# How close are we to reveal the etiology of Parkinson's disease?

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Parkinson's disease (PD) is a chronic, disabling neurodegenerative proteinopathy characterized by degeneration of the dopaminergic nigrostriatal system, involvement of many neuronal systems and organs causing motor impairment, non-motor, autonomic dysfunction and neuropsychological changes. Recent advances have delineated pathogenic mechanisms related to deposition of phosphorylated α-synuclein as Lewy bodies and neurites, the hallmarks of PD. The etiology of PD (and related synucleinopathies) is poorly understood, but the heterogeneous mechanisms leading to the majority of (sporadic) PD are linked. They are not the result of a single causative factor, but are rather multifactorial, resulting from interactions between genetic background and environmental factors. Future advances in understanding the etiological factors and molecular mechanisms of PD are essential for the development of disease-modifying treatments.

Determining the causes of Parkinson's disease (PD) has been a focus of modern neuroscience research. Considerable advances have been made concerning the etiology of this chronic, progressive, devastating neurodegenerative disorder, which is attributed to the understanding of the genetic and environmental factors that underlie the mechanisms by which misfolded α-synuclein (αSyn) is involved in the pathological processes linked to sporadic PD and the genetic defects responsible for rare the familial forms.

The etiology of PD is still poorly understood. Nevertheless, in the last decades, genetic, clinicopathological and animal model studies have advanced our understanding of the causative factors of this proteinopathy, which may be genetic and environmental factors that may directly or indirectly be related to the development of sporadic PD. It is a multiorgan disease characterized by progressive degeneration of the dopaminergic nigrostriatal system, many other neuronal systems and organs responsible for the core motor symptoms – rigidity, akinesia, rest tremor and postural instability – and a variety of non-motor and neuropsychological manifestations that affect the patient's quality of life. Much attention has been focused on abnormal αSyn, which represents the major component of many intracellular and intraneuritic deposits (Lewy bodies and dystrophic neurites, the morphological hallmark of PD [1,2]), while mutations in the αSyn locus and related genes can cause less-frequent inherited forms of PD [3,4]. Other etiologies underlying parkinsonisms, like tauopathies or other neurodegenerative disorders, are not considered here. Among exogenous lesions, traumatic brain injury in later life has been shown to increase the risk for PD [5] and the role of infections in the etiology of PD has been discussed recently [6].

The view of etiological factors in PD has changed from one of a purely sporadic basis to the view that both genetic and environmental factors contribute to the development of the disease, while increasingly genetic predisposition is probably a major contributor leading to molecular mechanisms of neurodegeneration. To date, more than 13 loci and nine genes have been identified in familial PD, as well as candidate genes in

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sporadic PD. Many of these findings show overlaps and may increase susceptibility to PD. Genetic predispositions, such as point mutations, duplications and triplications of the *SNCA* gene, can cause PD-like neurodegeneration, including many of the motor and non-motor features of PD, especially dementia [7]. Aging may also be critical for PD, and the different agents in the etiology of this illness are also involved in aging of nigral dopaminergic neurons [8]. Unfortunately, most concepts of cell death in PD ignore the contribution of aging, and in the vast majority of experimental studies, rather young animals are employed to model the disease process.

Environmental influences on the occurrence of PD range from industrial, plant-derived toxins, well water, bacterial and viral infections to exposure to organic solvents, carbon monoxide, cyanide, carbon disulfide, neurotoxic metal, pollutants and pesticides, although there are conflicting outcomes between individual human studies [9]. Many of these compounds including agrochemicals, namely, paraquat and rotenone, which are involved in oxidative damage, disruption of calcium homeostasis and other metabolic dysfunctions, recapitulate PD pathology in animal models [10]. The discovery of the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) provided a first viable model of the motor deficits of PD in primates. Although these and other experimental models suggested to shed light on the etiopathogenesis of PD and reproduced some key features of the disease, they did not succeed in reproducing both the pathology and progressive degenerative process in human PD [11]. However, circuitory loss and β-synchronization are shared by denervated animals and humans undergoing deep brain stimulation, and recent rotenone models combined with genetic PD models reproducing motor deficits, extranigral pathology and non-motor symptoms have shed light into the gen–environmental interactions [12].

