

Distinct subsets of T cells and macrophages impact venous remodeling during arteriovenous fistula maturation

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ABSTRACT

Patients with end-stage renal failure depend on hemodialysis indefinitely without renal transplantation, requiring a long-term patent vascular access. Although an arteriovenous fistula (AVF) remains the preferred vascular access for hemodialysis because of its longer patency and fewer complications compared with other vascular accesses, the primary patency of AVF is only 50% to 60%, presenting a clinical need for improvement. AVF mature by developing a thickened vascular wall and increased diameter to adapt to arterial blood pressure and flow volume. Inflammation plays a critical role during vascular remodeling and fistula maturation: increased shear stress triggers infiltration of T cells and macrophages that initiate inflammation, with involvement of several different subsets of T cells and macrophages. We review the literature describing distinct roles of the various subsets of T cells and macrophages during vascular remodeling. Immunosuppression with sirolimus or prednisolone decreases neointimal hyperplasia during AVF maturation, suggesting novel approaches to enhance vascular remodeling. However, M2 macrophages and CD4⁺ T cells play essential roles during AVF maturation, suggesting that total immunosuppression may suppress adaptive vascular remodeling. Therefore, it is likely that regulation of inflammation during fistula maturation will require a balanced approach to coordinate the various inflammatory cell subsets. Advances in immunosuppressive drug development and delivery systems may allow for more targeted regulation of inflammation to improve vascular remodeling and enhance AVF maturation. (*JVS—Vascular Science* 2020;1:207-18.)

Clinical Relevance: Patients with end-stage renal failure depend on successful AVF maturation to have a useful access. Inflammation occurs during fistula maturation and may be a therapeutic target to improve fistula maturation and utilization. Inflammation is mainly caused by T cells and macrophages, which have several subsets with distinct phenotypes and roles during vascular remodeling. Regulation of inflammation during fistula maturation requires a balanced approach to coordinate the various inflammatory cell subsets.

Keywords: Arteriovenous fistula; Inflammation; T-cells; Macrophages; Vascular remodeling

Arteriovenous fistulae (AVF) are the preferred vascular access for hemodialysis despite maturation success rates of only 50% to 60%,¹ creating a clinical need to find additional therapeutic targets to improve AVF maturation. Inflammation is one potential therapeutic target as it is

associated with various effects during venous remodeling.²⁻⁵ A retrospective observational study showed that high C-reactive protein and fibrinogen levels, indicating increased inflammation, were associated with unsuccessful AVF maturation.³ Similarly, another study showed that C-reactive protein was an independent risk factor for late AVF failure.⁶ Therefore, inhibiting inflammation may offer benefits to improve AVF maturation and patency. Although several clinical studies investigated the ability of several drugs to improve AVF maturation or patency, no study has shown that inhibiting inflammation improves AVF patency or success.⁷⁻¹⁰ This lack of efficacy may be due to the complex cellular and cytokine regulation of inflammation.

Inflammation in the maturing AVF is characterized by accumulation of T cells and macrophages.¹¹⁻¹⁵ Because inhibition of T cell and macrophage accumulation in the maturing AVF leads to AVF failure, accumulation of T cells and macrophages is critically important for AVF maturation.¹¹⁻¹³ T cells and macrophages have several subsets that play distinct roles to regulate inflammation during vascular remodeling.¹⁶⁻²³ Regulation of inflammation may need a more balanced approach to account for the diversity of T cells and macrophages that contribute to vascular remodeling. This review examines the roles of

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several types of T cells and macrophages during venous remodeling such as occurs during AVF maturation, supplements this with data from vein graft adaptation, and proposes several potential approaches to regulate distinct inflammatory cell types to improve AVF maturation.

DISTINCT SUBSETS OF INFLAMMATORY CELLS DURING VENOUS REMODELING

AVF maturation. After surgical creation of an AVF, the vein is exposed to the new environment of the fistula, including arterial pressure, shear stress and oxygen tension.^{24,25} Accordingly, the fistula adapts to this environment, characterized by an early phase and a late phase (Fig 1). The early phase occurs during the first several weeks after AVF creation during which the AVF undergoes adaptive remodeling, characterized by diameter expansion and wall thickening, enabling the vein to become usable for hemodialysis.²⁴ Failure of adaptive remodeling to occur, that is, failure of venous maturation, may be due to a lack of either outward remodeling or of wall thickening, although these processes are likely coordinated. Little is known about the normal physiology of the late phase of AVF remodeling, the time during which the AVF is used for hemodialysis; however, failure during the late phase is characterized by neointimal hyperplasia that can be associated with inward remodeling, and causes lumen loss, decreased flow, and a loss of access function. These two different times and mechanisms of AVF failure contribute to the high rate of access failure.

