The Journal of Physiology

TOPICAL REVIEW

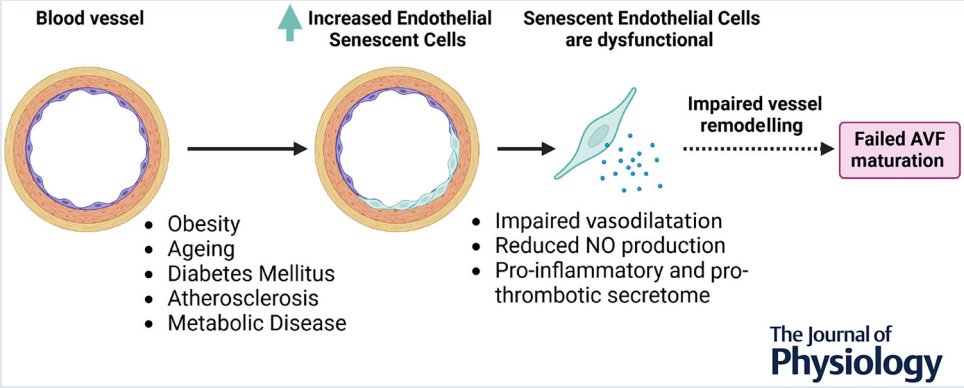
The role of cellular senescence in endothelial dysfunction and vascular remodelling in arteriovenous fistula maturation

Ignacia González and Rodrigo Maldonado-Agurto

Center for Biomedical Research (CIBMED), Faculty of Medicine, Universidad Finis Terrae, Santiago, Chile

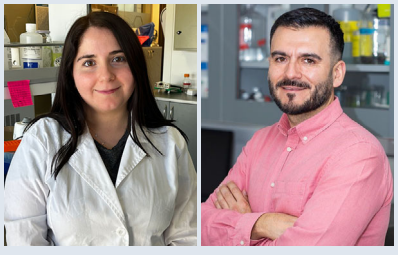
Handling Editors: Kim Barrett & Luis Sobrevia

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP287387#support-information-section)



Abstract figure legend Senescent endothelial cells accumulate in blood vessels due to risk factors such as obesity, ageing, diabetes mellitus, atherosclerosis and metabolic disease. These cells become dysfunctional, losing their ability to maintain endothelial homeostasis. This dysfunction is characterized by impaired vasodilatation, reduced nitric oxide (NO) production, and the secretion of a pro-inflammatory and pro-thrombotic secretome. As a result, senescent endothelial cells can potentially disrupt vascular remodelling, ultimately contributing to the failure of AVF maturation. This review highlights the need to characterize the role of senescent endothelial cells in AVF maturation and patency, as well as strategies to mitigate their negative effects.

Ignacia González is a Biochemist from Universidad de Santiago de Chile, working as a research assistant at Dr. Maldonado-Agurto's lab since 2023. **Rodrigo Maldonado-Agurto** earned his degree in Bioengineering and an MSc in Biochemistry and Bioinformatics from the University of Concepción, Chile. He completed a PhD in Biotechnology at the University of Manchester (UK), focusing on optimizing recombinant protein production in mammalian cells. His postdoctoral research investigated gene expression regulation mediated by non-coding RNAs. Since 2022, he has held a position as academic researcher at Universidad Finis Terrae, Chile, where he has started a lab as an independent researcher, focusing on the mechanisms controlling endothelial senescence through molecular biology, cell biology and bioinformatics approaches.



 DOI: 10.1113/JP287387

Abstract Haemodialysis (HD) is often required for patients with end-stage renal disease. Arteriovenous fistulas (AVFs), a surgical procedure connecting an artery to a vein, are the preferred vascular access for HD due to their durability and lower complication rates. The aim of AVFs is to promote vein remodelling to accommodate increased blood flow needed for dialysis. However, many AVFs fail to mature properly, making them unsuitable for dialysis. Successful maturation requires remodelling, resulting in an increased luminal diameter and thickened walls to support the increased blood flow. After AVF creation, haemodynamic changes due to increased blood flow on the venous side of the AVF initiate a cascade of events that, when successful, lead to the proper maturation of the AVF, making it suitable for cannulation. In this process, endothelial cells play a crucial role since they are in direct contact with the frictional forces exerted by the blood, known as shear stress. Patients requiring HD often have other conditions that increase the burden of senescent cells, such as ageing, diabetes and hypertension. These senescent cells are characterized by irreversible growth arrest and the secretion of pro-inflammatory and pro-thrombotic factors, collectively known as the senescence-associated secretory phenotype (SASP). This accumulation can impair vascular function by promoting inflammation, reducing vasodilatation, and increasing thrombosis risk, thus hindering proper AVF maturation and function. This review explores the contribution of senescent endothelial cells to AVF maturation and explores potential therapeutic strategies to alleviate the effects of senescent cell accumulation, aiming to improve AVF maturation rates.

(Received 6 August 2024; accepted after revision 29 January 2025; first published online 20 February 2025)
Corresponding author R. Maldonado-Agurto: Centre for Biomedical Research (CIBMED), Faculty of Medicine, Universidad Finis Terrae, Santiago, Chile. Email: rmaldonado@uft.cl

Generalities of the arteriovenous fistula maturation and failure

End-stage renal disease (ESRD) is a condition characterized by permanent failure or decline in kidney function, rendering the kidneys incapable of functioning independently. ESRD can occur in patients with chronic kidney disease (CKD), often due to conditions such as diabetes or hypertension. This condition is particularly common among older adults, as the prevalence of CKD and related risk factors tends to increase with age (Anand et al., 2014; Cheng et al., 2021). Consequently, individuals with ESRD require either haemodialysis (HD) or a kidney transplant for survival. HD involves the extraction of blood from the body through cannulation, directing it through an external dialysis machine. This machine filters out waste products and excess fluids from the blood before returning it to the body through pumping. Despite the fact that HD has been successfully used for years to save lives, the major difficulty for the application of this treatment is the need for vascular access to connect the patient's blood vessels to the dialysis machine. The preferred vascular access for haemodialysis is the arteriovenous fistula (AVF), which consists of surgically creating a direct connection between an artery and a vein (also called anastomosis), generally in the patient's arm. AVFs can be created in various configurations, depending on the specific vein and artery that are connected and the technique used to create the connection. The most commonly used configuration is the end-to-side anastomosis between the cephalic vein and the radial artery, typically performed at the wrist or forearm (Fig. 1*A*). This configuration will be used in the examples provided. AVF is the preferred vascular access for HD due to its long-term durability and low incidence of complications compared to other vascular access options (Hod et al., 2015). Moreover, patients with AVF experience lower morbidity and mortality compared to those with other vascular accesses, along with reduced maintenance costs (Sidawy et al., 2008). The aim of this procedure is to promote the remodelling of the vein that will serve as a point of access to receive the increased blood flow rates from the HD machine and the repeated cannulations (Wang et al., 2022). Two critical aspects of a successful AVF for HD are maturation and patency. The maturation process involves the vascular remodelling that must occur in the AVF before it can be used in HD. This involves the establishment of an increased blood flow and adequate vessel dilatation to withstand repeated cannulations, achieved through structural and functional changes (Fig. 1*B*). Typically, an AVF is expected to become mature between 4 and 6 weeks after surgery (Asif et al., 2006), resulting in an AVF with a diameter of at least 6 mm, positioned 6 mm below the skin surface, and with a flow rate exceeding 600 ml/min (Hu et al., 2016). The successful maturation of the AVF is influenced by several

