Chapter 13
Stem Cell Delivery for the Treatment of Arteriovenous Fistula Failure

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13.1 Introduction

Chronic kidney disease is associated with significant morbidity, mortality, and healthcare costs. The vast majority of patients with chronic kidney disease go on to develop end-stage renal disease (ESRD) [12]. There are several treatment options for patients with ESRD, including transplant and various forms of renal replacement therapy. However, the vast majority of patients rely on hemodialysis to survive.

Although hemodialysis has proven to be a lifeline for many patients, it requires a well-functioning vascular access. The maintenance and complications arising from vascular access are some of the most costly and often frustrating aspects of hemodialysis care for both the patients and providers. Over the past few decades, there has been progress in providing reliable vascular access, and more patients are receiving dialysis through the use of arteriovenous fistulas (AVFs). AVFs have fewer complications, namely, infection when compared with catheters [13, 14].

In addition to the decreased complication rate of AVFs, they can help preserve central access. However, arteriovenous fistulas often fail due to poor remodeling of the venous outflow. There are multiple factors implicated in AVF failure, including location, venous size, surgical technique, patient comorbidities, and others [13, 15].

Multiple studies examining fistula failure have shown that a majority of fistulas fail due to stenosis caused by venous neointimal hyperplasia (VNH). Venous neointimal hyperplasia occurs due to increased proliferation of smooth muscle cells, myofibroblasts, and inflammatory cells, which result in narrowing of the lumen of

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the vein. This negative remodeling can eventually result in clinically significant stenosis or thrombosis, leading to fistula failure [1].

There are multiple molecular pathways implicated in the development of VNH. As a whole, the process can be thought of as a stress response due to the inflammation and hypoxia during fistula placement. This coupled with the underlying uremic state of the patient with alterations in shear stress, actives multiple reactive cytokines. These, in turn, act on nearby fibroblasts, endothelial cells, smooth muscle cells, and macrophages. This runaway stress response leads to cellular proliferation, migration, and remodeling of the extracellular matrix, which ultimately narrows the lumen [16].

Many in vitro studies have demonstrated the capacity of stem cells, specifically mesenchymal stem cells (MSCs), to mitigate and counteract many of the mechanisms implicated in VNH. Preclinical in vivo studies have corroborated these findings demonstrating a reduction in inflammatory cytokines and VNH [11, 17, 18]. This chapter will explore the molecular mechanisms of VNH, the positive modulatory effects of stem cells), and the therapeutic potential of stem cells in the setting of arteriovenous fistula failure.

13.2 The Molecular Basis of Arteriovenous Fistula Failure

Pathological analysis of failed AVFs demonstrate thickening of the intima due to the presence of multiple cell types, including endothelial cells, fibroblasts, vascular smooth muscle cells, and macrophages [19, 20]. After the creation of the fistula, there is proliferation and migration of smooth muscle cells, derived from a combination of venous smooth muscle cells, arterial smooth muscle cells, adventitial fibroblasts and circulating progenitor cells. These changes are the result of multiple intertwined cellular signaling pathways [16, 20–22] (Fig. 13.1).

These pathways are complex and interwoven but can be grossly separated into several indistinct groups. One of the major drivers of fistula failure is hypoxia, which results from disruption of the vaso vasorum during fistula placement. Hypoxia increases the transcription of several key genes, including hypoxia-inducible factor-1 (HIF-1α) and radiation inducible immediate early gene (IEX-1). These activate multiple cascades resulting in upregulation of several downstream factors, including vascular endothelial growth factor A (VEGF-A), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), NADPH oxidase 2 (NOX-2), monocyte chemoattractant protein-1 (MCP-1), among others [23–27]. These downstream cytokines are responsible for a variety of functions, including angiogenesis, remodeling of the extracellular matrix and promoting inflammation. As a whole, these factors lay the groundwork for cellular proliferation and migration, discussed later in this section [26, 28, 29]. Several in vivo studies aimed at reducing hypoxia using hyperbaric oxygen and in vitro studies targeting these genes have shown decreased VNH and cellular proliferation, respectively. These studies provide further support for the multifactorial nature of VNH [30, 31].

