ABSTRACT

Synaptic degeneration is a common (early) pathology in several neurodegenerative disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD) and multiple sclerosis (MS). We hypothesized that synaptic biomarkers in cerebrospinal fluid (CSF) might closely reflect synaptic dysfunction in the brain, and thereby could contribute to improving diagnostic accuracy, monitoring disease progression, and serving as markers for assessing response to disease modifying therapies. The primary goal of this thesis was to identify biomarkers reflecting synaptic degeneration across neurodegenerative and neuroinflammatory diseases. We therefore investigated the potential of two well-known members of the contactin family, contactin-1 and contactin-2, as synaptic (or axonal) biomarkers for AD, PD and MS and their possible pathological relationships with these diseases.

In this thesis, we have developed and optimized assays and extensively characterized the concentrations of contactin-2 in CSF and contactin-1 in CSF and serum in several patient cohorts and the immunostaining patterns of these proteins in post-mortem human brain. Our results show that contactin-1 and -2 are decreased in the CSF of patients with AD, PD and MS (RRMS and SPMS) compared to relevant controls. CSF contactin-1 and -2 levels are correlated with levels of many proteins in CSF that are altered in these diseases such as amyloid beta species, beta secretase 1, neurogranin, total tau, phosphorylated tau, neurofilament (light and heavy) and alpha-synuclein. Lastly, we provided further support that synaptic degeneration is involved in MS pathogenesis that could also be detected in serum apart from CSF. In addition to decreases in levels of CSF contactin-1 and -2 in RRMS and SPMS, the decreases were associated with lower normalized brain volumes of MS patients. In summary, our findings indicate that there are overlapping features of synaptic pathology in AD, PD and MS. Moreover, contactin-1 and -2 are possible cross-diseases biomarkers for synaptic and axonal degeneration in neurodegenerative and neuro-inflammatory disorders.