Inflammation critically regulates both early and late phases of AVF adaptation to the fistula environment. Several types of inflammatory cells play a role during venous remodeling such as occurs during AVF maturation (Fig 1). Early and eccentric macrophage infiltration may play an important role in the pathogenesis of early AVF failure.^{14,15} In addition, low serum albumin and high C-reactive protein and fibrinogen, indicators of systemic inflammation, are found in patients with failed AVF maturation.^{3,6} Therefore, inflammation may be associated with poor Fig early AVF patency. However, recent studies have also shown the necessity of CD4⁺ T cell and M2 macrophage-driven inflammation for successful AVF maturation,^{11-13,26} suggesting that there are subsets of inflammatory cells with diverse contributions to venous remodeling. CD4⁺ T cells are necessary to maintain proper blood flow and outward remodeling during AVF maturation, as transfer of CD4⁺ T cells improved blood flow and outward remodeling in a T-cell-deficient rat AVF model.¹³ Different from CD4⁺ T cells, M2 macrophages have important roles in vascular wall thickening; reduction of M2 macrophages was associated with less vascular wall thickening.^{11,12} Thus, different subtypes of inflammatory cells may have different roles in AVF remodeling. Although it is still unclear about the roles of other inflammatory cells such as CD8⁺ T cells, M1

ARTICLE HIGHLIGHTS

- **Type of Research:** Literature review
- **Key Findings:** T cells and macrophages accumulate and create inflammation in the vascular wall during arteriovenous fistula (AVF) maturation. Inflammation is classically detrimental to AVF success; however, depletion of T cells and macrophages leads to AVF failure. This contradiction may be explained by the diversity of T cells and macrophages, because they have several phenotypes and distinct roles in vascular remodeling.
- **Take Home Message:** Inflammation from T cells and macrophages needs coordinated regulation for successful AVF maturation.

macrophages, circulating macrophages, natural killer T cells, monocytes, granulocytes, dendritic cells, and mast cells during AVF maturation, these inflammatory cells have distinct roles in vascular remodeling. Given the diversity of these inflammatory cells and cytokines that are involved in AVF maturation, it is likely that approaches to regulate inflammation should not focus on general promotion or suppression of inflammation, but rather will need regulation of specific cell types as well as of specific dosing and timing of therapeutics during different phases of venous remodeling.

Vein graft adaptation. Adaptation of a vein graft to the arterial environment is both similar to and different than fistula maturation.²⁵ Vein grafts are exposed to arterial flow, pressure, and oxygen tension distinctly different from the venous environment and subsequently develop vascular wall thickening and outward remodeling. Although vein graft adaptation is adaptive venous remodeling similar to AVF maturation, vein graft adaptation is different from AVF maturation, with vein grafts developing thicker vascular walls and less outward remodeling compared with fistulae; however, accumulation of T cells and macrophages in the venous wall are observed in both vein grafts as well as in AVF.^{25,27}

Vein graft remodeling that is predominantly characterized by wall thickening is, in part, regulated by locally released cytokines; however, differences in hemodynamics between the environments of vein grafts and AVF lead to the production of different cytokine profiles during vein graft adaptation and AVF maturation.^{28,29} During the early phase of vein graft remodeling, macrophages and T cells infiltrate through the endothelial layer into the vein wall.²⁷ In some patients, the macrophages and T cells in the vein wall then promote development of areas that form stenoses in vein grafts via crosstalk between macrophages and vascular smooth muscle cells (SMC).²⁷ Infiltrated T cells and

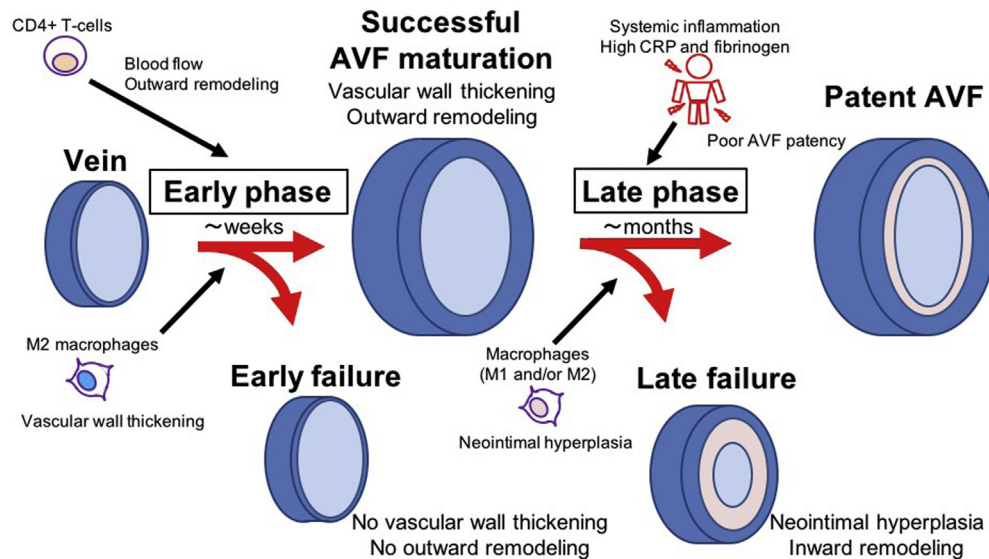


Fig 1. Associations between arteriovenous fistula (AVF) remodeling and inflammation. There are two phases of AVF remodeling, the early phase and the late phase. In the early phase, the remodeling AVF develops wall thickening and outward remodeling to become useable for hemodialysis. CD4⁺ T cells contribute to increased blood flow and outward remodeling, whereas M2 macrophages contribute to wall thickening. In the later phase, some AVF develop neointimal hyperplasia and inward remodeling and can eventually become unusable for hemodialysis. Systemic inflammation is associated with poor AVF patency. Macrophages are associated with neointimal hyperplasia. CRP, C-reactive protein.

