Tenascin-C: A key molecule in graft stenosis

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Coronary artery bypass grafting (CABG) using venous and arterial grafts is a standard surgical procedure for the treatment of advanced coronary artery disease. However, graft failure is common especially after transplantation of saphenous vein grafts, the first vessels used in CABG [1]. After one year up to 15% and after 10 years up to 50% of saphenous vein grafts are severely affected by neointimal thickening and advanced atherosclerosis. Improved long-term patency and survival in treatment of advanced coronary artery disease has been achieved by the use of arterial grafts from the left internal thoracic (mammary) artery and other arteries such as the right internal thoracic artery or the radial artery [1,2]. However, atherosclerosis and neointimal thickening especially at the site of anastomosis reduce the clinical success of by-pass grafting still today. Therefore, the search for novel therapeutic targets for prevention of graft failure continues. The paper by Sawada et al. [3] in the current issue of *Cardiovascular Research* addresses the role and origin of tenascin-C (TN-C) during neointimal hyperplasia in a mouse model of aorta-to-carotid artery interposition grafting.

Extracellular matrix (ECM) surrounding vascular cells is composed largely of different collagens, proteoglycans, and glycoproteins. TN-C is a member of the tenasin family of glycoproteins involved in vasculogenesis that displays a highly restricted expression pattern during embryogenesis. TN-C forms unique symmetrical hexamers (hexabrachions) consisting of six polypeptide chains that emanate from a central globular assembly domain where the monomers are disulfide-linked at their amino termini [4]. The TN-C monomers contain epidermal growth factor-like domains, fibronectin type-III domains, and a fibrinogen-like domain. This domain structure enables TN-C to associate with a variety of ECM molecules and cell surface receptors such as integrins that allow for different biological responses dependent on the cell type and the respective microenvironment [5]. The biological effects of TN-C comprise control of cell adhesion, migration, differentiation and proliferation. In the adult organism TN-C expression is very low but sharply re-expressed during wound healing and regeneration as well as during pathological processes such as vascular disease, tumorigenesis, and metastasis. TN-C is upregulated during neointimal hyperplasia and is associated with the synthetic, proliferative phenotype of vascular smooth muscle cells (VSMC) after balloon injury [6,7], in pulmonary vascular disease [8], and following aortotomy and vascular grafting [8,9]. TN-C is critically involved in the mitogenic response to growth factors such as EGF and FGF-2 [10] and is one of the downstream effectors of matrix metalloproteinase (MMP) activation. MMP activation generates denatured type-I collagen that induces TN-C expression via \( \alpha_v\beta_3 \) integrins. In turn, TN-C promotes SMC proliferation and prevents SMC apoptosis [11]. The concept of TN-C acting as both a growth and survival factor in vascular disease has been proven in vivo. By antisense/ribozyme constructs targeting TN-C,-specific inhibition of TN-C expression was achieved resulting in increased SMC apoptosis and inhibition of vascular thickening of pulmonary arteries [12]. In addition, TN-C-deficient mice display strong inhibition of neointimal hyperplasia [8]. Therefore, TN-C appears to be a central player during neointimal hyperplasia and vascular remodelling and a potent modulator of SMC-phenotype.

The current paper by Sawada et al. [3] investigates the role of TN-C during arterial grafting in mice. When aortas derived from wild-type (WT) mice were grafted to carotid arteries...
WT mice, TN-C was upregulated in the media and neointima, and VSMC proliferation as well as neointimal thickening occurred. Transplantation of TN-C-deficient aortic grafts into TN-C-deficient mice caused dramatic reduction of neointimal hyperplasia and VSMC proliferation compared with WT-to-WT grafting. Furthermore, even if only the graft or the recipient was TN-C-deficient, dramatic reduction of neointimal hyperplasia occurred. Thus, this study elegantly demonstrates that TN-C is an important promoter of neointimal hyperplasia in arterial grafts. In addition, the authors addressed the origin of neointimal TN-C in the grafts and demonstrated that cells from both the recipient and the donor contribute to neointimal TN-C deposition.

Strategies to treat vascular diseases such as atherosclerosis and the different forms of neointimal hyperplasia have largely been focussed on inhibitors of VSMC proliferation or anti-inflammatory drugs. With the exception of the local administration of rapamycin and paclitaxel via drug-eluting stents, most strategies failed after translation from laboratory animal research to human disease. An alternative target for therapeutic interventions that is still largely underexplored is specific manipulation of vascular ECM and ECM-mediated functions. Especially matricellular proteins such as TN-C appear advantageous because they are modulators of ECM assembly, including large structural components such as collagens, and at the same time are potent modulators of cellular function, as evidenced in the study by Sawada et al. Another group of molecules that possess similar potential are small leucine-rich proteoglycans (SLRPs) such as decorin and biglycan, which are anti-proliferative, increase the strength of collagen matrices, and inhibit growth factor signalling [13,14]. Strategies to interfere with the expression of matricellular proteins and SLRPs appear advantageous since they do not affect cell viability or disrupt collagen structure with the risk of adverse long-term remodelling. Instead, specific changes of matricellular proteins and SLRPs in the vascular ECM may towards formation of an extracellular microenvironment that is not permissive for VSMC proliferation and migration but is stable enough to fulfill hemodynamic functions and secure vessel integrity. One possibility to change the composition of vascular ECM is gene transfer, which has particular potential for vascular grafts that can be treated ex vivo before transplantation. In addition, dissection of specific pathways that regulate ECM accumulation during various vascular diseases will provide starting points for ECM-specific pharmacology. The expression of TN-C in the vascular wall is regulated by biomechanical factors, growth factors, cytokines, and vasoactive peptides. Recently, it has been shown that inhibition of phosphodiesterase III by cilostazol inhibits TN-C expression in VSMC and neointimal hyperplasia [9]. Furthermore, AT-1 antagonists and ACE inhibitors might also be effective inhibitors of vascular TN-C expression in hypertensive patients, since angiotensin II is a potent inducer of TN-C in VSMC. In conclusion, since TN-C is involved in remodelling of human vein grafts [15] and is associated with inflammation in human atherosclerosis [16], inhibition of TN-C expression represents a promising strategy for prevention of neointimal thickening and atherosclerosis of human vascular by-pass grafts that deserves further investigation.

References