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Von Willebrand Factor at the Crossroads of Hemostasis and Inflammation

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Abstract

Von Willebrand factor (VWF) is a large multimeric glycoprotein critical for hemostasis, mediating platelet adhesion to injured vessels and stabilizing circulating factor VIII. However, accumulating evidence reveals a complex, context-dependent role for VWF in inflammation and innate immunity that extends well beyond coagulation. VWF acts not only as a biomarker of endothelial activation but also as an active participant in immune responses. VWF directly interacts with major immune cell types—including macrophages, polymorphonuclear leukocytes (neutrophils), and dendritic cells—through both its endothelial-anchored and plasma forms. VWF facilitates leukocyte recruitment and transmigration across the vessel wall, while its interactions also promote macrophage and neutrophil activation as well as NET formation. VWF's immunomodulatory functions are further highlighted by its binding to extracellular DNA, smooth muscle cells, complement components (C1q and C3), and bacterial pathogens under flow conditions. Furthermore, VWF indirectly influences inflammation via its crucial role in Weibel–Palade body formation, a process that co-packages vital inflammatory mediators like P-selectin and angiopoietin-2. Markedly elevated VWF levels are consistently observed across acute and chronic inflammatory conditions such as sepsis, COVID-19, and autoimmune disorders, confirming its relevance as both a diagnostic marker and a therapeutic target. A comprehensive understanding of VWF's diverse functions in vascular inflammation is crucial for developing targeted therapeutics—including nanobodies, ADAMTS13 variants, and VWF interaction inhibitors—capable of modulating pathological thrombo-inflammation while preserving physiological hemostasis.

Keywords

- von Willebrand factor (VWF)
- inflammation
- innate immunity
- neutrophils
- macrophages
- leukocyte

Introduction

Von Willebrand factor (VWF) is a large multimeric glycoprotein that plays a pivotal role in hemostasis. It mediates platelet adhesion at sites of vascular injury and serves as a carrier for coagulation factor VIII, protecting it from premature degradation in the circulation.[1,2] Deficiencies or functional defects in VWF result in von Willebrand disease (VWD), the most common inherited bleeding disorder.[3,4]

VWF is synthesized in endothelial cells and megakaryocytes—the precursor cells of platelets. In endothelial cells, it is stored in specialized secretory organelles known as Weibel–Palade bodies (WPBs), where it colocalizes with proinflammatory and angiogenic molecules such as P-selectin and angiopoietin-2 (Ang2).[5,6] VWF is essential for WPB biogenesis, making it not only a mediator of hemostasis but also a key regulator of endothelial secretory function. Structurally, mature VWF comprises several distinct domains (D′, D3, A1, A2, A3,C1, C2, C3, C4, C5, C6, and CK),

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each mediating specific interactions with ligands such as platelets, collagen, and factor VIII.[2,7,8] The metalloprotease ADAMTS13 regulates VWF size and activity through proteolytic cleavage, maintaining the balance between hemostasis and thrombosis.[9] Notably, growing evidence suggests that VWF can also interact with additional ligands, including surface receptors on innate immune cells, implicating it in broader inflammatory and immunological processes.[10]

Beyond its established role in coagulation, increasing evidence indicates that VWF also participates in inflammation and immune regulation through both direct and indirect mechanisms. Directly, VWF interacts with key innate immune cells—including macrophages and leukocytes, particularly polymorphonuclear neutrophils (PMNs)—via its large multimers anchored to the endothelium or circulating in plasma (►Fig. 1).[11–13] It also binds to dendritic cells, complement proteins, and several bacterial species.[14–16] Indirectly, through intracellular mechanisms, VWF contributes to inflammation by orchestrating the formation and regulated exocytosis of WPBs, thereby modulating the vascular inflammatory milieu.[17]

This review discusses the expanding landscape of VWF's roles in inflammation, focusing on its interactions with immune cells, regulation of endothelial biology, and involvement in thromboinflammatory disease mechanisms. Furthermore, it highlights the therapeutic potential of targeting VWF-mediated pathways in inflammation-associated vascular disorders.

Direct Pro-inflammatory Functions of VWF: Interactions with Key Innate Immune Cells

In this section, we summarize current evidence on the direct cellular interactions of VWF with key innate immune and vascular cells. These include macrophages, neutrophils, dendritic cells, smooth muscle cells, and VWF's involvement in neutrophil extracellular trap (NET) formation via binding to extracellular DNA (►Fig. 1, ►Table 1). Together, these interactions highlight VWF's active role as a cellular modulator in inflammation.

