The use of percutaneous coronary intervention (PCI) for the treatment of ischemic coronary artery disease has dramatically increased during the past three decades. PCI also induces a marked inflammatory reaction in the injured vessel wall that leads to the development of neointimal thickening and restenosis. The proliferation of smooth muscle cells (SMCs) with the subsequent formation of an intimal thickening is a major event in the development of atherosclerotic lesions and is believed to contribute to the restenosis of arteries following balloon angioplasty. Immediately after endothelial denudation and medial wall injury following PCI, important triggers of the wound “healing” program occurred. Vascular SMCs retain remarkable plasticity and can undergo dedifferentiation to a synthetic phenotype. It enables the efficient repair of the vasculature after injury. As in many evolutionarily conserved processes, these properties can be disadvantageous and can predispose to abnormal responses after injury, contributing to restenosis.

Pentraxins, an essential component of the humoral arm of innate immunity, are a superfamily of acute-phase proteins highly conserved during evolution that are composed of short pentraxins such as C-reactive protein (CRP) and long pentraxins such as pentraxin 3 (PTX3). The latter has an unrelated long N-terminal domain coupled to the CRP domain and recognized ligands. PTX3 in humans, as CRP, is a marker of acute coronary syndrome and correlates with the risk of developing vascular events, including restenosis after the implantation of bare metal stents. PTX3 is stored in a ready-made form in neutrophils, localized in specific granules, and secreted in response to the recognition of microbial moieties and inflammatory signals. Cytokines and endotoxins induce endothelial cells, macrophages, and dendritic cells to synthesize PTX3. Similar to antibodies, PTX3 binds to pathogens, activates complement, and opsonizes particles. In addition to having recognition and effector functions, evidence shows that PTX3 can regulate inflammatory reactions.

In this issue of the Journal of Atherosclerosis and Thrombosis, Ishino et al. reported that PTX3 plays a role in preventing vascular remodeling function in a model of wire vascular injury in mice. This investigation was designed to assess the role of PTX3 in neointimal hyperplasia after wire vascular injury, taking the advantage of gene-targeted mice. The neointimal hyperplasia occurred twenty-eight days after the injury, with PTX3 being highly expressed at both mRNA and protein levels. In PTX3-deficient mice, the neointimal hyperplasia following the injury involved a higher number of macrophage infiltration than in wild-type mice. This was paralleled by a marked increase in the intima-to-media ratio at 4 weeks after the injury.

The in vivo role of PTX3 in inflammatory conditions has been investigated through the use of PTX3-overexpressing and -deficient mice. Cammozzi et al. demonstrated that PTX3 inhibits fibroblast growth factor 2 (FGF2)-dependent intimal thickening after vascular injury in mice. Deban et al. reported that endogenously secreted PTX3 bound P-selectin and affect leukocyte rolling in thrombin-stimulated vessels. PTX3-deficient mice are more susceptible to ischemia-reperfusion injury associated with more neutrophil infiltration. In a model of acute myocardial infarction caused by coronary artery ligation, PTX3-deficient mice showed exacerbated heart damage with a greater no-reflow area and increased inflammatory response. PTX3 and ApoE double knockout mice develop larger atherosclerotic lesions with overexpression of proinflammatory gene expression pattern in the vascular wall. In their gene expression pattern, adhesion molecules, cytokines, and chemokines in the...
vascular wall were induced. These findings suggest that PTX3 possesses a cardioprotective function to modulate the vascular-associated inflammatory response (Fig. 1, 2). The increased levels of PTX3 in cardiovascular disease could reflect a protective physiological response.

Although this study demonstrated that PTX3 has a protective function dampening inflammation in a model of restenosis after wire injury, there are several limitations. The study of balloon-injured mice femoral arteries permitted precise understanding of the kinetics of intimal thickening after this type of injury; however, the attempts to transfer this information to human restenosis met with considerable frustration. This disparity between the experimental injury of animal arteries and human restenosis is not surprising. The substrate of the animal studies was usually a normal artery rather than an atherosclerotic one, with all the attendant cellular and molecular differences highlighted earlier.

This study now clarifies that PTX3 may prove beneficial to prevent restenosis after percutaneous coronary intervention. Further studies are required to understand how PTX3 prevents intimal hyperplasia after vascular injury and to test the protective function of neointimal hyperplasia after mechanical injury in mice with atherosclerosis (e.g., ApoE knockout mice).

Conflicts of Interest

None.

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