

Chasing genes and proteins involved in disease progression in Parkinson's disease

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Research question and background

Intraneuronal abnormal alpha-synuclein aggregates are observed in peripheral and central nervous system in Parkinson's disease patients. During early disease stages, the alpha-synuclein pathology is confined to the brainstem and olfactory bulb. In more advanced stages of the disease, the pathology spreads to limbic and neocortical brain regions and contributes to both motor and non-motor symptoms, including cognitive decline. Severe nigrostriatal degeneration is already present at time of diagnoses and is accompanied by inflammation in PD. In our study, we aimed to identify the molecular mechanisms underlying the aggregation of α -synuclein and neurodegeneration in the early pre-motor stage and during disease progression in PD using transcriptome and proteome analysis.

Methods and tissues used

We studied the transcriptome of post-mortem olfactory bulb, medulla oblongata, locus coeruleus and substantia nigra of 27 PDs, 17 elderly with incidental alpha-synuclein pathology (iLBDs) and 21 controls using whole genome microarray technology (GeneChip® Human Genome U 133 Plus 2.0 arrays, Affymetrix). In addition, we studied the proteome of the locus coeruleus in PD. Subsequently, genes and proteins with different expression levels among the groups (p -value <0.05) were analyzed using IPA software and database DAVID (Database for Annotation, Visualization and Integrated Discovery) to discover altered functional pathways possibly linked to the disease course and validated using qPCR and immunohistochemistry.

Results and conclusion

Our results show that nigral neuronal loss is already observed in donors with iLBD, which may represent subjects at risk for PD. Autophagy, endocytosis and immune response are altered in all brainstem regions in iLBD, which suggests that these may contribute to the pathological cascade. Our results provide evidence that mitochondrial dysfunction, inflammation and protein ubiquitination pathway might be a secondary or later event in the progression of PD. These mechanisms might hold the key to altering disease progression in PD.