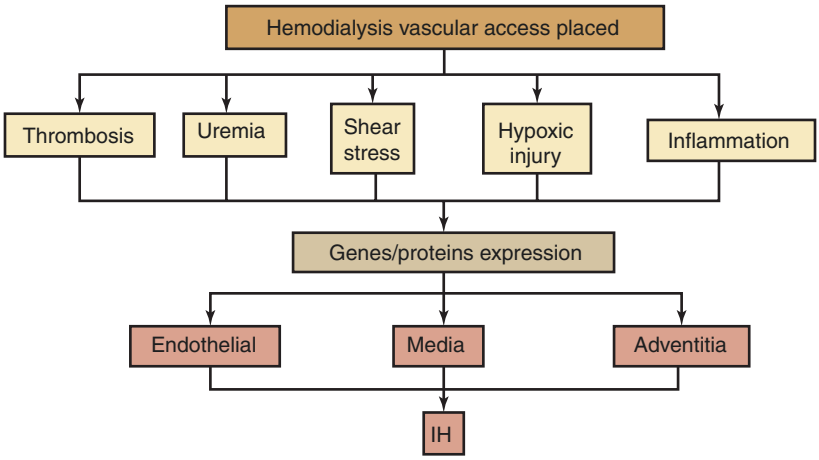

Fig. 13.1 Schematic of vascular injuries contributing to stenosis formation in hemodialysis vascular access. IH intimal hyperplasia. (Reprinted with permissions from Kidney International)

In addition to these factors activated secondary to hypoxia, there are many effects secondary to inflammation that occur during AVF placement. This inflammatory process drives macrophages which exacerbate cellular migration and proliferation [32]. These inflammatory factors share similar biochemical pathways with hypoxia response and both contributed to VNH [16].

One of the major drivers of this inflammatory phenomenon is MCP-1. In vitro and in vivo work has demonstrated that decreasing MCP-1 results in a decrease of proliferation and vein graft thickening [33]. Also, several clinical studies have linked higher levels of circulating MCP-1 with fistula failure [34]. MCP-1 has been shown to work through activation of transcription factors NF-κB implicated in immune responses and Activator Protein-1 (AP-1) implicated in the growth response. In addition to these, the cascade of pro-inflammatory markers includes plasminogen activator inhibitor-1 (PAI-1) and endothelin (ET)-1. ET-1 not only contributes to inflammation but also vasoconstriction [35]. Monocyte infiltration into the vascular wall has also been shown to increase transformative growth factor-beta 1 (TGF-β1), and tumor necrosis factor-alpha (TNF-α), and these are hypothesized to have a proliferative effect in the setting of fistula failure mediated through the NF-κB pathway [16].

In addition to the acute inflammatory response during fistula creation, there is an underlying heightened inflammatory state in patients with chronic kidney disease due to increased uremia [36]. In addition to uremia, patients with CKD often have other comorbidities, including diabetes, which also adds to dysregulation. Several clinical studies have shown that patients with an increased uremic burden have lower rates of fistula patency [34]. In vitro and animal work has also shown that uremia increases cellular proliferation [36–38]. For example, uremia has been shown to induce pro-inflammatory, M1 macrophages. This has been linked to multiple complex interactions [39]. One crucial factor is

Delta-like ligand 4 (DLL-4) release. DLL-4 is a Notch activating cytokine. Notch activation has been shown to increase cellular proliferation and migration. In addition, Notch activation can worsen the inflammatory response by transforming FSP-1-positive cells into macrophages [40, 41]. In vitro work has shown to suppress Notch activation and inhibit DLL-4 and reduce smooth muscle cell proliferation [42].

