”Assessing the proteome dynamics in healthy brain and neurodegenerative states using omics and imaging mass spectrometry”

HiLIFE, Meilahti Clinical Proteomics Core Facility
University of Helsinki, Finland

Institute of Bioorganic Chemistry
Polish Academy of Sciences
Department of Biomedical Proteomics, Poznan-Poland

Protein-protein interaction networks (PPI networks) constitute an important resource to elucidate protein function, structure and disease mechanisms. Phenotype or disease-oriented PPI networks provide tools to reveal candidate disease genes/modifiers, and underpin pathogenic mechanisms that could be targeted therapeutically.

In this talk, I will show some examples of these, with a focus on Huntington’s disease and protein quality control process in the brain. Disturbances in protein control mechanisms occur in many human disorders characterized by the accumulation of misfolded or mutant proteins. The two major protein-degrading systems in the cell are the ubiquitin proteasome system and the autophagy that are tightly regulated in the cell. Ubiquitin specific protease-14 (USP14) is one of three proteasome-associated deubiquitinating enzymes that plays a crucial role in protein degradation as shown in different models. We recently showed that USP14 affects ER signaling and the autophagy system in neuronal cells. Proteomic analysis revealed an interaction of USP14 with molecular chaperone, heat shock cognate 71 kDa protein (HSC70). USP14 and HSC70 were downregulated in mutant huntingtin-expressing striatal neurons, and USP14 levels were sensitive to inhibition of HSC70 by using the drug, VER-155008. A deeper understanding of how the protein quality control systems are regulated and coordinated by USP14 is crucial for design of molecular targets or drugs that may beneficially interfere with the pathophysiology of protein aggregation disorders and neurodegeneration.

The second part of my talk will be linked to Mass Spectrometry Imaging (MSI), which allows for multiplexed molecular measurements from biological specimens directly on tissue slices. MSI is capable of detecting analytes in the low pH concentration, shares a feature of spatial resolution with immunohistochemistry and capacity for tissue micro-extractions and multiplexing with liquid chromatography- mass spectrometry for downstream omics analysis. MSI is particularly suitable for imaging small molecules, such as peptides or drugs to which specific antibodies are difficult to generate. Some relevant examples of small molecules imaging in combination with downstream omics analyses in the brain will be presented.