patient-related factors such as age, sex and comorbidities (diabetes, hypertension, peripheral vascular disease, obesity) which can alter the concentration of several molecules in the blood (Hentschel, 2018; Siddiqui, Ashraff, & Carline, 2017). Diabetes is a primary risk factor for the development of ESRD and is characterized by chronic hyperglycaemia (Cheng et al., 2021). Elevated blood glucose levels increase the risk of ESRD, particularly when additional risk factors such as hypertension are present (Sim et al., 2014). Hyperglycaemia promotes the production of reactive oxygen species (ROS), chronic inflammation and advanced glycation end products, creating a pro-oxidative environment. This oxidative stress further promotes the oxidation of low-density lipoprotein (LDL), generating oxidized LDL (ox-LDL), which is strongly associated with endothelial dysfunction (Sakurai & Sawamura, 2003) and the development of atherosclerotic plaques (Gao et al., 2017; Hulthe & Fagerberg, 2002). On the other hand, AVF patency refers to the ability of an AVF to remain unobstructed, ensuring continuous blood flow between the artery and the vein. Patency is crucial for the effective utilization of the AVF in HD, as it guarantees that a sufficient blood volume is accessible for the dialysis process (Tabbara et al., 2016). Patency can be limited by AVF failure, which can be categorized into two types: early and late failure. Early AVF failure, characterized by the inability of the AVF to properly mature and become functional for HD following its surgical creation, is a significant concern in HD patients. It occurs in approximately 20–40% of cases (Ghorbani et al., 2009; McLafferty et al., 2007; Rezapour et al., 2018) and requires further interventions to facilitate maturation (Al-Jaishi et al., 2014; Cheung et al., 2017; Venkat Ramanan et al., 2022). A functional AVF can have a variable lifespan, lasting from months to several years, indicating their potential for long-term use (Liu et al., 2023). Nevertheless, AVFs can experience a loss of functionality after been successfully used for HD, which is known as late AVF failure. This type of failure is primarily caused by stenosis, which is the abnormal narrowing of the blood vessel, leading to reduced blood flow and eventual thrombosis within the AVF (Quencer & Friedman, 2017).

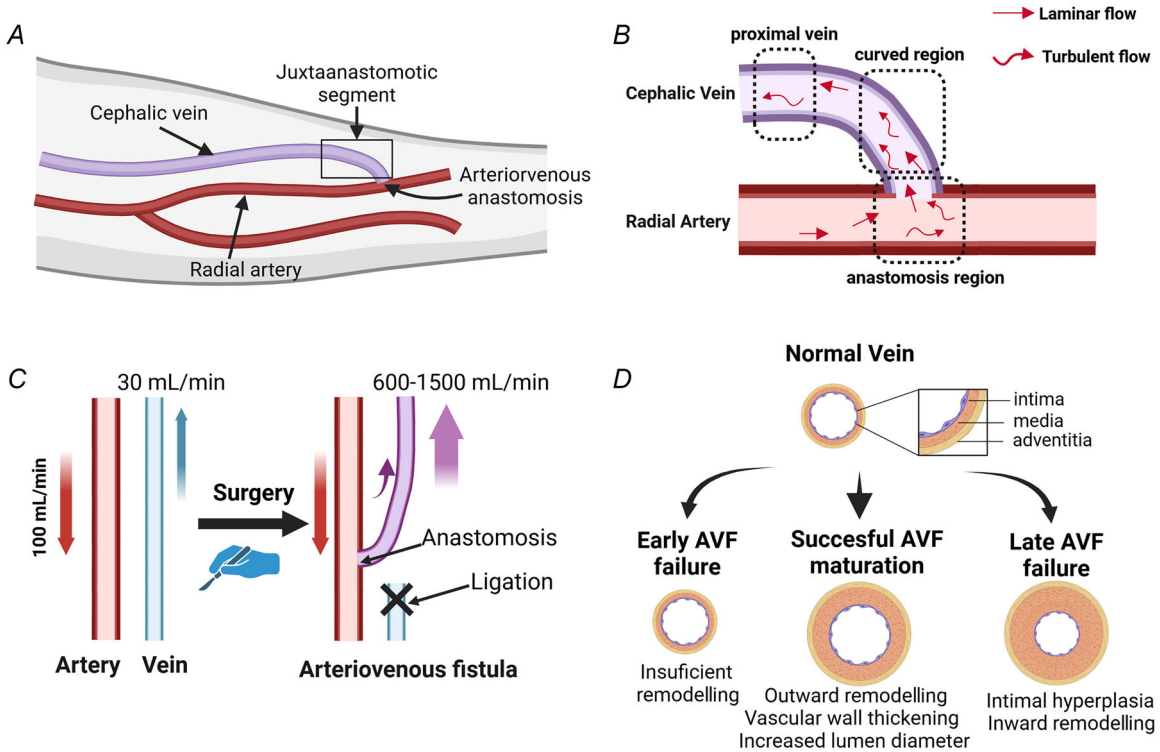


Figure 1. Schematic of arteriovenous fistula formation and flow dynamics
A, illustration of an arteriovenous fistula (AVF) showing the radial artery and cephalic vein. The anastomosis (connection) between the artery and vein is indicated, highlighting the portion of the cephalic vein that is immediately adjacent to the anastomosis (juxtaanastomotic segment) (modified from Quencer & Arici, 2015). *B*, depiction of flow dynamics within an AVF, with areas of laminar and turbulent flow labelled and stenosis prone regions in dashed boxes. *C*, comparison of blood flow rates in the artery and vein before and after surgery to create an AVF. Pre-surgery, the artery and vein flow rates are 100 and 30 ml/min, respectively. Post-surgery, the AVF results in increased flow rates of 600–1500 ml/min due to anastomosis and vein ligation (modified from Sadaghianloo et al., 2019). *D*, cross-sectional analysis of vein composition in native vein and remodelling possibilities that occur including successful AVF maturation, early and late AVF failure.

Stenosis is often caused by the development of intimal hyperplasia, a condition characterized by thickening of the intima, due to the accumulation of vascular smooth muscle cells (VSMCs), collagen and other components, resulting in a reduced vessel diameter (Mills et al., 2012; Vazquez-Padron et al., 2021). The blood vessel walls are continuously exposed to mechanical forces exerted by the continuous flow of blood. These forces include hydrostatic pressure, cyclic stretch and shear stress (Dessalles et al., 2021). Shear stress specifically refers to the frictional force exerted by the flow of blood on the endothelial cells (ECs) lining the inner walls of the vessels. This force is caused by the movement of blood as it flows over the surface of the endothelium. ECs are especially affected by shear stress since they are in direct contact with the blood flow (Souilhol et al., 2020). Furthermore, these haemodynamic forces are categorized into two main types: laminar flow, which is smooth and consistent, and non-laminar flow, which includes pulsatile, oscillatory, and turbulent flow. These forces play a critical role in vascular biology, influencing endothelial function, vascular remodelling and the development of various cardiovascular conditions (Dessalles et al., 2021; Souilhol et al., 2020). In AVFs, certain areas are more likely to develop intimal hyperplasia and stenosis. These areas include the anastomosis region, the curved parts of the vessel and the proximal segment of the vein (Fig. 1*C*) (Ding et al., 2023; Sivanesan et al., 1999). Due to their geometry, these regions experience unique flow dynamics, characterized by turbulent flow patterns. These turbulent flows disrupt the smooth, laminar movement of blood, resulting in areas of low and oscillatory shear stress (Yang et al., 2020). The low and oscillatory shear stress can stimulate endothelial cell dysfunction and the proliferation of VSMCs, promoting the deposition of lipids and inflammatory cells in the vessel walls that leads to stenosis (Chappell et al., 1998; Conklin et al., 2002; Fitts et al., 2014). Similar to these observations, certain regions of the arteries are exposed to disturbed blood flow due to specific vascular geometries (Morbiducci et al., 2016). These regions, characterized by oscillating and turbulent flow patterns, are more prone to developing atherosclerosis. Additionally, these regions exposed to disturbed flow have been associated with the local accumulation of senescent cells (Warboys et al., 2014).

