

von Willebrand disease and angiodysplasia: a wider view of pathogenesis in pursuit of therapy

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Abstract

Bleeding in the gastrointestinal tract in patients with von Willebrand disease continues to pose a therapeutic challenge for clinicians. It is associated with significant morbidity and mortality and represents the major unmet need in this disease. Defective angiogenesis in the gut is primarily responsible, resulting in angiodysplastic malformations making bleeding notoriously refractory to standard replacement therapy. A substantial body of evidence now shows that von Willebrand factor has a role in the regulation of angiogenesis but the mechanisms responsible for the formation of vascular malformations remain incompletely understood. Data from the wider field of vascular malformations may lend insight and point to novel therapeutic approaches. Here we review evidence linking von Willebrand factor to angiodysplasia, the associated molecular mechanisms and the implications for therapy.

Introduction

von Willebrand disease (VWD) is a hereditary bleeding disorder resulting from a deficiency of von Willebrand factor (VWF) function. The clinical bleeding manifestations are largely attributable to the loss of VWF adhesive function, platelet capture and the secondary reduction of factor VIII procoagulant activity. Therapeutically the deficiency can be effectively corrected by the use of VWF concentrates, although it is recognized that platelet, endothelial and extravascular VWF are not replaced by this approach. Recent work has identified numerous additional roles for VWF in non-hemostatic processes including immunity, cell proliferation, bone formation and inflammation, but also a role in angiogenesis.^{1,2} Defective angiogenesis in the gut may give rise to vascular malformations (angiodysplasia) that are responsible for a bleeding tendency which is frequently refractory to replacement therapy and represents the principal unsolved therapeutic problem in VWD today. This is a narrative review linking VWF to angiodysplasia, the associated molecular mechanisms and the implications for therapy.

von Willebrand disease and angiodysplasia

The epidemiology of VWD is often confusing. Although 2.5% of the population have a level of VWF function below the lower limit of normal, the point at which this becomes sufficient to cause abnormal bleeding is not agreed. It is usually estimated to be around 30 IU/dL but levels higher than this can nonetheless contribute to a bleeding tendency that may be multifactorial and in some schemes is also classified as VWD.³ Registries have found that the prevalence of gastrointestinal bleeding is approximately 2.5 times higher in those with VWD than in non-VWD cohorts.⁴ In the general population, angiodysplasia is the most common vascular abnormality of the gastrointestinal tract in subjects over 65 years old, with studies showing 11% of this population also have a diagnosis of VWD.⁵ Conversely, the reported prevalence of angiodysplasia in VWD is variable, ranging from 2-8%, and noted to be higher with increasing age.⁶ Angiodysplasia occurs most frequently in those with type 2A (39%) and type 3 (14.4%) VWD, the types characterized by loss of high molecular weight multimers (HMWM) of VWF, although it has been documented in all types.⁷ Interestingly, a 2024 retrospective review of gastrointestinal

bleeding in VWD found arteriovenous malformation to be the most predominant causative lesion, occurring in 35% of patients.⁸ This sets the problem of VWD-associated angiodysplasia as one not solely of hemostasis, but also one of vascular integrity and angiogenesis whose management may be best considered in parallel with that of other such vascular malformation syndromes.

The first suggestion that VWF might be responsible for vascular integrity and hence possibly involved in the pathogenesis of angiodysplasia emerged when the nail capillaries of VWD patients were found to show increased fragility, increased tortuosity, and defective contractility to trauma.⁹ Later, video capillary microscopy of nailfold vasculature of 100 patients with VWD confirmed the presence of vascular abnormalities with changes in capillary dilatation, extravasates and capillary torquation.¹⁰ The first mechanistic link between VWF and defective angiogenesis was provided by Starke *et al.* in 2011, who showed that inhibition of VWF expression in human umbilical vein endothelial cells led to increased proliferation, migration and angiogenesis.¹¹ This was confirmed in endothelial colony-forming cells sourced from VWD patients, although variability between patients has been reported.¹² *In vitro*, full-length VWF was able to normalize angiogenesis; *in vivo*, lack of VWF in VWF null mice resulted in increased constitutive vascularity.¹¹ Xu *et al.* showed the opposite effect in mice lacking ADAMTS13, in a model of revascularization after stroke, highlighting the importance of VWF HMWM for regulation of angiogenesis – a finding consistent with the epidemiology in VWD and acquired von Willebrand syndrome.¹³ Most notably, acquired von Willebrand syndrome with associated gastrointestinal bleeding has been described in patients with left ventricular assisted devices, aortic stenosis (Heyde syndrome) and most recently mitral regurgitation, where high shear stress facilitates cleavage of VWF by ADAMTS resulting in loss of HMWM.^{14,15} Acquired von Willebrand syndrome is corrected and bleeding stops when the cause of the pathological shear is removed.

