Inflammatory response is triggered when tissues are exposed to a variety of insults. This response consists of a cascade of events that includes release of various chemical mediators and recruitment of circulating blood cells (platelets, leukocytes, and monocytes) to the site of injury and their subsequent activation. The inflammatory response attempts to contain the damaging effects of the insult, leading to recovery from its injurious effects. However, when normal checkpoints that limit continuing or ongoing inflammation fail, inflammatory response can become a liability that leads to a diverse group of diseases, including atherosclerosis and thrombosis. A large body of evidence has implicated inflammation in the initiation, progression, and destabilization of atherosclerotic vascular disease, linking many of the known risk factors to atherothrombosis. However, the role of inflammation in other vaso-occlusive disorders, such as neointimal thickening after mechanical injury to arteries during angioplasty and/ or stenting, is not as well appreciated. Neointimal thickening after mechanical injury predominantly consists of a fibroproliferative reaction initially involving proliferating smooth muscle cells and later dominated by accumulation of extracellular matrix. Neointimal thickening plays a decisive role in restenosis after stenting because stenting essentially precludes constrictive remodeling, whereas postangioplasty restenosis involves elastic recoil and constrictive or negative vessel wall remodeling (vessel shrinkage) in addition to neointimal thickening. An improved understanding of the molecular mechanisms leading to neointimal thickening after mechanical injury would pave the way for development of novel therapeutic approaches for prevention of restenosis, which has remained the Achilles’ heel of endovascular interventions.

Several lines of evidence have suggested that platelet/fibrin deposition and activation of inflammatory genes, followed by increased leukocyte trafficking into the injured vessel wall, may provide a key stimulus for subsequent neointima forma-

tion. Although most experimental studies have identified mononuclear leukocytes (monocyte-macrophage lineage) as the primary inflammatory cell types, some models of balloon angioplasty have implicated neutrophils as well. The prevailing paradigm assigns the origin of proliferating neointimal smooth muscle cells to medial smooth muscle cells and/or adventitial myofibroblasts, which are thought to be attracted to the site of injured intima in response to chemotactic and mitogenic products released by arterial injury, and inflammatory cells. Recent experimental observations have challenged this dogma, suggesting that circulating progenitor cells derived from the bone marrow or other organs may actually home in to the site of vascular injury and transform into smooth muscle cells, contributing to neointima formation in diverse vaso-occlusive pathologies. This tantalizing and provocative concept needs further validation. Leukocyte trafficking into the vessel wall is regulated by a number of genes that include selectins (especially P-selectin and E-selectin) that stimulate initial rolling of leukocytes along the vessel wall; integrins such as Mac-1 and cell adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which cause mononuclear cells to adhere to the vessel wall; chemokines such as monocyte chemotactic protein (MCP)-1, interleukin-8, interferon gamma–inducible CXC chemokines, eotaxin, and possibly others that regulate interendothelial diapedesis of leukocytes into the subendothelial space; and colony-stimulating factors such as macrophage colony–stimulating factor (M-CSF) and granulocyte M-CSF, which activate resident mononuclear cells, enhancing their survival, proliferation, and mitogenic effects. Experimental studies examining the time course of cellular events in the injured vessel wall have demonstrated inflammatory cell recruitment in the early hours and days after mechanical injury, with persistence of inflammation for weeks and months with stenting, along with a strong direct correlation between the magnitude of inflammatory cell accumulation and the magnitude of subsequent neointimal mass. Similarly, inhibiting inflammatory cell accumulation by inhibiting genes that regulate leukocyte trafficking, such as Mac-1, vascular cell adhesion molecule-1, P-selectin, and MCP-1, has generally resulted in reduced neointimal mass, lending credence to the hypothesis that inflammation begets neointimal thickening. These results are further supported by experiments in knockout mice lacking key genes (Mac-1, P-selectin) or by using gene therapy with dominant negative mutants of MCP-1 gene therapy to suppress MCP-1. We have recently observed that M-CSF–null genotype in mice (op/op mice) nearly completely inhibits neointimal thickening after perivascular carotid injury, whereas local perivascular delivery of recombinant M-CSF

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restores neointimal thickening, implicating M-CSF as an obligate gene for neointimal response to injury in mice (Rajavashisth et al, Cedars Sinai Medical Center, Los Angeles, Calif, unpublished observations, 2003).