macrophages secrete proinflammatory cytokines, and chemokines such as tumor necrosis factor- α (TNF- α) and monocyte chemoattractant protein-1 (MCP-1) to enhance migration and proliferation of SMC that leads to neointimal hyperplasia,^{30,31} and depletion of macrophages significantly inhibits neointimal hyperplasia that forms in a rat vein graft model.³² In contrast, macrophages also produce inducible nitric oxide synthase (iNOS) that attenuates constrictive vascular remodeling and neointimal hyperplasia, and thus iNOS may have the potential to promote long-term patency of vein grafts.³³⁻³⁵ Altered shear stress affects early and transient interleukin (IL)-1 synthesis and delayed and persistent IL-10 production.³⁶ IL-1 contributes to outward remodeling³⁶⁻³⁸ and IL-10 contributes to vascular wall thickening^{12,36,39}; thus, there is a diversity of inflammatory cells and cytokines that regulate vein graft remodeling, similar to that which occurs in the venous wall during AVF maturation.

PHENOTYPES OF T CELLS AND MACROPHAGES

Helper, regulatory, and cytotoxic T cells. Distinct subsets of T cells are characterized by different cell surface markers, intracellular markers and secreted cytokines (Table 1).¹⁶⁻¹⁹ CD4 is the common marker of helper (Th) cells and regulatory (Treg) T cells, and CD8 is the marker of cytotoxic T cells (CTL).^{17,55,56} Arterial magnitudes of shear stress after AVF creation increases expression and secretion of interferon (IFN)- γ on the endothelial cells,

and IFN- γ activates major histocompatibility complex (MHC) II to activate both circulating and resident CD4⁺ T cells.⁵⁷ Activated CD4⁺ T cells are characterized as Th or Treg cells by their functions that are distinct with different effects on inflammation.

The main function of Th cells is to produce cytokines, and Th cells are divided into several subtypes such as Th1 or Th2, depending on the secreted cytokines.^{40-42,45} Th1 cells secrete IFN- γ and activate other inflammatory cells including M1 macrophages,^{40-42,45} and IFN- γ is involved in vascular remodeling (Fig 2).⁵⁸ M1 macrophages produce proinflammatory cytokines such as IFN- γ and TNF- α , which may damage vasculature integrity and promote inflammation.⁵⁹⁻⁶³

One of the primary functions of Th2 cells is secretion of IL-4.^{40-42,45} Interestingly, IL-4 exacerbates inflammation and decreases the integrity of the vascular endothelial barrier⁶⁴ that occurs with atherosclerosis,⁶⁵ yet Th2 cells seem to lessen the inflammation that occurs in diseased blood vessels.⁴³ In particular, Th2 cells promote polarization of M2 macrophages that promote wound healing (Fig 2).^{44,66} M2 macrophages have been shown to be necessary for AVF maturation^{12,43}; therefore, it is likely that a major role for Th2 cells to improve vascular remodeling is via induction of M2 macrophage polarization and differentiation.

Treg cells are anti-inflammatory T cells that are characterized by CD25⁺ and Foxp3⁺ markers (Table 1).^{19,46} Treg cells are induced by IL-2 that is derived from other

Table I. Types of T cells involved in vascular remodeling

	Cell surface and intracellular markers	Secreted cytokines causing vascular remodeling	Association with macrophages
Th1 ⁴⁰⁻⁴²	CD3, CD4, STAT4	IFN- γ , TNF- α	Activate M1
Th2 ^{43,44}	CD3, CD4, STAT5	IL-4	Activate M2
Treg ^{19,45-49}	CD3, CD4, CD25, Foxp3	IL-10, TGF- β	Suppress M1 Activate M2
CTL ⁵⁰⁻⁵⁴	CD3, CD8	IFN- γ , TNF- α	—

CTL, Cytotoxic T cells; IFN- γ , interferon- γ ; IL, interleukin; STAT, signal transducer and activator of transcription; Th1, T helper-1 cells; Th2, T helper-2 cells; Treg, regulatory T cells; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α .

