Toward New Therapeutic Strategies Against Neointimal Formation in Restenosis

François Mach

Physiopathology of Restenosis

Percutaneous transluminal coronary angioplasty (PTCA) has become the treatment of choice for severe cases of coronary artery atherosclerosis, and currently, >1 million PTCA interventions are performed each year worldwide.1 However, despite its overall value in achieving an immediate increase in lumen diameter, PTCA often triggers local arterial renarrowing (restenosis). This occurs in 20% to 50% of cases within 3 to 6 months and represents a major clinical and economic problem.2 Although several drugs have been shown capable of preventing or reducing the proliferative healing response after arterial injury in experimental animal models, only stenting has proved effective in reducing postinterventional restenosis in humans.3 Prevention of restenosis is therefore a major challenge, which highlights the need to better understand the interplay of the various components responsible for restenotic lesions.

Arterial restenosis after balloon angioplasty is a complex and multifactorial wound healing process that involves several redundant and overlapping mechanisms. Schematically, one distinguishes 4 interrelated issues.4,5 First, a vessel wall “elastic recoil” (vasoconstriction due to endothelial disruption) occurs, which tends to present within 24 hours of PTCA and which may be of predictive value for subsequent restenosis. Second, a mural thrombus forms, which occurs within 2 to 3 weeks and involves local platelet activation and thrombin secretion; an increase in smooth muscle cell activation, proliferation, and migration; and leukocyte recruitment at the site of balloon injury. This complex process then induces neointimal hyperplasia. Already beginning 48 hours after balloon injury, the major wave of neointimal growth occurs over the ensuing weeks to months, as smooth muscle cells continue to replicate and produce large amounts of extracellular matrix. Indeed, aberrant synthesis of extracellular matrix seems to contribute even more than does cell proliferation to the changes in volume and shape seen in restenotic lesions. Finally, after angioplasty, the vessel wall undergoes a major remodeling process, which is usually defined as a change in artery wall size without a change in artery wall mass. In the case of restenosis, a slow vasoconstriction (negative remodeling), occurring over weeks or months, results in luminal narrowing. This remodeling process can occur independently of “elastic recoil,” thrombus formation, or neointimal formation.

While there is no doubt that vessel wall recoil and mural thrombus contribute actively to restenosis, there has been some controversy regarding the respective contributions of neointimal formation versus negative arterial remodeling as the major cause of restenosis after balloon injury.2 For many years, the working hypothesis of restenosis had focused on neointimal hyperplasia. However, recent results from both animal and human studies have suggested that after angioplasty, the failure to maintain expansion of the artery wall rather than neointimal thickening was the main cause of restenosis.6,7

The Growing Importance of “In-Stent Restenosis”

These different views on the pathogenesis of restenosis are directly relevant to therapeutic strategies. Indeed, as almost all drug therapies directed against remodeling have failed to prevent restenosis after balloon angioplasty in humans, alternative intracoronary approaches with the use of stents have emerged to mechanically inhibit remodeling and thus, restenosis. Intracoronary stent placement has become the leading procedure in many interventional centers, and numerous clinical studies have demonstrated the benefit of stents in reducing postinterventional restenosis.2 Unfortunately, although stenting is clearly effective in preventing negative remodeling, long-term success remains limited by the occurrence of late in-stent restenosis with an incidence of 20% to 40%, depending on the stent design and the population studied.2 Interestingly, this “novel” restenosis pattern appears to be due purely to neointimal hyperplasia.8 Because of this high incidence of in-stent restenosis and of the essential role of neointimal formation, it is reasonable to reevaluate therapies that would limit neointimal growth, independent of any effect on the remodeling process.

