COMMENTARY

The Thalidomide renaissance

La renaissance de la thalidomide

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Nearly 50 years after an unprecedented sanitary tragedy, thalidomide makes a remarkable comeback. In a paper published last April in *Nature Medicine*, Franck Lebrin and his French, British and Dutch colleagues report remarkable results in the treatment of hereditary haemorrhagic telangiectasia (HHT) [1]. This genetic disease (see below) causes vascular malformations responsible for recurrent epistaxis, which can severely affect the quality of life and may be difficult to treat.

In the years 1957—1961, the drug, after tests on mice, was prescribed as a sedative to pregnant women with nausea. It resulted in widespread spontaneous abortion and severe birth defects in more than 10,000 babies, 40% of whom died before one year of age [2], and many are still alive. Thalidomide was withdrawn from the market in 1961 and remained so for more than 30 years. Since then, researchers have tried to uncover the mechanism(s) of the malformations and have discovered many fascinating biological properties of the drug [2]. A major finding is that the limb deformities caused by thalidomide in human embryos result from the drug’s ability to inhibit angiogenesis (the ability to build new vessels) [2,3]. As a consequence, thalidomide has been used with some success as an antiangiogenic agent in certain cancers, such as multiple myeloma, leukaemia and, recently, prostate cancer [4]. Because of anti-inflammatory properties, the drug has also been used in leprosy.

In this paper [1], Lebrin et al. describe a new promising application of thalidomide: prevention of severe nasal or gastrointestinal bleeding in patients with HHT. The elementary lesions in HHT are telangiectases, consisting in dilated and thin-walled vascular dysplasias of the capillary bed, which are prone to bleeding, mostly in the nasal mucosa and in the gastrointestinal tract. Some individuals also develop arteriovenous malformations in the liver, lungs or brain. These large and tortuous vessels replace the normal vascular bed of these organs, thus reducing vessel function and causing haemorrhage and stroke.

Excessive angiogenesis is probably the cause of telangiectases and arteriovenous malformations in HHT. In support of this hypothesis, anecdotal studies with the antiangiogenic drug bevacizumab, an antibody against the vascular endothelial growth factor (VEGF), have shown benefit in patients with HHT [5]. Even more spectacularly, a patient waiting for a liver transplantation for severe HHT could be taken out of the waiting list after treatment with the same agent [6]. Lebrin also explains that, with his colleagues, he started with the observation of a patient with cancer and HHT in whom both diseases improved under treatment with thalidomide [7].

Seven patients aged 18—75 years with severe and recurrent bleeding were treated with thalidomide, 100 mg daily. Treatment lowered significantly both the frequency (six of seven patients) and duration (three of four patients in whom the information was available) of epistaxis, all within one month of treatment. The average haemoglobin concentration in peripheral blood increased without additional iron supplementation in five of six patients. Before treatment, four individuals who suffered from 18 to 32 nosebleeds per week required between one and six blood transfusions per year to prevent anaemia. These patients did not require any blood transfusion after being treated with thalido-
mide with a follow-up of 6 months to five years. Six of the seven patients exhibited minor side effects: constipation, loss of libido, drowsiness and lethargy. One patient had to stop treatment because of peripheral neuropathy. Two others stopped treatment for reasons unrelated to side effects. In these three individuals, epistaxis returned and haemoglobin concentration dropped to pretreatment levels in two of the three subjects. Control subjects with HHT not receiving thalidomide had haemoglobin concentrations lower than the normal range and the treated patients.

Lebrin et al. next investigated how thalidomide might exert its antihaemorrhagic effect using several elegant models. In HHT, there is a communication defect between vascular endothelial cells and pericytes, which are connective tissue cells that surround and support blood vessels. HHT is mainly caused by mutations in two genes encoding receptors for ligands of the transforming growth factor-β (TGF-B) superfamily. One of these genes is ACVRL1, which encodes the activin-like receptor kinase-1 (Alk-1), an endothelial cell TGF-B type I receptor. The other gene is ENG, which encodes endoglin, an auxiliary receptor for TGF-B ligands. Normally, in response to TGF-B secreted by endothelial cells, the coordinate signalling pathways result in inhibition of endothelial cell growth and stimulation of myogenic differentiation of adjacent pericytes, thereby promoting normal angiogenesis.

Lebrin et al. first show that thalidomide promotes vessel maturation. They used both an in vitro model with spheroids of differentiating mouse embryonic stem cells, and an in vivo model of Eng+/− mutant mice which have only one copy of Eng (the endoglin gene in mice) and develop vascular lesions similar to those of HHT [8,9]. In both models, thalidomide has a dual effect: it inhibits endothelial cell proliferation and it stimulates pericyte recruitment and coverage of the vessels. These effects might stabilize blood vessels and thus prevent bleeding caused by rupture of the vascular malformations. In addition, Eng+/− mutant mice have “thin-walled” vessels, due to irregular layers of smooth muscle cells. This results in fragile vessels, prone to bleeding. The authors show that thalidomide rescues the arterial coverage with smooth muscle cells in these mice.