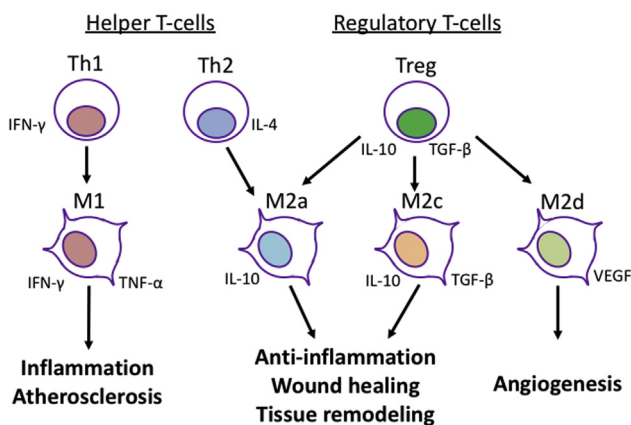


Fig 2. Associations between CD4⁺ T cells and macrophages. T-helper (Th) 1 cells secrete interferon- γ (IFN- γ) to induce M1 macrophages. M1 macrophages secrete IFN- γ and tumor necrosis factor- α (TNF- α) to promote inflammation. Th2 cells secrete IL-4 to induce M2a macrophages. Regulatory T cells (Treg) secrete interleukin (IL)-10 and transforming growth factor- β (TGF- β) to induce M2a, M2c and M2d macrophages. M2a and M2c macrophages secrete IL-10 and TGF- β to contribute to anti-inflammation, wound healing, and tissue remodeling. M2d secrete vascular endothelial growth factor (VEGF) to promote angiogenesis.

inflammatory cells; therefore, Treg cell differentiation functions as a negative feedback system to resolve inflammation.^{19,47} Treg cells secrete IL-10 and TGF- β not only to suppress other inflammatory cells including Th1, Th2, CTL, and M1 macrophages,^{48,49} but also to induce M2 macrophage polarization so that inflammation resolution, tissue healing and vascular remodeling are promoted (Fig 2).²⁰ Thus, Treg cells have important roles in maintaining the homeostasis of the vasculature during vascular remodeling.

CTL are characterized by expression of CD8 antigen on their cell surface. There are several phenotypes of CD8⁺ T cells, including naïve CD8⁺ T cells, CTL, exhausted T cells, and memory CD8⁺ T cells.⁵⁰ Different from CD4⁺ T cells, CD8⁺ T cells function independently from macrophages. Once CD8⁺ T cells recognize MHC I and pathogens, CD8⁺

T cells differentiate into CTL which secrete perforin, granzyme, and TNF- α to induce cell apoptosis.⁵¹ CTL are typically initially activated by coexistence of MHC I and pathogenic antigens that are presented by dendritic cells.⁵² In baseline conditions, vascular cells have MHC I, but are not activated because there are no dendritic cells presenting antigens; therefore, CTL are rarely detectable in the normal vascular wall. However, once the vascular wall is exposed to inflammation, CTL infiltrate into the vascular wall.⁵³ Because apoptosis of vascular cells causes reduced vascular wall barrier function, leading to vulnerability of the diseased vasculature, CTL promote vulnerable atherosclerotic plaques in apoE-deficient mice.^{53,54} In contrast, CD8⁺ cells protect against the development of neointimal hyperplasia and failure of vein grafts⁵³; CD8⁺ T cells improved vein graft patency whereas CD8⁺ T-cell-depleted mice showed increased apoptosis and higher rates of vein graft failure; surprisingly, the protective effect of CD8⁺ T cells on vein graft patency was independent of MHC and other antigens that are necessary for inducing CD8⁺ T cells to differentiate into CTL.⁵³ There may be other subsets of CD8⁺ T cells that contribute to vascular remodeling; methods to activate specific groups of CD8⁺ T cells during AVF maturation or vein graft adaptation that allows taking advantage of their protective effects are still unknown.

M1 and M2 macrophages. Different from circulating inflammatory cells that contribute to systemic inflammation, macrophages work within tissues to contribute to local inflammation. Macrophages are classically divided into one of two major subtypes, M1 or M2, and the polarization into a particular subset phenotype depends on the cytokine environment of the tissue^{5,23}; the commonly described macrophage subsets are summarized in Table II. M1 macrophage polarization is induced by Th1 cytokines such as IFN- γ , whereas M2 macrophage polarization is induced by Th2 and Treg cytokines such as IL-4, IL-10, and TGF- β (Fig 2). M1 macrophages are known as inflammatory macrophages because they secrete proinflammatory cytokines, such as IFN- γ and TNF- α , and may affect vascular remodeling. The proinflammatory cytokines may induce vascular cell apoptosis, dissolve extracellular matrix, induce breaks in elastic fibers,

Table II. Types of macrophages involved in vascular remodeling

	Cell surface and intracellular markers	Secreted cytokines	Main functions
M1 ⁵⁹⁻⁶³	CD68, iNOS, STAT1, IFN- γ receptor	TNF- α , IFN- γ , IL-1	Proinflammation
M2a ^{20-23,67}	CD68, CD206, TGM2, Arginase 1, STAT6	IL-10, TGF- β	Anti-inflammation Wound healing
M2b ²⁰⁻²³	CD68, IL-4 receptor	IL-1 β , IL-6, IL-10, TNF- α	Immunoregulation
M2c ^{20-23,67}	CD68, CD206, CCR2, Arginase 1	IL-10, TGF- β	Immunosuppression Tissue remodeling
M2d ²⁰⁻²³	CD68, iNOS	IL-10, VEGF	Angiogenesis

