A surgeon-scientist's approach to improving arteriovenous fistula patency

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Arteriovenous access is critical for survival among patients with end-stage kidney disease requiring renal replacement therapy with hemodialysis. Although arteriovenous fistulae (AVF) have superior outcomes compared with grafts and catheters, AVF remain imperfect, with multiple modes of failure that typically cause morbidity requiring multiple episodes of care with resultant patient suffering and healthcare costs; AVF failure—both early failure to mature as well as late failure of a functional conduit—is a critical issue for patients; vascular access for hemodialysis is an essential and under-recognized lifeline for patient survival.[1] Unfortunately, multiple approaches to improve outcomes of AVF have not translated into durable therapy. Our laboratory has taken the approach of understanding adaptive venous remodeling within the fistula environment, which is somewhat different than the adaptive remodeling of vein grafts within the arterial environment.[2-4]

Vascular identity is determined genetically, with arterial identity determined by ephrin-B2 expression and venous identity determined by Eph-B4 expression.[5,6] Interestingly, vascular surgeons can alter vascular identity; vein grafts lose venous identity,[7,8] whereas AVF gain a dual venous-artery identity.[9,10] Stimulation of Eph-B4 receptors in AVF results in thinner veins with increased patency[11]; however, a limitation of venous dilation in this model, likely via regulation of the Akt-eNOS axis, suggests that a strategy using Eph-B4 stimulation may not be easily translatable to human therapy for AVF failure, but may be more suited to address vein graft failure.

Because the Akt-mammalian target of rapamycin axis is also activated during Eph-B4 activation, we tested the effects of rapamycin on AVF patency. Similar to Eph-B4 stimulation, rapamycin improved AVF patency with thinner venous walls; however, there was no effect on venous diameter, suggesting that the effects of rapamycin during AVF maturation in humans may not be easily predictable.[12]

During early venous remodeling, smooth muscle cells (SMC) are a critical source of Akt activity.[9] SMC are also critical producers of extracellular matrix (ECM), which is vital to the strength of the fistula enabling needle puncture three times a week in the dialysis unit. The ECM is extremely finely regulated during venous remodeling, with phases of matrix breakdown, reorganization, and rebuilding[13]; tight coordination makes teleological sense, because mismatch of venous strength could lead to catastrophic loss of wall integrity with subsequent potentially fatal bleeding. Both noncanonical transforming growth factor β (TGF-β) signaling,[14] as well as canonical TGF-β signaling,[15] are critical regulators of ECM production during venous remodeling, suggesting that regulating TGF-β signaling, especially in the SMC, may be another translational approach to improve fistula patency and use.

The immune response is another critical regulator of venous remodeling.[16] Inflammation via the innate immune response is well-characterized, with macrophages present in the remodeling venous wall. MCP-1 increases M2-type macrophages in the AVF,[17] suggesting that this response is critical to adaptive remodeling. In addition, hypoxic signaling is active and is linked to the production of the ECM.[18,19] The prevention of hypoxic signaling by avoiding the relative wall hypoxia during surgical dissection of the veins, for example, avoiding dividing of the vasa vasorum, led to the concept of the radial artery deviation and reimplantation (RADAR) procedure, performing radial-cephalic AVF in an artery-to-vein configuration with minimal operative exposure of the vein.[20,21] RADAR shows increased primary patency (62.1% vs 37.6% at 36 months; $P < .0001$) and increased secondary patency (94.9% vs 66.8% at 36 months; $P < .0001$) compared with the traditional vein-to-artery configuration of an AVF; in addition, patients with RADAR required few interventions (30.1 per 100 person-years vs 39.9 per 100 person-

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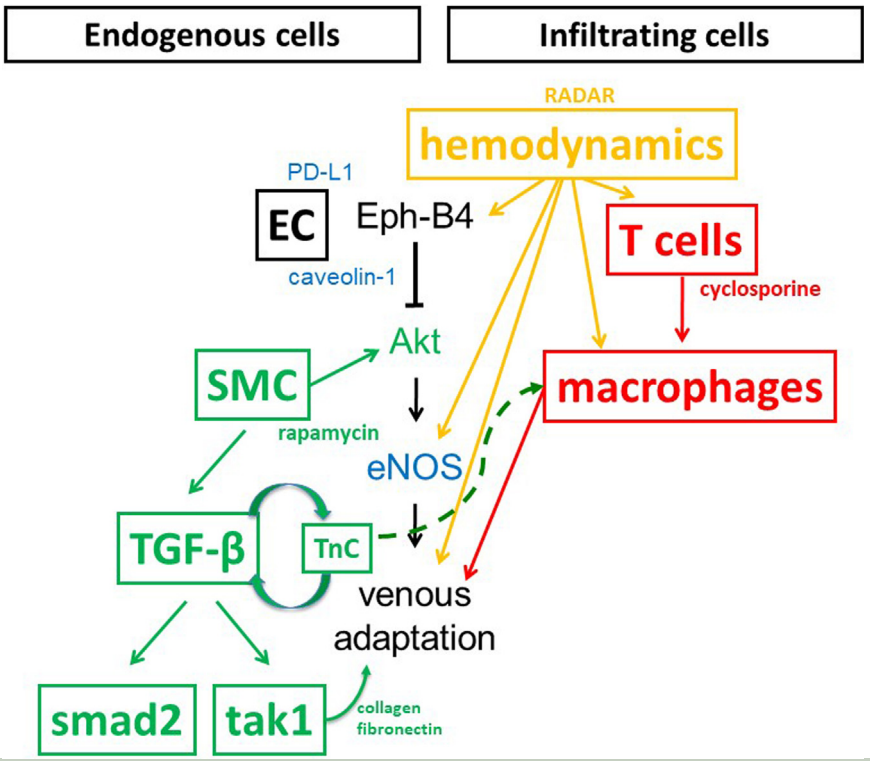

