The molecular mechanisms of hemodialysis vascular access failure

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The arteriovenous fistula has been used for more than 50 years to provide vascular access for patients undergoing hemodialysis. More than 1.5 million patients worldwide have end stage renal disease and this population will continue to grow. The arteriovenous fistula is the preferred vascular access for patients, but its patency rate at 1 year is only 60%. The majority of arteriovenous fistulas fail because of intimal hyperplasia. In recent years, there have been many studies investigating the molecular mechanisms responsible for intimal hyperplasia and subsequent thrombosis. These studies have identified common pathways including inflammation, uremia, hypoxia, sheer stress, and increased thrombogenicity. These cellular mechanisms lead to increased proliferation, migration, and eventually stenosis. These pathways work synergistically through shared molecular messengers. In this review, we will examine the literature concerning the molecular basis of hemodialysis vascular access malfunction.

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Arteriovenous fistulas (AVFs) and grafts were introduced over 50 years ago and have been used extensively to provide vascular access for patients requiring hemodialysis (HD).[1,2] AVFs have lower rates of infection and complications in comparison to other modes of HD access and are the preferred method of vascular access in dialysis patients.[1] The Fistula First Initiative has helped make AVFs the preferred method of HD vascular access.[3] As a result, there has been an increase in the number of patients in whom AVFs are placed worldwide, including Europe and Japan.[4,5] AVFs have also been recommended in the pediatric population.[6] In the United States alone, there are nearly 600,000 patients with end-stage renal disease (ESRD) and approximately 400,000 on HD.[7] These numbers are expected to grow in the coming years. Given the magnitude of renal disease, AVFs will continue to be an effective and necessary tool in the coming years.

Although AVFs have proven to be an essential tool, they are by no means without problems. One of the major weaknesses of AVFs is the time it takes for the fistula to mature. This time can be further worsened due to lack of patient education, predialysis planning, and follow-up care. As a result, many patients may need to use tunneled dialysis catheters, which are less favorable due to their associations with bacteremia, resulting in increased morbidity, mortality, and cost.[5,8,9]

Unfortunately, only 60% of AVFs will be functional at 12 months.[10–12] Several studies have shown that patency rates are linked to many variables, ranging from age, presence of diabetes, body mass index, smoking, cytomegalovirus infection, total plasma cholesterol, protein intake, peripheral vascular disease, vessel characteristics, mean arterial pressure, surgical technique, and the use of vascular staples, along with many others.[13–17] Despite the heterogeneity of the factors associated with AVF patency, it is suspected that many of them act through pathologically similar molecular mechanisms.

The histology of intimal hyperplasia (IH) is characterized by an abundance of contractile smooth muscle cells, myofibroblasts, fibroblasts, and macrophages, which eventually narrow the venous outflow leading to stenosis and a reduction in blood flow or in many cases thrombosis (Figure 1). There are many studies that have demonstrated that IH occurs because of several vascular biology pathways, including inflammation, uremia, hypoxia, shear-stress, and thrombosis.[2,18–22] These mechanisms are thought to work in concert through linked