Senescent cells are cells that have permanently stopped dividing but remain metabolically active, and present a characteristic secretome called the senescence-associated secretory phenotype (SASP). SASP includes growth factors, chemokines, cytokines and proteases, which can influence the local vascular environment (Campisi & D'Adda Di Fagagna, 2007; Gorgoulis et al., 2019; Hernandez-Segura et al., 2018). Despite the relevance of AVF for haemodialysis, the cellular and molecular mechanisms associated with AVF maturation and failure are not well understood. While various factors implicated in AVF failure such as vascular endothelial dysfunction (Siddiqui, Ashraff, Santos et al., 2017), inflammation (Zhang, Kong et al., 2024) and shear stress (Browne et al., 2015) have been reviewed, the role of cellular senescence in AVF maturation has not been examined. In this review, we will explore the role of cellular senescence in vascular remodelling and its impact on AVF maturation and failure.

Vascular remodelling within AVFs and shear stress

Physiologically, to maintain vascular homeostasis, the circulatory system can remodel blood vessels to accommodate increased blood flow to different organs, starting from early embryonic developmental stages (le Noble et al., 2004; Lucitti et al., 2007). Blood vessels, including arteries and veins, consist of multiple cell types distributed across three layers of tissue known as the tunica intima, tunica media, and tunica adventitia. Both veins and arteries are composed of these three layers, but their thickness and composition vary. The intima, the innermost layer, primarily comprises a single layer of ECs that come into direct contact with the blood flow within the vessel. The middle layer, the media, which is usually the thickest layer in arteries, is composed primarily of VSMCs, as well as elastic tissue and collagen. This layer is responsible for regulating the diameter of blood vessels – and thus blood flow and pressure – through vasoconstriction and vasodilatation. The adventitia, or outer layer, is the thickest layer in veins and consists of fibroblasts, collagen fibres and connective tissue. Following the creation of an AVF, the pressure gradient between the artery and vein increase blood flow through the vein side of the anastomosis, leading to changes in shear stress (Dixon, 2006; Wedgwood et al., 1984). Successful AVF maturation requires the blood vessels to adapt to these haemodynamic changes, which is achieved through an increased internal diameter and vessel wall thickening (Fig. 1*D*) (Remuzzi & Bozzetto, 2017). Blood flow and consequently shear stress regulate the luminal diameter of the blood vessels through mechanisms that induce the contraction and relaxation of VSMCs (Zhao et al., 2017) and through a process known as outward remodelling (Chatzizisis et al., 2007; He et al., 2023). Outward remodelling involves the structural reorganization of the vessel wall, increasing the external diameter of the blood vessel while maintaining or increasing the luminal diameter (Mulvany, 2008). This process helps to accommodate the increased blood flow and reduces the risk of vessel occlusion by mitigating the effects of neointimal hyperplasia and other obstructive processes.

The haemodynamic changes affecting both the artery and vein sides of the anastomosis are translated into

biochemical signals influencing the behaviour of several cell types, including ECs, VSMCs and fibroblasts. These signals lead to changes in the extracellular matrix (ECM), increasing inflammation, the production of growth factors and antioxidant stress (Browne et al., 2015). Typically, the remodelling process initiates post-anastomosis, setting off a cascade of cellular and molecular events to help blood vessels adapt to the new haemodynamic conditions (Pries et al., 2005). Initially, the abrupt increase in blood flow and pressure induces mechanical forces such as shear stress and circumferential stretch, which are sensed by the ECs lining the vessel walls. These mechanical stimuli are rapidly converted into biochemical signals through mechanotransduction pathways, initiating a series of cellular responses. ECs begin to secrete vasoactive substances like nitric oxide (NO) and prostacyclin, which promote vasodilatation and inhibit platelet aggregation, thus ensuring an increased luminal diameter and improved blood flow. Concurrently, VSMCs in the tunica media respond to the altered haemodynamic forces by shifting from a contractile phenotype to a synthetic state. In this synthetic state, VSMCs become capable of proliferating, migrating and secreting ECM components, contributing to the structural remodelling of the vessel wall. Fibroblasts in the tunica adventitia also participate in this process by producing collagen and other ECM proteins, which provide structural support to the expanding vessel. Additionally, increased blood flow activates a localized inflammatory response (Samra et al., 2022), leading to the recruitment of immune cells that release cytokines and growth factors. This inflammatory response further influences the behaviour of EC, VSMCs and fibroblasts (Kingston et al., 2003). Additionally oxidative stress, resulting from increased production of reactive oxygen species (ROS), has also been identified as a key factor in modulating cellular functions and signalling pathways during AVF maturation (Bezhaeva et al., 2017; Rai et al., 2022; Sadaghianloo et al., 2017). Together, these processes contribute to the outward remodelling and functional adaptation of the AVF, ultimately determining its maturation and patency. Despite efforts to characterize the factors that contribute to AVF maturation (reviewed in Gorecka et al., 2019; Yan et al., 2024), the exact sequence of cellular and molecular events leading to successful AVF maturation have yet to be fully elucidated, as reflected by the fact that 20–40% of AVFs do not reach maturity (Ghorbani et al., 2009; McLafferty et al., 2007; Rezapour et al., 2018). Recent research has focused on investigating how various signalling pathways influence the successful maturation of AVFs. From these, transforming growth factor β (TGF-β) signalling is one of the more studied pathways that can control several processes associated with vascular remodelling in AVF, including ECM remodelling, inflammation and cell proliferation (Hu et al., 2020; Laboyrie et al., 2023). TGF-β plays a dual role in AVF maturation: while it promotes key processes like ECM deposition and smooth muscle cell (SMC) proliferation necessary for initial vein wall thickening (Kobayashi et al., 2005; Tsai et al., 2009), excessive TGF-β activity can inhibit successful AVF maturation by driving pathological wall thickening and stenosis (Stracke et al., 2002). Interestingly, genetic inhibition of TGF-β signalling in mice reveals cell-type-specific effects. In SMCs, disruption of TGF-β signalling reduces collagen deposition but does not significantly affect SMC proliferation or wall thickness, suggesting limited impact on AVF maturation. Conversely, endothelial cell-specific inhibition of TGF-β signalling decreases both SMC proliferation and collagen deposition, leading to reduced wall thickness, enhanced outward remodelling and improved AVF patency (Taniguchi et al., 2022; Zhang, Gonzalez et al., 2024). The differential effects of TGF-β signalling in ECs *versus* SMCs highlight the complexity of the molecular pathways controlling AVF maturation and patency. Further studies are needed to elucidate how TGF-β influences other cell types involved in AVF remodelling, such as fibroblasts and immune cells, and their interactions during maturation. Additionally, it is well-established that AVF maturation and patency are influenced by sex differences, with females often experiencing lower success rates compared to males (Hoffstaetter et al., 2023). However, the underlying mechanisms driving these sex-specific AVF outcomes remain unclear (Chan et al., 2021; Liu et al., 2024; Satam et al., 2023). This represents another critical open question in AVF research, highlighting the need for further investigation into how sex-specific factors, such as hormonal influences and differences in vascular biology, impact AVF remodelling and patency (Chan et al., 2021; Liu et al., 2024; Satam et al., 2023).