Uremia has also been linked to decreasing circulating endothelial progenitor cells (EPCs) and decreased proliferation of EPCs. These cells are important for vascular reparative functions and uremia negatively affects the number, which likely exacerbates vascular disease and fistula failure in CKD patients [43, 44].

In addition to hypoxia and inflammation, alterations in shear stress on the endoluminal endothelial cells also contribute to fistula failure [45–47] (Fig. 13.2). Sustained unidirectional wall shear stress (WSS) activates several transcription factors that maintain a quiescent phenotype, including NO and Kruppel-Like Factor-2 (KLF-1). KLF-2 downregulates inflammatory cytokines, including IL-8 and MCP-1 [48, 49]. NO acts as a vasodilator and modulates matrix metalloproteinases toward maintaining the vessel wall. In contrast to this, altered WSS, as in some AVFs, leads to a decrease in KLF-2 and NO resulting in decreased vasodilation as well as upregulation of inflammatory cytokines and several of which are involved in remodeling of the extracellular matrix (ECM) [50]. These include TGF-B1, MCP-1, and IL-8, among others [47]. Overall these alterations promote cellular proliferation and migration leading to VNH [16, 27, 46].

Beyond these, there are many other cytokines and molecular pathways implicated in fistula failure, but overall the mix of stressors leads to an environment that favors cellular proliferation, migration, and adverse remodeling of the vascular wall. As a result of this, multiple clinical studies examining AVF failure have tried to reduce these cellular processes.

There have been several clinical trials examining the role of paclitaxel via drug-coated balloons with promising but mixed results [51–56]. Brachytherapy trials using endovascular radiation did demonstrate some initial benefit, but they were not durable at 1 year, nor was external beam radiation [57–60]. Multiple studies examining the impact of Omega-3 PUF and aspirin have demonstrated no durable benefit [61, 62]. Several studies have also examined the possible benefits of statins, but these have resulted in mixed largely inconclusive results [63]. Other studies examining antiplatelet therapy have shown similar mixed results [64]. Transdermal glyceryl trinitrate does increase blood flow in the perioperative period but did not demonstrate any durable benefit [65, 66]. In addition to these and several other studies using chemical and medical therapies, there are numerous studies examining technique, patient-based factors, cannulation, etc. These are primarily outside the scope of this chapter, but should be considered in the greater context of vascular access failure and when designing studies.

Overall the majority of these prior studies have focused on one or several mechanisms of AVF failure. Additionally, many targeted downstream cellular functions, such as paclitaxel. Stem cell therapy is different from these prior therapies in several ways. Stem cells can modulate the microenvironment using multiple paracrine