VWF–Macrophage Interactions

The interaction of VWF with platelets and its role in platelet adhesion and aggregation under shear stress are well established; however, VWF has also been shown to directly interact with key innate immune cells. Early studies demonstrated that VWF binds to macrophages, followed by rapid uptake and subsequent degradation of the internalized protein, thereby contributing to the clearance of the VWF/FVIII complex. This interaction is mediated mainly by binding of VWF to the low-density lipoprotein receptor-

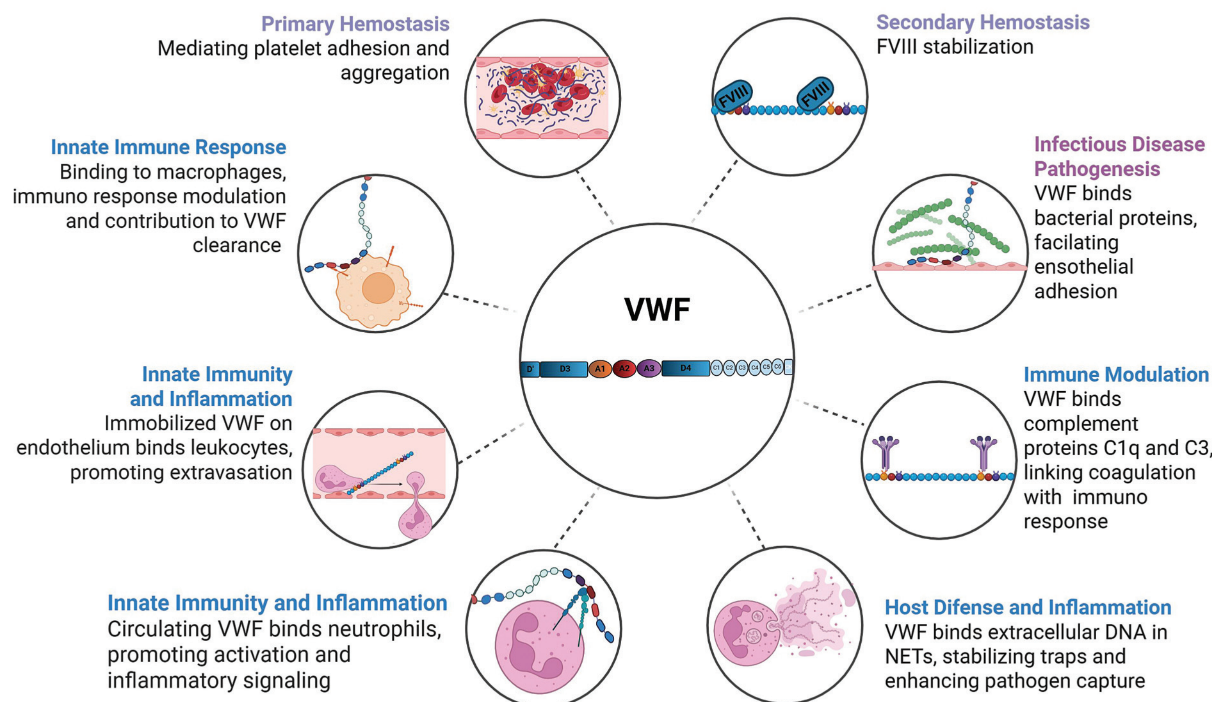

Fig. 1 Direct interaction partners of von Willebrand factor (VWF) in hemostasis and inflammation. This schematic illustrates VWF's central role at the interface of coagulation and innate immunity. VWF mediates platelet adhesion and stabilizes factor VIII in hemostasis, and directly interacts with macrophages and polymorphonuclear leukocytes (PMNs, neutrophils) to regulate inflammatory responses. It also binds neutrophil extracellular trap (NET)-derived DNA, complement components (C1q and C3), and bacterial pathogens under flow, highlighting its involvement in immunothrombosis and host defense. (Figure created with BioRender.com under an active publication license. Created in BioRender. Yadegari, H. (2025) https://BioRender.com/zxrcvw6.)

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Table 1 Direct interaction partners of VWF and associated functional consequences in innate immunity

Interaction partner in innate immunity	VWF binding domain	Receptor/Molecular target	Functional consequence
Macrophages	A1 domain (receptor-recognition site); A2 domain (glycans inhibit uptake)	LRP1, SR-A1 (and additional proposed receptors)	VWF internalization and clearance; modulation of macrophage function; increased cytokine production; M1-like activation
Polymorphonuclear leukocytes (PMNs, neutrophils)	A1–A3, D′D3 fragments	Mac-1 (CD11b/CD18), PSGL-1, SLC44A2	Leukocyte adhesion and transmigration; PMN activation (↑CD45, CD66b); NETosis induction; VWF uptake and degradation
Dendritic cells	–	–	Steric shielding of FVIII; prevention of FVIII endocytosis; reduced antigen presentation and immune activation
Smooth muscle cells	A2 domain	LRP4–αvβ3 axis	SMC proliferation and migration
Complement components	A domains	C1q, C3	Context-dependent complement regulation (activation or suppression)
NETs/extracellular DNA and histones	A1 domain	DNA–protein interaction	NET scaffolding; bacterial trapping; amplification of thrombosis
Bacteria (e.g., *S. aureus*, *S. pneumoniae*)	Stretched ULVWF multimers	VWbp, SpA	Adhesion under flow; vegetation and aggregation; contribution to infective endocarditis

