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Targeting the von Willebrand Factor–ADAMTS-13 axis in sickle cell disease

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1 | INTRODUCTION

Sickle cell disease (SCD) is the most prevalent inherited monogenic disease worldwide caused by a single nucleotide mutation in the gene coding for β-globin chain. This results in an abnormal form of hemoglobin, known as hemoglobin S (HbS). In low-oxygen conditions, HbS forms polymers in red blood cells (RBCs), making them rigid, adhesive, and prone to lysis [1] The primary pathologies of SCD are hemolytic anemia and vaso-occlusive episodes (VOEs), with other sequelae of inflammatory vasculopathy, coagulation activation and thromboembolism, stroke, acute chest syndrome (ACS), multiorgan failure, and shortened lifespan [1–3]; SCD affects more than 4 million people worldwide (85% of cases are concentrated in Sub-Saharan Africa and India), with approximately 100 000 patients in the United States, with an increasing frequency of reported cases in the United Kingdom and Europe [4,5].

VOEs are caused, in part, by the formation of multicellular aggregates of neutrophils, platelets, and sickled RBCs, which bind to adhesion molecules, including the well-described interactions of these cells with P-selectin and von Willebrand factor (VWF) on the activated endothelium [1,4]. These aggregates form vascular occlusions that can lead to tissue injury from ischemia reperfusion and release of cytokines, reactive oxygen species, and damage associated molecular patterns, such as free hemoglobin and heme [1]. Although VOEs can result in the clinical presentation of a pain crisis, the processes described here leading to end-organ damage are often distinct from a clinical syndrome of acute or chronic pain. Current treatment options for SCD are limited to hydroxyurea (which increases fetal hemoglobin production and limits HbS polymerization), L-glutamine (an antioxidant that reduces painful VOEs), crizanlizumab (a monoclonal antibody targeting P-selectin), and

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DECLARATION OF COMPETING INTEREST STATEMENT

There are no competing interests to disclose.

voxelotor (a small molecule that alters HbS binding to oxygen to decrease polymerization) [4]. Unfortunately, these treatments reduce the frequency of VOEs by only approximately 45% [6]. Although prospective studies are evaluating the potential benefits for end-organ health, neither crizanlizumab nor voxelotor has been demonstrated to prevent ACS or stroke. During an acute VOE, patients receive supportive therapy, such as pain medication (often in the form of opioids) and hydration [4], and all of the currently approved agents are preventative rather than therapeutic. Clearly, a better understanding of the mechanisms of VOEs and downstream consequences is crucial, and it is likely that a multimodal approach is the best therapeutic strategy to treat the complex pathophysiology of the disease. One pathway that has received increasing attention is the VWF–ADAMTS-13 axis.

2 | VWF–ADAMTS-13 IN SCD

The adhesion molecule VWF and its regulatory protease ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, number 13) play an important role in inflammatory and thrombotic conditions. The form of VWF present in endothelial cells is a multimerized polymer referred to as ultralarge VWF (ULVWF), and under flow conditions, these ULVWF multimers tend to form long strings and mesh-like structures within the vasculature [7]. The presence of ULVWF multimers was described first in patients with relapsing thrombotic thrombocytopenic purpura (TTP) [8]. The generation of plasma VWF multimers, which are found in a variety of sizes *in vivo*, is a result of proteolysis of VWF by ADAMTS-13 [9], a process that requires shear stress-induced unfolding of VWF [10,11]. ADAMTS-13 is a constitutively active enzyme with no known physiologic inhibitors, and its cleavage of ULVWF to smaller multimers is a requisite for normal hemostasis [12]. Under physiologic intravascular shear stresses, VWF undergoes a conformational change from a globular form to a more linear, extended chain, which in turn exposes cleavage sites for ADAMTS-13 [10,13,14]. This physiology creates a self-limiting system commonly termed the VWF–ADAMTS-13 axis.

