A proteomic and glycomic study of regional differences in Alzheimer disease brain

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Research question and background

AD is the most common neurodegenerative disorder and is characterized by progressive memory failure and severe cognitive deficits. The main neuropathological hallmarks are amyloid plaques composed of amyloid-beta peptides (Aβ) and tangles composed of hyperphosphorylated Tau. Today it is estimated that around 35 million people world-wide suffer from AD. Hence, a main challenge for the coming years is to find reliable biomarkers and effective treatments to conquer AD at an early stage in the pathogenesis. Several groundbreaking discoveries have been made in the field of AD over the years and possible pathogenic mechanisms have been suggested. Although extensive research has advanced the knowledge about the disease, all clinical trials conducted in the last years have failed to cure AD. This might be due to misinterpretations of findings from animal models. Another reason why the clinical trials have failed may be that the focus has not been directed to the right mechanisms and molecules.

Our research question is to elucidate which disease mechanisms that are involved in Alzheimer disease (AD) with a focus on proteins and the proteo-glycome. Both proteomics and glycomics are powerful methods to identify novel targets of disease progression. We utilize unbiased proteomics and glycomics, as well as targeted analysis of proteins and glycans of interest for AD. In our research projects, human brain material is crucial due to the fact that there are no animal models currently available that adequately mimic the progression of human AD.

Methods and tissues used

We utilize frozen brain sections from frontal cortex, hippocampus and cerebellum of six cases of non-demented and six cases of patients diagnosed with AD. The methodology that we are using includes laser capture microdissection, mass spectrometry, immunohistochemistry and proximity ligation assay.

Results and conclusion

We are currently performing immunofluorescence staining and proximity ligation assay in human brain sections to study the localization and interactions of proteins that we have shown to interact with the active γ-secretase complex, which is one of the critical enzymes for Aβ-formation. We also perform microscopy studies of proteins that we, by using laser capture microdissection/mass spectrometry, have shown to be altered in AD brain.

We are developing antibody and lectin based assays for studying differences in glycosylation in AD and control brain. Furthermore, we have developed highly sensitive mass-spectrometric methods for measuring AD induced alterations in the N-glycome.

We have not yet published any data using the samples from NBB.