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Review Article

Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis

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ABSTRACT

In order to better understand the pathogenesis of Parkinson's Disease (PD) it is important to consider possible contributory factors inherent to the aging process, as age-related changes in a number of physiological systems (perhaps incurred within particular environments) appear to influence the onset and progression of neurodegenerative disorders. Accordingly, we posit that a principal mechanism underlying PD is inflammaging, i.e. the chronic inflammatory process characterized by an imbalance of pro- and anti-inflammatory mechanisms which has been recognized as operative in several age-related, and notably neurodegenerative diseases. Recent conceptualization suggests that inflammaging is part of the complex adaptive mechanisms ("re-modeling") that are ongoing through the lifespan, and which function to prevent or mitigate endogenous processes of tissue disruption and degenerative change(s). The absence of an adequate anti-inflammatory response can fuel inflammaging, which propagates on both local (i.e.- from cell to cell) and systemic levels (e.g.- via exosomes and other molecules present in the blood). In general, this scenario is compatible with the hypothesis that inflammaging represents a hormetic or hormetic-like effect, in which low levels of inflammatory stress may prompt induction of anti-inflammatory mediators and mechanisms, while sustained pro-inflammatory stress incurs higher and more durable levels of inflammatory substances, which, in turn prompt a local-to-systemic effect and more diverse inflammatory response(s). Given this perspective, new treatments of PD may be envisioned that strategically are aimed at exerting hormetic effects to sustain anti-inflammatory responses, inclusive perhaps, of modulating the inflammatory influence of the gut microbiota.

1. The continuum of physiological aging and Parkinson's Disease (PD)

Age is a major risk factor for PD, the second most frequent common neurodegenerative disease [1], affecting approximately 1% of the population over 60 years of age [2]. Despite this evidence, the relationship between the molecular/cellular processes involved in physiological/healthy aging, and those contributory to the pathogenesis of PD is still unclear. For example, it could be hypothesized that PD is, at least in part, a type of "segmental" aging, in which specific, localized, and accelerated aging mechanisms, which for reasons at present largely unknown, markedly affect dopaminergic (DA) neurons in the pars

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compacta region of the midbrain substantia nigra (SnPC). Indeed, even physiological aging is characterized by a progressive decline of motor abilities and patho-anatomic features of neuronal degeneration in the brain, which in many ways are similar to key characteristics of PD (but which do not evoke clinically-relevant signs of PD). In this light, data collected from 2500 aged persons who were annually assessed for PD revealed global Parkinsonism was 18.6%. However, post-mortem patho-anatomical studies of 744 of these subjects (who did not have PD; mean age at death: 88.5 yrs.) showed that: a) about 1/3 had mild or more severe nigral neuronal loss; b) about 17% had Lewy bodies; and c) 10% showed both nigral neuronal loss and Lewy bodies. These findings suggest that there is an apparent continuum between physiological aging and age-related neurodegenerative motor disorders. Idiopathic PD manifests a combination of motor and non-motor features that can precede the onset of clinically relevant motoric signs by decades. These prodromal motor and non-motor features are thought to result from the combined effects of aging, genetic risk factors, and particular lifestyle/nutritional/environmental determinants, inclusive of exposure to potentially toxic substances [3]. At present, environmental and genetic risk factors that are directly contributory to PD remain somewhat vague, and are of limited clinical utility in the majority of sporadic PD patients [4]).

However, we propose that lifelong exposure to (exogenous and endogenous) stressors can stimulate local and systemic adaptive responses, including activation of the immune system to incur "physiological inflammation" [5]. This inflammatory response, which can be considered as "inflammatory tone", is highly conserved in evolution, and appears to be critical for survival. Thus, it may be that a sustained systemic inflammatory state represents a particular aging phenotype, which results from exposure to chronic stressors, perdurable inflammatory responses, and/or some combination of both. This condition, conceptualized as an important example of adaptive remodeling, is now referred to as "inflammaging" [6,7]. Recently, inflammaging was recognized as one of the seven pillars underpinning the aging process [8], and influential to many (if not all) major age-related diseases including those that are neurodegenerative [7]. It has been proposed that inflammaging can be regarded as both an age-related increase in inflammation, and a concomitant adaptive activation of anti-inflammatory processes [9].

