

Targeting von Willebrand Factor–Mediated Inflammation

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Aymé et al¹ provide new insights into the role played by von Willebrand factor (VWF) in modulating in vivo inflammatory responses. In particular, a single-domain antibody against the VWF A1 domain is shown to markedly attenuate leukocyte recruitment and vascular permeability in 2 distinct murine models of inflammation. Collectively, these findings support the hypothesis that VWF is involved in regulating inflammation and suggest that novel VWF-targeted therapies may be useful inhibitors of this critical step in inflammatory pathogenesis.

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VWF circulates in plasma as a large multimeric glycoprotein and plays critical roles in normal hemostasis.² At sites of vascular damage, VWF binds to exposed subendothelial collagen. Shear stress then triggers unwinding of the normal globular conformation of VWF, leading to conformational changes within the A domains and in particular exposure of the GPIIb α (glycoprotein IIb α)-binding site within the A1 domain. Consequently, tethered VWF can recruit platelets to the site of injury. In addition, VWF also acts as a carrier for procoagulant FVIII, protecting it against premature proteolytic degradation and clearance.³

Besides these important roles in maintaining hemostasis, recent studies have identified novel roles for VWF in modulating inflammatory responses.^{4–8} In vitro studies demonstrated that immobilized VWF binds directly to both polymorphonuclear leukocytes and monocytes under static and flow conditions.⁴ Under flow conditions, this VWF-mediated interaction involved transient rolling (mediated in part through VWF binding to leukocyte P-selectin glycoprotein ligand-1) followed by stable adhesion (mediated in part through VWF interaction with leukocyte β 2-integrins). VWF binding to P-selectin glycoprotein ligand-1 was dependent on the A1 domain, whereas several regions of VWF (including D'D3 and A1A2A3) were implicated in β 2-integrin binding.⁴

Roles for VWF in modulating inflammatory responses have also been observed in vivo.^{5–8} In an experimental sepsis model involving cecal ligation and puncture, Lerolle et al⁵ observed significantly enhanced overall survival in VWF^{-/-} mice compared with wild-type controls. Importantly, however, data derived from inflammation studies performed

in VWF^{-/-} mice are complicated by the fact that these mice also lack Weibel–Palade bodies and consequently have confounding P-selectin storage abnormalities. However, Petri et al⁶ showed that VWF-blocking antibodies significantly inhibited neutrophil recruitment into thioglycollate-inflamed peritoneum and keratinocyte-derived chemokine-stimulated exposed cremaster muscle. In both murine models, the ability of the VWF-blocking antibody in reducing neutrophil extravasation was critically dependent on the presence of platelets and GPIIb α .⁶ In addition to VWF-mediated leukocyte binding, in vivo studies have further demonstrated that VWF-associated platelets are important in regulating permeability of the endothelial cell wall and, thus, also influence neutrophil extravasation.⁶ VWF-blocking antibodies were also shown to attenuate neutrophil recruitment in a murine model of immune complex-mediated vasculitis.⁷ Interestingly, in contrast to the critical need for platelet GPIIb α in regulating VWF-induced neutrophil extravasation into inflamed peritoneum, Hillgruber et al⁷ showed that VWF-modulated neutrophil recruitment in cutaneous inflammation was GPIIb α -independent.

To further elucidate the role of VWF in regulating inflammation in vivo, Aymé et al¹ have developed a novel single-domain llama-derived antibody or nanobody that recognizes an epitope located within the A1 domain of VWF. Importantly, this A1 domain single-domain llama-derived antibody cross-reacts with both human and murine VWF. Consequently, a bivalent variant of the single-domain llama-derived antibody (KB-VWF-006bi) interfered with ristocetin-induced murine and human platelet aggregation and significantly attenuated VWF binding to collagen VI (but not to collagens I, III, or IV). In vivo, KB-VWF-006bi dose dependently increased bleeding time and blood loss in a tail-clip model and reduced the formation of occlusive thrombi in a ferric chloride-induced thrombosis model. In keeping with previous studies, KB-VWF-006bi was shown to markedly reduce leukocyte recruitment and vascular permeability in 2 distinct inflammation models of immune complex-mediated vasculitis and irritant contact dermatitis, respectively.¹ Given that KB-VWF-006bi binds only to the VWF A1 domain, this suggests that, at least in these animal models, the A1 domain plays a specific role in facilitating the proinflammatory effects of VWF. Perhaps unsurprisingly, this critical role for the A1 domain is at least partially dependent on the presence of platelets. Cumulatively, these findings suggest that VWF binding to GPIIb α serves to tether platelets, which, in turn, modulates endothelial cell barrier wall permeability and thus leukocyte tissue extravasation into the tissues.

These emerging data demonstrate that VWF influences multiple different aspects of inflammation in vivo (Figure). Further studies will be essential in defining the molecular mechanisms through which these VWF-mediated immunomodulatory effects are mediated. On the basis of the current

