Pathogenesis of Parkinson’s disease: Focus on lysosomes

Parkinson’s Disease (PD) is one of the most common neurodegenerative diseases. Patients display the classical motor symptoms of the disease, such as bradykinesia, tremor and rigidity, but also non-motor features, such as autonomic and sleep disturbances, cognitive decline and neuropsychiatric symptoms. The disease can only be partially managed, regarding motor symptoms, while there is no neuroprotective therapy available to delay its progressive course. The etiology of PD is mostly unknown. In recent years however, it has become clear that a considerable proportion of patients suffer from genetic/hereditary forms of the disease, while large Genome Wide Association Studies (GWAS) have revealed a significant genetic factor even in sporadic PD. The genes that are involved in hereditary PD are variable, but the most important one is the SNCA gene, encoding for the protein alpha-synuclein. Point mutations or multiplications of the gene locus lead to autosomal dominant PD. Furthermore, the alpha-synuclein protein, normally present in large amounts in presynaptic neuronal terminals, deposits abnormally in the brains of PD patients, creating the well-known Lewy Bodies. In Greece, the most common genetic/hereditary forms of PD are the p.A53T mutation in the SNCA gene, as well as mutations in the GBA1 gene, encoding for the lysosomal protein Glucocerebrosidase. A number of other genetic forms of the disease, as well as GWAS hits, appear to relate to lysosomal function, rendering it a central element in disease pathogenesis. Our lab has been working on the inter-relationship of lysosomal function with PD, focusing mostly on the Chaperone Mediated Autophagy (CMA) pathway and its role as a potential therapeutic target in PD and related synucleinopathies. Our work has shown reciprocal relationships between CMA function and alpha-synuclein accumulation, both in neuronal cell culture and in vivo settings. Furthermore, this work has led to the establishment of a novel PD-like rodent model, which may be used to probe relevant pathogenic mechanisms and implementing experimental therapies. More recent evidence suggests a more generalized systemic lysosomal dysfunction in PD. This works relates to the general theme that the inter-relationship of lysosomal dysfunction, and especially of the mechanisms of macroautophagy and Chaperone-Mediated Autophagy (CMA), with the abnormal conformations of alpha-synuclein, constitute a vicious cycle that leads to neurodegeneration in the context of PD.