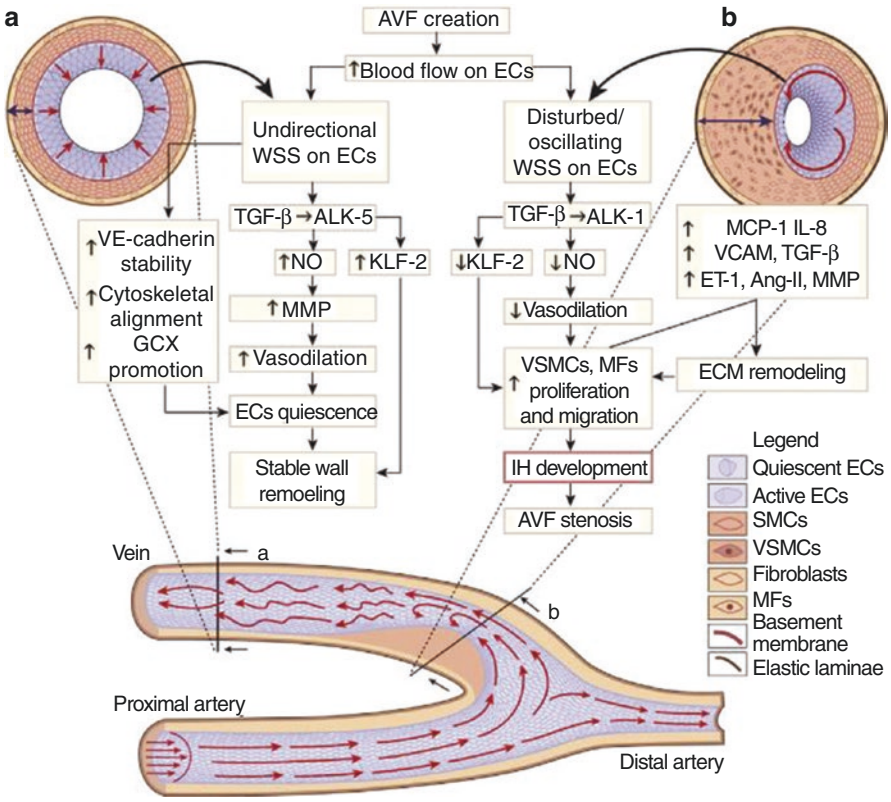

Fig. 13.2 Section of a side-to-end arteriovenous fistula (AVF). Laminar blood flow coming from the proximal artery stimulates the endothelial cells (ECs) with unidirectional wall shear stress (WSS) until the anastomosis level where the blood flow splits in two directions. At the vein curvature, the blood flow becomes unstable with disturbed and oscillating WSS and reverse flows at the inner curvature of the anastomosis. After the curvature, blood flow oscillations decrease and WSS returns to almost unidirectional. The different WSS patterns generated on the endothelium lead wall remodeling. At (a), the unidirectional WSS maintains vessel patency, while at (b) oscillating and reversing WSS impair ECs quiescence leading to intimal hyperplasia (IH). ALK-5 activin receptor-like kinases 1/5, Ang-II angiotensin II, ECM extracellular matrix, ET-1 endothelin 1, GCX glycocalyx, IL-8 interleukin 8, KLF-2 Krüppel-like factor 2, MCP-1 monocytes chemoattractant protein 1, MFs myofibroblasts, MMP metalloproteinase, NO nitric oxide, SMCs smooth muscle cells, TGF-β transforming growth factor β, VCAM vascular cell adhesion protein, VE vascular endothelial, VSMC vascular smooth muscle cells. (Reprinted with permissions from Kidney International)

effects to alter many pathways simultaneously and at higher levels of cellular signaling. These and other beneficial properties have allowed stem cells to be used in a variety of disease states with good results [3, 9, 10, 67–70]. Due to these properties, stem cells were hypothesized to serve as a potential treatment for AVF failure [2, 11, 17, 18].

13.3 Stem Cells

Several types of stem cells have been used in vascular applications. Earlier work involved adult stem cells derived from either tissue, blood, or bone marrow. These endothelial progenitor cells, such as blood outgrowth endothelial cells (BOECs), have multiple favorable vasculogenic properties and were used in several trials [7]. However, more recent work has incorporated the use of MSCs [9]. These cells have greater plasticity allowing for greater cellular differentiation. This along with several reliable methods of harvest and proliferation has made them a more desirable therapeutic option [7, 9].

MSCs are pluripotent and are able to differentiate themselves into several different cell types [71]. MSCs have several intrinsic properties, which have allowed them to serve as therapeutic agents in innumerable pathological diseases. The main therapeutic function of MSCs is through their paracrine immunomodulatory properties. There are multiple studies examining these proteins, transcription factors, and microRNA that induce a variety of responses. The signaling molecules and their effects depend on the existing environment [6, 67, 72]. However, in multiple studies, given a baseline inflammatory environment, MSCs serve an anti-inflammatory role. Overall, MSCs can drive differentiation of macrophages toward a M2 phenotype in the setting of inflammation. The M2 phenotype is associated with repair and anti-inflammatory cytokines, including TGF-B and IL-10. In contrast, M1 macrophages are associated with inflammation. These are tied linked to TNF-α, interferon-γ *(*IFN-γ*), MCP-1, IL-6, among others* [4].