Abbreviations: FVIII, coagulation factor VIII; LRP1, low-density lipoprotein receptor–related protein 1; LRP4, low-density lipoprotein receptor–related protein 4; Mac-1, macrophage-1 antigen (CD11b/CD18); NETs, neutrophil extracellular traps; PMNs, polymorphonuclear leukocytes; PSGL-1, P-selectin glycoprotein ligand-1; SLC44A2, solute carrier family 44 member 2; SMC, smooth muscle cell; SpA, staphylococcal protein A; SR-A1, scavenger receptor class A1; ULVWF, ultra-large von Willebrand factor; VWbp, von Willebrand factor–binding protein; VWF, von Willebrand factor.
Note: References supporting interaction mechanisms are detailed in the sections 'Direct Pro-inflammatory Functions of VWF: Interactions with Key Innate Immune Cells' and 'VWF Interactions with Pathogens and Peptides.

related protein 1 (LRP1), with shear stress enhancing the interaction.[18,19] Additional studies revealed that the A1 domain of VWF contains a receptor-recognition site critical for macrophage binding, while glycans within the A2 domain protect VWF from macrophage uptake.[20] Other surface molecules, including additional scavenger receptors, lectins, and integrin-related interactions, may also contribute to VWF binding depending on macrophage activation state and VWF conformation (►**Table 1**).[21,22]

Internalized VWF contributes to macrophage phenotypic changes, suggesting a context-dependent modulation of VWF–immune cell crosstalk, although the functional consequences of this process remained poorly understood. Recent work has shown that VWF binds to complement component C1q and modulates its immunological effects on human monocyte–derived macrophages. In the presence of cholesterol crystals, C1q–VWF complexes increased the expression of phagocytic receptors such as MerTK, LRP1, and SR-A1, yet paradoxically did not enhance phagocytosis of the crystals and suppressed caspase-1 activation, leading to diminished IL-1β secretion. These findings point to a potential anti-inflammatory role for VWF in certain contexts, such as atherosclerosis (►**Table 1**).[15]

In contrast, a major advance in understanding the pro-inflammatory functions of VWF came from the study by Drakeford et al, which demonstrated that VWF not only binds macrophages but also actively triggers intracellular signaling.[13] The authors proposed that VWF and monocytes circulate together in healthy blood with minimal interaction; however, at sites of vascular injury, VWF encounters tissue-resident macrophages and initiates pro-inflammatory responses. Exposure of human macrophages to ultra-large VWF multimers led to activation of the MAPK and NF-κB signaling pathways, increased production of pro-inflammatory cytokines such as IL-6 and TNF-α, induction of iNOS expression, and ROS generation. Furthermore, VWF stimulation promoted polarization toward an M1-like inflammatory phenotype and shifted macrophage metabolism toward glycolysis in a p38-dependent manner, mirroring the response typically observed with LPS.[13]

Collectively, these findings establish VWF as a pro-inflammatory ligand for macrophages, further supporting its role in bridging hemostasis and innate immune activation.

VWF–Leukocytes Interactions

Over the past two decades, accumulating evidence has demonstrated that VWF plays direct roles in regulating leukocyte recruitment and activation, both in vitro and in vivo. Seminal studies in the early 2000s revealed that immobilized or endothelial-anchored VWF interacts with polymorphonuclear leukocytes (PMNs, neutrophils) under both static and flow conditions. Under physiological flow, resting PMNs displayed short-lived, transient adhesive contacts with surface-bound VWF, mediated predominantly by P-selectin glycoprotein ligand-1 (PSGL-1). In contrast, PMA-stimulated PMNs exhibited firm adhesion, involving engagement of various β2 integrin isotypes, especially Mac-1 (αMβ2, CD11-b/CD18).[11,23] Additionally, recent studies suggest that

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SLC44A2 is another receptor on neutrophils that binds to VWF.[24,25] Domain mapping studies using recombinant VWF fragments further identified that the A1–A3 and D′D3 domains of VWF harbor binding motifs for these leukocyte receptors.[11] These findings were complemented by earlier work from Koivunen et al, who also reported VWF binding to leukocyte-specific β2 integrins (►Table 1).[23]

