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Review Article

Parkinson disease: from pathology to molecular disease mechanisms

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ABSTRACT

Parkinson disease (PD) is a complex neurodegenerative disorder with both motor and nonmotor symptoms owing to a spreading process of neuronal loss in the brain. At present, only symptomatic treatment exists and nothing can be done to halt the degenerative process, as its cause remains unclear. Risk factors such as aging, genetic susceptibility, and environmental factors all play a role in the onset of the pathogenic process but how these interlink to cause neuronal loss is not known. There have been major advances in the understanding of mechanisms that contribute to nigral dopaminergic cell death, including mitochondrial dysfunction, oxidative stress, altered protein handling, and inflammation. However, it is not known if the same processes are responsible for neuronal loss in nondopaminergic brain regions. Many of the known mechanisms of cell death are mirrored in toxin-based models of PD, but neuronal loss is rapid and not progressive and limited to dopaminergic cells, and drugs that protect against toxin-induced cell death have not translated into neuroprotective therapies in humans. Gene mutations identified in rare familial forms of PD encode proteins whose functions overlap widely with the known molecular pathways in sporadic disease and these have again expanded our knowledge of the neurodegenerative process but again have so far failed to yield effective models of sporadic disease when translated into animals. We seem to be missing some key parts of the jigsaw, the trigger event starting many years earlier in the disease process, and what we are looking at now is merely part of a downstream process that is the end stage of neuronal death.

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Abbreviations: SNc, substantia nigra pars compacta; PD, Parkinson disease; NMS, nonmotor symptoms; MAO-B, monoamine oxidase-B; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxy dopamine; GBA, glucocerebrosidase; STN, subthalamic nucleus; DBS, deep brain stimulation; LPS, lipopolysaccharide; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; PINK1, phosphatase and tensin homolog-inducible kinase 1; LRRK2, leucine-rich repeat kinase 2; GWAS, genome-wide association studies; mtDNA, mitochondrial DNA; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; UPS, ubiquitin–proteasome system; LAMP2A, lysosome-associated membrane protein type 2A; HLA, human leukocyte antigen; IL, interleukin; TNF-α, tumor necrosis factor-α

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Defining Parkinson disease

Parkinson disease (PD)[1] is the second most common neurodegenerative disorder after Alzheimer disease, with prevalence in industrialized countries of approximately 0.3% of the population. This rises with age from 1% in those over 60 years of age to 4% of the population over 80, illustrating the effect of aging. The mean age of onset is approximately 60 years; however, 10% of cases are classified as young onset, occurring between 20 and 50 years of age, which may represent a distinct disease group. PD is more prevalent in men than in women, with reports of ratios of 1.1:1 to almost 3:1 being quoted [135], which may be attributable to the protective effects of estrogen in women [121]. The socioeconomic cost of PD is high and in the United Kingdom is estimated to be approximately £3.3 billion. In the United States, the cost per patient per year is around $10,000, with a total economic burden of $23 billion. The greatest proportion of cost comes in the later stages of the illness for inpatient care and nursing homes and far less for medication [27].

This review aims to provide a current overview of the clinical, neuropathological, and biochemical features of PD, the genetic components of the disease, and risk factors for its development in relation to the pathogenic mechanisms thought to be involved in neuronal death. Currently drug treatment provides only symptomatic relief and we explore how knowledge of the pathogenic processes and the use of experimental models of PD interlink to assist in the search for neuroprotective/neurorestorative treatments.

Motor and nonmotor symptoms

Impaired motor function is classically used to make a clinical diagnosis of PD. The main features are bradykinesia, rigidity, tremor, and postural instability with an asymmetric onset spreading to become bilateral with time. Other motor features include gait and posture changes that manifest as festination (rapid shuffling steps with a forward-flexed posture when walking), speech and swallowing difficulties, and a masklike facial expression and micrographia [58]. A good response to dopaminergic medication is confirmatory of the diagnosis. Although this has been the classical textbook description of PD, more recently it has become recognized as a more complex illness encompassing both motor and nonmotor symptoms (NMS), such as depression, sleep disturbance, sensory abnormalities, autonomic dysfunction, and cognitive decline [74]. NMS affect all patients with PD, the frequency of which increases with disease severity, with late-stage patients exhibiting 6–10 NMS. NMS create the biggest demand on clinical resources, they are poorly diagnosed and treated and they are the major determinant of disease outcome, increasing disability, poor quality of life, and entry into long-term care [13]. Whereas the causes of motor dysfunction in PD are reasonably well understood (see later), the cause of NMS in PD remains poorly researched and they may largely relate to pathology outside of the basal ganglia.

From the perspective of this review, the most important feature of NMS is that some, for example, olfactory deficits, constipation, rapid-eye-movement sleep behavior disorder, and depression, may precede the onset of motor symptoms by many years (although they can occur at the same time as motor symptoms or follow the onset of motor abnormalities) [105]. NMS may in the future be used for the early diagnosis of PD, enabling neuroprotective strategies to be introduced at an early stage, and studies of large populations of apparently normal older individuals are ongoing at this time to enable such early detection to occur [6,143]. However, they provide another and perhaps vital clue to the search for the pathogenic processes that underlie PD, as they suggest that it is a disease of both the peripheral and the central nervous systems and that it is a multisystem disorder that spreads with time, affecting movement only at a relatively late stage in its course, and may thus be a target for early diagnosis and identification of at-risk populations. Current dopamine replacement strategies for treating PD are effective against the motor features of PD but are largely ineffective at addressing NMS. Hence a greater effort needs to be made not only in understanding the molecular mechanisms that cause NMS but also in how to treat them.

Spreading pathology

Neuronal loss in the substantia nigra pars compacta (SNc) and the subsequent loss of striatal dopamine content are accepted as being responsible for the classical motor features of PD. The neuropathological diagnosis of PD requires the detection of marked dopaminergic neuronal loss in the SNc and the presence of Lewy bodies, eosinophilic inclusions consisting of a dense core surrounded by a pale-staining halo of radiating filaments. The role of the Lewy body in pathogenesis remains unknown, but the discovery that misfolded α-synuclein is a major component of the radiating filaments and is also present in neuronal processes as Lewy neurites has altered views on their formation and role in neuronal loss and has led to a major shift in thinking about the onset and progression of the disease process from a pathological perspective and to the classification of PD as a synucleinopathy [21]. However, the neuropathological picture of PD has been known to be more widespread for many decades, with many nondopaminergic nuclei affected, including the locus coeruleus, reticular formation of the brain stem, raphe nucleus, dorsal motor nucleus of the vagus, basal nucleus of the Meynert, amygdala, and hippocampus [59]. Importantly, all of these nuclei degenerate with Lewy body pathology, suggesting a pathogenic process in common with that occurring in the SNc. It is the Lewy body pathology in these nondopaminergic areas that then results in some NMS. For example, hyposmia is associated with the presence of Lewy bodies and Lewy neurites in the olfactory bulb and brain centers such as the amygdala and perirhinal nucleus [78,162]. But it is the presence of Lewy bodies in peripheral tissues that takes the pathology associated with PD to another level. Orthostatic hypotension in PD is associated with

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