PD-PAM

Early indicators of nervous system dysfunction in gut-first and brain-first animal models of Parkinson's Disease

Parkinson's disease (PD) is characterized by pathological misfolding of the protein alpha-synuclein (asyn), which causes progressive neurodegeneration in the brain and subsequent motor symptoms. The spread of pathogenic asyn bidirectionally and trans-synaptically along the body-brain axis is believed to be a crucial pathogenic factor in PD. Next to a damaged brain, it is well-known that PD patients exhibit extensive nerve damage to peripheral organs, such as in the heart and the gut, causing debilitating non-motor symptoms up to 20 years before the motor symptoms occur. This early 'pre-motor´ disease phase is highly heterogeneous across patients with variable involvement of different neuronal systems. It is conceivable that the large variability in early disease phenotype could be attributed to the variability in disease initiation, i.e. body or brain. In our recently published imaging study of human patients, we hypothesized that PD can be divided in two subtypes: (1) a body-first type, where damage to the cardiac and enteric nervous system precedes damage to the brain, and (2) a brain-first type where neuronal loss in the brain precedes nerve damage to other organs. To date, no cure is available for PD and therapy is limited to symptomatic treatment of motor symptoms. Thus, it is crucial to establish animal models with a clear pre-motor phase (i.e. therapeutic window) that resemble human PD subtypes, which will allow testing of personalized treatment strategies per subtype. Here, we will emulate the two types of PD as observed in humans by injecting pathogenic asyn in the gut (= body-first) vs. in the amygdala (=brain-first) of transgenic or old wild-type mice. We will map the spatio-temporal spread of pathogenic asyn and progressive neuronal dysfunction from the initiation, via early disease stages to late disease stages, using a broad battery of in vivo and ex vivo techniques such as longitudinal in vivo functional imaging, autoradiography, symptom scoring, and thorough immunohistochemical analysis. We expect to show that these two animal models closely parallel observations in human patients with early involvement of the peripheral autonomic nervous system in body-first PD (i.e. as in isolated REM sleep behavior disorder patients) as opposed to brain-first PD, where peripheral organs are relatively spared at early disease stages. Besides asyn propagation and neuronal dysfunction, we aim to assess other cardinal features of PD pathogenesis in our models, such as reactive astrogliosis and lysosomal dysfunction. These pathogenic processes are reported to precede the formation of asyn pathology and neurodegeneration and could be suitable early disease indicators. Finally, we hypothesize that the phenotypic and histopathological variability between body-first and brain-first PD could result, apart from the different disease initiation site, from variation in the intrinsic structure of the asyn aggregates. The strain hypothesis in synucleinopathies postulates that each disease entity is characterized by a distinct conformation of pathogenic asyn, therefore, each PD subtype could be caused by a unique asyn structure or strain. In order to investigate this hypothesis, we will use a panel of thiophene-based ligands that produce a 'spectral fingerprint' of protein aggregates upon interaction. This interaction will be studied using cell models as well as tissue sections or biofluids. The identification of subtype-specific asyn aggregates in easily accessible peripheral fluids or tissues from our body-first or brain-first animals may enable stratification in different PD subtypes. Positive results will have important implications in translational research to stratify PD subtypes at early disease stages allowing personalized and disease-modifying treatment. Especially in the body-first PD subtype, where damage to the brain is limited at the early stage, early diagnosis would create a large therapeutic window. Thus, particularly for body-first PD, the identification of early disease biomarkers such as autonomic dysfunction, inflammation, lysosomal dysfunction and/or unique intrinsic asyn structure are beneficial as it would allow early therapeutic intervention. Thus, this project may contribute significantly to the development of early disease biomarkers and disease-modifying treatment targets.

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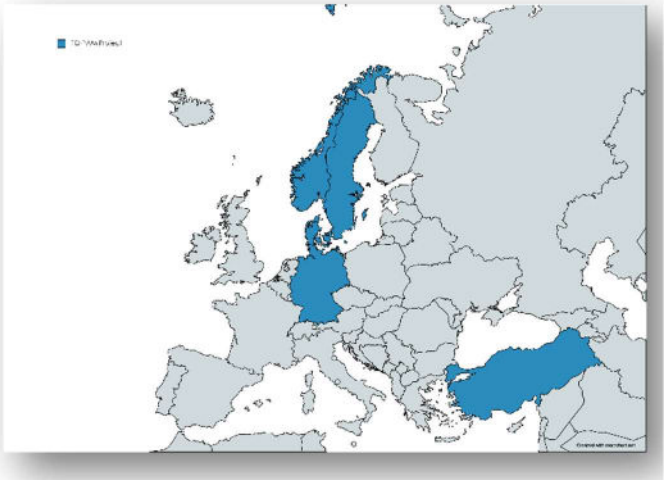

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