CCR, Chemokine receptor; *IFN- γ* , interferon- γ ; *IL*, interleukin; *iNOS*, inducible nitric oxide synthase; *LPS*, lipopolysaccharide; *M1*, M1-type macrophages; *M2*, M2-type macrophages; *TNF- α* , tumor necrosis factor- α ; *TGF- β* , transforming growth factor- β ; *TGM*, transglutaminase; *TLR*, toll like receptor; *VEGF*, vascular endothelial growth factor.

promote SMC apoptosis, and impair endothelial barrier function,^{59,60} resulting in accelerated atherosclerosis^{61,62} and aneurysm formation.⁶³ Although proinflammatory cytokines may be associated with adverse effects on the vascular wall to stimulate some vascular pathologies, however, proinflammatory cytokines play important roles in dissolving the venous wall extracellular matrix to enable outward remodeling during AVF maturation.^{68,69} iNOS is also produced by M1 macrophages, and iNOS attenuates constrictive vascular remodeling and neointimal hyperplasia of vein grafts in a rabbit model.^{33,34} From these data, the role of M1 macrophages during venous remodeling is unclear, because M1 macrophages may both inhibit AVF primary maturation as well as improve AVF long-term patency.

M2 macrophages, also known as prerepair macrophages, are polarized into the M2 phenotype by IL-4 secreted from Th2 cells and by IL-10 and TGF- β secreted from Treg cells.^{66,67,70} The main role of M2 macrophages is to resolve inflammation and promote tissue remodeling and wound healing. M2 macrophages are further categorized into M2a, M2b, M2c, and M2d macrophages (Table II).²⁰⁻²³ M2a and M2c macrophages seem to have important roles in vascular remodeling because they produce IL-10, TGF- β , and arginase 1, which have critical roles in vascular remodeling. IL-10 and TGF- β have important roles in maintaining the integrity of the vasculature as described elsewhere in this article (Table III). M2a and M2c macrophages also produce arginase 1, which promotes SMC proliferation and inhibits inflammation.⁸⁰ During the early phase of AVF maturation, SMC proliferation and vascular wall thickening are critically regulated by M2 macrophage infiltration,^{12,24} and thus arginase 1 may be associated with AVF primary maturation. In contrast, arginase 1 might have an adverse effect during the later phase of AVF maturation because arginase 1 also promotes neointimal formation in a rat common carotid injury model.⁸¹ Although arterial remodeling is different from AVF remodeling, arginase 1 may critically regulate the balance of vascular wall thickening and

neointimal formation, and may be either beneficial or deleterious during AVF maturation.

ETIOLOGY OF INFLAMMATION DURING VENOUS REMODELING

Shear stress as a trigger of inflammation. Shear stress is a hemodynamic force tangential to the endothelium whereas blood pressure is a hemodynamic force perpendicular to the vessel wall.^{82,83} The magnitude of shear stress in arteries is approximately 1 Pa, which is more than 300,000 times less than typical magnitudes of arterial blood pressure (300,000-500,000 Pa). Nevertheless, the effects of shear stress on the vascular wall are not negligible.^{82,83} Normal veins are typically exposed to less blood flow with lower magnitudes of shear stress compared with arteries, but veins are exposed to increased magnitudes of shear stress after AVF creation.²⁵ Exposure of veins to arterial magnitudes of shear stress and mechanical stretch promotes inflammation and remodeling.^{84,85} Because AVF are exposed to higher magnitudes of shear stress and lower arterial pressure compared with vein grafts,²⁵ AVF maturation and vein graft adaptation show different patterns of remodeling to normalize the hemodynamic forces, with AVF maturation characterized by more outward remodeling and less wall thickening compared with vein graft adaptation.²⁵ The arterial magnitudes of shear stress promote production of anti-inflammatory cytokines in vein grafts.²⁸ Because anti-inflammatory cytokines are necessary for maintenance of the normal architecture of vessels, it is possible that increased shear stress contributes to venous remodeling.^{25,28} In contrast, nonlaminar shear stress induces a proinflammatory response.⁸⁶ Low and oscillatory shear stress is characteristic of most vascular anastomoses and is associated with clinically significant stenosis in some patients.⁸⁷ Nonlaminar shear stress induces changes in endothelial cell gene expression, cytokine production, and cytoskeleton organization to increase secretion of MCP-1, and decrease nitric oxide secretion to cause activation and proliferation of SMC

Table III. Effector cytokines secreted by T cells and macrophages during vascular remodeling

	Effects on vascular wall	M1	M2	CTL	Th1	Th2	Treg
IL-1	Outward remodeling ³⁷ Vein graft wall adaptation ³⁸	++	+	+	+	+	-
IL-10	Maintenance of normal vasculature ^{12,36,39}	-	++	-	-	-	++
TNF- α	Endothelial barrier dysfunction ⁷¹ Increase vein graft neointimal hyperplasia (TNFR-1) ⁷² Reduce vein graft neointimal hyperplasia (TNFR-2) ⁷³	++	-	+	+	-	-
TGF- β	Promote SMC proliferation ⁷⁴⁻⁷⁹ Promotes neointimal hyperplasia ⁷⁹	-	++	-	-	-	++

CTL, Cytotoxic T cells; IL, interleukin; M1, M1-type macrophages; M2, M2-type macrophages; SMC, smooth muscle cell; TGF- β , transforming growth factor- β ; Th1, T helper-1 cells; Th2, T helper-2 cells; TNF- α , tumor necrosis factor- α ; TNFR, tumor necrosis factor receptor; Treg, regulatory T-cells.

within the vein wall.⁸⁶ Thus, maintaining arterial magnitudes and laminar character of shear stress is important to regulate inflammatory cells for AVF maturation without excessive neointimal thickening.