Evidence that VWF plays an important role in vascular development and angiogenesis is apparent, but the mechanisms by which it regulates angiogenesis and the reason for dependency on HMWM remain unclear. As with non-VWD age-related angiodysplasia, its development only in certain individuals and the predominance in the gut also require explanation.

von Willebrand factor and pathways regulating angiogenesis

Like many other biological processes, angiogenesis is controlled by a balance of pro- and anti-angiogenic factors via crosstalk between several signaling pathways, the disruption of which can favor angiodysplasia. Data suggest that some of these effects only become significant when endothelial

cells are also under the influence of various stressors such as age, muscular compression or inflammation and antigen exposure in tissues where endothelial cells express VWF. Such ‘second hits’ are more likely to be environmental in the context of VWD angiodysplasia, but it is possible that genetic second hits are also involved, as observed in many vascular abnormality syndromes.¹⁶

As an intracellular, matrix and plasma protein, VWF interacts with many molecules with the potential to regulate angiogenesis. Platelets, growth factors, matrix proteins and intracellular components are all implicated and while the contribution of some of these has been delineated, the picture remains incomplete.

Angiopoietin-Tie 2 pathway

Prior to release from endothelial cells, VWF is stored in organelles called Weibel-Palade bodies which are dependent on VWF for their formation. Numerous other proteins are also stored in Weibel-Palade bodies allowing VWF to modulate their release. Several of these proteins also bind to VWF and have roles in angiogenesis, most notably angiopoietin (Angpt)-2.

In the vasculature, the Angpt-Tie2 system regulates the balance between quiescence and angiogenesis. Angpt1, released by smooth muscle cells and pericytes, promotes vascular homeostasis, stability and quiescence by binding to Tie2, a receptor tyrosine kinase critical for endothelial cell function, which signals via the PI3K/AKT/mTor pathway.¹⁷ Angpt2 competes with Angpt1 for binding to Tie2, leading to vascular destabilization, a precursor to new vessel formation. The effect of Angpt2 is synergistic with the pro-angiogenic pathway of vascular endothelial growth factor (VEGF) and its receptor-2 (VEGFR2), promoting new vessel formation via endothelial cell proliferation and migration.¹⁸ Conversely, when VEGF is absent or inhibited, Angpt2 can promote endothelial cell death and vessel regression.¹⁷ Angpt2 also potentiates endothelial cell inflammatory responses, for example to the proinflammatory cytokine tumor necrosis factor (TNF) α ;¹⁹ this may be particularly relevant in the gut, given the high exposure of the gut-vascular barrier to antigens.²⁰ Interestingly, VWF binds to both Angpt1 and Angpt2 but does not prevent either from interacting with Tie2;²¹ similarly Angpt2 does not affect VWF-dependent platelet capture.²² Thus the functional relevance of these interactions is still unclear.

In vitro studies showed that VWF-deficient cells release high levels of Angpt2.¹¹ This was not reflected in plasma, since a study on a large cohort of VWD patients showed normal plasma Angpt2 levels but, interestingly, significant differences in the levels of Angpt1 and VEGF were observed between VWD subtypes.²³ The explanation of these findings is unclear; it is possible that released Angpt2 remains bound locally, or that increased release occurs only in specific vascular beds and therefore remains undetectable systemically.