Beneficial Effect of Anti–VCAM-1 Antibodies Against Neointimal Formation in a Mouse Model

Neointimal formation after balloon injury is largely due to vascular smooth muscle cell proliferation, migration, differentiation, and activation with secretion of extracellular matrix, as well as leukocyte recruitment. Several recent studies have documented that after arterial injury, not only endothelial cells but also vascular smooth muscle cells express the cellular adhesion molecules intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 (VCAM-1).2 In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology,
Oguchi and coworkers\(^9\) report the use of an anti–VCAM-1 antibody to prevent neointimal formation after arterial injury in a mouse model of atherosclerosis. Inhibition of VCAM-1 function by antibody treatment significantly and profoundly reduced neointimal formation and monocyte/macrophage infiltration after arterial injury. Because VCAM-1 interacts with the integrin αβ\(^1\) (very late–acting antigen 4 [VLA-4]) that is constitutively expressed on the surface of leukocytes, it is not surprising that blockade of the VCAM-1/VLA-4 pathway reduces monocyte infiltration. Other reports have shown that inhibition of this particular integrin-ligand pathway reduces inflammation in numerous pathologies, including the development of primary atherosclerosis.\(^10,11\) Moreover, prevention of primary atherosclerosis that was observed after blocking the CD40/CD40L pathway in vivo was associated with a strong reduction of VCAM-1 expression on vascular cells.\(^12\) Interestingly, Oguchi and colleagues\(^9\) also found that in vivo inhibition of VCAM-1 partially prevented the loss of α-actin expression by smooth muscle cells after vascular injury, a loss that is related to phenotypic modulation of these cells. In addition, the authors demonstrated that VCAM-1, which is thought to act primarily or only on leukocyte chemotaxis, may also play an important role in the migration of smooth muscle cells, very likely via VLA-4, which was recently identified on smooth muscle cells.\(^13\) These findings suggest that expression of adhesion molecules on smooth muscle cells influences their proliferation, differentiation, and migration and therefore, may actively contribute to the inflammatory neointimal formation process within the vascular wall after arterial balloon injury.

**New Targets and New Strategies for In-Stent Restenosis**

The complex mechanisms of restenosis and the redundancy of cellular migration and proliferation pathways allow us to define other potential targets for the prevention and reduction of in-stent restenosis after balloon injury. As demonstrated for primary atherosclerosis,\(^8\) neointimal hyperplasia after arterial injury involves numerous interrelated components, such as coagulation factors (eg, plasminogen activator inhibitor, tissue factor, and thrombin); growth factors (eg, platelet-derived growth factor, epidermal growth factor, and insulin-like growth factor-1); chemokines and their receptors (eg, interleukin-8, monocyte chemotactic protein-1, interferon-induced protein-10, CC-chemokine receptor-1 and -2, and CXC-chemokine receptor-3; matrix metalloproteinases-2, -3, -9, and -11; mediators of apoptosis [Bcl-x\(^L\]); and even infectious agents (eg, cytomegalovirus or *Chlamydia pneumoniae*). Experimental modulation of these different components and interactions by antibodies, selective genetic inactivation (preferably condition-\(^a\)), or other strategies will soon clarify their individual roles in neointimal hyperplasia and thus, help identify novel therapeutic targets for the prevention of in-stent restenosis.

Finally, the strategy of drug delivery might also be crucial in the treatment of restenosis after stent implantation. Indeed, for every localized coronary stenosis that justifies angio-plasty, the same patient also has other multiple, clinically silent lesions. Systemic delivery of agents that inhibit cellular proliferation and migration could have a negative effect and even induce pathology at those silent sites, even though they may succeed in reducing restenosis at the location of injury. Therefore, because the site of PTCA predicts exactly where subsequent pathology will develop and since treatment should prevent rather then cure restenosis, local drug delivery strategies (eg, gene therapy,\(^14\) irradiation,\(^15\) or stent-mediated drug delivery) during stent implantation should be seriously considered. This method would provide prolonged, potent, and locally active therapies to reduce the extent of restenosis and thus, contribute positively to the major limitation of PTCA.

**References**


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