Endothelial cells and shear stress

ECs lining blood vessels are in direct contact with the bloodstream and exposed to shear stress. To maintain normal vascular functions, ECs need to be able to sense and respond to highly dynamic biomechanical forces. They are key players in the vascular remodelling process as they can recognize changes in shear stress and convert these mechanical stimuli into biochemical signals (Dessalles et al., 2021; Li et al., 2005) that control several aspects of EC function, such as gene expression (Wragg et al., 2014), morphology (Butcher et al., 2004) and physiology (Espina et al., 2023). Impairment of ECs' response to changes in shear stress can lead to the development of vascular diseases, including hypertension (Iring et al., 2019), thrombosis (Yin et al., 2011) and atherosclerosis (Souilhol et al., 2020). Vascular geometry significantly impacts blood

flow and haemodynamic forces, resulting in considerable variations and non-uniformity within the vascular system. In straight segments, blood flow is typically undisturbed, laminar and parallel to the vessel wall, resulting in high shear stress. However, in curved, branched or bifurcated areas, blood flow is disturbed, leading to low shear stress. Furthermore, laminar shear stress promotes endothelial cell alignment in the direction of flow (Wang et al., 2013), inhibits endothelial cell proliferation (Kadohama et al., 2007) and enhances the production of nitric oxide (Ozawa et al., 2004), which helps maintain vascular homeostasis and prevent the development of vascular diseases. In contrast, disturbed or oscillatory shear stress, common in bifurcations and curved regions, leads to endothelial cell dysfunction by triggering the expression of pro-inflammatory genes, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Sorescu et al., 2003), increasing the production of ROS (Jo et al., 2006) and downregulating protective factors such as Kruppel-like factor 2 (KLF2) (Sun et al., 2019).

The role of haemodynamic forces in endothelial function was first suggested by the observation that atherosclerotic lesions develop preferentially at arterial branches and curvatures, where cells are exposed to a disturbed flow. Several studies indicate that such disturbed flow and the associated low and reciprocating shear stress activate atherogenic genes in ECs (Andueza et al., 2020; Passerini et al., 2004). In contrast, laminar blood flow and high shear stress in straight arterial segments downregulate atherogenic genes and upregulate protective genes in ECs. Furthermore, *in vivo* observations suggest that changes in shear stress, rather than the magnitude of shear stress, play critical roles in vascular homeostasis and remodelling (Chiu & Chien, 2011).

The precise mechanisms by which endothelial cells distinguish between uniform and disturbed flow are not yet fully understood. However, evidence indicates that various mechanotransducers respond to shear stress, including G-protein-coupled receptors (GPCRs), adherens junctions and flow-sensitive ion channels (Tamargo et al., 2023). Additionally, certain mechanosensitive transcription factors are known to be activated selectively in response to different flow types, modulating gene expression patterns in ECs depending on the flow environment (Niu et al., 2019). Although the complete signalling pathway connecting the activation of various membrane mechanotransducers with distinct mechanosensitive transcription factors is not understood, recent research has shed light on specific components of this process. For example, it has been shown that laminar shear stress activates the mechanosensitive channel Piezo1 in endothelial cells, which subsequently induces the release of ATP into the extracellular space. This ATP then binds to the purinergic P2Y2 receptor, a GPCR specifically linked with Gq/G11 proteins. Activation of the P2Y2 receptor initiates downstream signalling cascades involving Gq/G11, which elevate intracellular calcium levels, activate AKT, and promote phosphorylation of endothelial nitric oxide synthase (eNOS) (Wang et al., 2015, 2016). These signalling events increase nitric oxide (NO) production, supporting vasodilatation and exerting protective, anti-atherogenic effects by enhancing endothelial function and maintaining vascular tone. Nevertheless, the same proteins, Piezo1, P2Y2 and Gq/G11, have been shown to mediate the inflammatory response triggered by oscillatory shear stress (OSS). Under OSS, signalling through Piezo1 and Gq/G11 leads to the activation of integrin $\alpha5\beta1$, which subsequently triggers the focal adhesion kinase (FAK) pathway. This activation culminates in the stimulation of the transcription factor NF-κB, promoting the expression of pro-inflammatory molecules, including adhesion molecules VCAM-1 and ICAM-1, which facilitate immune cell attachment to the endothelium (Albarrán-Juárez et al., 2018). Similarly, a recent study has shown that OSS elevates Piezo1 expression in endothelial cells, particularly in the ApoE$^{-/-}$ mouse model of atherosclerosis. The activation of Piezo1 facilitates calcium influx into the cell, subsequently activating the calmodulin–Ca^{2+}/calmodulin-dependent protein kinase II signalling pathway. This pathway then activates FAK and Src, ultimately leading to the activation of the transcription factor YAP (Yes-associated protein). Chemical inhibition of Piezo1 using GsMTx4 has been found to slow the progression of atherosclerotic plaque formation and reduce inflammation caused by Piezo1 activation (Lan et al., 2024). In another publication it was shown that OSS activates the stimulator of interferon genes (STING) pathway in endothelial cells, a mechanism involved in sensing cytoplasmic DNA as a signal of cellular damage (Dong et al., 2024). OSS induces mitochondrial damage, which compromises mitochondrial membrane integrity and results in the release of mitochondrial DNA (mtDNA) into the cytoplasm. The released mtDNA is recognized by cyclic GMP-AMP synthase (cGAS), an enzyme that generates the second messenger cGAMP to activate STING. Once STING is activated, it drives the expression of type I interferons and pro-inflammatory cytokines and activates transcription factors, including NF-κB. These factors stimulate the expression of genes associated with the SASP, contributing to cellular senescence and endothelial dysfunction. In another study, the effects of low shear stress (LSS) and high shear stress (HSS) on the production of extracellular vesicles (EVs) was evaluated (Coly et al., 2024). The paper showed that ECs exposed to LSS released fewer EVs compared to those exposed to HSS. However, EVs produced by ECs under LSS conditions were taken up more efficiently by recipient endothelial cells than

those from HSS conditions. This increased uptake of LSS-EVs was attributed to an enrichment in adhesion molecules, such as platelet endothelial cell adhesion molecule-1 (PECAM-1) and melanoma cell adhesion molecule (MCAM), which facilitated their cellular uptake. Additionally, LSS-EVs presented mitochondrial and endolysosomal proteins, which were associated with the increase in reactive oxygen species (ROS) production observed in LSS-EV recipient cells, which was reduced when neutralizing antibodies against PECAM-1 and MCAM were applied, highlighting the role of these adhesion proteins in mediating the effects of LSS-EVs on recipient cells.

In AVFs, regions near the anastomosis experience significant haemodynamic changes as blood transitions from a high-pressure environment in the artery to a low-pressure environment in the vein (Ene-Iordache & Remuzzi, 2012; Hyde-Linaker et al., 2022). The endothelium, constantly exposed to the mechanical force of blood flow, relies on shear stress for maintaining its physiological function. Shear stress not only regulates endothelial cell integrity and permeability but also influences cellular senescence, a process wherein cells undergo irreversible growth arrest in response to various stressors, including mechanical forces and oxidative stress. Early studies demonstrated that senescent ECs tend to be increased in sites of atherosclerosis (Vasile et al., 2001). This accumulation is particularly evident in specific regions of blood vessels, such as bifurcations and curved areas, which are also exposed to disturbed flow and non-laminar shear stress (Warboys et al., 2014). Considering that in AVFs there are also regions exposed to disturbed flow like those observed in atherosclerotic regions prone to accumulating senescent cells, it is reasonable to suggest that a similar phenomenon occurs in AVFs.