Galectin-3

Galectin-3 (Gal-3) may also be implicated in VWF-dependent regulation of angiogenesis. Like Angpt2, Gal-3 is a component of Weibel-Palade bodies which binds to VWF intra- and extra-cellularly. It interacts with both VEGFR2 and integrin $\alpha\beta3$ to promote angiogenesis.²⁴ Saint-Lu *et al.* noted that in VWF-deficient mice, plasma Gal-3 levels were reduced compared to those in wild-type animals and this was corrected following hydrodynamic VWF gene transfer.²⁵ Contrary to Angpt2, plasma Gal-3 level was significantly higher in patients with gastrointestinal bleeding than in those with bleeding at other sites, suggesting unique and distinct roles for these two mediators in VWD-associated angiodysplasia.²³

Integrin $\alpha\beta3$ and vascular endothelial growth factor receptor 2

$\alpha\beta3$ integrin is the best-characterized endothelial receptor for VWF, expressed on endothelial cells and smooth muscle cells.²⁶ It is an obvious candidate for mediating the effect of VWF on angiogenesis because it is known to modulate VEGFR2 and VEGF-mediated increased endothelial cell proliferation via the PI3K/AKT/mTor, PLC γ /PKC/RAF/MEK/ERK and RAS/BRAF/MEK1/ERK pathways.²⁷ *In vitro* studies on VWF-deficient endothelial cells showed that $\beta3$ surface expression was decreased due to enhanced inter-

nalization, indicating that VWF binding to $\alpha\beta3$ stabilizes its surface expression. Whether VWF binding to $\alpha\beta3$ regulates downstream signaling and crosstalk with VEGFR2 signaling remains to be established. VWF can bind multiple angiogenic growth factors, including VEGF-A (see below)²⁸ and Angpt1-2 (see above). The ability of VWF to bind multiple receptors and ligands may result in VWF-dependent crosslinking of cell-surface receptors such as $\alpha\beta3$, Tie2 and VEGFR2, which would explain why its effects in angiogenesis are dependent on HMWM.²⁹ A role for VEGFR2 signaling in VWF-dependent angiogenesis is suggested by *in vitro*¹¹ and *in vivo* data.¹³ A model of VWF-dependent crosslinking endothelial cell surface receptors involved in angiogenesis is shown in Figure 1.

Growth factor binding

Recently, VWF was found to bind a surprising number of growth factors, including pro-angiogenic growth factors VEGF-A, placental growth factor, platelet-derived growth factor, basic fibroblast growth factor and others.²⁸ The binding was mapped to a short peptide in the A1 domain of VWF, the heparin-binding domain, which overlaps with the site for interaction with platelet glycoprotein Ib/IX. This is intriguing and raises the question of how VWF can sustain many multiple interactions in such a small region. Confusingly, the VWF heparin-binding domain appears to

