Editorial

What Benjamin Babington, William Osler, Frederick Weber, and Henri Rendu did not know

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Epistaxis is a reasonably common and usually minor condition, although in rare cases it can be severe and life threatening. Benjamin Guy Babington described a family with individual members in five generations who had commonly and at times severe epistaxis, and he recognized this as an inherited epistaxis syndrome [1]. Diagnostic acuity of the time was limited, leading to confusion between familial epistaxis and other hemorrhagic diatheses, especially hemophilia. Henri Rendu’s observations provided some clarification. He described the case of a 52-year-old male with frequent epistaxis and a similar history in his brother and mother. Moreover, Rendu recognized blanching angiomata on the nose, cheek, and lips of his patient [2]. A more detailed study of cases of the cutaneous-telangiectases-with-epistaxis syndrome was provided by William Osler and Frederick Parks Weber [3,4]. Osler noted that frequent and severe nose bleeds in these patients occur without similar bleeding from other minor injuries. One of the three subjects in Osler’s initial publication lost more than 1 L of blood from epistaxis, yet his coagulation time was reduced [3]. Hanes, a pathology resident at Johns Hopkins University Hospital, coined the term of hereditary hemorrhagic telangiectasia (HHT) for this familial disorder, which was later also named Osler–Weber–Rendu disease (OWR) [5]. Recently, progress has been made in defining the gene disorders underlying OWR. However, it remains poorly understood how these gene mutations relate to the molecular and cellular pathophysiology and to the clinical abnormalities in these patients. The seminal observations on blood outgrowth endothelial cells from OWR-patients in the studies by Fernandez-L and her associates in this issue of Cardiovascular Research provide novel insights into OWR pathogenesis and perhaps into general aspects of endothelial cell functions [6].

HHT or OWR disease is a relatively rare autosomal dominant disorder with an incidence estimated at 1 : 10,000 to 1 : 50,000. The disease is clinically characterized by repeated, spontaneous epistaxis that is associated with telangiectasias on the lips, tongue, and mucous membranes of the oral cavity and nose as well as the skin of the face and fingers. Internal organs can be involved with formation of arterio–venous malformations (AVM), which are typically found in the gastrointestinal tract (44% of patients), lungs (33%), liver (17%), and CNS (≤ 15%). AVMs can give rise to bleeding, with symptoms depending on the site of the bleed. Pulmonary AVMs can mature into larger shunts with increased risk for the passage of small thrombi that can give rise to CNS infarcts or (if thrombi are infected) brain abscesses. Pathologically, telangiectatic lesions begin as small dilatations in post-capillary venules and arterioles. The lesions are surrounded by mononuclear leukocyte infiltrates. Growth of the arteriolar and venular lesions leads to disappearance of the capillary segment and formation of an arterio–venous shunt [7].

Linkage studies of HHT families have revealed at least two distinct loci for the disease. Two genes were subsequently cloned: HHT1, encoding endoglin, and HHT2, encoding the activin receptor-like kinase-1 (ALK1) [8,9]. A third HHT locus has recently been identified in an OWR pedigree without an ALK1 or endoglin defect [10]. In addition, there is an overlap syndrome of juvenile polyposis and HHT (JPHT) due to loss-of-function mutations in Smad4. ALK1, endoglin, and Smad4 are involved in the signaling of transforming growth factor-β (TGFβ).

The TGFβ superfamily of multifunctional cysteine-knot cytokines includes TGFβ1, TGFβ2, TGFβ3, bone morphe-
genetic proteins (BMPs), activins/inhibins, growth differentiation factors, and Müllerian inhibitory factor (MIF). These proteins initiate signaling by binding to one of several constitutively active type II receptors, inducing recruitment and activation of a type I receptor by transphosphorylation on serine/threonine residues. The activated type I receptor phosphorylates intracellular substrates, classically receptor Smads (R-Smads). Once activated, R-Smads heterodimerize with Smad4, undergo nuclear translocation and regulate transcription at Smad-sensitive transcription regulatory gene elements. Smad4 is thought to serve as a transcriptional co-activator in collaboration of the R-Smad transcription activator and other co-regulatory proteins. In this simplified paradigm, functional selectivity is provided on multiple levels beginning with the cytokine concentrations. Moreover, limitations in the affinity to different type II receptors and the ability to recruit one of several type I receptors into a complex determine which R-Smad(s) are activated by phosphorylation. ALK2, ALK3, and ALK6 are activated by BMPs and give rise to intracellular signaling through Smad1, -5, and/or -8 as R-Smads. There may be further signal specificity in some tissues: for example, BMP7, which has functions that are antagonistic to TGFβ-dependent profibrogenic activities, utilizes mainly Smad5, at least in some tissues [11]. ALK5 is the ‘classic’ TGFβ-activated type I receptor that associates with the TGFβ type II receptor (TBRII), initiating signaling through Smad2 and -3. Smad3 is thought to be the TGFβ mediator for many events associated with fibrogenesis, including transcriptional upregulation of extracellular matrix proteins. ALK1 was initially categorized as an ‘orphan’ type I receptor, but was subsequently found to recognize TGFβ1 and TGFβ2 in the presence of TBRII as well as activin A in the presence of ActRII or ActRIIB and perhaps other, yet unidentified ligands [12].