Several studies have demonstrated decreased levels of TNF- α and IL-6 in models of acute kidney and lung injuries after administration of MSCs. This is likely being mediated through tumor necrosis factor receptor-1, which effectively neutralizes circulating TNF-α and subsequently reduces IL-6 and IFN-γ. Other studies have demonstrated that TNF-α induced protein 6 and high levels of prostaglandin 2 release, which acts on the EP2 and EP4 receptors of macrophages may be responsible. This concomitant decrease is also tied to the increased release of anti-inflammatory factors such as IL-10, which drive cells toward an M2 phenotype [68, 73–76]. In vivo studies using MSCs to treat fistula failure have demonstrated a reduction in inflammatory markers such as MCP-1 and CD-68. This reduction supports the anti-inflammatory properties of MSCs in the setting of fistula failure [11].

It is important to note that in several studies examining ischemia and damaged organs that MSCs have been shown to increase levels of angiogenesis and cellular proliferation [68]. Some of these factors may negatively impact fistula remodeling such as VEGF-A [77]. It is likely that the MSCs aid in a reparative process that varies based on the surrounding microenvironment. Thus in some cases, it may promote angiogenesis, while in others it may serve to attenuate the process [68, 78]. Overall, work in this area is limited with regard to MSCs in the setting of AVF failure. Future studies may shed light on these additional factors.

MSCs also migrate toward sites of inflammation, though several cytokines including parts of the complement cascade and chemokines including CXCR4 [5,

79, 80]. CXR4 is also implicated in multiple other downstream immunoregulatory pathways [81]. This migratory process has been tied to matrix metalloproteinases, immunoglobulins, and transcription factors several of which are implicated in fistula failure [82]. MSCs delivered to the adventitia migrate to the lumen in murine arteriovenous fistulae [11]. This intrinsic migratory propensity toward inflammation adds to their therapeutic value.

13.4 Isolation and Safety of Mesenchymal Stem Cells

MSCs can be derived from a number of different sources, including umbilical cord blood, bone marrow, and adipose tissue [8]. However, given the minimally invasive nature of adipose tissue extraction and the availability of reliable MSCs using good manufacturing practice compliant production, supported the use of adipose-derived MSCs in preclinical experiments. Additionally, using these established practices was thought to facilitate an easier transition to clinical trials [83, 84]. There are some challenges in harvesting stem cells from patients with renal dysfunction. Uremia, along with common comorbidities such as diabetes and cardiovascular disease, negatively affects MSCs. However, there are several preconditioning techniques and chemicals that can be used to increase the function of MSCs, including hypoxic preconditioning and statins. In the future, more robust techniques including epigenetic programming might be employed [70].

MSCs are also a safe therapeutic option. There have been multiple studies examining the safety of adipose-derived MSCs in multiple settings. Countless studies across many disciples have demonstrated the safety and therapeutic potential of stem cells [3, 9, 85]. Initially, given the pluripotency of MSCs, there was some concern that therapy with MSCs might lead to neoplasms or that these cells may undergo malignant transformation. Hover, several studies have not found any meaningful evidence to support this [86, 87].

13.5 Drug Delivery Technologies Applied to and Available for Fistula Failure

There are several drug delivery and treatment options that can be applied in the setting of fistulae and grafts. These can be broadly divided into two types, endovascular and perivascular.

The most commonly used endoluminal delivery device is a balloon. The standard of care to treat fistula failure is plain balloon angioplasty; however, balloons have also been used for cryotherapy, brachytherapy, and drug delivery via drug-coated balloons [59, 88, 89]. There have also been several animal studies delivering gene therapy into the lumen via infusion of viral vector and temporary clamping of the

vessel to allow for transfection [90–92]. Similar techniques have been used with high-dose vitamin D [93]. Viral vectors and other therapies requiring endoluminal infusion and incubation have the potential to be used at the time of fistula placement or with the use of an occlusion balloon in an existing fistula. In addition to balloons, intraluminal delivery of drugs can be performed using micro infusion catheters. These devices, upon inflation, puncture the vessel with a small needle and can deliver a therapeutic agent into the vessel wall [94]. This latter method may be useful for the delivery of stem cells or cytokine containing exosomes in the future.