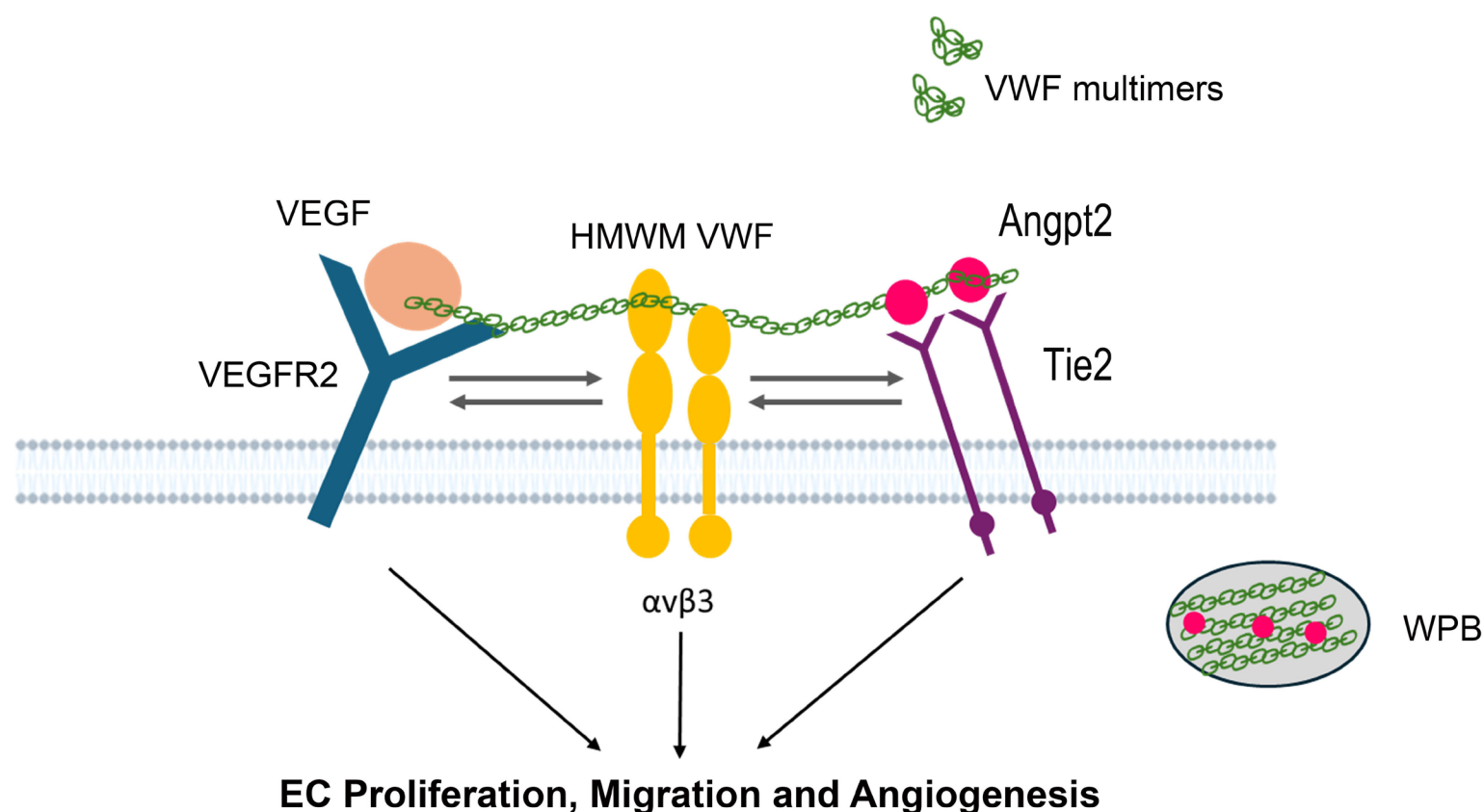


Figure 1. Model of von Willebrand factor regulation of angiogenesis. von Willebrand factor (VWF) is likely to modulate angiogenesis via various pathways. VWF is critical to the formation of Weibel-Palade bodies that store the growth factor angiopoietin-2 (Angpt2). Loss of VWF leads to increased Angpt2 release from endothelial cells and subsequent increased Angpt2 signaling. Upon its release, Angpt2 can bind the tyrosine kinase receptor Tie2 which promotes angiogenesis by synergizing with vascular endothelial growth factor (VEGF) signaling. VWF can also bind to integrin $\alpha\beta3$ on the endothelial cell surface which modulates VEGF receptor 2 (VEGFR2) signaling downstream. However, loss of VWF decreases $\alpha\beta3$ surface expression which might modify sensitivity to VEGF/VEGFR2 signaling. The ability of VWF to bind multiple receptors and ligands may result in VWF-dependent crosslinking of cell surface receptors $\alpha\beta3$, Tie2 and VEGFR2, which may explain why its effects in angiogenesis are dependent on high molecular weight multimers. EC: endothelial cell; HMWM: high molecular weight multimer; WPB: Weibel-Palade body.

have a pro-angiogenic effect in a model of wound healing, by recruiting growth factors to the site of the wound. It is possible that full-length VWF and its fragments may have opposite effects. This dual role is not unique to VWF: for example, $\alpha v\beta 3$ itself can have both pro-angiogenic and anti-angiogenic effects.²⁶ Whether the role of the heparin-binding domain is dependent on the microenvironment is not known. More studies are required to understand the role of VWF in growth factor signaling and angiogenesis.

