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Endothelial dysfunction in von Willebrand disease: angiogenesis and angiodysplasia

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ABSTRACT

In recent years, new functions for the haemostatic protein von Willebrand Factor (VWF) have emerged. Amongst these is the ability to modulate the development of new blood vessels, a process called angiogenesis. The subtle effects that VWF exerts on blood vessel formation and stability may be relevant for the small but significant fraction of patients with von Willebrand disease (VWD) who also present with vascular malformations (angiodysplasia) in the gastrointestinal tract, often responsible for intractable bleeding. This review will briefly summarise the evidence and discuss the molecular pathways involved.

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von Willebrand disease and acquired von Willebrand syndrome

von Willebrand disease (VWD), the most common inherited bleeding disorder in humans (reviewed in [1]), is caused by congenital decrease or dysfunction of von Willebrand factor (VWF), a large glycoprotein best known for its role in haemostasis. The classification of VWD identifies 3 main types and a number of subtypes. VWD can also be acquired (acquired von Willebrand syndrome or AVWS), due to dysfunction or degradation of VWF, often in association with malignant disorders, aortic valve stenosis or left ventricular assist devices (reviewed in [2,3]).

Vascular abnormalities in patients with VWD or AVWS

Up to 20% of patients with VWD present with gastrointestinal (GI) bleeding [4] which can be severe and not responsive to VWF replacement therapies [5]. GI bleeding has been linked to the presence of angiodysplasia [6,7]. The true prevalence of angiodysplasia in VWD or AVWS is not known, partly because of the risk of complications from the invasive endoscopic techniques required for diagnosis. Angiodysplastic lesions are thought to develop due to dysregulated angiogenesis, leading to the production of fragile vessels prone to bleeding [8]. Angiogenesis is a complex, multistep process which involves numerous pathways acting in concert to produce a stable blood vessel (reviewed in [9]). Loss of balance between proliferation and stabilization may result in excessive, unstable and dysfunctional new vessels, such as those found in angiodysplastic lesions. Interestingly, vascular malformations outside the GI track have also been reported in patients with VWD [10,11]. Until recently, the pathological mechanism underlying angiodysplasia in patients with VWD was unexplained. The discovery that VWF regulates angiogenesis [12] has provided a novel prospective on this syndrome and opened the way to new strategies for the treatment of angiodysplasia.

von Willebrand factor, angiogenesis and angiodysplasia: molecular mechanisms

VWF is a multifunctional glycoprotein best known for its essential roles in haemostasis, as a mediator of platelets adhesion and as carrier for coagulation Factor VIII. VWF is present in three pools: cells (endothelial cells [EC] and megakaryocytes); plasma (mostly from EC release) and subendothelium (through release from EC). In EC, VWF is stored in organelles called Weibel Palade Bodies (WPB) [13,14], as multimeric molecules which reach a molecular weight (MW) up to 20,000 kDa. Both the multimeric size and the conformation of VWF determine its platelet binding activity (reviewed in [15]). Besides its well-characterised role in haemostasis, VWF is increasingly been implicated in other biological processes, from inflammation to permeability and cell survival (reviewed in [16]). We recently identified a role for VWF in the control of angiogenesis [12]. *In vitro* studies on EC showed that inhibition of VWF expression using siRNA resulted in increased proliferation, migration and *in vitro* angiogenesis [12]. A similar overall pattern is found in blood outgrowth endothelial cells (BOEC) from patients with VWD [12,17], although differences in the cellular phenotypes have been observed depending on different molecular defect. In VWF deficient mice, angiogenesis and vascular density were increased in several *in vivo* models [12], whilst recruitment of VSMC, a sign of arterial maturation, was delayed in the developing retinal vasculature [18].

Because of the numerous molecular interactions and functions of VWF in the vasculature, multiple molecular pathways

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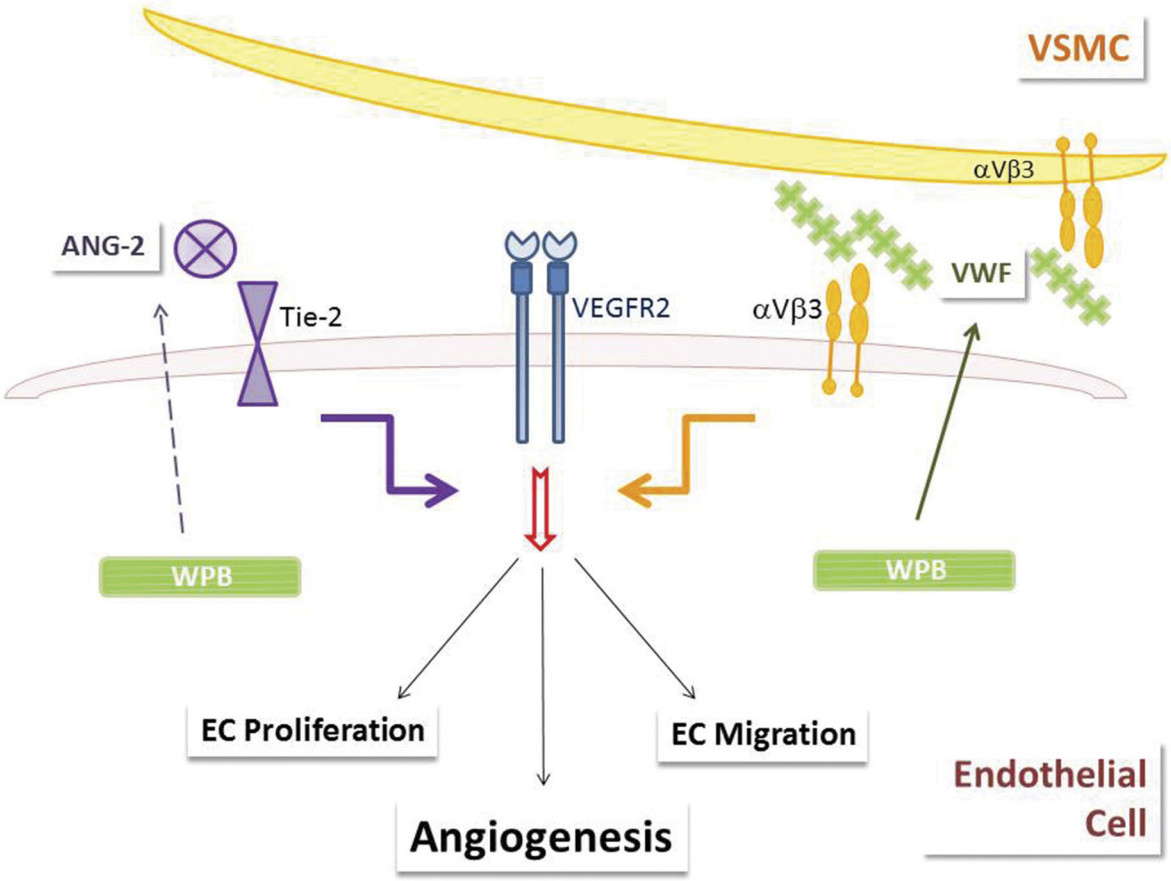