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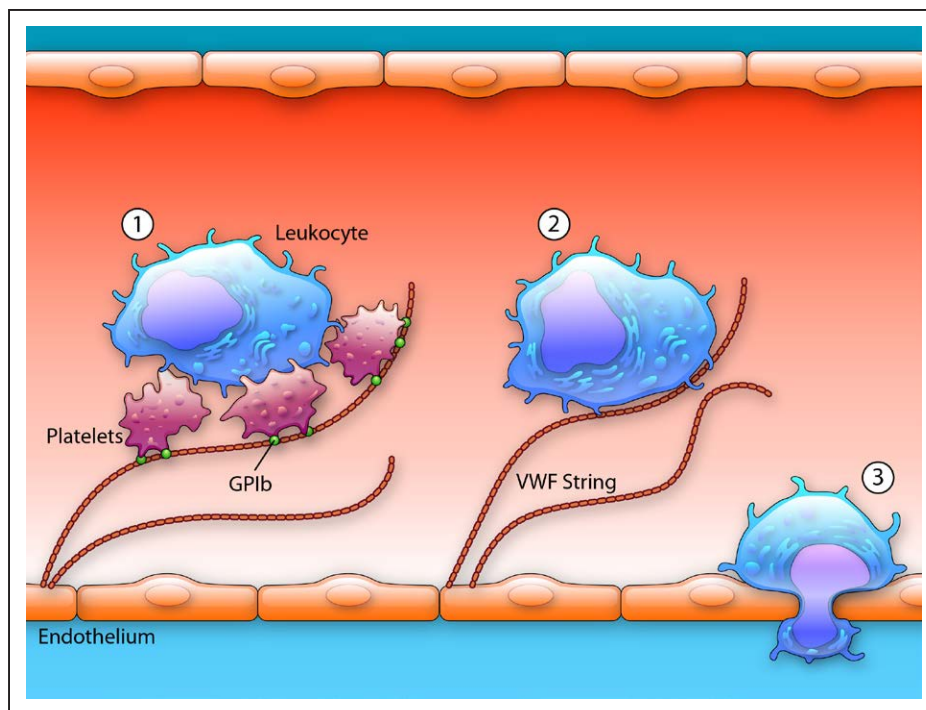


Figure. von Willebrand factor (VWF) modulates inflammation through multiple different mechanisms. (1) VWF released from activated endothelial cells, or bound to collagen at sites of vascular injury, interacts with platelet GPIb α (glycoprotein Ib α) and recruits platelets. The VWF-tethered platelets subsequently enable neutrophil recruitment. (2) VWF can also recruit leukocytes in a platelet-independent manner by directly interacting with leukocyte cell surface receptors including β 2-integrins and P-selectin glycoprotein ligand-1. (3) VWF regulates endothelial wall permeability and influences leukocyte extravasation.

evidence, VWF clearly modulates inflammation through platelet-dependent and platelet-independent pathways.^{4–8} Moreover, although the underlying biology remains unexplained, the animal data further suggest that the relative importance of these discrete VWF-mediated pathways varies between different types of inflammation. Further insights into the role played by VWF in regulating leukocyte extravasation and endothelial cell permeability and the complex cross-talk that exists in vivo between hemostasis and inflammation will undoubtedly emerge in the near future. Given the significant morbidity and mortality associated with inflammatory pathology, defining the roles of VWF may offer exciting opportunities to develop novel therapies to address a critical unmet clinical need.

Disclosures

None.

References

1. Aymé G, Adam F, Legendre P, Bazaa A, Proulle V, Denis CV, Christophe OD, Lenting PJ. A novel single-domain antibody against von Willebrand factor A1 domain resolves leukocyte recruitment and vascular leakage during inflammation—brief report. *Arterioscler Thromb Vasc Biol.* 2017;37:1736–1740. doi: 10.1161/ATVBAHA.117.309319.
2. Lenting PJ, Christophe OD, Denis CV. von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. *Blood.* 2015;125:2019–2028. doi: 10.1182/blood-2014-06-528406.
3. Terraube V, O'Donnell JS, Jenkins PV. Factor VIII and von Willebrand factor interaction: biological, clinical and therapeutic importance. *Haemophilia.* 2010;16:3–13. doi: 10.1111/j.1365-2516.2009.02005.x.
4. Pendu R, Terraube V, Christophe OD, Gahmberg CG, de Groot PG, Lenting PJ, Denis CV. P-selectin glycoprotein ligand 1 and beta2-integrins cooperate in the adhesion of leukocytes to von Willebrand factor. *Blood.* 2006;108:3746–3752. doi: 10.1182/blood-2006-03-010322.
5. Lerolle N, Dunois-Lardé C, Badirou I, Motto DG, Hill G, Bruneval P, Diehl JL, Denis CV, Baruch D. von Willebrand factor is a major determinant of ADAMTS-13 decrease during mouse sepsis induced by cecum ligation and puncture. *J Thromb Haemost.* 2009;7:843–850. doi: 10.1111/j.1538-7836.2009.03313.x.
6. Petri B, Broermann A, Li H, Khandoga AG, Zarbock A, Krombach F, Goerge T, Schneider SW, Jones C, Nieswandt B, Wild MK, Vestweber D. von Willebrand factor promotes leukocyte extravasation. *Blood.* 2010;116:4712–4719. doi: 10.1182/blood-2010-03-276311.
7. Hillgruber C, Steingraber AK, Pöppelmann B, Denis CV, Ware J, Vestweber D, Nieswandt B, Schneider SW, Goerge T. Blocking von Willebrand factor for treatment of cutaneous inflammation. *J Invest Dermatol.* 2014;134:77–86. doi: 10.1038/jid.2013.292.
8. Adam F, Casari C, Prévost N, Kauskot A, Loubière C, Legendre P, Repéant C, Baruch D, Rosa JP, Bryckaert M, de Groot PG, Christophe OD, Lenting PJ, Denis CV. A genetically-engineered von Willebrand disease type 2B mouse model displays defects in hemostasis and inflammation. *Sci Rep.* 2016;6:26306. doi: 10.1038/srep26306.

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