These mechanistic insights were further substantiated by in vivo studies demonstrating the involvement of VWF in leukocyte recruitment and vascular inflammation. Petri et al showed that administration of polyclonal anti-VWF antibodies in wild-type mice markedly reduced neutrophil recruitment—by approximately 50%—in models such as thioglycollate-induced peritonitis and KC-stimulated cremaster inflammation. These effects were independent of platelet P-selectin but required platelet presence and engagement of the VWF receptor glycoprotein Ibα (GPIbα), suggesting that VWF-associated platelets facilitate leukocyte extravasation, possibly by destabilizing the endothelial barrier.[26] Complementing these findings, Hillgruber et al demonstrated that both genetic VWF deficiency and antibody-mediated VWF blockade significantly inhibited leukocyte recruitment and vascular leakage in models of cutaneous inflammation, including immune complex–mediated vasculitis and irritant contact dermatitis. Interestingly, in contrast to the peritonitis model, the VWF–GPIbα axis appeared dispensable in these skin inflammation models.[27] These observations underscore the context-dependent role of VWF in leukocyte trafficking and highlight its contribution to inflammation through mechanisms extending beyond canonical platelet interactions. Further supporting this concept, Adam et al employed a VWD type 2B knock-in mouse model expressing the constitutively active p.V1316M VWF variant. In a reverse passive Arthus reaction, these mice exhibited markedly increased leukocyte recruitment accompanied by enhanced hemorrhage. Notably, platelet depletion reduced leukocyte infiltration despite persistent bleeding, indicating that the increased recruitment reflected an active VWF-mediated process rather than passive leakage. The authors proposed two mechanisms: (i) enhanced binding of mutant VWF to PSGL-1 via its A1 domain and/or (ii) the presence of preformed VWF–platelet complexes that promote leukocyte extravasation more efficiently than wild-type VWF. These findings suggest that conformational activation of the A1 domain can potentiate the inflammatory capacity of VWF.[28] More recently, Aymé et al provided additional insight into the VWF–platelet axis in leukocyte recruitment. The authors generated single-domain antibodies directed against the human and murine A1 domain, effectively blocking VWF–platelet interactions. Administration of these antibodies in inflammatory models markedly reduced leukocyte recruitment to background levels or abolished it entirely, underscoring the central role of the A1 domain in this process. Although the contribution of other VWF domains cannot be excluded, platelet depletion did not further diminish leukocyte recruitment, suggesting that the A1–platelet interaction is the principal driver of VWF-dependent leukocyte recruitment.[29]

Collectively, these animal studies establish a pivotal role for VWF in promoting leukocyte recruitment across diverse inflammatory settings. Nevertheless, the precise contribution of platelets remains incompletely understood: while some models demonstrate a strict requirement for platelet–VWF interactions (e.g., peritonitis), others indicate platelet-independent pathways (e.g., cutaneous inflammation). Clarifying these context-specific mechanisms will be critical for designing targeted anti-inflammatory strategies that modulate VWF-driven inflammation without impairing hemostasis. It also remains conceivable that binding motifs within the VWF A1 domain, essential for GPIbα interaction, may likewise serve as contact sites for leukocyte receptors such as PSGL-1 or β2 integrins. Although still speculative, this dual functionality of the A1 domain highlights its central role at the interface of hemostasis and inflammation and warrants further structural and functional investigation.

Beyond interactions of endothelial-bound VWF, our recent ex vivo work provides novel insights into how unbound plasma VWF interacts directly with human neutrophils. We demonstrated that soluble VWF binds to neutrophils via the β2 integrin Mac-1 (CD11b/CD18), and that this interaction is enhanced under flow and upon stimulation with inflammatory mediators such as IL-8, TNF-α, or PMA.[12] These findings extend prior work by Pendu et al by showing that circulating—not just immobilized—VWF can engage neutrophil integrins. Binding of VWF was associated with increased expression of CD45 and CD66b, markers of neutrophil activation, suggesting a potential regulatory role via outside-in signaling mechanisms. In addition, we showed that neutrophils internalize and degrade plasma VWF.[11,12] These observations suggest a previously unrecognized cellular mechanism for VWF clearance involving neutrophils. Given that neutrophils also internalize plasma proteins such as albumin and fibrinogen during inflammation, it remains to be determined whether this VWF-clearing function occurs mainly under inflammatory stress or also contributes to basal VWF homeostasis.

Building on its interaction with neutrophils, VWF has also been implicated in the formation and stabilization of NETs—web-like DNA structures composed of histones and proteases, released during a specialized form of neutrophil cell death known as NETosis. Although NETs serve protective functions by trapping pathogens, they can also promote tissue injury and thrombosis. NETs provide a scaffold for platelets, fibrin, and VWF itself, thereby linking innate immunity to thrombus formation.[30,31] VWF directly binds to extracellular DNA released from leukocytes as well as to histones through its A1 domain, and anchors NETs to the vascular wall under shear stress (►Table 1).[32–34] These interactions underscore the dual pro-inflammatory and pro-thrombotic functions of VWF. Finally, our recent ex vivo work demonstrated that VWF binding can actively enhance NET formation by neutrophils, highlighting a direct feed-forward loop between VWF and neutrophil activation during inflammation.[12]

Together, these insights emphasize that both endothelial-immobilized and circulating VWF actively coordinate central

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innate immune mechanisms, namely, leukocyte adhesion, activation, and NETosis.