Stent placement is another commonly used endovascular treatment option for arteriovenous fistula failure. Overall stents have been less commonly used due to the risk of thrombosis, fracture, and migration. Additionally, stenting can limit further intervention in cases of in-stent restenosis [95–97]. Future developments, including drug eluting and bioabsorbable stents, may prove to be durable treatment options [96, 98]. Currently, there is limited technology to allow for the reliable intraluminal delivery of stem cells, which would allow them to integrate into the vascular lumen. Additionally, MSCs need to be kept viable in a suitable media. There is promising work with regard to stem cell impregnated stents [99]. However there are several challenges with stent-based delivery including the risk of washing cells away or damaging them during delivery with mechanical, immune, and chemical stressors [99–101]. Additionally, stem cell behavior can vary based on the surrounding structure and potential stent material. These effects should be considered when designing delivery methods and devices [102–104].

Perivascular treatment delivery can be used during fistula creation or after placement. This method avoids the need for endovascular instrumentation and predominantly treats the adventitial and medial vascular layers, thought to be the predominant source of cells leading to venous neointimal hyperplasia. One of the more well-studied perivascular delivery systems is the use of biodegradable gels. These can be altered or used with other technologies such as nanoparticles to optimize the release kinetics of the therapeutic agent [105]. Several in vivo studies have used gels to deliver paclitaxel, sirolimus, peptides, vitamin D, and stem cells, among others [30, 106–108].These studies have had promising results. In addition to gels, perivascular wraps have also been utilized in a variety of in vivo models and in several clinical trials [109–111].

MSCs can be grown in gels, and artificial matrices, which can be optimized for perivascular delivery, serve as a vascular wrap [69, 112]. These delivery mechanisms can be applied to the fistula under direct visualization or with the use of imaging guidance. Given the ease of use and the ability to easily deliver cells either at the time of fistula placement or afterward allows for therapeutic flexibility. Perivascular delivery of MSCs for AVF failure is the most feasible. Additionally, it does not necessitate the use of a durable implant and allows for greater flexibility, should the patient require future therapy or a revision.

Beyond these, there are several other treatment delivery methods, systemic, topical, etc. [113]. While these may be useful for other therapeutic agents, they are not particularly efficacious for stem cells, which require proximity to exert their paracrine effects. Although MSCs do have homing properties toward inflammation, a

higher number might be needed to generate the desired effect especially in patients with multiple comorbidities. However, systemic treatment may be more feasible in the future [5, 79, 80].

13.6 Preclinical Work

Early in vitro work utilized BOECs. Although BOECs exhibit less plasticity than embryonic and induced pluripotent stem cells, they exert similar effects [2, 7]. When co-cultured with fibroblasts in a hypoxic environment, BOECs reduced angiogenic cytokine production and resulted in decreased conversion of fibroblasts to smooth muscle cells. This demonstrated the potential for blood endothelial outgrowth cells to reduce angiogenesis, a major hypoxia driven response implicated in VNH (Fig. 13.3) [17, 23].

These findings were corroborated in a porcine model of fistula failure. In this model, uremia was induced by partial renal infarction and PTFE grafts were placed between the carotid and jugular to create a fistula. BOECs were delivered to the adventia with a polyglycolic acid scaffolding. Compared with controls fistulae which had been treated with BOEC, demonstrated reduced neointima (Fig. 13.4). There was also decrease in HIF-1α. Interestingly many of the BOEC cells had migrated to neointima of both the treated and contralateral control sides underscoring the homing proprieties of these cells to seek out areas of tissue damage and hypoxia likely through factors like HIF-1α [18]. These studies eventually paved the way for more streamlined work using adipose-derived stem cells in a murine models.

