Tracing the fibrillation mechanism by nanospectroscopic profiling of structure-dependent tau protein aggregation

Alzheimer's disease (AD) is the most common form of dementia (50–60% of total dementia cases). In 2020, c.a. 50 million people worldwide were suffering from dementia and the global economic cost related to dementia in 2015 was $818 billion that represented 1.09% of global GDP that year. Because of a worldwide aging population and prolonged life expectancy, the problem is expected to grow worse. The number of dementia cases has been estimated to almost double every 20 years.

The presence of intraneuronal tau neurofibrillary tangles (NFTs) and extra-neuronal amyloid-β (Aβ) plaques in the brain is the major histopathological hallmark of neurodegeneration implicated in Alzheimer's disease. Despite the years of research effort in numerous scientific disciplines, the mechanisms leading to the presence of aggregates in the brain of AD patients remain elusive. Still, there is no cure for neurodegenerative disorders.

Therefore, the main aim of this project is to evaluate the influence of the structural variability of tau protein (tau isoforms, tau protein mutants, and phosphorylated tau) on the mechanism and dynamics of tau protein aggregation. The understanding of the tau protein aggregation mechanism is extremely important, because it will help in designing therapeutic strategies against AD.

The research of the aggregation mechanism was limited for a long time due to the lack of research techniques able to deliver the information regarding the structure in respect to single molecules. In recent years the major progress of nanospectroscopic techniques has been beneficial due to the possibility of studying chemical structure at the level of single aggregates. Nanospectroscopy combines the chemical sensitivity of conventional spectroscopy (Raman or infrared spectroscopy) with the resolution of Scanning Probe Microscopy (SPM) techniques. In this project, I propose to incorporate tip-enhanced Raman spectroscopy (TERS) as the most sensitive technique allowing to study the chemical structure of individual tau aggregates and to detect local chemical rearrangements, and Fourier transform infrared nanospectroscopy (nanoFTIR) as a complementary method. Structural rearrangements at the level of single molecules during the aggregation process will provide the insight into the mechanistic aspects of this process. Moreover, the influence of factors like tau protein mutations, its phosphorylation and the presence of aggregation inhibitor on the tau protein aggregation scheme will also be studied. Atomic force microscopy (AFM) and nanospectroscopy will enable to study the dynamics of the aggregation process, and to determine the influence of different tau aggregates (monomers, oligomers, annular protofibrils or fibrillar filaments) on the integrity of biological membranes. To support the experimental findings, I propose to incorporate the molecular dynamics (MD) simulations to study aggregation susceptibility of different tau protein variants at the initial stage of tau protein aggregation (the formation of tau oligomers). These simulations will allow determining the interactions between tau protein molecules that lead to the aggregation.

The results of this project will allow to gain essential knowledge about the abnormal aggregation of tau protein and the differences in mechanism and dynamics of tau aggregation mechanism resulting from structural variability of tau protein (mutations, phosphorylation). Thus, it will be possible to determine which modifications of tau protein are the most dangerous ones. Moreover, the knowledge of the exact aggregation pathway will be extremely beneficial regarding the design of effective therapeutic strategies to prevent the destructive neurodegenerative symptoms.