The role of senescent cells in vascular remodelling of AVFs

Cellular senescence is a state of permanent cell cycle arrest that occurs in response to various stressors, including DNA damage, oxidative stress and telomere shortening (Campisi & D'Adda Di Fagagna, 2007). Although these cells no longer proliferate, they remain metabolically active and secrete a variety of pro-inflammatory cytokines, chemokines, growth factors and metalloproteases, collectively known as the SASP (Coppé et al., 2008). This phenotype has significant effects on the tissue microenvironment, influencing neighbouring cells and contributing to tissue remodelling and inflammation (Ohtani, 2022). The SASP also facilitates the recruitment of immune cells to eliminate senescent cells from tissues (Prata et al., 2018). Senescent cells that are transiently present participate in various homeostatic processes, such as embryonic development and wound healing. During embryo development, senescent cells play a crucial role in tissue patterning and remodelling, by promoting macrophage infiltration aiding in the removal of cells that are no longer needed and ensuring proper organogenesis (Muñoz-Espín et al., 2013; Storer et al., 2013).

In wound healing, senescent cells contribute to the repair process by promoting tissue regeneration and remodelling through the secretion of pro-inflammatory cytokines that recruit immune cells to clear damaged cells and pathogens (Demaria et al., 2014). However, as organisms age, the efficiency of clearing these senescent cells declines, contributing to their accumulation in various tissues, including endothelial tissue (Idda et al., 2020; Jeyapalan et al., 2007; Pantsulaia et al., 2016). The persistent accumulation of senescent cells alters the tissue microenvironment through the effects of the SASP, resulting in chronic inflammation and paracrine-induced senescence of neighbouring cells (Admasu et al., 2021; Ferreira-Gonzalez et al., 2018). This process contributes significantly to endothelial dysfunction and is a hallmark of age-related diseases. (Bloom et al., 2023; Graves & Baker, 2020; Han & Kim, 2023). The number of senescent cells increases with age, and metabolic diseases, such as diabetes and obesity, can accelerate this process (Spinelli et al., 2023). More specifically, it has been shown that transplanting a small number of senescent cells into young mice can lead to significant physical dysfunction and accelerated ageing, with the transplanted cells inducing senescence in nearby tissues (Xu et al., 2018). Importantly, the study suggests that there appears to be a threshold number of senescent cells required to produce these deleterious effects, as the physical dysfunction was only detectable when the number of transplanted senescent cells exceeded a certain limit. This threshold was lower in older mice and in those with additional comorbidities, such as obesity, indicating that ageing and metabolic stress can enhance the impact of senescent cells. Since young mice are typically less inflamed than older or obese mice, transplanting senescent cells into young mice helps to isolate the direct effects of senescent cells, in contrast to the chronic inflammation that is associated with ageing and metabolic conditions. These findings suggest that even a small burden of senescent cells can drive systemic dysfunction, particularly in the context of ageing and disease. In patients undergoing HD, where ageing and comorbidities such as diabetes often coexist, the process of cellular senescence can be accelerated, increasing the burden of senescent cells within the vasculature. For instance, elevated glucose levels in diabetes promote the formation of glycation end-products and oxidative damage in ECs (Cheng et al., 2023), further exacerbating endothelial dysfunction and accelerating the accumulation of senescent cells. Similarly, hypertension

induces mechanical stress and inflammation, further contributing to the endothelial senescent cell burden (Minamino et al., 2004). Chronic kidney disease (CKD) itself, along with the associated uraemia, raises oxidative stress and induces endothelial cell senescence, leading to endothelial dysfunction and cardiovascular disease (Yang et al., 2012). Chronic inflammation, prevalent in renal failure, releases cytokines like tumour necrosis factor-α and interleukins that directly induce EC senescence (Bolton et al., 2001; Khan et al., 2017; Shen et al., 2012). Consequently, patients undergoing haemodialysis tend to have an increased burden of senescent cells with respect to healthy individuals.

Unlike other cell types, ECs are directly exposed to the blood and its contents, including the shear stress resulting from blood flow (Fig. 2). ECs respond differently to shear stress based on its magnitude and pattern. ECs exposed to sustained high laminar shear stress in straight arteries show reduced DNA synthesis (Lin et al., 2000), indicating decreased proliferation. Furthermore, disturbed blood flow, characterized by low and oscillatory shear stress, is common in blood vessels with complex geometries such as bifurcations and branches. Under these low shear stress conditions ECs proliferate, leading to an accelerated shortening of telomeres, the protective caps at the ends of chromosomes. As with each cell division telomeres shorten, they eventually reach a critical length that triggers a DNA damage response that leads a permanent cell cycle arrest called replicative senescence (Ando et al., 1987; Chang & Harley, 1995; Mavromatis et al., 2000). On the other hand, in regions where cells are exposed to laminar shear stress (inhibiting EC proliferation), EC turnover can take up to 60 years (Akimoto et al., 2000; Hobson & Denekamp, 1984). However, although cells with low turnover do not develop replicative senescence, these ECs are exposed to several circulating agents in the blood for extended periods. This chronic exposure to potentially harmful molecules increases their susceptibility to accumulating damage over time, which can lead to DNA damage and induce premature senescence, for example. Consequently, both long-lived and short-lived ECs can become senescent from different stimuli. Patients requiring HD are typically older and present one or more comorbidities that can lead to CKD and ESRD, likely already having an increased number of senescent ECs due to ageing and the stress associated with metabolic disease.

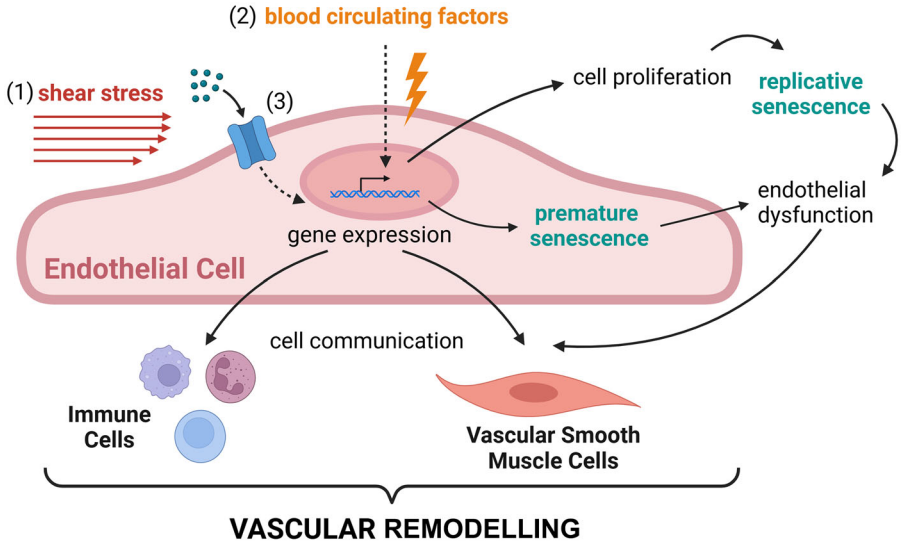


Figure 2. Endothelial senescence may affect cell communication during vascular remodelling
Endothelial cells (ECs) are continuously exposed to various types of shear stress (1) and circulating blood factors (2) that activate intracellular signalling pathways (dashed lines), leading to changes in gene expression associated with key processes such as proliferation, adhesion, and senescence. Shear stress, in particular, plays a critical role in shaping EC behaviour. ECs sense shear stress through mechanosensory proteins located in the cell membrane (3), including Piezo1, a channel protein that opens in response to mechanical forces, allowing calcium influx and initiating a signalling cascade that activates mechanosensitive transcription factors (not shown) that induce the expression of their target genes. Importantly, EC phenotype is highly responsive to shear stress patterns: disturbed flow promotes EC proliferation, which can eventually lead to replicative senescence. Additionally, circulating factors in the blood can induce cellular stress, triggering premature senescence and the expression of senescence-associated genes, including those linked to the senescence-associated secretory phenotype (SASP). Regardless of the inducing mechanism, senescent ECs exhibit dysfunction that compromises vascular homeostasis. The SASP and other senescence-related changes disrupt cell-to-cell communication with neighbouring cells, such as immune cells and vascular smooth muscle cells, impairing proper vascular remodelling.

