Molecular pathology of hereditary cerebral hemorrhage with amyloidosis-Dutch type

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Summary

Hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D) is an early onset hereditary form of Cerebral amyloid angiopathy (CAA) caused by a point mutation of the Amyloid Precursor protein (APP). CAA refers to the accumulation of amyloid β (Aβ) peptide, resulting from APP protein cleavage, in intracerebral vessels. CAA pathology is present in the majority of Alzheimer's disease (AD) brains and is associated with intracerebral hemorrhages in the elderly. The general aim of this thesis is to decipher the molecular pathogenesis of HCHWA-D. Since no proven therapeutic treatment exists to prevent or even delay the disease onset, the understanding of underlying pathomechanisms in HCHWA-D is important. It may help discovering new therapeutic targets and biomarkers that can be used to assess the efficacy of candidate drugs in treatment trials.

Chapter 1 is a general introduction of HCHWA-D covering the clinicopathological and neuropathological aspects of the disease as well as the known pathogenesis and the importance of HCHWA-D studies for the CAA field. **Chapter 2** reviews other hereditary APP mutations and describes how the Aβ mutation of HCHWA-D patients modifies Aβ properties regarding aggregation, binding to cerebral vessel wall cells, interplay with extracellular matrix, proteolysis, and clearance, and how these altered characteristics lead to HCHWA-D pathogenesis.

Former research in the CAA field indicates the existence of factors able to influence Aβ accumulation predominantly in vessels rather than in brain parenchyma, such as TGFβ. Identification of aggravating factors of CAA pathology are therapeutic target of interest and therefore we explored in **Chapter 3** the TGFβ pathway deregulation in HCHWA-D. We discovered that in HCHWA-D brain material TGFβ1, its receptors and TGFβ-induced genes are upregulated. Using histology and compared to sporadic CAA, the actual activation of the TGFβ signaling cascade in the hereditary form is confirmed by the accumulation of its activated transcription factor phospho-SMAD2/3 (pSMAD2/3) in some angiopathic vessels which also correlates with the disease severity.

Understanding the underlying pathology of neuroimaging features in patients is essential for a precise diagnostic and follow-up of the disease. Therefore we investigated a recently described MRI neuroimaging feature of advanced disease stage in HCHWA-D. We used an histopathologic correlates in **Chapter 4** to reveal that cerebrovascular iron accumulation and calcification are the cause of the *in vivo* observed MRI abnormalities. We identified calcifications as a novel MRI marker of interest for clinical CAA severity evaluation in hereditary as well as sporadic CAA patients.

Because calcifications are a feature of severe CAA pathology (Chapter 4) and CAA severity is linked with TGFβ deregulation (Chapter 3), we investigated in **Chapter 5** the calcified CAA vessels in HCHWA-D with a focus on TGFβ-related disease progression. Besides pSMAD2/3 immunomarker, we quantified in patients with different severity the presence of osteopontin (OPN) and collagen 1 (col1), potential modulators of vascular calcification responsive to TGFβ. We described an accumulation of OPN and pSMAD2/3 in calcified CAA vessels as well as the association of col1 protein, a fibrotic protein with vascular amyloid load. Chapter 5 tightly link the TGFβ pathway deregulation to CAA progression and calcification in HCHWA-D.

Finally, **Chapter 6** is an transcriptomic study in human *post mortem* brain to identify major deregulated pathways in HCHWA-D and broaden our comprehension of molecular pathogenesis. By comparing the changes that we found in the human transcriptome with the transcriptome of young APP-E693Q mice at the pathway level, we could identify an overlap in the upregulation of ECM-related pathways, which is in mice prior to the onset of CAA pathology and suggests an early TGFβ1-mediated fibrosis. In addition, we identified a mitochondrial dysfunction, a feature of neurodegenerative diseases not yet described in HCHWA-D.

The discussion in **Chapter 7** summarizes the main finding of this thesis namely that TGFβ deregulation plays a central role in HCHWA-D pathogenesis. Therefore the beneficial and detrimental aspects of TGFβ on the vascular and parenchymal brain components are reviewed and the possible causes of TGFβ activation in HCHWA-D as well as its implication for future studies and therapeutic intervention are discussed.