Figure. Working model for arteriovenous fistula (*AVF*) maturation. Venous adaptation is comprised of outward remodeling (increased diameter) and increased wall thickness. Increased diameter may be altered by endothelial ntiric oxide (*eNOS*) production of nitric oxide. Increased wall thickness is due to both increased numbers of cells as well as increased extracellular matrix (ECM). *EC*, endothelial cell; *Eph*, ephrin; *PD-L1*, programmed cell death ligand 1; *SMC*, smooth muscle cell; *TGF-β*, transforming growth factor β; *TnC*, tenascin-C. Dashed arrow indicates unpublished observations.

years; $P = .03$).[22] Although the RADAR procedure was originally thought to decrease hypoxic signaling, it is not clear whether this mechanism is responsible for increased patency; similarly, it is not clear whether laminar or spiral flow within the transposed arterial segment confers resistance to the development of juxta-anastomotic stenosis, although similar hemodynamics may be present in arteriovenous grafts that have significantly decreased patency. It is possible that the favorable hemodynamics in the RADAR configuration promote favorable changes in vascular identity or in infiltrating immune cells, but these conjectures require additional data.

We recently showed that the adaptive immune response contributes to venous adaptive remodeling. T cells mediate wall thickening during venous remodeling, and cyclosporine promotes favorable remodeling.[23] Interestingly, programmed cell death ligand 1 promotes T regulatory cell differentiation to induce M2-type macrophages, and inhibition of programmed cell death ligand 1 with checkpoint inhibitors increases thrombosis and inflammation in the AVF.[24] These studies suggest a role for the adaptive immune response that we did not anticipate; there is no clearly identified foreign antigen that should stimulate the adaptive immune response as happens after organ transplantation. However, the complexity of the adaptive immune response may underlie some of the complexity of fistula remodeling, and thus understanding these mechanisms may help us to understand some of the patient variability in venous remodeling.

Central to these studies has been the use of a mouse aortocaval AVF model that recapitulates human AVF maturation,[25,26] including showing a sex difference with lower patency in female mice,[27] which is linked to sex differences in immunity.[28] Lower AVF patency in human female patients has been attributed to smaller diameter vessels; however, women requiring AVF have both smaller vessels as well as reduced circulating monocytes compared with men,[29] suggesting that previous studies may not have examined confounding sex differences in the immune response in this patient population. Our mouse model shows multiple sex differences, including decrweased basal arterial and venous shear stress, increased AVF diameter, and decreased AVF wall thickness in female mice, as well as multiple alterations in circulating and infiltrating immune cells and increased interluekin-10 and tumor necrosis factor-α in the AVF

walls in female mice.[28] The parallel changes in the mouse aortocaval model with human patients suggests the continued potential usefulness of this mouse model.

Although the mouse AVF model is relatively easy to perform technically and the outflow vein—the inferior vena cava—is easy to analyze, interestingly, analysis of the juxtaanastomotic area is more challenging because it is small and complex. We have recently characterized this area to show that the juxtaanastomotic area is characterized by focal endothelial loss, thrombus formation, and, ultimately, increased neointimal hyperplasia compared with the outflow vein,[30] corresponding with the important human juxta-anastomotic area that causes prevention of fistula maturation, as well as neointimal hyperplasia with fistula failure. The mouse AVF model is versatile, allowing the use of many genetic knockdown strains, as well as the use of a hypertension model.[31] In addition, bioinformatics studies can be performed.[32] A working model of AVF maturation, based on data in the mouse AVF, is presented in the Figure.

Surgeon-scientists are uniquely poised to solve clinical problems and address bedside issues at the bench.[33] Twenty years of laboratory investigation of venous remodeling have brought 4 solutions to increase the efficacy of venous remodeling and potentially increase AVF patency in patients (Eph-B4 stimulation, rapamycin, RADAR, and cyclosporine), of which one of these strategies has already been brought to use in humans (RADAR). Funding for surgeon-scientists is challenging,[34,35] but showing the productivity and value of these translational investigations is important to maintain the presence of surgeon-scientists, ultimately allowing translation of ideas into human therapies. There are several Society for Vascular Surgery-sponsored venues for developing and showing the work of vascular-surgeon scientists; the journal *JVS-Vascular Science* (www.jvsvs.org), the annual Vascular Research Initiatives Conference, and the William J. von Liebig Forum plenary session at the Vascular Annual Meeting that presents the James S.T. Yao Resident Research Award, as well as the Society for Vascular Surgery Foundation career development awards. These venues continue to be successful in their missions, enabling our community to lead in its mission to improve the mortality, morbidity, quality of life, and costs of vascular disease.

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