Senescent endothelial cells can alter the function of the neighbouring vascular endothelium

EC senescence can lead to endothelial dysfunction by dysregulation of key vascular cell functions including vasodilatation and haemostasis, induction of oxidative stress, and inflammation (Fig. 3*A*). Vascular endothelium maintains normal vascular homeostasis by producing several paracrine factors, including NO and endothelin-1 (ET-1). NO serves as a potent vasodilator and plays a pivotal role in inhibiting platelet adhesion, suppressing VSMC proliferation and reducing leukocyte adhesion. The physiological stimuli for NO production are primarily wall shear stress and alterations in blood flow. In senescent ECs, there is a notable reduction in NO production (Matsushita et al., 2001), which can potentially decrease vasodilatation, leading to increased vascular resistance and elevated blood pressure (Li et al., 2015; Shesely et al., 1996).

Additionally, senescent ECs exhibit an increased production of ET-1, a potent vasoconstrictor, further exacerbating vascular tone (Donato et al., 2009). In the context of AVFs, the presence of senescent ECs can negatively affect vascular remodelling due to the decreased production of NO in response to haemodynamic changes post-anastomosis. The reduced availability of NO impairs vasodilatation and contributes to neointimal hyperplasia, as NO normally inhibits the proliferation of VSMCs (Herrera et al., 2010). Moreover, SASP factors such as interleukin (IL)-6 (Bent et al., 2016) and IL-8 (Hampel et al., 2006), secreted by senescent ECs, along with other proteins that show increased expression in senescent cell, such as E-selectin (SELE) (Yanaka et al., 2011), monocyte chemoattractant protein-1

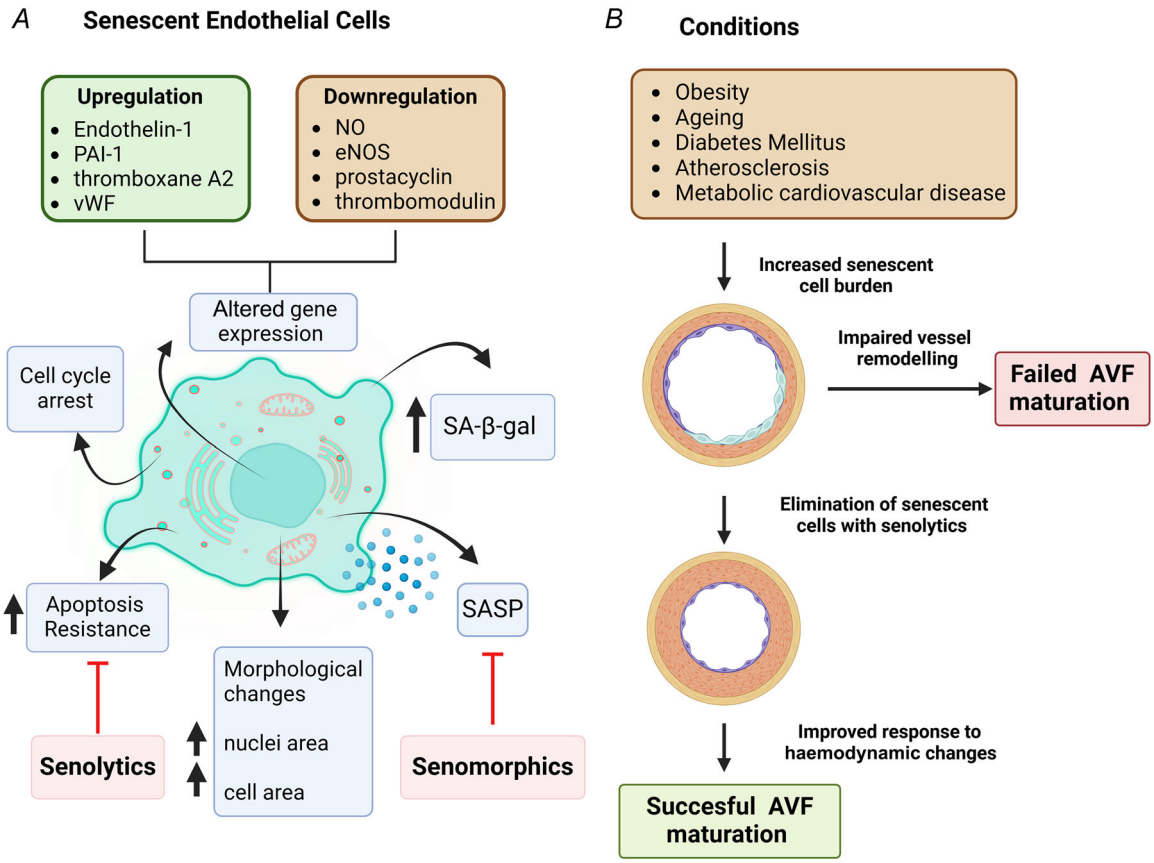


Figure 3. Impact of endothelial cell senescence on AVF maturation and therapeutic strategies
A, schematic representation of senescent endothelial cells phenotype. Senescent ECs are characterized by the upregulation of pro-thrombotic genes and downregulation of molecules that prevent this. Senescent ECs exhibit features such as cell cycle arrest, altered gene expression, SASP and the increased activity of senescence-associated β-galactosidase (SA-β-gal). These cells show increased resistance to apoptosis and morphological changes, including increased nuclear and cell area in cell culture. *B*, the contribution of various diseases to senescent EC burden. The increase of senescent ECs leads to impaired vessel remodelling, contributing to AVF failure. Removal of senescent cells through senolytics improves the response to haemodynamic changes, potentially leading to successful AVF maturation. EC, endothelial cell; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; SASP, senescence-associated secretory phenotype; vWF, von Willebrand factor.

(MCP-1) and VCAM-1 (Piga et al., 2007), can create a pro-inflammatory environment that attracts immune cells, such as macrophages and neutrophils, to the site of the AVF. These immune cells can further exacerbate inflammation, promoting a phenotypic switch in VSMCs, characterized by increased protein synthesis, proliferation and migration (Gerthoffer, 2007; McDonald et al., 2010; Weber & Noels, 2011).

Under these conditions, VSMCs migrate from the medial layer to the vessel intima, where they produce abundant ECM components and proteins, such as matrix metalloproteinases (MMPs). This phenotypic switch of VSMC not only increases the risk of neointimal hyperplasia but also leads to ECM remodelling, contributing to vessel wall thickening and narrowing (Déglise et al., 2023).