Other Direct Cellular Interactions: VWF Interactions Beyond Classical Innate Immune Cells

In addition to its well-characterized roles in leukocytes/neutrophils and macrophages, VWF engages other cell types relevant to vascular immunity and inflammation. Dendritic cells (DCs), as professional antigen-presenting cells, bind VWF, which modulates the uptake and peptide presentation of FVIII, thereby reducing its immunogenicity (►Table 1).[35–37] Mechanistically, VWF prevents FVIII endocytosis by DCs, likely via steric hindrance or stabilization of the FVIII structure, thus limiting antigen processing and $CD4^+$ T cell activation. Peptidomic studies further show that VWF alters the repertoire of FVIII-derived peptides presented on MHC-II, which may explain the lower immunogenicity observed in patients treated with plasma-derived FVIII–VWF complexes compared to recombinant FVIII.[16,38] Furthermore, a recent study provided evidence that VWF modulates the formation and effector functions of FVIII-containing immune complexes and attenuates the secondary immune response to FVIII in hemophilia A mice.[39]

Beyond immune cells, VWF also interacts with vascular smooth muscle cells (VSMCs). It promotes VSMC proliferation and migration via the LRP4–αvβ3 integrin axis, particularly through its A2 domain (►Table 1).[40] In vivo, VWF deficiency impairs outward remodeling and reduces VSMC and macrophage accumulation during arteriovenous fistula (AVF) maturation, highlighting VWF's contribution to vascular inflammation and repair.[41] These findings suggest that VWF may modulate sterile inflammation by linking endothelial injury to immune cell infiltration and vessel wall remodeling.

VWF Interactions with Pathogens and Peptides

VWF Interactions with Pathogenic Microorganisms

VWF plays a complex and dual role in microbial pathogenesis and immune regulation. It directly binds to several pathogenic bacteria, including *Streptococcus pneumoniae* and *Staphylococcus aureus*, facilitating their adhesion to endothelial cells under flow conditions.[14,42] In *S. aureus*, surface proteins such as protein A (SpA) and VWF-binding protein (VWbp) enable firm attachment to stretched VWF multimers on activated endothelium (►Table 1). This hijacking of the host's hemostatic system promotes bacterial aggregation and vegetation formation, contributing to diseases such as infective endocarditis and sepsis. VWF-mediated bacterial clustering amplifies endothelial inflammation and immune activation, leading to microvascular occlusion and, ultimately, multiorgan failure in systemic infections. Furthermore, as discussed earlier, VWF contributes to NET formation, which aids pathogen capture but may also aggravate vascular inflammation and thrombosis.

VWF Interactions with Complement Components

VWF also directly interacts with key complement components, particularly C1q and C3, thereby linking coagulation with innate immunity.[43] These interactions, mediated by the A domains of VWF and enhanced under shear stress, can have divergent effects depending on the context. For example, VWF and C1q colocalization on surfaces such as cholesterol crystals can dampen macrophage cytokine release, whereas C3 binding to ultralarge VWF multimers (ULVWF)—especially in ADAMTS13 deficiency—facilitates C3 and C5 convertase assembly, driving excessive complement activation and microvascular thrombosis as seen in thrombotic microangiopathies.[15] Thus, direct binding of VWF to C1q and C3 exerts a context-dependent influence on the interplay between coagulation and immunity, shaping both pro- and anti-inflammatory responses (►Table 1).

Beyond these molecular interactions, complement activation and bacterial components (e.g., LPS) can induce WPBs exocytosis, thereby secondarily increasing VWF release and amplifying the thromboinflammatory milieu.[42]

Indirect Role of VWF in Inflammation: Regulation of Inflammatory Cargo Storage in WPBs

WPB Biogenesis and Inflammatory Cargo Packaging

VWF is synthesized in endothelial cells and stored in specialized rod-shaped organelles called WPBs, which are found throughout the vascular endothelium but absent in lymphatic vessels.[17] VWF is not only the principal cargo but also a structural scaffold essential for WPB biogenesis. It provides the molecular framework around which other WPB-resident proteins are organized during organelle formation. In its absence, WPBs are malformed or fail to form entirely, leading to misrouting or unregulated secretion of their cargo.[44–49]

WPBs function as specialized, tightly regulated storage organelles for a diverse array of pro-inflammatory and vasoactive molecules. In addition to their principal contents—P-selectin and VWF—they contain Ang2, interleukin-8 (IL-8), interleukin-6 (IL-6), eotaxin-3 (Eo-3, CCL26), growth related oncogene α (Groα), endothelin 1 (ET-1) and monocyte chemoattractant protein-1 (MCP1).[17,50] Upon endothelial activation by inflammatory cytokines or hemodynamic stress, WPBs undergo rapid exocytosis, releasing these mediators into the vascular lumen or onto the cell surface. Each cargo molecule contributes distinct yet complementary functions: P-selectin mediates leukocyte rolling and adhesion and increases endothelial permeability; Ang2 destabilizes endothelial junctions and heightens sensitivity to cytokines; IL-8, IL-6,Eo-3, and MCP1 act as potent chemoattractants for neutrophils and monocytes; and ET-1 regulates vasoconstriction and vascular tone.[50–52] Collectively, these mediators coordinate endothelial–leukocyte interactions, modulate vascular integrity, and drive localized tissue inflammation (►Fig. 2).

