Maastricht University

White matter really matters in cerebral small vessel disease

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Summary

Cerebral small vessel disease (cSVD) is a vascular risk factor associated disorder characterised by white matter lesions. These lesions are associated with cerebral hypoperfusion and increased blood-brain barrier (BBB) permeability. The cellular and molecular mechanisms underlying small vessel dysfunction and loss of white matter integrity remains largely unknown. In that context both endothelial cells (ECs) and oligodendroglia are key players, as ECs have a critical role in cerebral perfusion and BBB permeability and oligodendrocytes and oligodendrocyte precursor cells (OPCs) are responsible for myelination in the brain. Although EC dysfunction could affect oligodendrocytes and OPCs and lead to white matter damage, the role of their interplay is poorly studied in context of cSVD.

In this thesis, we identified Wnt7a as a potential modulator of EC-OPC interaction in a systematic literature search (Chapter 2). We studied the effects of Wnt7a and β-catenin signalling on endothelial barrier integrity in vitro, demonstrating its impact on the expression of tight junction proteins (Chapter 3). Our transcriptomic analysis revealed the role of Wnt7a in regulating a signalling pathway of importance for OPCs. We showed that Wnt7a suppressed *Cxcl12* in ECs but had no influence on expression of CXCL12 receptor *Cxcr4* in OPCs (Chapter 4). Finally, we demonstrated that cerebral hypoperfusion in mice leads to hypoxia in OPCs and an increased BBB permeability. In vitro experiments with OPCs exposed to hypoxia resulted in upregulation of *Vegfa*, rather than Wnt7a, via *Hif1a* and *Epas1* signalling. We also showed in a retrospective human study that higher VEGFA plasma levels were associated with increased BBB permeability in normal appearing white matter of cSVD patients (Chapter 5).

Taken together, our findings support *(a)* a role for Wnt7a in regulating BBB integrity and OPC migration and *(b)* an early role for OPC-derived VEGFA in hypoxia contributing to BBB impairment and possibly white matter lesion development in cSVD patients.