Even before the discovery of numerous endothelial and subendothelial ligands implicated in RBC adhesion [15], it had been demonstrated that clinical disease severity in SCD correlates with increased adhesion of erythrocytes to the endothelium [16]. These early findings prompted a sustained and ongoing interest in targeting these interactions for therapeutic purposes, with several such drugs currently being investigated [17]. The introduction of crizanlizumab in 2019 established an important precedent in the SCD treatment paradigm by demonstrating therapeutic impact on VOEs and quality of life despite not addressing the underlying hemoglobin disorder directly but rather an important cell adhesion ligand [12]. Despite some notable failures to treat acute VOEs with similar agents [18,19], the success of crizanlizumab has indelibly imprinted on the clinical and research landscape, with more promising targets on the horizon. One such potential therapeutic target is VWF, which is implicated in adhesion and thrombotic processes in SCD [20–22]. The chronic vascular inflammation present in persons with SCD stimulates the secretion of VWF, and these patients demonstrate abnormal *in vivo* dynamics of ADAMTS-13 and VWF [14,20,23] Specifically, ULVWF multimers are present in higher proportion both at steady state and in crisis in persons with SCD than in persons without SCD [24,25]. *In vitro* studies investigating this phenomenon have shown that free hemoglobin and thrombospondin 1

bind to VWF, transiently inhibiting its cleavage by ADAMTS-13. Although this seems to be a primary driving mechanism, lower ADAMTS-13 activity is observed in a subset of people with SCD as well, which is attributed to possible exhaustion and reduced synthesis of the enzyme, as is observed in thromboinflammatory conditions such as sepsis [26–29]. These mechanisms seem to cumulatively explain the abnormal *in vivo* dynamics and presence of larger VWF multimers [29,30], which have, in turn, been long recognized to adhere more readily to RBCs [21,31].

3 | TARGETING THE VWF–ADAMTS-13 AXIS TO TREAT VOES

Evidence has accumulated in recent years suggesting that the VWF–ADAMTS-13 axis might play a role in the pathology of VOEs in SCD. Because VWF can adhere sickle RBCs to the endothelium *in vitro* [21] and bind to platelet GPIb in patients with SCD during VOE [20], it suggests that VWF can mediate the events involved in the pathogenesis of VOEs. In a recent study by Shi et al. [32] published in Proceedings of the National Academy of Sciences, this hypothesis was investigated in a mouse model of SCD via comprehensive experiments. The authors used a well-characterized model of VOEs induced by tumor necrosis factor α (TNFα) [33,34] in humanized sickle cell mice [22]. In this model, TNFα administration worsens anemia and thrombocytopenia, increases plasma levels of VWF antigen, and leads to the formation of VWF-positive vascular occlusions and ischemic and necrotic changes in several organs of mice with SCD (HbSS) mice. To determine the role of (endothelial) VWF in this model, the authors transplanted HbSS bone marrow into von Willebrand factor knockout (VWF^{KO}) mice, generating VWF-deficient sickle mice VWF-deficient sickle mice exhibited less severe anemia and a significant reduction in vascular occlusions in the tissue. To investigate whether ADAMTS-13–mediated cleavage of VWF contributes to VOEs, HbSS mice received recombinant ADAMTS-13 (rADAMTS-13) either before or after TNFα challenge. Both strategies significantly reduced the number of vascular occlusions and organ damage in HbSS mice. These findings are notable because they suggest that rADAMTS-13 might be beneficial as a treatment for a patient during a VOE to protect against organ damage. The authors also found that rADAMTS-13 reduced fibrin deposition after TNFα administration, suggesting that it may also reduce thrombotic complications in SCD.

Coincidentally, the VWF–ADAMTS-13 axis was investigated in another recent study in which a VOE was induced by exposing Townes HbSS mice to hypoxia/reoxygenation (H/R) [35]. In this model, H/R increases VWF antigen and reduces ADAMTS-13 activity, thereby causing acute organ damage and inflammation. Consistent with the article by Shi et al. [32], this study found that administration of rADAMTS-13 before H/R attenuated inflammation, oxidative stress, and organ damage and reduced the presence of thrombi in the vasculature. A limitation of this study is that rADAMTS-13 was only given prophylactically, and future studies should focus on administration after a VOE is induced. These 2 recent studies build on an earlier observation that heme-induced stasis was reduced by an anti-VWF antibody in HbSS mice [36]. Altogether, 3 independent models of VOEs in HbSS mice support a role for the VWF–ADAMTS-13 axis. Given the recent advances in the treatment of TTP using rADAMTS-13, this is an interesting therapeutic strategy for SCD.

