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# Parkinson's Disease: New Insights

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Neurodegenerative disorders are characterized by the atrophy of central or peripheral structures, leading to progressive nervous system dysfunction. Among them, Parkinson's Disease (PD), originally described by the English doctor James Parkinson in 1817 [1], is featured with disabling symptoms such as tremor and rigidity accompanied by postural instability. The hallmark of the disease is represented by the presence of Lewy bodies in neurons, i.e. large inclusions containing α-synuclein, leading to impaired formation/activity of dopamine-secreting cells.

The impact of genetic defects on PD, consisting in mutations in several crucial genes such as α-synuclein, parkin (PKN), leucine-rich repeat kinase 2 (LRRK2), PTEN-induced putative kinase 1 (PINK-1), accounts for only about 10% of patients [2,3]. The vast majority of PD cases are sporadic, with unknown etiology and possible causes spanning from the exposure to environmental toxins (e.g. herbicides, pesticides) [4] to inflammation [5], immune deficiency [6] and head trauma [7].

Looking for the molecular determinants of PD onset, special attention has been paid to the relevance of oxidative stress in driving neurological abnormalities [8,9]. In fact, as recently reviewed [10-13], not only the excessive production of Reactive Oxidative Species (ROS) is considered as a causative event leading to the neuronal death, but it reflects the status of mitochondria, which are the main intracellular district responsible for ROS generation [14,15].

The evidence of a correlation between PD and mitochondrial dysfunction arises from a number of considerations, including the following: i) mutations in the neuroprotective genes PINK-1 [16-18] and LRRK2 [19-21] affect mitochondrial homeostasis as well as the biochemical reactions ensuring basic functions such as energy supply, calcium buffering, respiratory activity etc., the impairment of which can drive neurodegeneration; ii) the activity of kinases involved in regulating mitochondrial biology under the influence of ROS (Akt, JNK, ERK, c-JUN, PINK-1) is generally altered in PD patients or PD experimental models, possibly promoting mitochondrial dysfunction [22]; iii) given that the loss-of-function of mitochondria is often associated to deletions of mtDNA, the exogenous introduction of mtDNA restores mitochondria bioenergetics [23].

A promising approach to the study of PD has been so far represented by the use of animal models, including mice, for which expression profiles and data from proteomics and metabolomics are available [24], zebrafish, which shows orthologs of many PD-associated genes and can respond to toxins with a PD phenotype [25,26] and Drosophila that reproduces PD in a very accurate manner [26].

In summary, significant progress has been made in deciphering PD pathogenesis, although this is true more for the familial form of the disease than for the sporadic cases. The evidence that ROS and mitochondria are the major players of neurodegeneration could open new perspectives of research and therapy. The availability of PD animal models renders the dissection of the different pathways leading to PD occurrence more accessible. Finally, it has to be mentioned that new molecular tools have been applied to this research field, leading to the finding that miRNAs play an important role in the pathophysiology of PD by regulating crucial factors at the transcriptional/post-transcriptional level [27,28], thus opening a new route to investigate the mechanism of the disease through the miRNA-based strategy.

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