Endoglin is a TGFβ receptor partner that can interact with both ALK1 or ALK5. It appears to regulate the formation of the ALK1/TBRII and ALK5/TBRII complexes by TGFβ, thereby balancing downstream Smad2/3- and Smad1-dependent events. Similar to BMP7 (via Smad5), TGFβ-induced Smad1 signals antagonize TGFβ-induced, Smad3-mediated events [11,13]. Endoglin and high levels of ALK1 expression appear to be limited to the endothelium, but lower levels of ALK1 are also expressed in other cell types. This may suggest some dependence on both of these proteins for the ‘fine tuning’ of TGFβ effects in endothelial cells, whereas perhaps in certain other (epithelial) cells, TGFβ/Smad3 effects are balanced by BMP7/Smad5. Haploallelic loss-of-function mutations in endoglin or ALK1 would be expected to result in a vascular phenotype, as is indeed observed in OWR.

TGFβ is a pluripotent cytokine with many apparently opposing effects. In epithelial cells, this protein reduces cell cycle transition by reversible late-G1 arrest, reduces the incidence of mitosis, and accelerates apoptosis. In contrast, TGFβ is a true mitogen-growth factor for some mesenchymal-derived cells such as fibroblasts. Recent studies have demonstrated that TGFβ utilizes a Smad2/3-independent mitogenic pathway specifically in fibroblasts involving the p21-activated serine/threonine kinase PAK2 and the non-receptor tyrosine kinase ableson (abl) [14,15]. Whether this alternative pathway is also active in endothelial cells and whether it can be activated downstream of ALK1 is not known.

Such models of TGFβ function in endothelial cells may explain some but not all aspects of clinical findings in HHT syndromes. For example, why are the microvascular lesions limited to some areas of the skin (face, hands) and mucous membranes (mouth, nose) and do not involve all of the skin and mucous membranes? Why are AVMs formed rather selectively in lungs, liver, and gastrointestinal tract and, less commonly, in the CNS but not in other vascularized tissues? And what is the difference, if any, between the activation of Smad1 by TGFβ (via ALK1), by activin A (via ALK1), or by BMPs (via ALK2, -3, or -6)? Several experiments have been performed in different laboratories to address such questions, especially as they relate to the pathogenesis of OWR. Fernandez-L and associates have developed an elegant in vitro model to study questions related to the functions of endoglin and ALK1, especially in the case of – but not limited to – HHT. These investigators used blood outgrowth endothelial cell cultures from affected patients [6]. As expected, HHT1 endothelial cells had reduced endoglin. Surprisingly, endoglin was also reduced in OWR subjects with haploallelic loss-of-function mutations in ALK1. Fernandez-L and co-investigators show that TGFβ transcriptionally activates endoglin through an ALK1/Smad1 pathway. Moreover, normal ALK1 and endoglin levels are required for the maintenance of ALK5, and the latter TGFβ type I receptor is reduced in endothelial cells that are defective in either ALK1 or endoglin. First, these findings give rise to the possibility that the critical biochemical abnormality in both forms of HHT is endoglin deficiency. Second, the findings from these studies may help to explain why telangiectasias in OWR patients occur only at selective sites and not diffusely throughout the body. Perhaps the TGFβ signals that are transmitted through ALK1/Smad1 and ALK5/Smad2/3 are sufficiently balanced except in certain parts of the microcirculation that experience additional stress that shifts this ratio towards ALK5 signal predominance. Since insufficient ALK1/endoglin levels lead to disruption of the actin cytoskeleton, this may contribute together with reduced proliferative capacity of endothelial cells to structural weaknesses, causing angiomata formation. These changes in the cytoskeleton of endothelial cells are reminiscent of some of the phenotype changes that occur during TGFβ-induced epithelial-mesenchymal transdifferentiation, which is also ALK5 dependent.

The findings of Fernandez-L and co-investigators may extend beyond better understanding of the cellular pathophysiology of OWR. They may also provide lessons applicable to the regulation of TGFβ function in general.
TGFβ effects in endothelium downstream of ALK5 are probably ‘fine-tuned’ by parallel activation of the ALK1/Smad1 pathway and in other tissues such as epithelium by other, competing Smad pathways such as Smad5 downstream of BMP7 [11]. In this respect, it is worth noting that genetic defects in ALK1 or the type II BMP receptor, BMPRII, can be associated with increased pulmonary arteriolar resistance, causing pulmonary hypertension. Although uncommon, pulmonary hypertension can also develop in Osler–Weber–Rendu’s disease. The availability of blood outgrowth cultures from patients with genetic disorders involving endothelial cells such as HHTs, primary pulmonary hypertension, and others will provide a useful tool to unravel further the molecular, biochemical, and cell physiological mechanisms of common as well as rare vascular diseases.

References