Other possible mechanisms

Other mechanisms which might be implicated in VWF regulation of angiogenesis include the VWF-LRP4- $\alpha v\beta 3$ axis, in which low density lipoprotein receptor-related protein (LRP) was identified as a binding partner for VWF on vascular smooth muscle cells, resulting in proliferation of these cells via activation of p38MAPK.³⁰ VWF has also been shown to interact with insulin-like growth factor binding protein-7, another Weibel-Palade body component, which modulates angiogenesis via VEGF expression and signaling.³¹

VWF and angiogenesis mechanisms: a summary of possible pathways

To summarize, it is not yet possible to provide a complete explanation for the development of angiodysplasia in VWD, but several elements are clear:

- Loss of VWF leads to increased Angpt2 release from endothelial cells; increased Angpt2 signaling (depending on context) promotes angiogenesis by synergizing with VEGF signaling; increased Angpt2 likely mimics and/or accentuates inflammaging in the gut.
- VWF binding to $\alpha v\beta 3$ on the endothelial cell surface could modulate VEGFR2 signaling; VEGFR2 activity is increased in VWF-deficient endothelial cells.
- The effects of VWF on angiogenesis are at least partly dependent on HMWM.
- A fragment of VWF (the heparin-binding domain) interacts with multiple growth factors and is required to recruit growth factors at the site of skin wound healing.
- Platelets store multiple regulators of angiogenesis, both promoters and inhibitors of the process; hence they are very likely to play an important role in VWF-dependent angiogenesis which, as yet, has not been delineated.

Why the gut? Local mechanisms for angiodysplasia

Local factors are likely to explain why the gut is the predominant site of angiodysplasia in patients with and without VWD. Firstly, chronic exposure to high levels of antigen may result in endothelial activation. Although the prevailing dogma is that vascular endothelial cells are quiescent in the adult, recent data indicate that the gut microvascula-

ture is more prone to angiogenesis, possibly because of the oxygen gradient present in the intestinal villi.³² Secondly, aging is associated with a loss of pericytes in the murine colon vasculature; this has been attributed to upregulation of Angpt2 production in endothelial cells in response to increased macrophage infiltration and TNF α production (inflammaging).³³ The resulting increase in Angpt2-Tie2 signaling leads to loss of pericytes, vascular instability and leakiness. These effects could be accentuated in VWD, as described above.

Secondly, vascular instability may be compounded by the repeated muscular compression of the gut, where increased contractility of the muscularis propria can cause congestion and failure of the precapillary sphincters.³⁴ It can also produce a chronic hypoxic state triggering the release of pro-angiogenic factors such as VEGF. Mechanical and inflammatory factors are both consistent with the increased frequency of angiodysplasia in old age. Emerging data from single-cell RNA sequencing of gut endothelium will allow analysis of VWF expression in endothelial subtypes in the gut.³⁵

The possible importance of dysregulated angiogenesis at other sites in VWD is largely unexplored. For example, abnormal vasculature may contribute to the high frequency of heavy menstrual bleeding (90%) and slightly increased miscarriage rate in women with VWD.³⁶ Angiodysplasia in the uterus has been demonstrated in non-pregnant pigs with type 3 VWD with a decrease of integrin $\alpha v\beta 3$ and increase in VEGF expression.³⁷ Porcine models have revealed significant alterations in VEGF/VEGFR-2 signaling and $\alpha v\beta 3$, Angpt1, Angpt2 and Tie2 expression during placentation in animals with type 1 VWD compared to wild-type ones.³⁸

Parallels with other vascular abnormality syndromes

Angiodysplasia is regarded as an acquired disorder, but there are numerous congenital disorders of vessel formation whose genetic basis may help us to understand angiodysplasia in VWF and aid in the development of therapy. Some of these disorders also show progression with age. The variable phenotypes suggest interaction with other genetic variants, which would help to explain why only some patients with VWD develop angiodysplasia. In some cases, a somatic second-hit mutation is required for phenotypic expression. These factors have not been explored in VWD; the mutations involved reveal key signaling pathways and the pathophysiological basis of the associated angiogenic malformations.