Preclinical work using a murine carotid jugular model of AVF failure and human adipose-derived MSCs has demonstrated the feasibility and utility of treating AVF failure with MSCs. In this study B6.Cg-*Foxn1*^{nu}/J mice (Charles River Laboratories, Wilmington, MA, USA) were used. These mice lack a thymus and

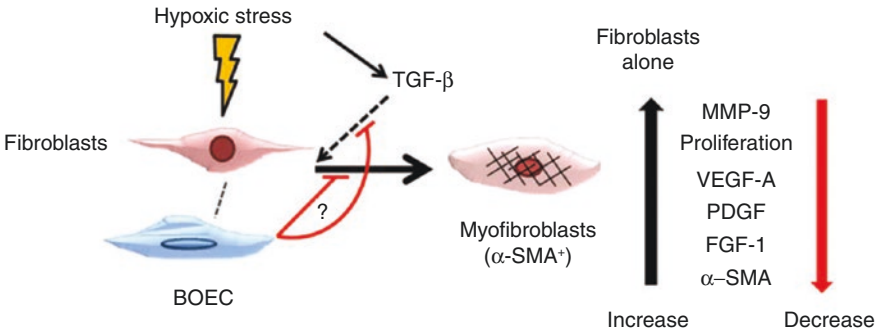

Fig. 13.3 Schematic of proposed interaction by BOEC under hypoxic conditions changes. (The final, published version of this article is available at http://www.karger.com/?doi/10.1159/0003699290)