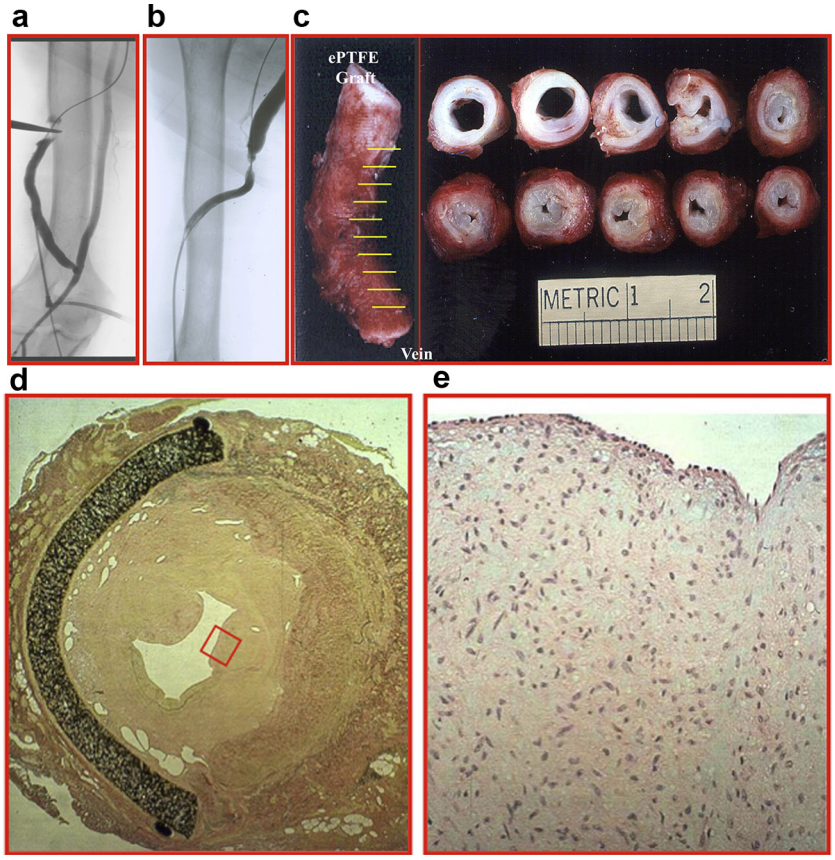

Figure 1 | (a, b) Fistulograms showing a stenosis at the polytetrafluoroethylene graft anastomosis to the basilic vein. (**c**) A gross specimen from a different patient showing thickening of the vein to graft anastomosis. Hematoxylin and eosin stain (**d**) at 10× magnification demonstrating a thickened neointima and (**e**) at 40× magnification (red box in **d**) showing increased cellular proliferation. ePTFE, expanded polytetrafluoro-ethylene.

cytokine cascades and possibly epigenetic changes that induce negative remodeling to occur, leading to fistula failure (Figure 2).[23] This review will focus on the events triggered by renal failure as well as vascular access (VA) surgery that frequently lead to AVF failure. Because hemodynamic forces play an important role in vascular tone regulation and inflammation, we will review specifically the relation between vascular vessel wall stresses and the molecular mechanisms that are responsible for vessel wall changes and ultimately for AVF dysfunction.[23]

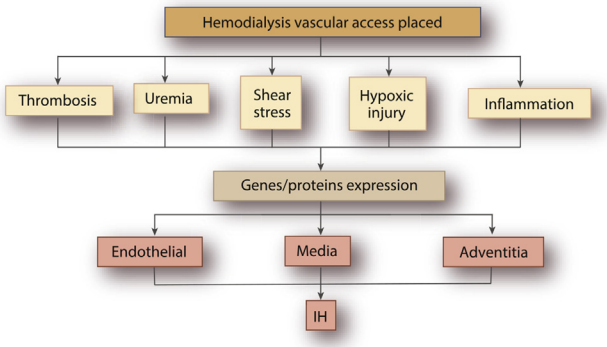

Figure 2 | Schematic of vascular injuries contributing to stenosis formation in hemodialysis vascular access. IH, intimal hyperplasia.

Animal models

Given the complex nature of AVF failure in the setting of chronic kidney disease (CKD), several animal models have been established to study this phenomenon. There are many *in vitro* models utilizing cell culture. Whereas these models are useful for studying isolated phenomenon, they fail to capture all of the factors at play in AVF failure. Initial work in AVF and arteriovenous graft failure utilized carotid artery to jugular vein and also femoral artery to femoral fistulas and grafts. This was performed in pigs, rats, and mice. All of them showed significant IH at varying time points.[24–27] However, these did not account for the systemic effects of CKD that play a significant role in AVF failure.[28] In order to capture these systemic effects, models with induced kidney failure were developed. These models induced CKD in the animals via complete and/or partial nephrectomy. One kidney would be removed or embolized and/or the upper pole of the remnant kidney would also be ligated or embolized. These one-half or five-sixths nephrectomy models allowed for progression of CKD. Blood urea nitrogen was noted to be elevated for up to 8 weeks after nephrectomy. In the porcine