TGF- β , BMP9-10/ENG/ALK1/SMAD4 pathway

Hereditary hemorrhagic telangiectasia (HHT) is a vascular abnormality syndrome which has parallels with VWF-angiodysplasia. Much like VWD, telangiectasias develop pro-

gressively into adulthood in the gastrointestinal mucosa, with 25% of patients suffering from gastrointestinal bleeding after the age of 50. Variants in *ENG* (endoglin), *ACVRL1* (ALK1) and rarely *SMAD4* are responsible for HHT and reduce signaling via the transforming growth factor (TGF)- β signaling pathway causing increased endothelial cell migration, proliferation and vessel development. There are overlaps between these pathways and those associated with VWF: for example, TGF- β has been shown to preserve vascular stabilization via Angpt1-Tie2 and VEGF-VEGFR2 signaling in human umbilical vein endothelial cells.³⁹ Furthermore, Angpt2 inhibition was able to alleviate the formation of arteriovenous malformations in an *in vivo* model of HHT.⁴⁰

RAS/RAF/MEK/ERK pathway

Parkes-Weber syndrome is a rare capillary malformation syndrome observable as cutaneous flat lesions overlying arteriovenous malformations with bone and soft tissue overgrowth. Transmission is in an autosomal dominant manner, caused by mutation in *RASA1*, which gives rise to prolonged RAS/MAPK/ERK signaling. Vascular malformations related to the RAS signaling pathway or 'RASopathies' are varied and generally dissimilar from angiodysplasia. Nonetheless, VEGF and Angpt1 can stimulate the RAS-MAPK pathway in endothelial cells, indicating possible shared molecular pathways with VWD vascular abnormalities.⁴¹

PI3K/AKT/mTOR signaling pathway

Naturally occurring *TEK* mutations causing arteriovenous malformations, such as Klippel-Trenaunay syndrome, lead to ligand-independent hyperphosphorylation of the receptor and a permanent activation of the PI3K/AKT/mTOR signaling pathway.¹⁶ An interaction between Angpt and Tie2 is central to the activation of the PI3K/AKT/mTOR pathway: Angpt1 binding to Tie2 (encoded by *TEK*) results in PI3K/AKT/mTOR activation. A similar effect may occur in HHT, in which reduced signaling via the TGF β /ALK1 pathway leads to loss of its inhibitory action on AKT/mTOR.

Therapies and healthcare impact

VWF replacement therapy is effective for most bleeding in patients with VWD but notably less so for gastrointestinal bleeding and often has little impact when angiodysplasia is present.⁴² This experience comes largely from use of plasma-derived VWF concentrates in which the multimer composition is degraded to a variable extent.⁴³ Given the importance of HMWM to hemostasis and vascular integrity, recombinant VWF which contains ultra-large VWF might be more effective. To date there is a single case report in the literature documenting its successful use in a patient with systemic sclerosis and (acquired) type 2A VWD and gastrointestinal bleeding unresponsive to plasma-derived VWF/factor VIII concentrates.⁴⁴

For many years, thalidomide has been the most frequently used and effective anti-angiodysplasia agent. In 2023 a multicenter, double-blind, randomized, placebo-controlled trial demonstrated a significant reduction in bleeding episodes with 100 mg or 50 mg thalidomide daily compared to placebo.⁴⁵ Thalidomide's efficacy has been attributed to suppression of VEGF and possibly TNF β expression.⁴⁶ In the context of VWD angiodysplasia, a further benefit might be derived from its capacity to increase VWF HMWM via inhibition of the degradation of thrombospondin-1 which promotes VWF multimerization.⁴⁷

Bevacizumab, the monoclonal antibody against VEGF, has been efficacious in two cases of gastrointestinal bleeding associated with acquired von Willebrand syndrome and Heyde syndrome^{48,49} as well as in a single-institute study of five cases of acquired von Willebrand syndrome secondary to insertion of left ventricular assisted devices.⁵⁰ Bevacizumab has been used more widely in HHT and has demonstrated benefit by increasing hemoglobin concentrations and reducing transfusion requirements in the international multicenter INHIBIT-BLEED HHT randomized controlled trial.⁵¹

