Establishment of an arteriovenous fistula (AVF) is an important step in providing hemodialysis in patients with chronic renal failure. However, over a period of months or years fistulous patency is compromised and that puts a tremendous constraint on hemodialysis therapy. Thus it is imperative to delineate the mechanisms that lead to the vascular access failure since such patients with dysfunctional AVFs require frequent clinic visits and hospitalizations, which becomes an immense burden on the health care cost (1, 10, 11). The article by Caplice et al. (2) in this issue highlights some of the pathogenetic mechanisms operative during the lifespan of the AVF that culminate in its renal failure.

Given the natural history of AVF studied in humans and various animal model systems, it seems that the vascular access failure involves at least two major pathological changes that occur in its venous segment: stenosis due to neointimal thickening and thrombosis (1, 10, 11). Along similar lines, Nath’s laboratory (8) demonstrated comparable anatomic changes in a rat model of an AVF created simply by needle puncturing the aorta and inferior vena cava. Neointimal thickening included smooth muscle cell proliferation and extracellular matrix amassing, which at times was accompanied by thrombosis. Interestingly, in the early phase, induction of genes that are proinflammatory (monocyte chemoattract protein-1; MCP-1), procoagulant (plasminogen activator inhibitor-1; PAI-1) and vasoconstrictive (endothelin-1; ET-1), and subsequently profibrogenic genes (transforming growth factor-β1; TGF-β1) were induced in the venous limb of this model (8). This would mean that MCP-1 is a pivotal cytokine in the induction of neointimal cell hyperplasia since it is known to mediate chemotaxis of monocytes and macrophages, which, in turn elaborate cytokines that stimulate smooth muscle cell proliferation and induce an inflammatory response and promote cycles of thrombosis and organization, leading to the formation of an intimal plaque/protuberance (8). In the present study, Caplice et al. (2) described neoangiogenesis in this protuberance besides cellular hyperplasia. Neoangiogenesis implies new blood vessel formation, which is often seen in many vasculitides, including during the genesis of atherosclerotic plaque (5, 12). Neoangiogenesis is believed to be stimulated by relatively reduced levels of oxygen in localized tissues and is an adaptive response to nourish the cells in the diseased vasculature (5, 12). Unfortunately, the new vessels are relatively fragile and can rupture, with ensuing hemorrhage and acceleration of the vascular injury. Conceivably, these events also occur in humans as well since the presence of such microvessels in vascular access has been described in patients undergoing hemodialysis (9, 13).

Besides neoangiogenesis, the overarching question addressed by Nath’s team (2) in the current study was to determine the origin of cells lining these new vessels of AVF. The cells lining the microvessels of the intimal protuberance/plaque and adventitia expressed c-Kit, a protein marker for bone marrow-derived cells. Intriguingly, the c-Kit-expressing cells assumed phenotypes that included both a smooth muscle and an endothelial phenotype, as shown by the coexpression of calponin or endothelial nitric oxide synthase (eNOS), respectively. Based on these observations, the authors concluded that the new vessels are created in the venous limb by the local influx of bone marrow-derived cells, which then differentiate to either one of the two major cell types that make up the vasculature of the intimal plaques. The basis for such recruitment of bone marrow-derived cells in this model is unclear as the angiogenic cytokines in the venous wall, such as vascular endothelial growth factor (VEGF) or stromal cell-derived factor-1 (SDF-1), were not upregulated nor were their plasma levels or those of other angiogenic species, cytokine-induced neutrophil chemoattractant-1 (CINC-1) and MCP-1. Nevertheless, the duality in the phenotype of bone marrow-derived progenitor cells is quite captivating. The notion that bone marrow is the source of endothelial stem/progenitor cells stems from studies in a canine bone marrow transplantation model, where cells lining the dacron graft transplanted in the aorta were found to be derived from donor marrow (reviewed in Ref. 7). Further studies revealed that the endothelial stem cells (ESCs) like hematopoietic stem cells (HSCs) are CD34 positive; however, the latter lack receptors for VEGF. Similarly, the stem cells capable of de- or transdifferentiation into various phenotypes have been identified in other organs as well. To add further complexity to the stem cell biology, bone marrow contains multipotent adult progenitor cell (MAPC) with an extremely rare frequency (1 in 10^7 to 1 in 10^8 marrow cells), which could contribute to the neovascularization of intimal plaque or protuberance. An interesting suggestion is raised in the current study that the previously recognized marked upregulation of MCP-1 in this model may be involved in recruiting bone marrow-derived cells, possibly MAPC, because MCP-1 is known to recruit progenitor cells (3) as well as to promote angiogenesis (4). Despite the rarity of MAPC, it is perhaps a realistic possibility that such a recruited cell can transdifferentiate into either a smooth muscle or endothelial cell phenotype, thereby authenticating the functional duality of the cells influxing into the injured adventitia/intima of the AVF (2).

The findings in this study also raise a number of other interesting issues. The first relates to the significance of neoangiogenesis in the background of vascular injury in the AVF. Do these changes represent an alteration that contributes to progressive neointimal hyperplasia? Do these new vessels undergo rupture and hemorrhage, and are thrombosis and organization that can result from such hemorrhage the features...
that drive neointimal hyperplasia? On the other hand, is it possible that neoangiogenesis may be a beneficial adaptive change? In this context, it was recently reported that neoangiogenesis is decreased in stenotic AVFs (6). Another question raised by this study is the nature of the signal that draws bone marrow-derived cells into the venous limb of the AVF, and thus examining the role of MCP-1 would certainly be of great interest. Finally, these studies were undertaken in a nonuremic environment, and raising the issue as to how these changes are modified in a uremic environment would also be worth investigating.

To sum up, the novelty of the current study is that it demonstrates that bone marrow-derived progenitor cells are recruited to the venous limb of AVF, and they participate in the neogenesis of vessels as well as exert considerable influence on smooth muscle cell proliferation, resulting in the formation of an intimal plaque/protuberance and thereby AVF dysfunction.

GRANTS

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