

Parkinson's disease as a systemic pathology

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Parkinson's disease is a progressive neurodegenerative disease characterized by the presence of proteinaceous aggregates containing α -synuclein termed Lewy bodies and neurites, and cell death of the specific vulnerable dopaminergic neurons (DAn) in the midbrain substantia nigra which are associated with the cardinal motor symptoms symptoms of tremor, rigidity and bradykinesia in PD. Although the DAn nigral neurons are the ultimate targeted cells related with these clinical motor symptoms there are also Lewy bodies in other extranigral neurons that differ in their susceptibilities to develop disease-related alterations. This DAn selective vulnerability has been suggested to be related with the oxidative stress caused by metabolism of dopamine, the presence of neuromelanin deposits as a consequence of dopamine metabolism, and the large dendrite arborization requirements of these neurons in humans. In addition, the presence of PD-associated biological changes has been described not only in brain but in peripheral autonomic nerves [1]. Moreover, recent studies have been described presence of whole expression changes in non nervous tissues like blood from PD patients [2]. Recently, we found large global gene expression changes in a cell model of cultured fibroblasts carrying mutations in the Parkin (*PRKN*) gene [3] supporting the view of PD as a systemic disease that affect peripheral non-neural tissues. A possible explanation of these findings in cultured skin cells from PD patients is that it would exist an intrinsic alteration in each individual cell of skin, and potentially in any cell of the body. These transcriptomic alterations could be originated by the specific Parkin mutations and/or the environmental history of the subjects conserved in the fibroblast cell model. Yet these changes would not cause any apparent skin or blood phenotype in PD patients although the presence of latent subclinical alterations would be possible.

The presence of transcriptomic alterations in cultured fibroblast has been described in other neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis [4]. Thus it is possible that the presence of systemic alterations in non-neural tissues could be a common hallmark of a variety of neurodegenerative diseases as it has been suggested previously [5]. In addition, and taking into account the cell inaccessibility of DAn from living patients, primary

fibroblast cultures obtained by skin biopsy from PD patients have been proposed as a cellular model to investigate molecular alterations in PD because their advantages of easy availability and robustness as cell system genuine to PD patients [5]. In our study the differentially expressed genes identified in fibroblast from PD patients with mutations in Parkin gene were related with extracellular matrix organization, cell adhesion and axon guidance pathways. Interestingly, the molecular processes involved in filopodia formation are common in fibroblast and neurons ultimately leading in the later to the formation of axonal processes. In addition, we found deregulation of the same pathways in fibroblasts from both, sporadic PD and PD patients carrying mutations in *LRRK2* gene (own unpublished findings). We also found deregulated these pathways in a previous study where we analyzed the transcriptome of induced pluripotent stem cell (iPSC)-derived dopaminergic neurons (DAn) from sporadic and *LRRK2* PD patients generated by cell reprogramming of somatic skin cells [6]. Again, independent studies also found enrichment of deregulated genes related with these cytoskeleton-associated pathways in postmortem dopaminergic brain tissues from PD patients [7].

In summary, the large overlap of altered biological pathways detected in fibroblasts, iPSC-derived DAn and postmortem brain tissues from PD patients support that fibroblasts could be a good surrogate cell model to investigate the biological basal processes occurring in brain from PD patients. In addition, our findings support the view of PD as a systemic disease in which molecular alterations occur not only in the central and peripheral nervous system but also in peripheral non-neural tissues such as the skin.

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