TGFβ signalling in HCHWA-D: exploring new therapy targets against CAA

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Research question and background

HCHWA-D (Hereditary Cerebral Haemorrhage With Amyloidosis–Dutch type) is an autosomal dominant hereditary disease caused by a point mutation in the Amyloid Precursor Protein (APP) gene leading to the formation of Amyloid beta (Aβ) proteins with the ‘’E22Q Dutch mutation’’. The particular properties given by that mutation have been extensively studied and are causing an early onset amyloid deposition in cerebral blood vessels called Cerebral Amyloid Angiopathy (CAA), resulting in cell death and vessel wall integrity loss.

CAA is also a frequent lethal cause of intracerebral hemorrhages in the elderly and is associated with Alzheimer disease (AD) in at least 80% of cases. The exact mechanism leading to CAA is not known and there is no actual therapy to alleviate or delay amyloids deposition.

One possible therapy target is the TGFβ signalling pathway. CAA has been shown to be correlated with TGFβ1 level both in mouse models (overexpression in astrocytes) and in AD human brain material. We want thus to first investigate the differences in TGFβ signalling in HCHWA-D in comparison to age-related control individuals. As the CAA is starting in the occipital lobe, we are also comparing this area with the frontal lobe where the pathology has a milder form. In addition to the requested frozen control material, we also asked for the related paraffin block (frontal and occipital) in order to have a better set of control material for our immunohistochemistry study. The same investigation will be conducted in AD and age-related control donors later.

Methods and tissues used

Tissue from the LUMC pathology department (7 HCHWA-D patients and 2 controls) was also included in the study. We requested 7 additional controls (below 65years) and 2 additional HCHWA-D donors.

Immunohistochemistry and RNA analysis were used.

Results and conclusion

Both immunohistochemistry and qPCR showed differences in the TGFβ signalling pathway between controls and HCHWA-D patients. Studies are still ongoing to further assess gene expression differences between these groups.