Rolling of leukocytes along activated endothelium or on activated platelets at sites of endothelial denudation followed by firm adhesion is an early event before leukocyte recruitment into the vessel wall. This early rolling and adhesion of leukocytes to the vessel wall is regulated by a number of genes, which include P-selectin.16,18 P-selectin is expressed by activated platelets that adhere to sites of endothelial denudation early after arterial injury and is also expressed by activated endothelium and regenerating endothelium a few weeks after arterial injury. P-selectin supports leukocyte rolling and adhesion by interacting with its main ligand (P-selectin glycoprotein ligand [PSGL]-1) expressed by leukocytes. An inhibitory effect of P-selectin–null genotype on inflammatory cell recruitment and subsequent neointimal thickening in mouse carotid and femoral artery injury models suggests an important role for this molecule in arterial response to injury.16

In the present issue of Circulation, Phillips et al19 provide further confirmatory evidence in support of this hypothesis. The authors used hypercholesterolemic apolipoprotein E–null mice fed a Western diet a week before and for 4 weeks after wire-induced carotid injury and administered a single intraperitoneal injection of monoclonal antibodies to P-selectin (2 doses) or PSGL-1 (1 dose) or an isotype control IgG 3 hours before injury. Compared with controls, P-selectin antibody significantly reduced both macrophage immunoreactivity and neointimal thickening 4 weeks after injury in a dose-dependent fashion (50% to 80% reduction in neointima), whereas the single dose of PSGL-1 antibody produced a 55% reduction in neointimal thickening. The magnitude of macrophage immunoreactivity correlated well with neointimal thickening both in controls and in treated mice. The striking differences in neointimal thickening were noted despite similar degrees of hypercholesterolemia and the initial extent of arterial injury among the various groups of mice. The authors appropriately concluded that their results confirm an important if not obligate role for P-selectin–mediated inflammatory cell recruitment in neointima formation in the murine model. Although generally supporting a causal link between inflammation and neointimal thickening, this study raises some questions. First of all, while murine models of vascular injury involving normal arteries without underlying atherosclerotic plaque and with severe hypercholesterolemia have improved our understanding of molecular events triggered by injury in the vessel wall, how well these events reflect or correlate with biology of post-PTCA or post-stent neointimal thickening is unknown. Limited morphological observations in human examples of coronary stenting have provided data to support the link between inflammation and neointimal hyperplasia.7 These observations are further supported by recent evidence suggesting an increased risk of restenosis in humans when systemic markers of inflammation such as C-reactive protein or MCP-1 are elevated.5,20,21 Furthermore, results from experimental and clinical trials that have shown markedly reduced rates of in-stent restenosis with local delivery of rapamycin (a potent antiproliferative and antiinflammatory drug) via drug-eluting stents have also helped corroborate this hypothesis.22

Second, one needs to consider how well this strategy for inhibition of neointimal hyperplasia can be translated to the clinical setting. The durability of the results from a single injection of an antibody observed in this study needs to be verified with more prolonged observation, especially in view of the fact that endothelial regeneration 3 to 4 weeks after injury may provide a renewed source of P-selectin and leukocyte trafficking at a time when the inhibitory antibody is no longer around. This is particularly relevant in the case of stenting, which is the most commonly performed endovascular intervention in humans, where peri-stent inflammation is prolonged, highlighting the need for prolonged antiinflammatory therapy.5,7 Similarly, unlike nonatherosclerotic murine arteries used in this model, human atherosclerotic lesions often already contain a variable number of chronic inflammatory cells, especially when the lesions are lipid rich; hence, a strategy that targets the earliest steps for leukocyte entry into the vessel wall would work in this setting also remains unclear. In atherosclerosis, adventitial and intimal vascularity is increased, providing another potential portal of entry for inflammatory cells, and it is not clear whether P-selectin–targeted strategy would also block this route of leukocyte entry into the vessel wall. Finally, activation of redundant pathways utilizing redundant genes regulating leukocyte entry into the vessel wall may also thwart attempts to block leukocyte entry when therapies target one gene early in the leukocyte entry cascade. Notwithstanding these potential limitations, Phillips and colleagues19 have provided yet another piece of data to support the dictum that “when leukocytes roll, the arteries thicken,” thus strengthening the inflammatory paradigm of neointimal thickening and restenosis. However, translation of such concepts to prevention of restenosis in humans must take into account the numerous nuances that separate animal models of injury of normal arteries from the complexities inherent in models of injury involving human atherosclerotic arteries.

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References


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