To gain insight into the molecular mechanisms involved in these effects, the authors measured mRNA expression of growth factors and receptors regulating angiogenesis and pericyte recruitment in the retina of thalidomide-treated and untreated Eng+/− mice and their normal littermates. They show that thalidomide upregulates platelet-derived growth factor-β (PDGF-B). Since pericytes express PDGF receptor-β (PDGFR-B), they reasoned that upregulation of PDGF-B might enhance pericyte recruitment by a paracrine mechanism. To test this, they took advantage of the Pdgfb+/−/−ret mouse model, in which PDGF-B is secreted but not retained by the extracellular matrix. In this model, thalidomide did not rescue pericyte recruitment. This supports the idea that PDGF-B is required for thalidomide-mediated pericyte recruitment, establishing PDGF as a key mediator of thalidomide effect. It thus appears that the major effect of thalidomide is to bypass the TGF-β1-endoglin-Alk-1 signalling pathway, which is defective in HHT; thalidomide administration stimulates PDGF-B expression independently of the TGF-β1-endoglin-Alk-1 pathway, thereby bypassing the requirement for this pathway in vessel maturation and stability (Fig. 1).

Finally, Lebrin et al. confirmed in humans the findings in mice models by examining human nasal mucosal biopsies. They stained sections for endoglin and α-smooth muscle actin (α-SMA) as markers of endothelial cells and vascular smooth muscle cells, respectively. They compared sections from untreated patients to those of a patient treated with a daily 100 mg dose of thalidomide. There were many more smooth muscle cells layers around the blood vessels of the treated individual than around those of the untreated patients, showing that thalidomide stimulates vessel coverage in humans as well as in mice.

In brief, this study demonstrates that thalidomide acts on pericytes (and their precursors) surrounding the vessels to stimulate vessel maturation. It restores endothelial cell-pericyte communication, which is profoundly altered in HHT. Thereby, it corrects vessel fragility and significantly improves bleeding tendency.

These new insights into the molecular mechanisms of action of thalidomide are of considerable importance. Knowing how drugs like thalidomide work on angiogenesis will help informed decisions about other therapies, possibly with

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![Figure 1](image-url)  
**Figure 1**  Cross-talk between endothelial cell and vascular pericyte and the effect of thalidomide. A: normally, angiogenesis is dependent on the TGF-1-endoglin-alk-1 pathway, which is essential for endothelial cell-pericyte adhesion and vessel stability. B: in hereditary haemorrhagic telangiectasia, mutations of endoglin or Alk-1 inhibit this pathway and suppress endothelial cell-pericyte adhesion, thereby altering vessel stability. C: thalidomide treatment stimulates PDGF-B expression and rescues endothelial cell-pericyte adhesion and vessel stability independently of the TGF-1-endoglin-alk-1 pathway.
similar effects on the vessels but without side effects. Moreover, applications other that HHT can be considered. For example, of special interest to hepatologists, thalidomide could be a promising drug in chronic liver disease (CLD). Recent experimental and clinical studies have convincingly established that hepatic angiogenesis takes place in CLD, irrespective of aetiology [10]. CLD is characterized by perpetuation of liver cell injury, inflammatory response and progressive fibrogenesis, leading eventually to cirrhosis. Angiogenesis and related changes in liver vascular architecture, that in turn lead to increased vascular resistance, portal hypertension and decreased parenchymal perfusion, have been proposed to favour fibrosis progression toward cirrhosis. Hepatic angiogenesis has also been proposed to modulate the development of portosystemic shunts and increase splanchnic blood flow [11], thus potentially leading to complications of cirrhosis. A number of cellular and molecular mechanisms governing the cross-talk between angiogenesis and fibrogenesis have been identified, with a specific emphasis on the crucial role of hepatic stellate cells (the liver vascular pericytes), particularly when activated to the myofibroblast-like profibrogenic phenotype [12]. Finally, anti-angiogenic therapy with sunitinib and sorafenib has been proven to be effective in limiting the progression of fibrosis in animal models of cirrhosis [13,14]. Sorafenib has also shown some benefit in patients with hepatocellular carcinoma [15,16].

Thalidomide might not be ultimately the drug of choice for HHT or other conditions with altered angiogenesis. But understanding the molecular pathways that regulate both cell autonomous and cell-to-cell cross-talk mechanisms is crucial for designing new drugs with possibly a better efficacy and fewer side effects [17]. A new large avenue for future treatments is undoubtedly opened.

Conflict of interest statement

None.

References


