Hereditary haemorrhagic telangiectasia: from physiopathology to future treatments

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I ADDENDUM

English summary

Hereditary Haemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare vascular disorder characterized by various vascular malformations ranging from bleeding telangiectasis to large arteriovenous malformations. Despite being clinically observed over a century and scientifically studied over four decades, effective treatment remains elusive. This is not only due to the complexity of the disease, but also to the lack of technology and biomarkers for assessing drug efficacy on blood vessels located deep inside the body. This thesis makes significant contributions to better understanding the disease mechanism, finding new treatments, and developing novel monitoring techniques.

The clinical features, genetic basis, and mechanisms underlying the formation of vascular malformations in HHT is reviewed in **chapter 1**, highlighting the role of Transforming Growth Factor-β (TGF-β) and Vascular Endothelial Growth Factor (VEGF) signalling in driving disease development and progression. **chapter 2** explores why vascular malformations occur in specific tissues of HHT type 1 patients, a subtype of the disease due to a mutation in the *ENG* gene, despite the fact that all blood vessels in the body carry the HHT mutation. We showed that organs with low levels of endoglin, such as the skin, lungs and brain, are more prone to the development of vascular malformations.

In **chapter 3** a novel HHT disease mechanism is elucidated. We showed that in HHT type 2, a subtype of the disease due to a mutation in the *ALK1* gene, VEGF Receptor 1 is downregulated leading to excessive angiogenesis and vascular malformation, hence explaining why anti-angiogenic therapies such as anti-VEGF are promising to treat HHT patients. **Chapter 4,** provides detailed insight into the mechanism of HHT type 1, with a specific focus on pericyte-endothelial cell interactions. We discovered how the *ENG* mutation in endothelial cells induces pericyte detachment from the blood vessel wall, which leads to cerebral blood flow deregulation. This hemodynamic defect has been revealed by a revolutionary ultrasound imaging technique that has the potential for future clinical use. In **chapter 5**, we investigated chemical compounds that stimulate pericyte-endothelial cell interactions and demonstrated their efficacy in treating both mouse models of HHT and neurodegeneration. In this chapter we also confirmed the critical role of Platelet Derived Growth Factor B (PDGF-B) signalling in enhancing pericyte-endothelial cell interactions and established, for the first time, the importance of Wnt signalling in increasing endothelial-

endothelial cell interactions to prevent blood-brain barrier damage. These findings have allowed us to design new compounds that could potentially treat HHT and other diseases associated with defects in pericyte-endothelial or endothelial-endothelial cell interactions. **Chapter 6** summarises the results presented throughout this thesis and provides new perspectives on the findings.

In summary, this thesis presents a ground-breaking and comprehensive exploration of the mechanisms driving HHT. By uncovering previously unknown disease pathways and developing novel therapeutic strategies, this thesis contributes to overcoming the long-standing challenges of treating this complex disease. Furthermore, the development and application of advanced imaging techniques which are described in this thesis for the use in HHT, provide a powerful new way to monitor disease progression and assess treatment efficacy, with the potential to transform clinical practice. The research not only deepens our understanding of HHT, but also lays the foundation for new, targeted treatments for HHT patients and paves the way for breakthroughs in other cardiovascular diseases. Hence, this work represents a significant step forward in both basic science and potential clinical disease management of HHT.