Biochemical abnormalities identified in postmortem sporadic PD revealed a complex cascade of multiple noxious factors in the etiopathogenesis of sporadic PD, most of which have already been identified in mutations of various genes such as *SNCA*, *LRRK2*, Parkin, *PINK1*, *DJ-1* and others identified as causes of familial PD [4,13]. These dysfunctions include protein mishandling, in particular, misfolded αSyn and its oligomers, accumulation of which is triggered by presynaptic dysfunction [14], perturbation of protein degradation systems, such as the ubiquitin-proteasomal system, formation of free radicals, defects in translation and/or protein turnover, oxidative, nutritive, and proteolytic stress. Other factors are production of reactive oxidative species and advanced glycation products, mitochondrial dysfunctions, alterations in vesicular transport proteins, impaired bioenergetics, lipid peroxidation, nuclear RNA deficits, protein–iron and neuromelanin–iron interactions, and transcriptional αSyn dysregulation. Disorders of calcium homeostasis, excitotoxicity from increased glutamatergic input and neuroinflammation are other factors. Many interactions between these and other noxious factors are well documented [1,13,15]. Disturbed calcium homeostasis, abnormal cortical metabolism and other molecular changes due to the convergence of multiple deficits have been observed in early stages of PD [16]. Overwhelming evidence has emerged showing that deposition of misfolded αSyn and its oligomers in the cytoplasm of selected neuronal populations, as well as their interaction with other proteins, particularly in their oligomeric forms, which might synergistically promote their mutual aggregation and vice versa, play a critical role in amplifying neuronal damage [1,2,13,15]. However, the basic mechanisms leading to the intimate association and synergism of these proteins, suggesting a dualism or triad of amyloidogenic neurodegeneratiom await further clarification.

The major components inducing neuronal dysfunction and ultimately cell death are: presynaptic and/or axonal αSyn aggregation, synaptic and axon degeneration [17]; mitochondrial dysfunction; environmental oxidative stress; neuroinflammation; and other noxious factors and their complex interactions. Despite speculations as to how aberrant protein activity might lead to neurodegeneration, it is not certain that αSyn aggregation is the primary cause or an epiphenomenon in the etiopathogenic process of PD [1,13].

Recent work using animal models has added decisive evidence that misfolded proteins can induce a self-propelling process that leads to amplification and a prion-like cell-to-cell spreading of pathologic protein assemblies [18]. Distinct αSyn strains display differential seeding capacities, inducing strain-specific pathology and neurotoxic phenotypes [19]. Cell-to-cell transfer of αSyn can explain the formation of Lewy bodies and neurites, but may not account for the full spectrum of PD including the involvement of multiple non-dopaminergic neuronal populations, although correlations exist between the degrees of neuronal degeneration in some of them [1]. Mounting evidence implicates that αSyn interacts with other proteins and propagates neurodegeneration by a transneuronal spread, which may provide an acceptable explanation for the stereotypic distribution of Lewy pathology in PD [1,15,19,20]. However, the causes of formation of neurotoxic soluble and oligomeric species of αSyn and other noxious proteins, the exact mechanisms underlying the prion-like spread and the contribution of αSyn and other self-propagating proteins in the development and propagation of PD require further elucidation.

## Five-year view

Although major advances have been made in our understanding of the etiology (and pathogenesis) of PD (and related synucleinopathies) over the last 20 years, it remains as much an enigma as when James Parkinson first described its clinical features. Current knowledge of this devastating disease, its causes and development continues to evolve and will be challenged by future scientific discoveries. The clinical course, diagnosis, neuropathology, biochemistry and relevant biomarkers are well known, but its etiology is far from being fully understood. Recent evidence suggests that the heterogeneous causal mechanisms leading to sporadic PD are linked and that this progressive disorder is not the result of a single causative factor, but is rather multifactorial, integrating the effects of genetic and

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environmental factors and a complicated cascade of molecular events to work in concert with many cellular and subcellular systems to induce progressive degeneration not only in vulnerable neuronal populations but also in many other organs, resulting in a multiorgan disease.

Much has been discovered in terms of identifying the causes of sporadic PD and the genetic backgrounds of hereditary PD, their complex interactions and clinicopathological features, but many open questions still require further studies to be answered. Among the most challenging problems are: further elucidation of the causative factors of αSyn aggregation in this disorder, its genetics, and development of experimental models with better reproducibility of the human disorder; detection of causal factors leading to cell dysfunction and death in the nigrostriatal system and other neuronal (and extraneuronal) circuits; elucidation of the molecular factors for the mutual interaction of αSyn with other neurotoxic and self-propagating proteins; elucidation of the etiological background of triggers for the mislocation and accumulation of αSyn and the resulting neuroinflammation; better knowledge on the dysfunction or protein surveillance identified by the susceptibility genes; and deciphering the interplay of specific gene mutations and genetic susceptibility factors with environmental noxious compounds. Better insights into these and other problems related to the etiology of PD (and other synucleinopathies) are needed to enable the development of reliable biomarkers for early diagnosis, optimal animal models, disease-modifying treatments and this hitherto incurable devastating disorder.

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