Plasticity of endothelial identity. Veins and arteries have different molecular identity that is most easily identified in the endothelium. Both embryonic and adult arterial endothelial cells express Ephrin-B2 and delta-like protein 4 (dll-4) whereas venous endothelial cells express Eph-B4.^{88,89} After vein grafts are exposed to the arterial environment, they lose Eph-B4 expression, but do not express Ephrin-B2 and dll-4, consistent with venous endothelial cells losing venous identity but not acquiring arterial identity during adaptation to an arterial environment.⁸⁹ Interestingly, changes of endothelial identity during AVF maturation are different from those that occur during vein graft adaptation; the AVF expresses Ephrin-B2 and dll-4 arterial markers in addition to increasing Eph-B4 expression, consistent with the AVF gaining arterial as well as venous identities.⁹⁰ This change in endothelial identity is likely to affect the inflammatory response during vascular remodeling because ephrin-Eph signaling regulates cell proliferation, survival and migration,⁹¹ as well as regulation of T-cell and monocyte activation.⁹² Monocytes also express Eph-B4 on their cell surface, and Eph-B4 binds to endothelial Ephrin-B2 to induce adhesion of monocytes.⁹³ Monocytes then migrate into the vascular wall and differentiate into macrophages,⁹³ promoting inflammation. Additionally, dll-4, which is an arterial marker, simulates macrophage activation, MCP-1 production and nuclear factor-kappa B activation. In particular, dll-4 induces polarization of macrophages to the M1 phenotype.⁹⁴ Thus, acquiring arterial identity may play an important role in regulating inflammation during AVF maturation.

Adhesion molecules promote inflammatory cell infiltration into the vascular wall. Mechanical stretch, endothelial injury and arterial shear stress also lead to vascular inflammation.^{95,96} Arterial shear stress regulates expression of cell surface molecules that stimulate leukocyte

adhesion and migration, such as vascular cell adhesion molecule 1 (VCAM-1) and E-selectin.⁹⁷ In a mouse venous arterialization model, expression of endothelial VCAM-1 and E-selectin was present early after surgery, concomitant with the presence of neutrophils and monocytes/macrophages in the vascular wall.⁹⁸ In AVF that fail owing to thrombosis, there is greater infiltration of macrophages and higher expression of adhesion molecules such as VCAM-1; VCAM-1 and proinflammatory macrophages may be associated with impaired endothelial antithrombotic functions.⁹⁹ E-selectin initiates rolling of leukocytes including monocytes and T cells followed by infiltration of these cells into the vascular wall.¹⁰⁰⁻¹⁰² Infiltrated monocytes and T cells will then differentiate into different subtypes of macrophages and T cells, depending on the cytokines and chemokines present in the vessel wall.¹⁶⁻²³ Unlike VCAM-1, which is associated with endothelial barrier functions, E-selectin is associated with adventitial inflammation¹⁰³; inhibition of E-selectin expression decreases adventitial inflammatory cells and attenuates neointimal hyperplasia in a rat carotid balloon injury model.¹⁰³ These data suggest that E-selectin regulates infiltration of inflammatory cells into the vascular adventitia after an endothelial injury and contributes to neointimal hyperplasia during the process of vascular wall healing. Moreover, E-selectin also contributes to leukocyte recruitment in a mouse vein graft model.⁹⁵ Although the vascular environment within an AVF is different from the arterial environment,²⁵ E-selectin may also have an important role during AVF remodeling to promote infiltration of inflammatory cells and contribute to vascular wall thickening or neointimal hyperplasia during AVF maturation.

Effector cytokines during venous remodeling. An important role of infiltrating inflammatory cells during venous remodeling is the production of effector cytokines that promote inflammation. Although some data are available regarding the types of these cytokines as well as their effects on venous remodeling (Table III; Fig 3), additional mechanistic understanding of how these cytokines regulate remodeling is still needed.

