Influencing the homing and differentiation of MNCs in hereditary hemorrhagic telangiectasia

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Stellingen behorend bij het proefschrift getiteld: 'Influencing the homing and differentiation of MNCs in hereditary hemorrhagic telangiectasia'

1. The decrease in myocardial function observed in our HHT1 animal model is not solely caused by a disturbed endothelium response, but also in part by impaired MNC function (this thesis).

2. Homing of MNCs to the ischemic myocardium could be restored by systemic DPP4 inhibition (this thesis).

3. Macrophage-specific deletion of *Eng* did not result in similar levels of cardiac deterioration as found in *Eng*+/- animals, implying a multifactorial nature of HHT1. This emphasizes the need for endoglin heterozygosity to be present in all cell types of the heart to recapitulate the HHT1 disease phenotype (this thesis).

4. Together with our observation of decreased homing capacity of the MNCs, HHT1 now proves to affect other cell types and functions as well, in particular the lymphocytes and monocytes (this thesis).

5. The absence of endoglin may skew the tight balance that often exists between TGFβ and BMP signaling, and inhibition of the BMP type I receptor kinases may push this balance towards enhanced TGFβ signaling, thereby restoring M2 macrophage differentiation (this thesis).

6. The impaired differentiation towards the regenerative M2 macrophage subtype -due to endoglin heterozygosity- could be restored by LDN stimulation, inhibiting the BMP type I receptors, confirming both BMP-dependent and non-canonical modulation of macrophage function in HHT1 (this thesis).

7. The inflammation and stress-related signaling aberrations found in *Eng*+/- macrophages highlight the complexity of the immunological defects present in HHT1. Whereas in this study we focused on macrophages, the effects of DPP4 inhibition on other immune cells and tissue cells is still largely unknown (this thesis).

8. DPP4 inhibition is able to positively direct wound healing in *Eng*+/- mice by decreasing the pro-inflammatory signaling in the macrophages and injured tissue. Further research should focus on finding a direct correlation between canonical/non-canonical TGFβ signaling and DPP4 inhibition, and could lead to revealing new mechanisms in the pathogenesis of HHT1 (this thesis).

9. Hereditary Hemorrhagic Telangiectasia type 1 is a haploinsufficient genetic vascular disorder caused by mutations in the transforming growth factor beta (TGFβ) co-receptor endoglin.

10. MNC homing and differentiation into inflammatory and regenerative macrophages is important for proper tissue repair.

11. The influx of circulating monocytes is important for cardiac repair post-MI and contributes to the revascularization of ischemic tissue.

12. Murine models have given valuable insights into the mechanism behind the mutations found in HHT patients.

13. Endoglin heterozygous mice can develop the same clinical features as HHT1 patients.

14. As is true for me and most people working in basic science; I can believe things that are true and things that aren't true and I can believe things where nobody knows if they're true or not. (Adapted from: Neil Gaiman, *American Gods*, 2001)