Hemodialysis vascular access failure: novel pathophysiological mechanisms and therapeutic strategies

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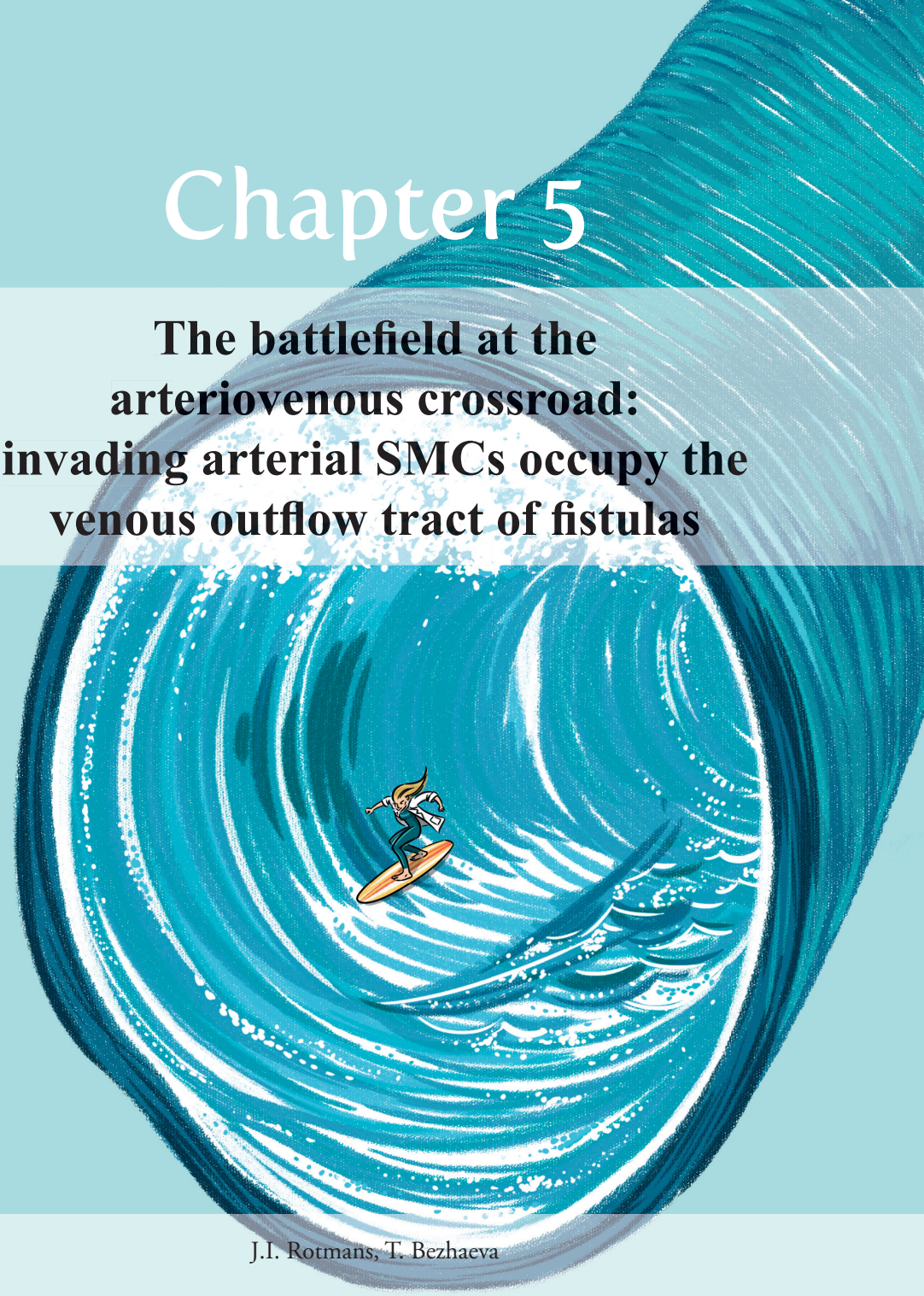
Chapter 5

The battlefield at the arteriovenous crossroad: invading arterial SMCs occupy the venous outflow tract of fistulas



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Abstract

There is an ongoing debate about the anatomical origin of the neointimal cells that are responsible for venous stenotic lesions in arteriovenous fistulas. Liang and coworkers show that vascular smooth muscle cells from the feeding artery contribute substantially to venous intima hyperplasia in murine AVF model. In addition, they show that increased Notch-signaling is the driving force behind FSP-1 mediated migration of these cells to the venous outflow tract.

More than 50 years after the first vascular access device for maintenance hemodialysis was introduced by Scribner, the options for vascular access conduits have witnessed substantial improvements. Currently, native arteriovenous fistulas (AVFs) are considered the preferred option for vascular access in view of their lower complication rate, when compared to prosthetic arteriovenous grafts (AVG) and central venous catheters. However, AVF-related complications still constitute a major cause of morbidity for patients on chronic hemodialysis, as the durability of AVFs is far from optimal with 1-year primary patency rates of 60-65%[1].