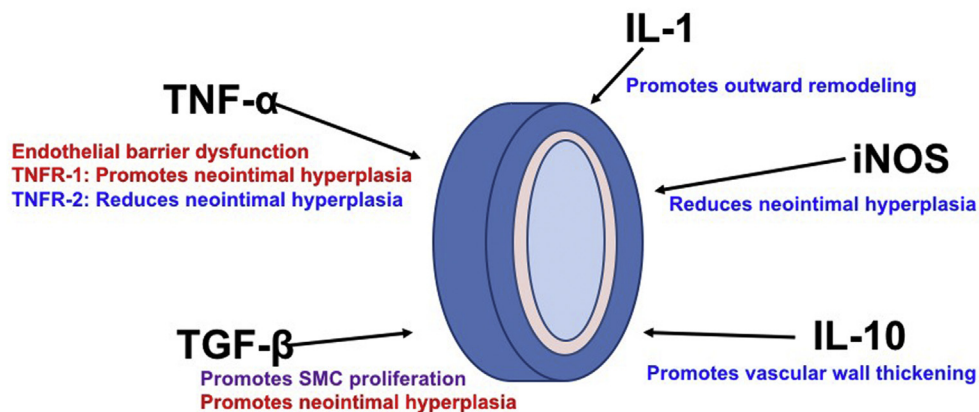


Fig 3. Associations between effector cytokines and venous remodeling. Tumor necrosis factor- α (*TNF- α*) causes endothelial barrier dysfunction. Tumor necrosis factor receptor (*TNFR*)-1 signaling promotes neointimal hyperplasia, but *TNFR*-2 signaling reduces neointimal hyperplasia. Transforming growth factor- β (*TGF- β*) promotes vascular smooth muscle cell (*SMC*) proliferation and neointimal hyperplasia. Interleukin (*IL*)-1 promotes outward remodeling. Inducible nitric oxide synthase (*iNOS*) decreases neointimal hyperplasia. *IL*-10 promotes vascular wall thickening. Factors promoting adaptive venous remodeling are shown in blue and factors inhibiting adaptive venous remodeling are shown in red. Factors having both effects on venous remodeling are shown in purple.

After exposure of a vein to arterial blood flow, increased wall shear stress affects early *IL*-1 production and delayed *IL*-10 signaling during vein graft remodeling.³⁶ *IL*-1 regulates matrix metalloproteinases expression to promote outward remodeling,³⁷ and a lack of *IL*-1 signaling results in perturbed early vein graft wall adaptation in a mouse vein graft model.³⁸ Although there is no study that shows the significance of *IL*-1 during AVF maturation, early production of *IL*-1 may have a critical role during AVF maturation because outward remodeling at early time points is essential for AVF maturation. *IL*-10 is an anti-inflammatory cytokine secreted by M2 macrophages and Treg cells. *IL*-10 inhibits the adhesion of leukocytes to endothelial cells.¹⁰⁴ In addition to preventing leukocyte adhesion, it appears that *IL*-10 is essential for the maintenance of normal vasculature.³⁹ *IL*-10 is also an essential cytokine that regulates vascular wall thickening during AVF maturation.¹²

TNF- α is a proinflammatory cytokine secreted by Th1 and M1 macrophages. *TNF- α* contributes to endothelial dysfunction and neointimal hyperplasia.⁷¹ Interestingly, vein graft neointimal hyperplasia is exacerbated by *TNF* receptor-1 signaling, but attenuated by *TNF* receptor-2 signaling.^{72,73} Because *TNF- α* plays a role in both exacerbation and attenuation of neointimal hyperplasia, direct inhibition of *TNF- α* may not be a translatable therapy; however, selective inhibition of *TNF* receptor-1 may be a potential strategy to inhibit neointimal hyperplasia, and targeting *TNF* receptors may therefore be a strategy to improve AVF patency.

TGF- β is an anti-inflammatory cytokine produced by Treg cells and M2 macrophages. *TGF- β* can suppress Th1 and Th2 cell differentiation, proliferation and

cytokine secretion, but induces differentiation of Treg cells.¹⁰⁵⁻¹⁰⁷ *TGF- β* also independently contributes to vascular remodeling by promoting *SMC* proliferation and extracellular matrix and collagen production to maintain the integrity of the vasculature.⁷⁴⁻⁷⁶ Therefore, *TGF- β* has functions that may promote AVF primary maturation. In contrast, *TGF- β* is also associated with AVF failure in the late phase of AVF remodeling⁷⁷⁻⁷⁹; *TGF- β* stimulates vascular *SMC* proliferation and promotes neointimal hyperplasia formation in AVF.⁷⁸ Because neointimal hyperplasia is a risk factor for late AVF failure, elevated expression of *TGF- β* may be a risk factor for AVF failure.⁷⁹ Thus, although *TGF- β* may promote early venous remodeling, such as occurs during AVF maturation, higher levels of *TGF- β* were associated with increased risk of AVF failure⁷⁹; this may be secondary to *TGF- β* 's role in promotion of neointimal hyperplasia. The exact roles of *TGF- β* in early or late venous remodeling are currently under investigation.

