in humans is the different ways restenosis is measured.11

Previously, Harmon et al12 demonstrated differences among mouse strains in response to a different type of arterial injury. In contrast to the endothelial denudation caused by a catheter probe, as used by Kuhel et al6, Harmon and colleagues12 ligated the carotid artery to prevent blood flow, and they measured separately arterial remodeling and neointimal hyperplasia, both of which occurred in the response to this injury. Combining the results reported in both studies6,12 with work from our laboratory,13,14 we summarize the susceptibilities of several strains to these three disease processes that can each narrow the coronary artery: atherosclerosis, neointimal...
Restenosis occurs in atherosclerotic arteries. In part, this occurs because the response to injury in these arteries is different from that in normal arteries. In human coronary arteries, angioplasty is typically successful, whereas in rat and mouse models of restenosis, the underlying cellular and molecular mechanisms are similar to those in the normal vessel wall. This finding suggests that differences in the underlying cellular and molecular mechanisms are responsible for the differences in restenosis susceptibility between the two species.

Hyperplasia, and arterial remodeling (Table). Susceptibilities to these three processes are not correlated with each other among the strains and must thus be under independent genetic control. In further genetic studies, it will be an advantage to measure each of these processes. Not only are different genes and molecular mechanisms likely to be involved, but the genetics leading to coronary artery narrowing, involving as it does all three, will necessarily be more complex than the genetics of the individual components.

Kuhel et al.6 also demonstrated that preexisting increased LDL and decreased HDL levels, which are significant risk factors for atherosclerosis, do not affect neointimal hyperplasia. The degree of hyperplasia was similar in mice fed low- or high-fat diets despite large lipoprotein differences between the two groups, a result consistent with human studies showing no association of plasma lipids and restenosis.15

Restenosis studies in rat and mouse models are criticized for being conducted in normal arteries, whereas human restenosis occurs in atherosclerotic arteries. In part, this problem can be solved by either feeding mice with a high fat diet for a period of time long enough to induce significant atherosclerosis, or by using ApoE- or Ldlr-targeted mutant mice, both of which develop spontaneous atherosclerosis. Still, the fatty streaks and lesions induced in such models are different from the fibrous plaques and advanced lesions typical of the human arteries in which angioplasty is performed.

Other animal models of restenosis exist: rat, rabbit, swine, canine, and nonhuman primate models. The major differences among these models are the size of the coronary artery lumen, the inducibility of preexisting atherosclerosis before experimental injury, and the similarity of the response to injury with that in humans. In these regards, mouse models are not the best, but they have some unique advantages that become especially important if for restenosis, as for many other pathologies, the underlying cellular and molecular mechanisms are alike in mouse and human. First, because there are many well-characterized inbred mouse strains, strain surveys of the susceptibility to restenosis can be made relatively easily, as shown by the work of Kuhel et al.6 Second, perhaps more importantly, it is realistic to use these differences in the mouse to begin the identification of the genes involved and from that the critical cells and molecules. The relevant genes can be mapped by crossing strains with phenotypic differences in a process known as quantitative trait loci (QTL) mapping. Murine QTL can be found relatively quickly and inexpensively. This strategy has been used to find at least 16 murine QTL for atherosclerosis (R. Korstanje and B. Paigen, unpublished data, 2002). When QTL are found, several approaches can be used to find their underlying genes.16 The completion of human and mouse genome sequencing, the advancement of new technologies, such as DNA microarray, and the availability of more sophisticated statistical tools such as those for detecting gene-gene interactions,17 have greatly accelerated and simplified the process of identifying QTL genes.

In their initial backcross between C57L and C57BL/6, Kuhel et al.6 showed that neointimal hyperplasia is a complex trait controlled by multiple genes. When the responsible murine genes are identified, we will know more about the mechanism and may be able to extrapolate these findings to human restenosis. If the mouse genes are relevant to human, their human counterparts can be located by comparative genomics.18,19 Finding the underlying genes will help identify patients for whom treatments will be successful, may lead to therapies that do not aggravate atherosclerosis, and may even provide new targets for gene therapy.

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References


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