Propanolol and angiogenesis inhibition in hereditary haemorrhagic telangiectasia

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Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant vascular disorder, which occurs at a frequency of about one in 5,000 people (1–3). Vascular malformations in HHT patients range from regions of capillary dilation (telangiectases) in the nasal septum, oral mucosa, skin, or gastrointestinal tract, to large arterial-venous malformations (AVM) in organs such as lung, brain, or liver. The lesions can give rise to spontaneous recurrent nasal or gastrointestinal bleeding, leading to significant blood loss. Therapeutic options include surgery, or manipulation of coagulation and fibrinolytic pathways (2). However, these treatments are insufficient, and novel therapies are needed.

The most frequent cases of HHT are caused by mutations in the Endoglin (ENG) or ALK1 genes. Endoglin and ALK1 are cell surface receptors for members of the TGF-β family of cytokines. The biology of TGF-β is complex and many of the observed activities are dependent on the biological context (4); notably, TGF-β can either stimulate or inhibit angiogenesis. Yet, genetic studies in mice have provided clear evidence for a role of Endoglin and ALK1 in vascular development and malformation. Mice carrying heterozygous mutations in the ENG or ALK1 genes develop HHT-like vascular phenotypes. The current hypothesis suggests haploinsufficiency of these genes as the major cause of HHT in men (1, 3). However, the development of the vascular lesions in HHT has not only been attributed to decreased TGF-β signalling but also to increased activity of the pro-angiogenic VEGF pathway. Treatments that result in elevated TGF-β signalling or in angiogenesis inhibition might reduce pathological endothelial cell activation in HHT lesions and appear promising.

Various candidate drugs have been proposed for the treatment of HHT on the basis of these considerations. For example, estrogen therapy using raloxifene has been shown to increase the expression of ENG and ALK1 in cultured endothelial cells, and to improve endothelial cell functions like tubulogenesis and migration. This suggests that raloxifene counteracts the haploinsufficiency of ENG and ALK1 and may be beneficial for epistaxis treatment in HHT menopausal women (5).

Inhibitors of VEGF, a key regulator of physiological and pathological angiogenesis, are obvious candidates for angiogenesis inhibition. The VEGF-specific antibody bevacizumab, which is approved for the treatment of several malignancies, can be beneficial for the treatment of epistaxis and anaemia in HHT patients (6). However, VEGF has important functions in the healthy adult organism, and inhibiting its activity can have undesired effects. Cancer patients who received bevacizumab therapy suffered from fever, headache, rash, or chills; notably, also epistaxis occurred (7). Although these events were generally mild to moderate in severity, caution is necessary.

This is also true for thalidomide. This drug was originally used to treat nausea during pregnancy, but was removed from the market after severe congenital defects became overt, which were attributed to its anti-angiogenic activity resulting in defective vascular development (8). However, thalidomide enjoys a renaissance in medicine recently. It was reported to inhibit gastrointestinal bleeding in a HHT patient who received the drug as anti-cancer therapy (9), and to reduce the frequency of nosebleeds in HHT patients (8). Although these effects might be attributed to thalidomide’s anti-angiogenic activity, a recent study revealed an alternative potential mechanism of action which may guide the development of novel therapeutics for HHT (8). Thalidomide was shown to promote vessel maturation in ENG+/- mice which develop HHT-like lesions, as well as in nasal mucosal biopsies of HHT patients. Vessel maturation involved enhanced pericyte and vascular smooth muscle cell coverage in a PDGF-B dependent manner.

Ideally, drugs for anti-angiogenesis or normalisation of the endothelium in HHT lesions should be in clinical use without severe side effects. In this issue of Thrombosis and Haemostasis, Albinana et al. propose the use of the β-blocker propanolol for the treatment of HHT (10). This non-selective β-adrenergic receptor antagonist inhibits β1 and β2 adrenergic receptors. It causes vasodilatation and has been used for the treatment of cardiovascular disorders like hypertension, angina, or cardiac arrhythmias. Propanolol has in addition antiangiogenic properties: it can reduce the expression of VEGF and inhibits typical angiogenic responses in endothelial cells, such as VEGFR-2 phosphorylation, cell proliferation and migration, as well as tube formation (11). Recently, propanolol has been reported to improve capillary haemangiomas of infancy (12). These vascular tumours are formed by endothelial cells that proliferate under the influence of elevated VEGF levels. The question arises whether propanolol might be useful for the treatment of HHT as well. Albinana and colleagues address this question by studying endothelial responses in vitro. Apart from confirming the antiangiogenic activity of pro-
propanolol using various in vitro angiogenesis assays, they have a closer look at the TGF-β signalling system. Yet—and somewhat surprisingly—from the perspective of TGF-β as a stimulator of angiogenesis: inhibition of angiogenic responses in a microvascular endothelial cell line after propanolol treatment was associated with decreased ALK1 and ENG expression, as well as reduced promoter activity of these genes. Propanolol treatment had also a profibronotic activity by decreasing the expression of plasminogen activator inhibitor-1 and thereby favouring plasmin activity; and it induced signs of apoptosis in these cells.

However, findings obtained with more or less normal endothelial cells cannot simply be extrapolated to pathological condition, associated with abnormal, genetically altered endothelial cells. Albinana et al. therefore studied the effect of propanolol on endothelioma cells and HHT human umbilical vein endothelial cells (HUVEC). Here, inhibition of endothelial cell proliferation was even more pronounced, as determined by delayed closure of a scratch wound in vitro, and cells were even more prone to induction of apoptosis.

However, these results also provoke questions. If one assumes that HHT results, at least in part, from reduced TGF-β signalling, it is not obvious at all why reducing ENG and ALK1 expression with propanolol should be beneficial. In fact, Albinana et al. report unpublished cases from the Spanish HHT Association where two HHT patients who received systemic propanolol showed increased epistaxes which improved following withdrawal of the drug. Therefore, systemic administration of propanolol is not recommended, due to the profibronotic effect of this drug. However, the authors show that topical application of propanolol on the nasal mucosa might reduce abnormal vascularisation, and should be combined with an antifibronotic drug to counteract bleeding.

Considering the beneficial effects observed in infantile haemangioma, the well-studied β-blocker propanolol appears at first sight to be an attractive therapeutic option for interfering with deregulated angiogenesis and inducing vessel normalisation in HHT lesions. In vivo studies, for example using mouse models of HHT, will be necessary to find out whether this promise can hold true.

The effects of antiangiogenesis have most extensively been studied in tumours. An important conclusion drawn from studies with VEGF inhibitors was that part of their effects resulted from vessel normalisation, rather than from angiogenesis inhibition. Recent research fosters the idea that it should be feasible to achieve vessel normalisation, without interfering with the process of angiogenesis (13). Such approaches might turn out to be useful for future therapies of HHT as well.

Conflicts of interest
None declared.

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References
10. Albiñana V, Recio-Poveda L, Zarrabeitia R, et al. Propranolol suppresses angiogenesis in vitro: in vivo studies, for example using mouse models of HHT, will be necessary to find out whether this promise can hold true.