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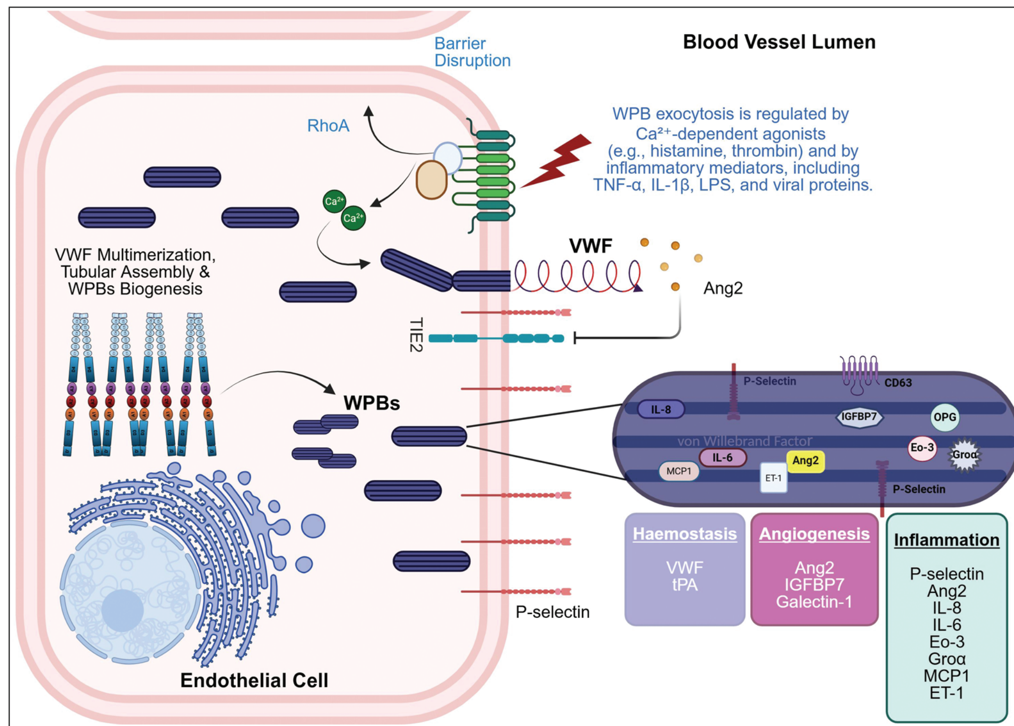

Fig. 2 **Indirect role of von Willebrand factor (VWF) in inflammation through regulation of inflammatory cargo storage within Weibel–Palade bodies (WPBs).** VWF serves as a structural scaffold for WPB formation and packaging of inflammatory mediators such as P-selectin, angiopoietin-2 (Ang2), IL-6, IL-8, MCP-1, eotaxin-3 (CCL26), and endothelin-1 (ET-1). The figure illustrates WPB biogenesis at the trans-Golgi network and Ca^{2+}-dependent exocytosis. Upon stimulation by Ca^{2+}-mobilizing agonists—including histamine, thrombin, bradykinin or by inflammatory triggers such as TNF-α, IL-1β, LPS, and SARS-CoV-2, WPBs release their cargo, promoting leukocyte recruitment and increasing endothelial permeability. Figure created with BioRender.com under an active publication license.

Regulation of WPB Trafficking and Exocytosis

WPB biogenesis begins at the trans-Golgi network, where VWF multimerization and tubulation shape the characteristic elongated organelle. During maturation, WPBs acquire endolysosomal proteins such as CD63 and are regulated by Rab GTPases (Rab3D, Rab27a) that coordinate their trafficking toward the cell periphery.[53,54] Exocytosis is triggered by Ca^{2+}- or cAMP-dependent pathways, activated by agonists such as thrombin, histamine, or epinephrine. While Ca^{2+} signaling promotes junctional disruption via RhoA, cAMP strengthens barrier integrity through Rap1, enabling the endothelium to fine-tune its inflammatory response.[6,55] Inflammatory mediators like IL-8 and Eo-3 are not constitutively stored but are routed to WPBs upon stimulation with cytokines such as IL-1β or IL-4, creating a regulated reservoir for rapid release.[53]