Based on our current knowledge, perhaps the most likely novel therapies that may be of value for VWD patients with angiodysplasia target the VEGFR2 and Angpt-Tie2 pathways, and include antibodies against Angpt-2 alone as well as those capable of neutralizing both Angpt2 and VEGF simultaneously, such as the bispecific monoclonal antibody faricimab which has received approval for use in retinal vascular diseases.⁵² In addition, the anti-angiogenic tyrosine kinase inhibitor pazopanib was reported to have been of benefit in three patients with VWD angiodysplasia.⁵³ Considering the multiple overlapping routes to vascular malformations, parallels with other vascular abnormality syndromes may point to therapeutic alternatives in VWD (Figure 2). In HHT, thalidomide's undesirable side effect profile has led to its analog, pomalidomide, being very recently investigated in the PATH-HHT study with encouraging outcomes.⁵⁴ The PI3K/AKT/mTOR signaling pathway provided the first genetic targeted therapy for vascular malformations, rapamycin, which has shown efficacy in various vascular malformation syndromes. mTOR is downstream of the activating *TEK* mutations causing Klippel-Trenaunay syndrome and, as predicted, rapamycin has shown efficacy in Klippel-Trenaunay syndrome.⁵⁵ Since this pathway might also be downstream of VWF via modulation of Angpt2-Tie2 signaling, this drug might also be of benefit in VWD. However, more data in VWD-related models are required to confirm this, before its use in patients could be advised. Interestingly, the PI3K/AKT/mTOR pathway has also been shown to be enhanced in HHT and novel agents such as apselisib and miransertib, targeting PI3K and AKT inhibition, respectively, are currently in development.¹⁶

The emerging role of the RAS/MAPK pathway also provides potential for targeted therapy. Trametinib is an