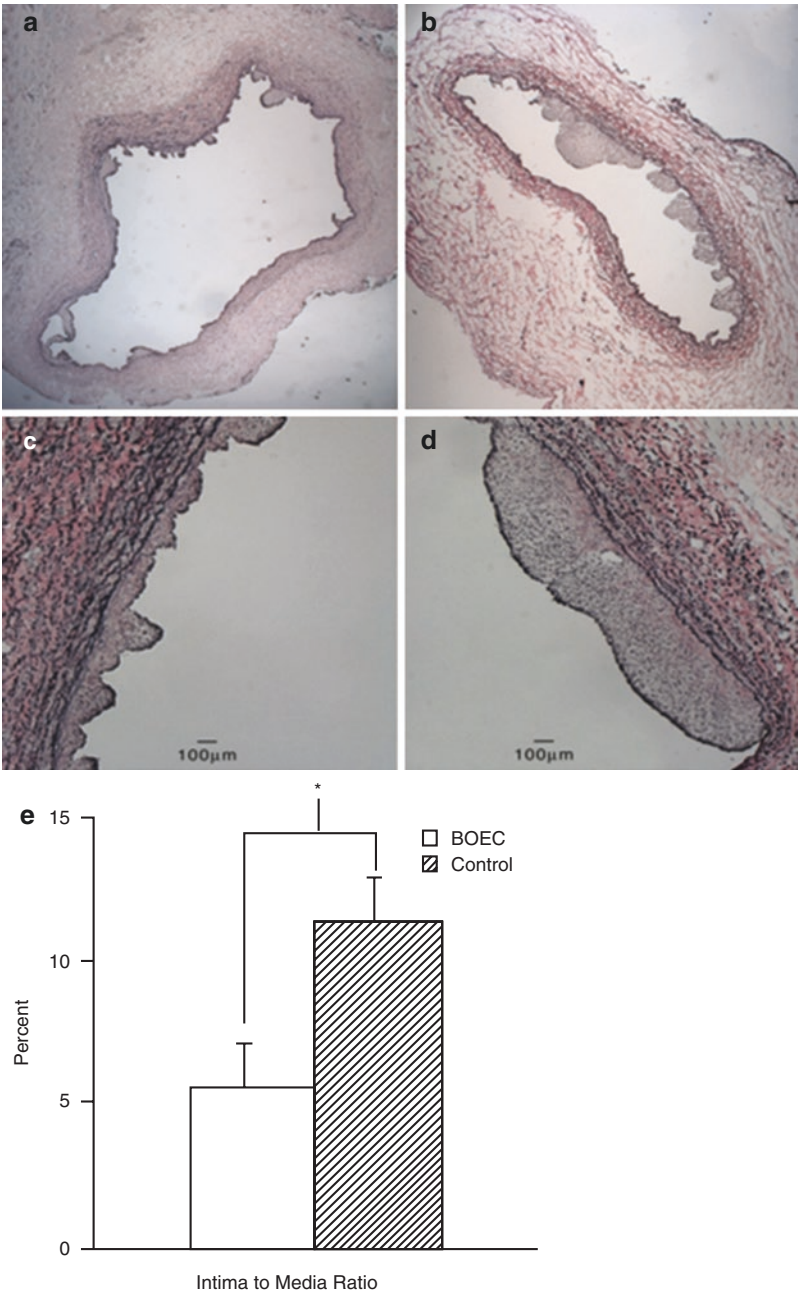

Fig. 13.4 Verhoeff's van Giesen staining was performed at the venous stenosis (section V1, see Figure Figure1C)1C) from the cushioning region of the BOEC-transplanted (**a**, **c**) and contralateral non-transplanted (control) veins (**b**, **d**). A and B are 5× and C and D are 40× magnification. The lower panel (**e**) shows that there was a 50% decrease in the intima-to-media ratio in the BOEC-transplanted samples when compared to controls ($P < 0.05$). Data are mean ± SD. (Reprinted with permissions from Nephrology Dialysis Transplantation)

thus cannot mount an immunogenic response to certain cells, namely, human-derived MSCs, which made them suitable for the xenograft study. Carotid-jugular AVFs were created in these mice. At the time of a creation, GFP and ^{89}Zr-labeled stem cells were delivered perivascularly to the adventitial of the outflow vein, in culture media. Approximately 250,000 cells from healthy adult donors were delivered. These cells were confirmed using several markers and used in several clinical trials [11].

These animals were followed to several weeks and sacrificed for genetic and histomorphological analysis. ^{89}Zr labeling was used to evaluate the retention of cells, approximately 90% of this tracer was present at the fistula site at 4 days, and this slowly translocated to the bones over the course of several weeks. GFP labeling was used to evaluate the local response and the majority of cells were present at the site, including a significant amount that had migrated toward the lumen. This confirmed that a majority of the cells delivered to the adventitia were retained at the site and locally migrated to the lumen. Genetic analysis also showed a decrease in MCP-1 and HIF-1α expression compared to controls at 7 days. Markers of fibroblasts and smooth muscle cells, FSP-1 and α-SMA, were also decreased at day seven and day 21 [11].

These findings were consistent with morphometric analysis at 7 and 21 days showed a decrease in neointimal area and cell density, compared with controls. Overall, these findings support an anti-inflammatory effect of the MSCs, resulting in decreased cellular proliferation and migration. Overall, these adipose-derived MSCs resulted in favorable remodeling [11]. This body of promising work, combined with our understanding of VNH and clinical use of these adipose-derived MSCs, make up the foundation for translation into clinical trials.

13.7 Conclusion

AVFs are an essential lifeline for patients with ESRD. In the past few decades, there has been an increased understanding of arteriovenous fistula failure and progress in improving AVF outcomes. However, a majority of AVFs still require repeated intervention due to stenosis. Multiple prior studies have identified out several intertwined mechanisms leading to fistula failure and possible targeted solutions. Stem cells, specifically MSCs, have been shown in multiple studies to modulate and counteract the mechanisms of fistula failure. This along with reliable methods of harvest and their use in multiple clinical paradigms supports the use of MSCs in the setting of AVF failure. Several animal models have confirmed the efficacy of MSCs to reduce venous neointimal hyperplasia. Overall, MSCs are a promising therapy with the potential to significantly reduce the number of interventions needed to maintain AVF function and improve the lives of those with ESRD.

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