The pro-thrombotic state induced by senescent ECs can also plays a role in AVF dysfunction. Senescent ECs upregulate pro-coagulant factors such as von Willebrand factor, thromboxane A2, and plasminogen activator inhibitor-1 (PAI-1), while downregulating several key antithrombotic proteins, including thrombomodulin, eNOS and prostacyclin. The increased production of these molecules significantly raises the risk of thrombosis within the AVF (Bochenek et al., 2016; Silva et al., 2017). This pro-thrombotic environment can further hinder blood flow and contribute to AVF failure. Additionally, the increased production of ROS by senescent ECs can contribute to oxidative stress in adjacent cells. This occurs because senescent cells can secrete ROS into the extracellular space, thereby impacting neighbouring non-senescent ECs (Nelson et al., 2012). Moreover, ROS production can contribute to a pro-thrombotic environment through several mechanisms. ROS can induce endothelial dysfunction, impairing the endothelium's ability to regulate vascular tone and prevent platelet aggregation, leading to an imbalance in vasodilators and vasoconstrictors that favours thrombosis (Incalza et al., 2018). Additionally, ROS can activate platelets (Qiao et al., 2018), which are crucial for blood clot formation, causing them to adhere to the endothelium and to each other, releasing pro-thrombotic substances that amplify clotting. Furthermore, ROS can stimulate leukocytes, which exacerbate vascular inflammation by releasing enzymes and cytokines that damage the endothelial lining and promote further platelet activation. ROS can also alter coagulation and fibrinolysis by enhancing tissue factor expression, initiating the coagulation cascade and impairing fibrinolysis, which favours clot formation and persistence (Gutmann et al., 2020). Finally, ROS affect blood flow by promoting vasoconstriction and reducing vascular elasticity, leading to impaired circulation and creating areas prone to clot formation. These combined effects significantly elevate the risk of thrombotic events.

Identification of senescent cells requires the assessment of multiple markers

Despite the importance of cellular senescence in various pathological processes and the potential benefits of eliminating them to ameliorate the detrimental characteristics of their accumulation, the clinical application of this knowledge is hindered by the heterogeneity of senescent cells and the lack of universal markers for their identification (González-Gualda et al., 2021). Therefore, there is a need to generate tools that can accurately determine the number of senescent cells present in an individual or organ with a specific condition. To accurately characterize the senescent cell burden in patients of varying ages and comorbidities, it is essential to identify these cells either *in vivo* or *ex vivo*. This approach will enable a comprehensive understanding of the abundance of senescent cells across different tissues and contexts. Such markers will provide critical insights, facilitating the translation of these findings into clinical applications. However, identifying senescent cells is a complex task due to the lack of universal markers and the heterogeneity of senescent phenotypes, which vary depending on cell types and the specific inducers of senescence (Basisty et al., 2020; Hernandez-Segura et al., 2017). This diversity requires careful selection of biomarkers derived from the hallmarks of cellular senescence for accurate detection and analysis, particularly in *in vivo* settings where detecting senescent cells can be more challenging compared to *in vitro* or *ex vivo* environments. Thus, a multi-biomarker approach is often required to enhance the specificity and accuracy of senescence detection (Kohli et al., 2021; Rabinowitz & Cui, 2023). The development of robust tools to study the diverse phenotypes of senescent cells is essential for comprehensively understanding the impact of cellular senescence on various diseases.

The detection of cellular senescence is generally accomplished through the measurement of several biomarkers associated with the hallmarks of senescence (Hernandez-Segura et al., 2018). These biomarkers are evaluated using various techniques such as quantitative PCR (qPCR), western blotting, immunohistochemistry, enzyme-linked immunosorbent assays and chemical staining. Commonly used markers include increased activity of the enzyme senescence-associated β-galactosidase (SA-β-Gal) (Dimri et al., 1995), elevated levels of cyclin-dependent kinase inhibitors like $p16^{INK4a}$ and $p21^{CIP1/WAF1}$, persistent expression of DNA damage response markers, such as γ-H2AX and 53BP1, and secretion of SASP factors (González-Gualda et al., 2021).

There are various characterizations of the secretome of senescent cells that have contributed to defining a general SASP profile (Basisty et al., 2020; Hernandez-Segura et al., 2017). However, in endothelial cells, the specific

SASP factors evaluated often vary by study. Commonly included markers across studies are typically divided into cytokines (e.g. IL-6, IL-1β), chemokines (e.g. IL-8), growth factors (e.g. vascular endothelial growth factor A, granulocyte–macrophage colony-stimulating factor), and metalloproteinases (e.g. MMP-9), along with other proteins such as PAI-1. This categorization highlights the diversity of SASP components commonly studied in endothelial cells, reflecting both their inflammatory and their tissue-remodelling roles.

However, the ubiquitous expression of some of these markers, which are also present in other cellular contexts, complicates the precise identification of senescent cells, particularly in vivo. This challenge is further compounded by the heterogeneity of senescent cells, which exhibit diverse phenotypes and molecular profiles. As a result, the accurate identification of senescent cells requires the use of multiple markers to reliably establish their identity and distinguish them from other cell states. For instance, SA-β-Gal activity, although widely used, can be expressed in non-senescent cells under certain conditions (de Mera-Rodríguez et al., 2021). Similarly, $p16^{INK4a}$ and $p21^{CIP1/WAF1}$ are involved in other cellular processes like cell cycle regulation and can be upregulated in cells experiencing transient stress responses. DNA damage markers like γ-H2AX indicate the presence of double-strand breaks, which may occur in non-senescent cells undergoing DNA repair. Nevertheless, in senescent cells, there is a persistent DNA damage response characterized by sustained activation of the DNA damage response pathway and the formation of persistent γ-H2AX foci (Pospelova et al., 2009; Siddiqui et al., 2015). Different cell types can exhibit distinct senescent phenotypes (Hernandez-Segura et al., 2017), and the pathway leading to senescence – whether through oxidative stress, telomere shortening, oncogene activation or chemotherapeutic agents – can influence the SASP factors produced (Basisty et al., 2020). Thus, employing a multifaceted approach that integrates various markers is essential for accurately identifying and studying senescent cells in diverse biological contexts. Recent advances in spatial biology technologies offer a detailed way to study senescent cells in tissues. Spatial biology technologies enable high-resolution imaging of RNA and proteins, allowing simultaneously visualization and measurement of multiple biomarkers at the subcellular level (Gurkar et al., 2023). This technology has been applied to formalin-fixed paraffin-embedded tissue samples, offering detailed spatial maps of cellular and molecular interactions within tissues. This comprehensive strategy ensures that senescent cells can effectively be distinguished from other cell types, facilitating better understanding and targeting of senescence in physiological and pathological conditions. In the context of AVF, spatial biology technologies will allow researchers to correlate the presence and abundance of these cells in the different layers of blood vessels previous to anastomosis, with successful maturation, failure and/or patency of the AVF (Martinez et al., 2019).

Therapeutic strategies for mitigating senescent cell burden and improving AVF maturation

Senescent ECs are dysfunctional and their numbers in patients requiring HD are most likely increased. Consequently, removing these cells, which may not respond properly to haemodynamic changes, could potentially improve vascular remodelling in AVF. In this context, senotherapeutics present a promising strategy to mitigate the adverse effects of cellular senescence (Fig. 3*B*). Senolytics, which selectively induce apoptosis in senescent cells (Lelarge et al., 2024), and senomorphics, which suppress the SASP without killing the cells (Zhang et al., 2023), both target the detrimental effects of cellular senescence. Senolytics have shown potential in preclinical models by reducing the senescent cell burden and alleviating associated dysfunction (Xu et al., 2018). This approach can potentially enhance healthspan and alleviate age-related pathologies such as cardiovascular disease, Alzheimer's disease, osteoarthritis, diabetes, macular degeneration, chronic obstructive pulmonary disease and cancer (Fuhrmann-Stroissnigg et al., 2017; Xu et al., 2018; Zhang et al., 2023).