The utility of AVFs is hampered by two distinct causes of failure: (1) initial failure to mature and (2) dysfunction of mature AVFs due to stenotic lesions in the venous outflow tract. The exact pathophysiology of both these types of AVF failure is unclear, although excessive intimal hyperplasia (IH) is thought to be a major cause of narrowing of the (venous) lumen, ultimately leading to AVF failure[2]. The vast majority of venous intimal cells are VSMCs and myofibroblasts, cells that both express alpha smooth muscle actin (α-SMA) whereas smooth muscle myosin heavy chain (SMMHC) is solely expressed by VSMCs. The stimuli responsible for the formation of IH in AVF are multifactorial and include hemodynamic factors such as turbulent flow, surgical injury as well as platelet activation due to repetitive cannulation. From an evolutionary point of view, veins are obviously not designed to cope with these excessive stimuli in AVF. To some extent, the outward remodeling and thickening of the intima in the venous outflow tract could therefore be considered as a physiological adaptive response that is needed to withstand the high hydrostatic pressure and flow.

Currently, there is an ongoing debate about the anatomical source of the neointimal cells in the venous outflow tract. While in the past, migrated VSMCs from the venous tunica media were considered to be the most prominent source of neointimal cells, more recent studies suggest that venous adventitial fibroblasts, circulating vascular progenitor cells as well as arterial VSMCs might contribute as well (Figure 1).

In a paper in the present issue of *Kidney International* [3], Liang and coworkers aimed to further unravel the cellular origin of venous intimal cells in a murine model of AVF failure. In a set of complex and elegant experiments in a murine uremic model of AVF failure, they focused on VSMCs in the feeding artery as important contributors to venous IH. For this purpose, transgenic mice were used that express green-fluorescent protein (GFP) in VSMCs in the carotid artery while venous VSMCs do not express GFP in these mice. This approach allowed the researchers to trace the arterial VSMCs in the development of venous IH in murine AVF. Histological analysis of the venous outflow tract of the murine AVFs at 2-4 weeks after surgery, revealed that half of intima cells in the AVF were GFP-positive and most of them expressed α-SMA, suggesting that VMSCs from the anastomosed artery contributed to as much as 50% of the VSMC compartment in the venous intima.

Next, the researchers aimed to identify the underlying mechanisms that stimulate arterial VSMCs to migrate to the venous intima. They hypothesized that increased Notch signaling could be the major driving force for arterial VSMC migration, as the Notch

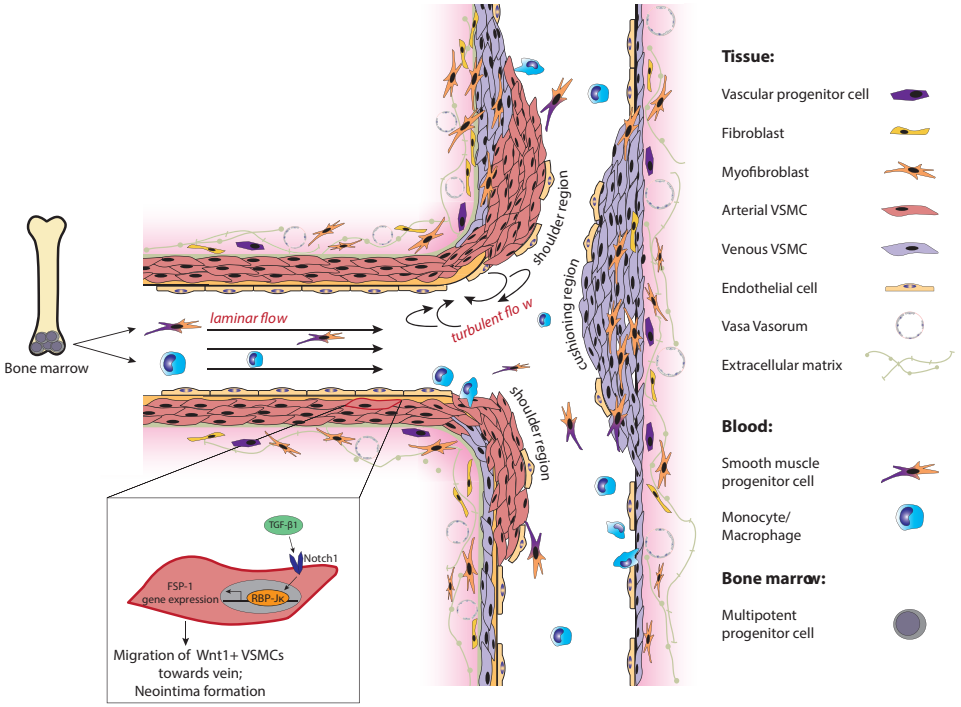

Figure 1. Schematic representation of peri-anastomotic neointima formation in AVFs.
A variety of cells have been designated as contributors to IH in AVF including venous VSMCs, venous fibroblasts that differentiate into myobroblasts, circulating vascular smooth muscle progenitor cells resident vascular progenitor cells and arterial VSMCs. With respect to the latter cells, FSP-1 mediates the migration towards the venous outflow tract in response to Notch activation. RBP-J: recombination signal binding protein for immunoglobulin kappa J region.

