Commentary: Late venous graft failure: Mystery solved?

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Sept 11, 2018; accepted for publication Sept 11, 2018; available ahead of print Oct 29, 2018.

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J Thorac Cardiovasc Surg 2019;157:2252-3

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2018.09.038>

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Central Message

The determinants of venous graft patency are multifactorial. Targeting the genes responsible for smooth muscle proliferation may reduce neointimal hyperplasia and provide a novel therapeutic option.

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The long-term patency of the venous graft is extremely clinically relevant and influences coronary artery bypass graft (CABG) procedure outcomes. Neointimal hyperplasia (NIH) results in accelerated atherosclerosis and vein graft failure. An alteration of vascular smooth muscle cell (VSMC) phenotype from a mature contractile to an excessive proliferative state is a key pathogenetic mechanism.¹⁻³ MicroRNA-145 has been extensively studied as it inhibits VSMC-specific overexpression and has been shown to limit the proliferative phenotype phase.⁴

Nishio and colleagues⁵ performed an elegant animal study to evaluate the effectiveness of a specific vector in the ex vivo delivery of microRNA to VSMC, namely microRNA-145-loaded polylactic-co-glycolic acid nanoparticles. Rabbit internal jugular veins were used as interposition grafts to the common carotid artery with ligation of the internal carotid artery to create poor distal runoff and facilitate venous NIH. Histochemical analysis in the venous grafts 2 weeks after implantation showed that the microRNA-145-loaded polylactic-co-glycolic acid nanoparticles were effective in getting into VSMCs and in reducing their proliferative activity as well as vein graft NIH.

Ex vivo gene transfer has rigorously been evaluated as among the promising preventative measures of arterialized vein graft disease. The Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) IV randomized controlled trial⁶ studied the influence of the transcription factor decoy edifoligide. There was no difference between groups with respect to saphenous vein graft failure compared with placebo 1 year post-CABG. These data suggest that late venous graft patency is a complex multifactorial process as also shown by other trials.⁷ Myriad anatomic and surgical factors including the quality and size of the coronary artery target vessel and vein harvesting technique as well as secondary preventative strategies (eg, antiplatelet agents and statins) contribute to the development of vein NIH and occlusion following CABG. These factors were not and could not be accounted for in the study by Nishio

and colleagues,⁵ and a potential future clinical application is severely compromised by the extremely multifactorial nature of long-term human venous graft failure. Moreover, the ultimate result of NIH—namely vein graft atherosclerosis—occurs after several years and is difficult to investigate in animal models that typically examine processes within days or weeks of the initial injury. Furthermore, it is unknown whether adequate durable long-term microRNA-145 expression within VSMCs occurs.

Despite these limitations, the authors should be congratulated for investigating a potentially compelling therapeutic option that may neutralize the final common pathway of vein graft failure irrespective of etiology. This study reignites enthusiasm for the field of focal gene delivery with potentially colossal clinical consequences. The use of arterial conduits for CABG with their superior late patency may be a simpler solution to overcome the long-term consequences of vein graft disease.

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