Impact of VWF Deficiency on WPB Formation and Inflammatory Signaling

Multiple studies have demonstrated that VWF deficiency disrupts the intracellular trafficking and secretion of inflammatory mediators. In endothelial cells lacking VWF—either generated via CRISPR/Cas9 or derived from patients with VWD—proteins normally stored in WPBs are misrouted to the constitutive secretory pathway or accumulate intracellularly.[46–48] For example, in one of our studies using ECFCs from a patient harboring a large in-frame deletion of VWF (exons 4–34), WPBs were malformed, Ang2 aberrantly localized to the nucleus, and P-selectin displayed altered intracellular trafficking.[47] Transcriptomic analysis of these cells revealed dysregulation of genes involved in inflammatory signaling pathways. In another study, ECFCs derived from a patient with a homozygous splice-site mutation in VWF—resulting in complete absence of WPB formation—exhibited perinuclear and membrane-associated accumulation of Ang2.[46] Additionally, Schillemans et al reported peripheral relocation of Ang2 colocalized with Tie2 and alternative trafficking and secretion of other WPB proteins, including CD63, syntaxin-3, IL-6, and IL-8 in VWF-knockout ECFCs generated via CRISPR.[48] This heterogeneity in intracellular trafficking patterns and downstream responses likely reflects the specific type and severity of VWF defects, which differentially affect WPB biogenesis and the regulated storage of inflammatory cargo. Consistently, studies in VWF-deficient mice revealed defective WPB formation and partial mislocalization of P-selectin to lysosomes, resulting in reduced leukocyte rolling and recruitment in models of cytokine-induced meningitis and early wound healing.[56] A recent multi-patient study further showed that ECFCs from VWD patients exhibit intracellular VWF retention, reduced WPB numbers, and proteomic signatures enriched for inflammatory and EndMT-associated markers such as TGFB1 and ALDH1A1.[57] Although a uniform inflammatory phenotype was not observed, these findings suggest that WPB biogenesis defects are accompanied by broader endothelial reprogramming and inflammatory responsiveness.

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Together, these findings establish that VWF, beyond its hemostatic role, orchestrates endothelial inflammatory responses by enabling the packaging, storage, and regulated release of pro-inflammatory mediators within WPBs. The specific mechanisms by which VWF deficiency modulates inflammatory responses remain incompletely understood and warrant further investigation.

VWF as a Biomarker of Inflammation and Mediator of Thromboinflammation

In response to inflammatory cytokines or hemodynamic stress, endothelial cells rapidly release VWF into the circulation via regulated exocytosis of WPBs. Consequently, plasma VWF levels rise markedly during both acute and chronic inflammation, making it a sensitive in vivo marker of endothelial activation. Importantly, this increase is not merely a byproduct of inflammation but actively contributes to thromboinflammatory responses, linking vascular injury, immune activation, and coagulation.

VWF in Acute Inflammatory and Infectious Diseases

Elevated VWF levels are a hallmark of systemic inflammatory conditions such as sepsis, systemic inflammatory response syndrome (SIRS), and acute respiratory infections including COVID-19. Similarly, persistently elevated VWF has been reported in HIV/AIDS, where it correlates with cardiovascular and thrombotic risk.

A meta-analysis of 17 studies involving 1,187 COVID-19 patients showed markedly higher VWF antigen (VWF:Ag) levels compared to controls (306% vs. normal 50–200%), with the highest levels observed in fatal cases (448%).[58] In parallel, a reduced ADAMTS13 activity/VWF:Ag ratio has been noted in hospitalized patients, suggesting a dysregulated VWF axis contributing to microvascular thrombosis.[9,59] Supporting this, several *in vitro* studies have shown that expression of SARS-CoV-2 proteins—including Spike (S), ORF7a, nsp2, and nsp7—in endothelial cells (e.g., HUVECs) consistently induces VWF secretion. Although secretion is robustly elevated, the degree of VWF mRNA upregulation, protein synthesis, and multimer formation varies among studies.[60–62] These findings support the concept that SARS-CoV-2–mediated endothelial activation includes a VWF release component, contributing to the thromboinflammatory phenotype of COVID-19.

In SIRS, VWF levels can increase up to 11-fold relative to healthy controls. Although total VWF is not predictive of mortality, higher levels of the conformationally active form correlate with 28-day mortality, suggesting potential prognostic relevance.[63,64] In the context of HIV, a nested case–control study found that elevated VWF levels independently predicted ischemic stroke in patients receiving effective antiretroviral therapy. Even after adjusting for age and sex, both higher plasma VWF and viral load were significantly associated with increased stroke risk.[65]

Together, these observations illustrate how acute infectious triggers rapidly engage the endothelial VWF axis, ultimately leading to thromboinflammatory states.

VWF in Chronic Inflammatory Disorders and Endothelial Dysfunction

Chronic inflammatory diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) are characterized by persistent immune activation, endothelial dysfunction, elevated VWF levels, and thrombosis. In these conditions, VWF serves not only as a sensitive marker of vascular injury but also as an active mediator of thromboinflammatory complications, which promote microvascular damage and pathological clot formation.[66–69]

In SLE, immune complex deposition and complement activation trigger marked endothelial activation, reflected by increased circulating VWF and P-selectin. Concomitant reductions in ADAMTS13 activity and the accumulation of ultra-large VWF multimers further amplify microvascular thrombosis, particularly in patients with antiphospholipid antibodies.[66,67]