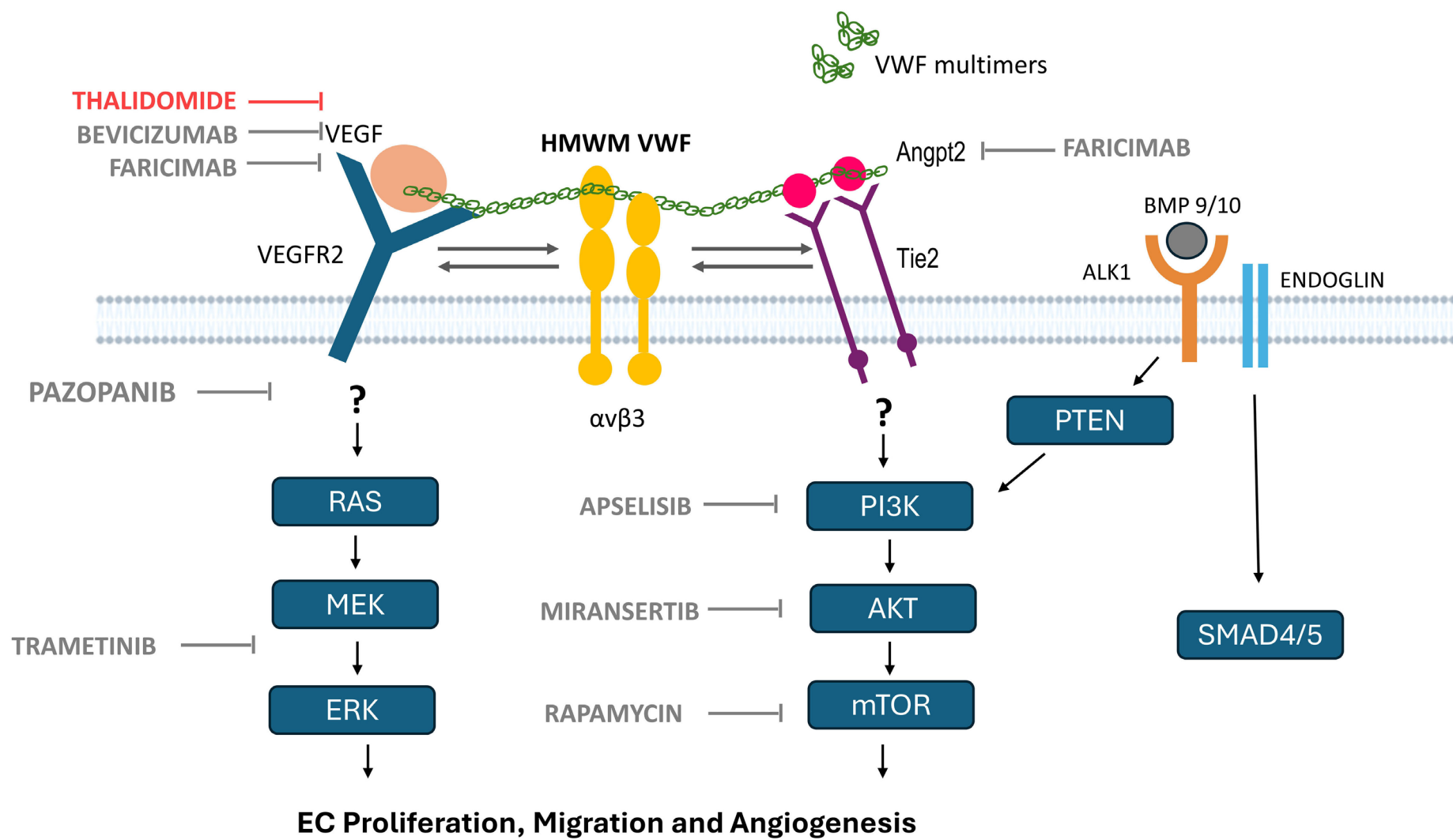


Figure 2. Therapeutic targets in vascular malformation syndromes with possible relevance to von Willebrand disease angiodysplasia. There appear to be multiple overlapping routes to vascular malformations which may help to identify overlaps between von Willebrand disease (VWD) and other vascular abnormality syndromes. The place of von Willebrand factor (VWF) in this web of molecular pathways remains unclear but may point to therapeutic alternatives in VWD. The figure shows current therapeutic alternatives that have targets within established VWF pathways (red) and those within pathways of other established vascular malformation syndromes (gray). HMWM: high molecular weight multimers; Angpt2: angiotensin-2; Tie2: tyrosine kinase receptor; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2; RAS: rat sarcoma; MEK: mitogen-activated protein kinase kinase 1; ERK: extracellular signal-regulated kinase; PI3K: phosphoinositide 3 kinase; AKT: serine-threonine protein kinase; mTOR: mammalian target of rapamycin; BMP: bone morphogenetic protein; ALK1: activin receptor-like kinase 1; PTEN: phosphatase and tensin homolog; SMAD: mothers against decapentaplegic homolog; EC: endothelial cell.

oral inhibitor of MEK1 and 2 by blocking Erk phosphorylation. A prospective phase II trial, TRAMAV, investigating trametenib in refractory arteriovenous malformations is underway.⁵⁶ Overall, the field of vascular malformations has delivered numerous novel treatments based on the definition of the molecular pathways underlying the disorders; these hold great promise for translation to angiodysplasia and gastrointestinal bleeding in VWD. Given the complex web of molecular pathways, it also highlights the need to validate the role of these potential targets in the development of VWF-dependent angiogenesis and angiodysplasia before they can be safely translated to patients. Although it is not yet possible to predict whether any of these novel agents will provide the answer to the challenge of intractable gastrointestinal bleeding from VWD-associated angiodysplasia, the crucial advance has been to understand that the role of VWF is more than simply hemostatic. By broadening our view of this complex molecule's

important roles to include regulation of angiogenesis we can utilize understanding from a number of other areas to pursue targeted therapy beyond simple replacement. The frustration of physicians, individual patients enduring prolonged and recurrent inpatient admissions as well as a large economic burden all provide encouragement in pursuit of this goal.⁵⁷

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Contributions

CC-T and AMR wrote the manuscript. ML conceived and wrote the manuscript. All authors read and approved the final version of the paper.

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