4 | POTENTIAL IMPACT AND FUTURE DIRECTIONS

Currently, a phase 1 clinical trial is investigating the role of this pathway in SCD. The rADAMTS-13 In Sickle Cell Disease (RAISE) study is enrolling adult patients with SCD (NCT 03997760). This is a double-blind, placebo-controlled, phase 1 interventional study investigating the safety profile of rADAMTS-13 infusion and determining the pharmacokinetics of ADAMTS-13 activity and other disease severity markers. The current study evaluated the use of rADAMTS-13 both for prophylaxis and the treatment of VOEs. Successful treatment of VOEs would fill a much-needed gap in SCD management. rADAMTS-13 is also currently being evaluated for its use in individuals with congenital TTP in phase 3 trials (NCT03393975 and NCT04683003).

SCD is a hypercoagulable state with a high incidence of venous thromboembolism [3,37] and increased levels of plasma biomarkers of coagulation activation, such as thrombin-antithrombin complexes and D-dimer [38,39]. As noted in the preclinical models described earlier in the article, rADAMTS-13 attenuated the formation of fibrin- and platelet-positive thrombi in the vasculature of HbSS mice during an experimental VOE [32,35]. Future studies should investigate the effects of rADAMTS-13 on the biomarkers of coagulation activation and other thrombotic complications as well as the effect of rADAMTS-13 on the formation of multicellular aggregates, ACS, and other complications of SCD.

Notably, ADAMTS-13 might not be the only pathway by which VWF is cleaved. Using plasma of patients with SCD in an *in vitro* system, Hunt et al. [40] found ADAMTS-13–independent cleavage of VWF. Their data suggest that other proteases, such as matrix metallopeptidase 9, may also play a role in VWF processing in SCD. Recent work by de Maat et al. [41] has also shown the ability of plasmin to cleave VWF, a strategy that has been employed to degrade microthrombi. This strategy could feasibly be used for any VWF-mediated microvascular process, although it has no preclinical or clinical data on SCD.

A functioning VWF–ADAMTS-13 axis is known to maintain endothelial integrity and function [14]. It is unknown whether exogenous administration of ADAMTS-13 in persons with an elevated inflammatory milieu could adversely affect endothelial health. For example, persons with type 3 von Willebrand disease and acquired von Willebrand disease may develop arteriovenous malformations, a long-observed clinical phenomenon now understood to be explained by the demonstrated role of VWF in the regulation of angiogenesis [42–44]. Cleaving ULVWF multimers could conceivably lead to bleeding complications as well given the primacy of large multimers in hemostasis. However, excessive bleeding has not been observed to date in studies evaluating the use of rADAMTS-13 in patients with congenital TTP. Although reassuring, the administration of the drug in that case represents restoration of a more profoundly perturbed VWF–ADAMTS-13 axis than that seen in SCD and warrants careful research [45]. Given the benefits of rADAMTS-13 shown in mouse models in recovery after ischemic stroke and correction of hypercoagulability associated with COVID-19 [46], it is likewise possible that clot stability could be affected because venous thromboembolism in SCD tends to be more resistant to fibrinolysis by tissueplasminogen activator [47].

It is additionally unknown whether alloimmunization to exogenous rADAMTS-13 could develop, as in the case of persons with nonsevere hemophilia receiving exogenous factor. If one were to develop an inhibitory antibody to rADAMTS-13, a TTP-like physiology could potentially be produced iatrogenically in persons without a congenital absence of ADAMTS-13 [48]. Although there are concerns with any potentially promising therapy, these are largely speculative at this point. Similar concerns existed before the clinical adoption of crizanlizumab and voxelotor; however, as others have noted in recent commentary, they have not manifested in our patients [49,50].

With promising preclinical data such as these driving the field, we remain cautiously optimistic about the potential of therapy to target the VWF–ADAMTS-13 axis in SCD, a disease in which mitigating therapies remain potentially critical.

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