Neointimal hyperplasia, vein graft remodeling, and long-term patency

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NEOINTIMAL HYPERPLASIA is generally considered as the major cause of vein graft stenosis and is the leading pathological sign of vein graft disease. Most research on this problem has focused on the inhibition of neointimal growth, based on the hypothesis that the inhibition of neointimal hyperplasia would improve long-term patency of the vein graft. However, the inhibition of cell proliferation-mediated early neointima accumulation does not translate into clinical benefits (5). In small animal models, neointimal hyperplasia is an early event lasting as long as several weeks after vein graft implantation (9). There is no direct scientific evidence showing that an early inhibition of neointimal hyperplasia will result in improving long-term patency. Neointimal formation is also regarded as a pathophysiological adaptation to increased cyclic intramural tension. Moreover, as stenosis is defined as a +50% reduction in luminal diameter (2), the neointima established in many vein graft animal models does not result in a significant loss of luminal area. In the clinic, long-term (up to 15 years) and progressive vein graft disease is of much more concern compared with the acute neointimal hyperplasia that usually occurs within one year (1).

In the American Journal of Physiology-Heart and Circulatory Physiology, Jiang and colleagues’ study (3) extends our understanding of chronic fibrotic remodeling in the established neointima. The authors show that cell proliferation-mediated neointimal formation predominated in the first month, whereas further neointimal expansion (~6 mo) was mediated by the accumulation of extracellular matrix via TGF-β/connective TGF-dependent pathways. Consistently, a knockdown of TGF-β in vein graft results in a reduced neointimal area and collagen content at 12 wk in a rat model, whereas an overexpression of TGF-β showed opposite results (7). The chronic fibrotic remodeling expressed in this model warrants further use as a comparable animal model for the study of chronic vein graft remodeling. However, since this study was conducted with healthy animals, the vein grafts appeared healthy up to 6 mo and may have a very good prognosis for long-term patency. Combining this model with experimental protocols that include a high-fat diet or transgenic animals with cardiovascular diseases could provide additional insights relevant to understanding chronic vein graft disease.

Jiang et al. (4) have previously reported that increased cyclic intramural tension in vein grafts could be the driving force of enhanced TGF-β production that occurs as early as a few days after vein graft implantation and is associated with the recruitment of α-actin-positive myofibroblasts in the adventitia (4). Although this is regarded as an adaptation to the increased cyclic stress, the authors argued that the accumulation of myofibroblast and collagen content may also limit early outward remodeling if the production of TGF-β is not well regulated; this may have deleterious effects on long-term patency. Interestingly, in the current study, an enhanced TGF-β production persisted up to 6 mo coupled with continuous outward remodeling. Thus the fibrotic remodeling could be a beneficial adaptation for the following reasons: 1) the passive cyclic intramural tension is proportional to the luminal diameter under the same pressure (6), and the outward remodeling resulted in an increased cyclic intramural tension; 2) the rabbit jugular vein is very thin and less muscular, and thus increased extracellular matrix is helpful to withstand the arterial blood pressure; and 3) the ratio of neointimal area-to-luminal area or the neointimal thickness was stable over time without progressive neointimal cell proliferation, which was critical for maintenance of the vein graft patency. This raises the question, Is the increased cyclic intramural force the predominant regulator for TGF-β production and fibrotic remodeling? If this is the case, the regulation of TGF-β production may result in unexpected outcomes. As no intervention of TGF-β production was applied in the current study, more investigation is needed to understand the regulation of the persistent elevation of TGF-β and chronic fibrosis in vein grafts.

Matrix metalloproteinases (MMPs), in addition to TGF-β, are important in controlling the balance in the extracellular matrix. Temporal levels of MMPs were also tested by Jiang et al. Although MMP-2 and -9 were significantly elevated at 1 mo, the enzymatic activity of MMPs is diminished despite the persistent elevation of TGF-β production. Logic suggests that this combination contributes to extracellular matrix accumulation. However, others have reported that the upregulation of both TGF-β and MMPs, which correspond with macrophage infiltration and luminal expansion, was exacerbated by a high-fat diet (8). In this case, the fibrotic remodeling is more complicated with the presence of obvious inflammation. With the presence of macrophage infiltration/inflammation, the activated MMPs did not counterbalance the TGF-β-induced fibrosis but put the vein graft at serious risk for the development of atherosclerosis.

This article suggests that the previous research focus on inhibition of acute neointimal hyperplasia should be expanded to include more detailed examination of chronic remodeling on the long-term patency of vein grafts. Jiang and colleagues’ work suggests that some important factors contributing to the acute effects, i.e., TGF-β, can also be involved in the chronic pathology of neointimal hyperplasia. Expanding the current study to include an examination of mechanical, cellular, and molecular alterations occurring in vein grafts may help to predict long-term patency. A careful selection of proper time windows and interventions will also aid in the elucidation of the subtle mechanisms that drive remodeling in vein graft disease.

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