pathway plays a critical role in vascular development, for instance by determining arterial versus venous vessel formation. In addition, increased Notch signaling has previously been associated with neointima formation[4]. In their previous work in the murine AVF model, researchers from the group led by Jizhong Cheng in Houston have already shown that blockade of the Notch-signaling pathway in endothelial cells prevented AVF failure in uremic mice[5]. In their present paper, Liang and colleagues confirm that Notch activation is increased in AVFs created in CKD mice, when compared to AVF in mice with normal renal function. In additional *in vitro* experiments, they elegantly show that transforming growth factor β1 (TGF-β1)-mediated upregulation of fibroblast-specific protein-1 (FSP-1) in VSMCs is partly dependent on the same Notch-signaling pathway. The latter is of particular interest since FSP-1 is an important regulator of VSMC migration. Subsequently, the investigators provided additional evidence for a central role for FSP-1 in VSMCs migration in AVF, by showing that IH was significantly reduced in FSP-1 knock out mice when compared to wild type mice. Finally, they evaluated human venous samples of failed AVFs and AVGs which revealed marked expression of both N1ICD (a marker of Notch activation) as well as FSP-1 in α-SMA$^+$ venous neointimal

cells, thereby illustrating the clinical relevance of their observations in mice.

Altogether, Liang and colleagues' findings underscore the importance of the feeding artery as cellular source of migrating VSMCs that contribute to the formation of stenotic lesion in the venous outflow tract of AVFs. This observation might have important implications for local therapeutic strategies to inhibit IH, which thus far primarily focused on the draining vein as pivotal source of proliferating and migrating VSMCs and fibroblasts. However, one should be cautious in extrapolating promising results from murine studies to potential benefit for hemodialysis patients. In general, the translation rate from preclinical studies to the bedside remains low, most likely due to differences in physiology and molecular pathways. In this respect, it should be noticed that the end-to-end configuration that was utilized by Liang and coworkers for the construction of the murine AVFs, differs from the anatomical configuration that is commonly used in humans. Indeed, AVFs in hemodialysis patients are usually constructed by anastomosing the end of a vein to the side of an artery. The exact configuration is a crucial characteristic of the AVF since it determines the hemodynamic profile in the AVF and affects blood flow rate, wall shear stress (WSS) levels, endothelial dysfunction and subsequent development of IH[6]. To circumvent this limitation of the end-to-end configuration, we recently developed a novel murine AVF model with a configuration similar to the one used most frequently in humans[7]. In addition, we should keep in mind that the geometrical orientation of the arterial and venous parts of the AVF in the described end-to-end model differs from an end-to-side anastomosis. Indeed, arterial VSMCs can relatively easily migrate towards the venous segment in the end-to-end configuration, whereas in the end-to-side model, the anatomical distance between the arterial segment and especially the cushioning region of the vein (see Figure 1) is larger. Interestingly, previous studies that were performed using an end-to-side configuration in rats, failed to demonstrate a substantial contribution of arterial VSMCs to venous IH in AVF[8]. As Liang and coworkers primarily focused on peri-anastomotic IH, the contribution of arterial VSMCs in more downstream stenotic lesions as well as in venous lesion of AVGs, remains to be determined. Future studies should reveal if the arterial VSMCs indeed have the capacity to make such long-distance trips.

The question arises how the presented data on the Notch/FSP-1 signaling in arterial VSMCs could translate into novel therapeutic approaches to improve AVF patency. An interesting option would be to evaluate the efficacy of Notch-inhibitors that have been developed in the field of oncology. These small-molecules could be applied to the arterial adventitia during AVF surgery, for instance using a hydrogel-based local delivery system that facilitates sustained release of the compound. In this respect, it is important to recognize that complete inhibition of VSMC proliferation and migration in the early phase after AVF surgery do not necessarily translate into a better functional outcome of AVFs, as (limited) VSMC proliferation might be a prerequisite for adequate outward remodeling of the involved blood vessels[9]. Therefore, the timing of the application of novel interventions to inhibit VSMC proliferation could be crucial for its effect on the functional outcome of the AVF.

Nevertheless, the latter complicating issues should not distract from the fact that these mechanistic studies on the pathophysiology of AVF failure open up a new perspective on potential therapeutic strategies, aimed to modulate the suboptimal vascular response in AVFs for hemodialysis access. Liang and coworkers should be congratulated which their excellent work which hopefully can be translated into local interventions that improve the performance of this 'lifeline' of hemodialysis patients.

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