EDITORIAL

Critical Analyses of Mechanism-Based Therapies Against Parkinson's Disease: Concepts and Perspectives

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Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects more than 6 million people worldwide. It is considered a multifactorial disease in which aging, environmental and genetic factors contribute to the clinical manifestation onset. Subsequent to the discovery of monogenic, hereditable forms of the disease, representing 5-10% of all cases, in the last years massive efforts have been made to delineate the molecular pathways that lead to this pathology. The pathways described until now include impairment of the intracellular protein-degradation and kinase activities, protein aggregation, mitochondria dysfunction, oxidative damages and neuroinflammation. While, the multifactorial nature of the disease hampers the discovery of a single treatment able to prevent neurodegeneration or to stop disease progression, the finding of different cellular processes involved in PD pathogenesis allowed the definition of different therapeutic strategies that, could hinder the advancement of the disease.

The aim of this thematic issue is to critically analyze the existing literature on potential therapeutic approaches, evaluating the results obtained in *in vivo* studies and, when present, in clinical trials.

Mutations in the gene coding for the protein leucine-rich repeat kinase type 2 (LRRK2) are linked to autosomal-dominant forms of PD and represent one of the most common familial forms of PD. LRRK2 is a complex multidomain protein which contains a catalytic core showing both GTP-ase and kinase activity.

J.-M. Taymans and E. Greggio review the experimental evidence implicating LRRK2 kinase activity in the pathogenesis of PD and the effects of LRRK2 pharmacological inhibition both *in vitro* and *in vivo*. Several inhibitors of the LRRK2 kinase activity are described in the review, some of them possessing interesting therapeutic potentials such as low nanomolar range potency, excellent selectivity profiles and good brain penetrance. Undesirable side effects appearing in preclinical studies are also described in the review and alternative strategies for the treatment of PD are critically presented.

One of the main pathological hallmarks of PD is the presence in the brain of intracellular inclusions, known as Lewy bodies, that have been shown to contain large amounts of fibrillar α-synuclein, another protein responsible for dominantly inherited forms of the disease. Since the discovery of the involvement of α -synuclein in familial forms of PD, a significant body of research has appeared concerning its physiopathological role. Coherently, α -synuclein has become an extremely attractive target for the development of therapeutic strategies.

K. Sivanesam and N. Andersen review the approaches proposed to inhibit the amyloidogenesis of α-synuclein and to reverse the cytotoxicity of the protein. The strategies described by the authors are either directed to maintain α -synuclein in its native random conformation or aimed at redirecting the pathway to less toxic aggregates. All of these approaches have allowed the identification of "inhibitors" that have shown promising results both *in vitro* and in cellular assays.

The presence of Lewy bodies in sporadic PD patients is compatible with the impairment of the degradative systems of cells, which include ubiquitin-proteasome system (UPS) and autophagy.

P. Rivero-Rios *et al*. thoroughly review the experimental evidence linking autophagic dysfunction to PD. Specifically, the authors describe how both the autosomal dominant and autosomal recessive PD-

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associated genes are linked to in autophagic/lysosomal pathways. Then, the authors focus on current approaches targeting this pathway, emphasizing their beneficial therapeutic effects, but also describing the drawbacks associated to pharmacological manipulation of autophagy.

A selective form of autophagy is mitophagy, a process which controls the elimination of dysfunctional mitochondria. Two proteins involved in recessive inherited forms of PD, PINK1 and Parkin, are now recognized to co-participate in the mitochondrial quality control pathway.

A. Nardin *et al*. review the molecular mechanisms underlying this process, analyzing in depth the ubiquitination process mediated by Parkin, which tags dysfunctional mitochondria for clearance. The review also describes the role of de-ubiquitinating enzymes (DUBs) that oppose Parkin in the ubiquitination of its targets. As DUBs can participate to and modulate the mitophagic process, the authors analyze the potential therapeutic use of DUBs activator and inhibitors as a strategy to eliminate dysfunctional mitochondria.

Strictly associated to mitochondrial dysfunction is oxidative stress. Robust evidence now exists indicating that oxidative stress plays a central role in the progression of the disorder. For this reason, antioxidant molecules have been considered attractive therapeutic drugs to cure PD.

R. Filograna *et al*. review the results obtained with antioxidant treatment in PD patients or animal models of the disease. From this analysis, it appears that the effects attained in clinical trials with antioxidants are often modest. Moreover, many antioxidants effective in animal models of PD do not show significant effects in humans. The authors analyze several issues that could rationalize these substantially negative results, reaching the conclusion that antioxidant might still need reconsideration as promising therapeutic approach against the progression of PD.

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