ABSTRACT

Tau protein, a microtubule-associated protein localized in axonal projections of neurons, is a key molecule in the pathology of Alzheimer´s disease (AD), the most common cause of dementia in the elderly population. Tau belongs to the group of natively unfolded proteins without globular structure and is prone to numerous posttranslational modifications (PTMs). Under pathological conditions, abnormal PTMs and misfolding of tau protein occurs and leads to oligomerization and aggregation into paired helical filaments forming neurofibrillary tangles, the histopathological hallmark of AD.

Currently available drugs applied in AD treatment can only slow the disease progression and those, which halt the AD-specific neurodegenerative processes, are still missing. Very promising and evolving therapeutic approach is immunotherapy, and even immunomodulation by administration of intravenous immunoglobulin (IVIG) products, a reservoir of natural antibodies from the plasma of healthy donors, has been already tested. The discovery of naturally occurring antibodies directed to tau (nTau-Abs) in body fluids of both AD and healthy subjects and their presence in IVIG begin the investigation of their therapeutic potential. Considering a wide range of possible modifications of tau and of various tau species (oligomers, aggregates etc.), the characterization of nTau-Abs is crucial step in understanding their physiological role and possible involvement in AD pathogenesis.

The main project goal was to isolate natural tau-reactive Abs from the plasma of AD patients, healthy controls, and IVIG product and compare them. Differences in IgG subclass distribution, avidities, and reactivity with various tau protein forms among these tau-reactive antibodies obtained from AD and healthy controls were revealed and discussed.

Phosphorylation is the most studied PTM of tau significantly participating in the modulation of its function and interactions. Abnormal phosphorylation is tightly connected with alterations of tau biology associated with the formation of neurotoxic tau species and aggregates. Thus, the second aim of the project was to prepare tau protein phosphorylated at residues specific for AD in high purity, which could further serve as a model protein in sensitive immunoassays applied with natural tau-reactive antibodies studies. Kinase-loaded magnetic beads prepared and characterized in our lab were applied for sequential *in vitro* phosphorylation of tau.

The thesis gives an overview about the biology of tau protein, enzymes involved in its (hyper)phosphorylation or truncation, and naturally occurring antibodies directed to tau as well as contains an experimental part composed from four key publications summarized our basic research regarding tau properties, phosphorylation, and its naturally occurring antibodies.