Figure 1. von Willebrand factor (VWF) controls angiogenesis and vascular maturation through multiple pathways: model. VWF modulates endothelial proliferation, migration and angiogenesis through intracellular and extracellular endothelial pathways, which converge to control vascular endothelial growth factor receptor (VEGFR)-2 signalling. *Intracellular pathway*: within endothelial cells (EC), VWF is essential for the formation of WPB, organelles which store the growth factor Angiopoietin (Ang)-2. Decrease in intracellular VWF results in increased release of Ang-2 from the EC. Upon release, Ang-2 can bind to the tyrosine kinase receptor Tie-2 and trigger signals which synergize with VEGFR-2 signaling to destabilize blood vessels and promote angiogenesis. *Extracellular pathway:* VWF, either in plasma or released into the subendothelial space, can interact with integrin αvβ3, a heterodimeric adhesion receptor with multiple ligands, involved in angiogenesis and vascular homeostasis. In EC, αvβ3 integrin modulates VEGFR-2 activity and downstream signaling. On the EC surface, VWF stabilizes integrin αvβ3 expression. Loss of VWF in EC results in decreased αvβ3 expression, which may causes over-sensitivity to VEGF/VEGFR-2 signalling, leading to formation of disrupted and immature blood vessels, similar to those described in angiodysplasia. Finally, during vascular development, expression of αvβ3 can also be upregulated in vascular smooth muscle cells (VSMC). VWF binding to αvβ3 on VSMC is required for their recruitment, thus promoting arterial maturation during vascular development. Thus lack of VWF may result in defective vascular maturation also because of reduced VSMC recruitment.

are likely to be involved in the regulation of angiogenesis by VWF. So far, the evidence points to VWF modulating angiogenesis through extracellular and intracellular pathways, schematically summarized in Figure 1.

VWF control of angiogenesis: extracellular pathways

In vitro, plasma-derived VWF inhibits endothelial tube formation in a basic model of angiogenesis [12], indicating the existence of an extracellular pathway. On endothelial cells, VWF binds to integrin αvβ3 [19], a heterodimeric adhesion receptor with multiple ligands, which plays a critical but complex role in angiogenesis and vascular homeostasis [20,21]. Pharmacological inhibition of αvβ3 inhibits angiogenesis in experimental models; however, genetic β3 deficiency results in enhanced angiogenesis *in vivo*. αvβ3 appears to exert a bimodal effect on angiogenesis, both as activator and inhibitor, playing different roles possibly depending on phases of angiogenesis, different ECM ligands, cross-talk and/or interaction with other receptors (reviewed in [21]). Multiple pathways downstream of αvβ3 link this receptor to regulation of gene expression and crucially to vascular endothelial growth factor receptor-2 (VEGFR)-2 signaling. A complex, reciprocal relationship exists between VEGFR-2 and αvβ3 integrin (reviewed in [22]). VEGFR2–αvβ3 integrin association is important for full VEGFR-2 activity and activation of downstream signalling [23]; however, lack of endothelial β3 causes over-sensitivity to VEGF leading to immature blood vessels [24]. As well as binding to αvβ3, VWF controls its expression by stabilizing its surface levels [12]. The effect of VWF on the pathways above is unknown and requires further investigation. Interestingly, VWF has been shown to interact with αvβ3 also on vascular smooth muscle cells (VSMC), in a pathway which involves Notch signaling [18]. This process has been proposed to promote arterial maturation during vascular development, thus providing a further mechanism through which VWF may modulate blood vessel formation. The observation that vascular malformations are most frequent in patients with AVWS and with type 2A VWD [5] suggests that VWF high MW multimers, which are crucial for haemostasis, may also be important for the control of angiogenesis, perhaps by enhancing VWF binding to EC.

VWF control of angiogenesis: intracellular pathways

VWF drives the formation of WPB, the endothelial storage organelles which contain multiple proteins, including the angiogenesis regulator as Angiopoietin-2 (Ang-2) [13,25]. *In vitro*

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