PhD thesis abstract by Kirstine Louise Bendtsen

Parkinson’s disease (PD) is the second most common neurodegenerative disorder, affecting millions of people around the world, and today there is no cure, only ways to relief the symptoms. One of the major hallmarks of PD is the presence of pathological Lewy Bodies, protein inclusions found in affected neurons in the brain, which mostly contain aggregated and fibrillated alpha-synuclein (aSN). aSN is a 140-residues, intrinsically disordered protein (IDP), mostly located at the pre-synaptic terminals in the neurons. The physiological function of aSN is not well-understood, but it is believed to be involved in trafficking and vesicle fusion. The fibrillation process of aSN and its link to neurodegeneration has been widely studied. However, much remains to be understood about PD, including the possible mechanisms for the spreading of PD pathology in the body and the brain.

Recently, it was found that the membrane protein Lymphocyte Activation Gene 3 (LAG3) plays a role in the cellular uptake of fibrillar aSN species. LAG3 is mostly expressed on cells related to the immune system, and is highly involved in the regulation of activation of T cells. Pathologically, LAG3 has been found to be involved in several types of cancer, viral infections and now also PD. Fibrillar aSN species which binds to LAG3 are endocytosed into neurons, in which they can catalyze the fibrillation of endogenous aSN.

In this PhD thesis the aim was to characterize the isolated interaction of aSN and LAG3 in vitro, as the previous studies were conducted in cellular assays, by employing several biophysical and structural techniques. The ambition was to be able to discriminate between different species of aSN and their binding to LAG3.

Here, it was found that monomeric aSN species do not interact with the extracellular domains of LAG3, whereas fibrillar species of aSN do. Preliminary results further suggest that N-acetylation of aSN increases the interaction with LAG3. These results support the previous binding studies conducted with cellular assays. A characterization of the isolated extracellular domain of LAG3 further reveal that the protein adopts the immunoglobulin superfamily fold in its four sub-domains with the presence of an additional unstructured loop, and that the outermost sub-domain tends to fold towards the other domains. Whether this loop and the movement of the sub-domain are related to the interaction with fibrillar aSN remains to be further investigated.