The arteriovenous fistula (AVF) is the preferred type of vascular access for maintenance hemodialysis because AVFs that mature successfully require fewer interventions, have lower rates of infection, and function longer than synthetic arteriovenous grafts or central venous catheters. However, the advantages of this vascular access type are less compelling if one considers that up to 60% of AVFs fail to mature sufficiently to provide adequate dialysis. 1

Maturation refers to changes in the feeding artery and draining vein that must occur for an AVF to withstand three times per week cannulation and have a blood flow rate that is high enough to support the extracorporeal hemodialysis circuit. Creation of an arteriovenous anastomosis causes a marked reduction in resistance accompanied by an increase in arterial and venous blood flow. An immediate vasodilatory response to the higher flow rate is followed by slow vascular remodeling with additional increase in vessel diameters and structural changes in the vein wall, including accumulation of smooth muscle cells, that allow the AVF to withstand high hydrostatic pressure. The frequent angiographic finding of stenosis in AVFs with maturation failure together with recent histologic demonstrations of marked neointimal hyperplasia with luminal narrowing in failed AVFs has led to a view by many, but not all, investigators that excessive neointima formation is an important cause of AVF maturation failure. 2 Neointima formation, which has been best studied in arteries subjected to endothelial injury, is principally caused by the excessive accumulation of smooth muscle cells and matrix. Recent observations that substantial intimal hyperplasia is present in veins of patients with ESRD before AVF creation have generated interest in understanding the contribution of uremia to AVF stenosis formation. 3

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Notch Ties a Knot on Fistula Maturation

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The current understanding of molecular events underlying AVF maturation or maturation failure is limited. Creating suitable experimental models is challenging because of the interaction of multiple relevant factors, including artery and vein biology, hemodynamic and rheological forces, surgically-induced trauma, and uremia. In this issue of JASN, Wang et al. 4 present a series of experiments to investigate the role of Notch signaling in AVF maturation failure. By incorporating both genetic manipulation and kidney function impairment into the mouse models, Wang et al. 4 were able to evaluate the role of the Notch pathway in a uremic milieu (i.e., a setting that presumably resembles the setting in which AVFs are created in patients).

Notch is an evolutionarily conserved membrane receptor that interacts with Delta and Jagged family ligands to make cell fate decisions and direct cell differentiation into specific lineages. 5 Notch ligands, expressed by the signal-sending cells, initiate the signaling cascade by interacting with receptors on the signal-receiving cells. Receptor–ligand interaction results in the intramembrane proteolytic cleavage of the Notch receptor and the translocation of the Notch intracellular domain into the nucleus. 6 Adjacent cells expressing either the Notch ligand or the Notch receptor can take on different fates. For example, Notch plays a critical role in determining arterial versus venous vessel formation. Jagged1 expression on endothelial cells directs the vessel into an arterial phenotype. Endothelial cells that express Jagged1 will interact with surrounding mural cells that express the Notch receptor. 7 This interaction induces the mural cells to take on a smooth muscle phenotype. By a positive feed-forward loop between Jag1 and Notch1, multiple layers of muscle cells will be induced to surround a single endothelial layer. Through transgenic expression or deletion of Notch ligands and receptors, we can selectively induce an arterial or venous phenotype, indicating that inherent molecular signals rather than physical forces (for example, wall tension) are critical for vessel wall formation. 7

In the present study, Wang et al. 4 examined the role of Notch signaling in AVF neointima formation in control mice and mice with CKD induced by subtotal nephrectomy. As has been observed in patients, Wang et al. 4 found that AVFs in mice with CKD develop substantial neointima formation and luminal narrowing, which they interpreted as an indicator of maturation failure. Wang et al. 4 found that expression of Notch pathway proteins was increased in endothelial cells of uremic mice that developed neointimal hyperplasia. Failed AVFs obtained from patients also had increased Notch expression, supporting the clinical relevance of these findings. Endothelial cells of uremic animals expressed mesenchymal markers, including α-smooth muscle actin and fibroblast-specific proteins. Notch expression was also associated with increased infiltration of inflammatory cells.
Genetic deletion of the transcriptional coactivator of Notch signaling, recombination signal-binding protein for Igκ J region, specifically from endothelial cells prevented smooth muscle cell accumulation, which was evident as markedly reduced neointima formation compared with controls. Notch interacted with TGF-β signaling that regulated the Notch ligand and receptor expression on endothelial cells. In summary, the increased Notch activation observed in the setting of CKD induced excessive accumulation of smooth muscle cells in AVFs, causing neointimal hyperplasia. The model is consistent with the developmental role of Notch of directing vessels into an arterial fate. Although some degree of smooth muscle accumulation in the venous limb of new AVFs is likely to be beneficial by allowing the vessels to accommodate high pressures, excessive Notch activation seemingly causes neointimal hyperplasia and lumen narrowing. Toxins or proteins that accumulate in uremia could contribute to excessive Notch activation.

The demonstration that interrupting Notch signaling reduced AVF neointima formation in mice with CKD is particularly exciting because it provides a preliminary indication that therapeutic manipulation of the pathway could facilitate AVF maturation. Small-molecule inhibitors of Notch have been developed and are being tested in clinical trials for several types of cancer. Determining the ligand- and isoform-specific pathways most appropriate for pharmacological intervention will be necessary, because it is likely that global or even endothelial-specific inhibition of Notch signaling will have significant toxicities given that de novo angiogenic pathways depend on Notch signaling. Because hemodialysis vascular access is a setting well suited for local administration of pharmacological or biologic interventions, reduction of off-target effects of Notch inhibition should be possible. Modulation of the degree of Notch inhibition with therapeutic agents will also be important if some degree of arterialization of the venous limb of the AVF is desirable.

It is important to recognize that, although intuitively appealing, we do not really know from animal or human studies if treatments that reduce neointimal hyperplasia will actually translate into improved outcomes for AVFs. Neointimal hyperplasia and stenosis formation may accompany other contributors to maturation failure, such as inadequate vessel dilation, or they may even be a consequence rather than a cause of maturation failure. A next step for Wang et al. in their investigation of the role of Notch blockade could be measurement of AVF blood flow to determine whether recombination signal-binding protein for Igκ J region knockdown in CKD mice improves AVF function in addition to altering structure. Additionally, assessment of the relevance of Notch pathway activation to humans with CKD might be possible using primary cultures of endothelial cells obtained from patients at the time of AVF creation to perform the mesenchymal cell marker expression studies and endothelial cell barrier function assays, which were performed in the work by Wang et al. using mouse cells.

Through a series of elegant experiments that incorporated in vivo and in vitro studies, surgical creation of mouse AVFs, genetic manipulation combined with CKD, and examination of AVF tissue from patients, Wang et al. have made a strong case for the involvement of Notch in neointimal formation after AVF creation. Although additional work is needed to clarify the clinical and therapeutic implications of the findings, Wang et al. should be congratulated on the necessarily complex approach that they have taken to this complex biologic problem.

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