RA is characterized by systemic inflammation that, although primarily affecting the synovial joints, promotes endothelial activation. This leads to elevated VWF antigen levels, endothelial dysfunction, and accelerated atherosclerosis, significantly increasing cardiovascular risk.[69]

IBD, encompassing Crohn's disease and ulcerative colitis, involves chronic gastrointestinal inflammation often complicated by bleeding and thrombosis. Evidence highlights significantly elevated VWF levels along with upregulation of the mediators of angiogenesis in IBD, reflecting marked endothelial activation. Although VWF's exact mechanistic role remains unclear, these high levels are likely to contribute to local microvascular dysfunction and thrombus formation.[68,70]

In addition, endothelial dysfunction is also a key pathogenic mechanism in other chronic conditions, including atherosclerosis, diabetes, and hypertension. In such settings, VWF functions both as a biomarker of vascular injury and as a mediator of ongoing thromboinflammation. Similar mechanisms are observed during vascular aging, which is associated with progressive endothelial deterioration and elevated basal VWF levels.[71,72]

VWF in Cancer-associated Thromboinflammation

In malignancy, elevated VWF levels are reported across various tumor types and correlate with thrombotic risk, metastasis, and poor prognosis. Tumor-driven endothelial activation, inflammatory cytokines, and hypoxia promote VWF release, which may facilitate tumor cell adhesion, angiogenesis, and vascular dissemination, reinforcing its role as a driver of cancer-associated thromboinflammation.[73]

However, recently another mechanism has been identified in which shear-stretched VWF binds tumor-derived extracellular vesicles (EVs) in a size-selective manner. This EV–VWF–platelet interaction promotes platelet aggregation and may support the capture of circulating tumor cells, contributing to cancer-associated thrombosis.[74]

Overall, these observations emphasize that VWF is not only a marker of endothelial perturbation but also an active participant in vascular inflammation and thrombosis.

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Therapeutic Perspectives and Future Directions

Insights from biomarker and disease-association studies have directly informed the development of novel targeted therapeutic strategies designed to modulate pathological VWF activity while preserving physiological hemostasis. The dual role of VWF in coagulation and inflammation positions it as a compelling target for innovative therapies aimed at disrupting pathological thromboinflammation without increasing bleeding risk.

Novel approaches—including recombinant ADAMTS13, anti-VWF nanobodies, inhibitors of VWF–cell interactions (e.g., with leukocytes, platelets, or pathogens), and siRNAs designed to normalize VWF levels—have shown promising results in preclinical and clinical models.[75–77] Rebalancing the VWF/ADAMTS13 axis represents a key therapeutic avenue: recombinant ADAMTS13 effectively reduces ultra-large VWF multimers and restores microvascular integrity in thrombotic microangiopathies and severe inflammation-associated thrombosis.[75] In parallel, the success of the A1-domain-blocking nanobody caplacizumab in immune-mediated TTP provides proof-of-concept for selective blockade of pathological VWF activity.[76] Moreover, RNA-based approaches, including allele-selective siRNA therapies, offer additional precision avenues for controlling pathogenic VWF expression.[77]

Future directions include the development of shear- and inflammation-specific VWF inhibitors to attenuate disease-driving VWF functions while minimizing interference with normal hemostasis. One promising concept involves selective targeting of oxidized VWF, which exhibits resistance to ADAMTS13 cleavage in inflammatory environments. Computational work suggests that certain molecular agents may preferentially inhibit oxidized VWF, offering a strategy for site- and context-specific intervention.[78]

The evolution of VWF-focused therapeutics will likely require a multi-pronged strategy integrating precision medicine, innovative delivery systems, and combination approaches. Precision-based interventions will leverage deeper insights into VWF post-translational modifications, context-dependent activation states, and patient-specific genetic backgrounds to inform individualized therapy. Advances in delivery modalities—such as subcutaneously administered monoclonal antibodies or allele-selective siRNAs—may improve convenience, adherence, and therapeutic durability compared with current intravenous regimens. Together, these emerging approaches hold strong potential for developing safer, more selective, and more effective therapies for thromboinflammatory disorders.

Conclusion

Beyond its established role in hemostasis, VWF is a critical modulator of inflammation and immune responses. Through its direct interactions with PMNs (neutrophils), macrophages, pathogens, and complement, and its involvement in NET formation, VWF is uniquely positioned at the intersection of coagulation and innate immunity. VWF also plays an indirect role in innate immunity by facilitating the formation of WPBs and sequestering inflammatory molecules within the endothelium. This complex function drives the pathogenesis of many thrombo-inflammatory conditions, including acute and chronic inflammatory diseases and vascular complications. A deeper understanding of VWF's context-dependent activities—how it acts protectively under normal circumstances versus pathogenically when dysregulated—is essential for future therapeutic strategies. Selective targeting of VWF represents a promising approach to mitigate pathological inflammation and thrombosis while preserving vital hemostatic functions. Further research into VWF's intricate immunothrombotic mechanisms is critical for developing the next generation of precision therapies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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