In this context, it has been shown that long-term treatment with the senolytic dasatinib and quercetin (D + Q) improves vasomotor function and reduces senescent cell markers in aged and hypercholesterolaemic mice (Roos et al., 2016). The treatment enhanced NO bioavailability and sensitivity to NO, reduced aortic calcification and osteogenic signalling, but did not significantly change intimal plaque fibrosis. Genetic clearance of senescent cells in aged mice showed similar improvements. In a recent study, the implications of cellular senescence in the pathophysiology of AVFs within a CKD mouse model were assessed. This research reveals a notable accumulation of senescent cells, particularly within the venous segments of AVFs, which is correlated with an increased expression of senescence-associated markers, such as $p16^{INK4a}$. This cellular senescence is implicated in endothelial dysfunction and the exacerbation of neointimal hyperplasia, thereby compromising AVF maturation and function. The study further highlights the therapeutic potential of senolytic agents in mitigating senescent cell burden, thereby enhancing the structural and functional integrity of AVFs (Nath et al., 2018). These findings propose a novel therapeutic avenue, suggesting that targeting cellular senescence could significantly improve AVF outcomes in CKD patients undergoing haemodialysis. Moreover, positive effects in restoring

endothelial function have also been observed using *in vitro* blood–brain barrier models, further supporting the potential of senolytics for enhancing vascular health (Ya et al., 2023). Despite their potential benefits, there are several unknowns regarding the systemic effects of senolytics, especially the long-term impact of its use on tissue homeostasis and regeneration. Furthermore, certain types of senescent cells play essential roles in maintaining organ structure and integrity. Removing these cells in mice can result in tissue damage and organ dysfunction (Grosse et al., 2020). Additionally, senescent cells play beneficial roles in processes like wound healing and tumour suppression, raising concerns about the consequences of their removal. Thus, while senolytics hold great promise, their long-term effects and optimal use require further investigation to ensure safe and effective therapeutic applications. In this context, the modulation of SASP via senomorphics offers a way to contain the negative effects of senescent cells without killing them (He & Sharpless, 2017). It has been shown that senomorphics can reduce inflammation and improve vascular function (He & Sharpless, 2017; Lorenzo et al., 2023). Although senomorphics can mitigate the detrimental impacts of senescent cells, their long-term efficacy in altering the SASP and their overall impact on cellular health require further investigation. The optimal timing, dosage and duration of senotherapeutic treatments need further exploration to ensure a balance between efficacy and safety. The heterogeneity of senescent cells across different tissues also presents a challenge for developing targeted therapies.

Future directions and limitations

This review introduces the concept of cellular senescence with a particular emphasis on endothelial cell senescence and its implications for vascular remodelling. Vascular remodelling is a critical process for the maturation and long-term patency of AVFs, which serve as essential vascular access for patients with ESRD undergoing haemodialysis. By exploring the interplay between endothelial cell senescence and vascular remodelling, this work underscores the broader impact of cellular senescence on the health outcomes of individuals dependent on haemodialysis. However, the role of senescence in the vasculature, beyond its contributions to atherosclerosis, remains poorly understood. A critical knowledge gap involves the response of senescent endothelial cells to shear stress, a key regulator of vascular health. In non-senescent endothelial cells, laminar shear stress promotes anti-inflammatory and anti-thrombotic effects, contributing to vascular homeostasis. However, senescent cells exhibit impaired functions, such as resistance to apoptosis and pro-inflammatory secretions, raising questions about their capacity to respond to shear stress effectively. Dysregulated responses in senescent cells could exacerbate vascular pathologies, including AVF failure, where shear stress plays a pivotal role in remodelling. Understanding the differential mechanotransduction responses of senescent *versus* non-senescent ECs is essential for designing targeted therapies that enhance vascular function. To address these challenges, future research should prioritize the characterization of endothelial cell senescence in AVFs, focusing on patient-derived samples from both successful and failed fistulas. Comprehensive analyses of senescent cell burden, secretory profiles and shear stress mechanotransducers before and after AVF surgery are critical. Comparative studies using human samples and animal models will provide insights into the mechanistic links between endothelial cell senescence, shear stress and AVF maturation. Moreover, manipulating shear stress experimentally could reveal novel therapeutic strategies to improve AVF outcomes.

A limited number of studies have demonstrated the presence of senescent endothelial cells in AVFs, primarily relying on rodent models. This gap highlights the necessity of translating findings from these models to human physiology. Future research should confirm the presence of senescent cells in human AVFs and investigate their relationship with AVF maturation, long-term patency and the influence of ESRD-related comorbidities on the accumulation of senescent cells. If human studies align with preclinical evidence suggesting that senescent cell clearance improves AVF outcomes, the next steps would involve identifying appropriate senolytic therapies tailored for this context. Potential strategies could include systemic senolytic treatments or localized approaches, such as drug-coated balloons used in angioplasty, to target endothelial senescence.

Although preclinical evidence supports the efficacy of senolytics in ameliorating cardiovascular dysfunction, significant challenges remain. For instance, prominent senolytic agents like ABT263 (navitoclax) and dasatinib are associated with severe toxicities in clinical settings (Sweeney et al., 2023). Moreover, there is limited evidence regarding the systemic and tissue-specific effects of senolytic treatments on vascular systems in humans. The long-term impacts of senescent cell clearance – both systemic and localized – on cardiovascular health are also unclear. Additional research is needed to refine the duration, dosage and targeting mechanisms of senolytic therapies to ensure safety and efficacy.

Current challenges in senolytic therapy development include the lack of specificity, as many compounds inadvertently affect non-senescent cells, leading to potential damage in healthy tissues. Additionally, some senolytics exhibit significant toxicity or fail to effectively target senescent cells due to the presence of senescent cell anti-apoptotic pathways (SCAPs). These pathways are a

network of survival mechanisms that allow senescent cells to resist apoptotic signals, making them less responsive to conventional cytotoxic drugs. While preclinical studies in animal models have shown promising results, the clinical efficacy of many senolytics remains moderate, underscoring the need for improved strategies. To overcome these challenges, researchers are developing innovative therapeutic approaches, such as small molecules, prodrugs designed to activate selectively within senescent cells, and immunotherapies, including engineered immune cells and vaccines targeting senescence-specific markers (Lelarge et al., 2024). These advances aim to improve the precision and effectiveness of senolytic treatments while minimizing adverse effects.

Conclusion

The failure of AVFs to mature remains a major barrier for patients with end-stage renal disease, often prolonging dependence on central venous catheters and increasing the risks of infection, thrombosis and other complications. Additional interventions to salvage or replace non-maturing AVFs further heighten these risks, delaying adequate dialysis and exacerbating patients' overall health conditions.

A deeper understanding of endothelial senescence and its mechanotransduction, along with the exploration of senolytic therapies, presents a promising avenue for improving AVF maturation. Senescent endothelial cells significantly influence vascular remodelling, a process critical for AVF functionality. However, despite notable progress in understanding AVF maturation, a substantial proportion still fail to mature successfully. Comprehensive characterization of endothelial senescence in patients – both pre- and post-surgery – could enable the development of personalized strategies to minimize the harmful effects of senescence while preserving its adaptive roles.

Ultimately, a multifaceted approach that integrates human studies, mechanistic insights and therapeutic innovation may lead to paradigm-shifting strategies for enhancing vascular access. This could significantly improve treatment outcomes, increase AVF patency and enhance the quality of life for this vulnerable population.

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

R.M.A. was responsible for the concept of the article. R.M.A. and writing the manuscript. I.G. wrote sections of the first draft of the article and figures. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

This research was supported by Proyecto FONDECYT de Iniciación 11220698 to R.M.A.

Acknowledgements

We extend our sincere gratitude to Dr Fabian Pardo, Dr Glauben Landskron and Dr Arturo Chavez-Reyes for their invaluable feedback on early drafts of this manuscript. We would also like to thank Magdalena Castro, RN, MSc, for sharing her clinical knowledge and experience with haemodialysis patients.

Keywords

arteriovenous fistulas, endothelial dysfunction, endothelial senescence, shear stress, vascular remodelling

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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