In this light, centenarians provide good example(s) of the complex regulation of pro- and anti-inflammatory pathways/products, as these individuals have largely avoided or postponed major age-related diseases, and in particular, neurodegenerative syndromes. Studies on centenarians have revealed increased plasma levels of inflammatory molecules such as interleukin IL-6, IL-18, IL- 15, C reactive protein (CRP), serum-amyloid A, fibrinogen, von Willebrand factor, resistin and leukotrienes [9–11]. However, such increased levels of pro-inflammatory mediators were also frequently accompanied by a concomitant elevation in anti- inflammatory molecules (*i.e.* adiponectin, Transforming Growth Factor (TGF)-b1, IL-1 receptor antagonist (IL-1RA), cortisol, and anti-inflammatory arachidonic acid-derived compounds, such as HETE and EET) [12–16]; for a detailed review on inflammaging and longevity, see: Monti et al. [17]. These findings suggest that those who age "well" demonstrate anti-inflammaging mechanisms (and biomarkers) that likely counteract the adverse immune response of inflammaging. Modulating this crucial balance of pro- and anti-inflammatory processes has become a major focus of new geroscientific approaches that are attempting to more successfully treat – or prevent – major age-related diseases [8].

2. Genetic risk factors, neuroinflammation, and oxidative stress in PD

PD-related pathological changes include progressive degeneration and loss of DA neurons in the SNpc, reduction in DA content in the corpus striatum, and formation of eosinophilic inclusions (i.e.- Lewy bodies) containing α-synuclein, primarily in the remaining DA neurons [18]. While such features are noteworthy, and perhaps pathognomic. At present a complete understanding of the pathogenesis of PD remains lacking.

Still, five genes that are suspected to be highly correlated to, if not "causal" for PD have been identified via observation of rare multi-generational pedigrees in which PD segregates in a Mendelian pattern. These include: (SNCA [α-synuclein], LRRK2 [leucine-rich repeat kinase 2], PARK2 [parkin], PINK1 [PTEN induced putative kinase 1], and PARK7 [DJ-1]) [19]. The involvement – and functional roles – of these genes suggest that a dysregulation of diverse cellular processes, including mitochondrial respiratory chain function, kinase signaling, and ubiquitin-mediated protein degradation, may be potentially pathogenic in PD [19].

It is important to stress that mutations in these five genes account for no more than 2% of PD in populations of European ancestry. Recent large-scale collaborative studies have now implicated common variants in two genes, SNCA and MAPT [microtubule-associated protein tau] as susceptibility factors in PD [20,21]. These latter data are particularly intriguing because common variants in MAPT also modify risk for Alzheimer's dementia (AD), progressive supranuclear palsy, and corticobasal degeneration, suggesting the possibility of a shared pathophysiological mechanism among neurodegenerative diseases. There also is emerging evidence that mutations in the glucocerebrosidase (GBA) gene may increase the risk for both PD and Lewy Body dementia [19]. Moreover, it has been shown that the presence of GBA variants can predict a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD [22].

The discovery of genetic risk factors for PD sheds light on valuable information that can be used to create new experimental models, identify promising targets for therapeutic interventions, and to select subgroups of patients and at risk subjects who may be appropriate for specific clinical trials. Preclinical and clinical studies reported a link between neurodegenerative diseases, activation of the immune system and neuroinflammation [23]. These common neuroinflammatory aspects, in both animal and human models of PD, are represented by reactive astrocytes and activated microglia, involvement of the innate and adaptive immune system, over-expression of pro-inflammatory chemo- and cytokines, and increased concentrations of reactive oxygen and nitrogen species (ROS/RNS) [24].

It has been shown that the age-related increase of both peripheral inflammation and neuroinflammation contribute to the prodromal phase of PD [25]. We hypothesize that peripheral and/or central inflammatory stimuli, affecting the brain, could induce inflammatory changes that shift microglial function toward neurodegeneration, are inductive for, and operative in PD, and thereby lead to PD signs, symptoms and progression. Data reveal that peripheral immune system activation exacerbates inflammatory responses in the brain, and may incur or increase neurodegenerative processes. However, it is unclear if the mechanisms involved in peripheral inflammation are directly or indirectly influential to – and/or involved in – those in the CNS [26].

Activation of microglial cells is, on the one hand, beneficial for neuronal tissue, as it stimulates clearance of cell debris and prompts secretion of several neurotrophic factors. But on the other, microglial inflammatory mediators modulate immune cells, act on neurons, and have been shown to contribute to neurodegenerative effects [27]. Thus, while activation of inflammatory responses is fundamental for tissue functioning and homeostasis, it can also contribute to neuronal insult. Until quite recently, the brain was considered to be an immunologically privileged organ due to the presence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex class II (MHCII) proteins, and the apparent lack of cerebral lymphatic vessels.

Currently, however, this view has changed [24,28]. Louveau and colleagues have demonstrated the presence of lymphatic vessels in mouse brain [28], which could support the possibility of bi-directional peripheral-CNS entry and exit of immune cells; these findings have