FUTURE DIRECTIONS TO IMPROVE AVF PATENCY

Targeting inflammation. Sirolimus and tacrolimus are immunosuppressant drugs that decrease neointimal hyperplasia in animal models. Sirolimus improves experimental AVF patency by decreasing wall thickening while attenuating the Akt1-mTORC1 signaling pathway in *SMC* and macrophages.¹¹ Because sirolimus has been used clinically in human patients in conjunction with coronary stents to preserve lumen diameter and decrease restenosis after coronary artery stenting,¹⁰⁸ sirolimus should have potential to decrease neointimal hyperplasia in AVF; because the arterial and venous environments are different, additional research in this area

will be needed. Interestingly, the combination of sirolimus and tacrolimus is associated with a greater decrease in vascular narrowing¹⁰⁹; because tacrolimus acts specifically on T cells, these data also suggest that T cells are associated with excessive SMC proliferation, and that macrophages are inhibited by sirolimus. Prednisolone is another anti-inflammatory drug used in human patients and that could be used to modulate AVF maturation; a murine AVF model showed prednisolone attenuated infiltration of lymphocytes and M1 macrophages and enhanced outward remodeling of the AVF wall.¹¹⁰

Because immunosuppressive drugs have multiple effects on inflammatory cells, additional evidence is still required to determine which subset of inflammatory cells is the optimal cell type to target to improve AVF maturation. Treg cells are one potential therapeutic target.^{48,49} Treg cells secrete IL-10 and TGF- β to suppress inflammation that is associated with AVF failure^{3,6,111}; therefore, inducing the number of Treg cells and/or their function could be considered a potential treatment to improve the success of AVF in human patients. Interestingly, because sirolimus can induce Treg cell differentiation,¹¹² sirolimus's success in improving AVF patency might be due to its upregulation of Treg cell activity.¹¹

Antibodies targeting inflammation have therapeutic potential during AVF remodeling. For example, a selective anti-CD4⁺ T-cell epithelial growth factor receptor antibody induces T-cell anergy and reduces atherosclerosis.¹¹³ Because antibodies can specifically target single cell types such as antigen expressing cells or M1 macrophages, targeted therapeutic antibodies may be able to both provide additional mechanistic understanding of venous remodeling as well as regulate inflammation during AVF maturation in more sophisticated ways.

Local therapy to control inflammation. Local delivery of anti-inflammatory agents may help to minimize adverse effects such as immunosuppression and severe infection that are associated with systemic administration of these therapies. Local injection of virus vectors has been successful in gene transduction without an inflammatory response.¹¹⁴⁻¹¹⁶ Sendai virus causes less inflammation than other viruses, and has been used in patients with peripheral arterial disease.¹¹⁷ The use of nanoparticles for local drug delivery is also effective in humans.¹¹⁸ In animal models, treatment of vein grafts with imatinib nanoparticles before graft implantation inhibits development of focal areas of stenosis,¹¹⁹ and nanoparticle-mediated delivery of irbesartan promotes cardioprotection from myocardial ischemia-reperfusion injury.¹²⁰ Thus, local drug delivery systems with virus vectors and nanoparticles show efficacy in some cardiovascular diseases, and therefore could potentially be used for patients with AVF. Pluronic gel, a thermoreversible hydrogel, is another medium used for local drug delivery to the adventitia; pluronic gel is delivered as a liquid at room temperature and

hardens at body temperature. After pluronic gel is applied around the perivascular wall, there is sustained release of drugs.¹²¹ Animal models have shown the usefulness of this delivery system in AVF maturation and vein graft remodeling.^{11,12,122}

An endovascular delivery system can be used to infuse drugs locally into the arterial adventitia.¹²³ Although this system has been used to deliver dexamethasone into an arterial wall,¹²³ treatment of the thinner venous wall may not be possible, especially prior to maturation; however, since perivascular inflammatory cells play an important role during AVF maturation, immunosuppressive drug delivery into the venous adventitia might help treat AVF stenoses to increase secondary patency. A double balloon catheter system has been used to deliver drugs directly to the intima¹²⁴; the balloons are inflated to isolate a vessel segment, and drugs are infused between the two balloons.¹²⁴ Because endothelial cells regulate the infiltration of inflammatory cells, local drug delivery with the double balloon catheter may be feasible to locally control endothelial function to improve AVF remodeling. Although balloon catheters induce neointimal hyperplasia, the double balloon catheter may deliver drugs to inhibit neointimal hyperplasia and therefore contribute to improved secondary AVF patency. With local drug delivery systems, patients with an AVF may be treated more specifically to maximize therapeutic effects and minimize systemic adverse effects.

CONCLUSIONS

T cells and macrophages play critical roles during AVF maturation with distinct effects attributed to each of these cells. From the limited evidence to date, Th2, Treg, and M2 macrophages are necessary for primary AVF maturation, but are also associated with late AVF failure. Th1 and M1 macrophages are associated with primary AVF failure, but may also contribute to long-term patency by inhibiting neointimal hyperplasia. The nuanced roles of T cells and macrophages during venous remodeling such as occurs during AVF maturation and vein graft adaptation have yet to be adequately understood owing to the great functional diversity of these cells. Regulation of specific inflammatory cells and their functions during the different phases of AVF remodeling with selective immunosuppressive drugs and local drug delivery systems may offer therapeutic promise to improve AVF maturation, the numbers of working fistulae and long-term AVF patency.

AUTHOR CONTRIBUTIONS

Conception and design: YM, GK
Analysis and interpretation: YM, GK, AF, JL, AD
Data collection: YM, GK, AF, JL, AD
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Critical revision of the article: AD
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