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Emerging roles of microglial activation and non-motor symptoms in Parkinson's disease

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ABSTRACT

Recent data has indicated that the traditional view of Parkinson's disease (PD) as an isolated disorder of the nigrostriatal dopaminergic system alone is an oversimplification of its complex symptomatology. Aside from classical motor deficits, various non-motor symptoms including autonomic dysfunction, sensory and cognitive impairments as well as neuropsychiatric alterations and sleep disturbances are common in PD. Some of these non-motor symptoms can even antedate the motor problems. Many of them are associated with extranigral neuropathological changes, such as extensive α-synuclein pathology and also neuroinflammatory responses in specific brain regions, i.e. microglial activation, which has been implicated in several aspects of PD pathogenesis and progression. However, microglia do not represent a uniform population, but comprise a diverse group of cells with brain region-specific phenotypes that can exert beneficial or detrimental effects, depending on the local phenotype and context. Understanding how microglia can be neuroprotective in one brain region, while promoting neurotoxicity in another, will improve our understanding of the role of microglia in neurodegeneration in general, and of their role in PD pathology in particular. Since neuroinflammatory responses are in principle modifiable, such approaches could help to identify new targets or adjunctive therapies for the full spectrum of PD-related symptoms.

Contents

Abbreviations: PD, Parkinson's disease; L-Dopa, levo-dopa; SN, substantia nigra; REM, Rapid eye movement; RBD, rapid eye movement sleep disorder; LBs, Lewy bodies; α-syn, alpha-synuclein; TNFα, tumor necrosis factor-alpha; IL, interleukin; I-MIBG, I-meta-iodobenzylguanidine; PARK gene, Parkinson disease gene; LRRK2, Leucine-rich repeat kinase 2; PINK1, PTEN (Phosphatase and tensin homolog)-induced putative kinase 1; hWT, human wild-type; ROS, reactive oxygen species; NADPH, Nicotinamide adenine dinucleotide phosphate; Nurr1, nuclear receptor related-1; NF-κB, nuclear factor-κB; LPS, lipopolysacharide; AD, Alzheimer's disease; NSAIDs, non-steroidal anti-inflammatory drugs; iNOS, inducible nictric oxide synthase; NO, nitric oxide; MHC-II, major histocompatibility complex class 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinel; IFNγ, interferon-gamma; CD, cluster of differentiation; AAV, adeno-associated virus; TGFβ, tumor grow factor-beta; BDNF, brain derived neurotropich factor; GDNF, glia-derived neurotrophic factor.

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Nomenclature

alpha	α
beta	β
gamma	γ
kappa	κ

1. Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder that affects about 1-2% of the population over 65 years of age. PD was first described by James Parkinson in 1817 in his monograph '*An Essay on the Shaking Palsy*' (Alves et al., 2008; Parkinson, 2002). PD was, and still is, primarily considered a movement disorder characterized by increasingly disabling motor symptoms that include bradyskinesia, tremor, and rigidity (Dauer and Przedborski, 2003). Underlying these motor symptoms is a progressive and selective loss of dopaminergic neurons in the substantia nigra pars compacta, which causes striatal dopamine deficiency. In the early disease stages, dopamine replacement therapy by levodopa (L-dopa) and/or dopamine agonists can significantly ameliorate the motor symptoms. In more advanced stages, most patients develop motor response fluctuations and/or levodopa-induced dyskinesias (Björklund and Dunnett, 2007). Moreover, many patients eventually suffer from levodopa-resistant symptoms including progressive balance problems and freezing.

In the past few years, also the non-motor symptoms of PD have gained considerable attention. The clinical features include neuropsychiatric symptoms, autonomic dysfunction, sensory and cognitive impairments as well as pain and sleep disturbances (Gaenslen et al., 2011; Dickson et al., 2009; Reichmann et al., 2009; Grinberg et al., 2010; Tysnes et al., 2010; Shulman et al., 2001; Aarsland and Kurz, 2010; Halliday et al., 2011). Some of these non-motor symptoms, in particular hyposmia and REM sleep behaviour disorder (RBD), can even antedate the motor deficits (Postuma et al., 2009; Ponsen et al., 2004). Notably, the non-motor symptoms of PD are largely refractory to dopaminergic drugs (Lloyd et al., 1975; Poewe, 2009).

Recent developments indicate that the characterization of PD as a more or less isolated disorder of the nigrostriatal dopaminergic system is an oversimplification of the complex pathogenesis and does not explain the full clinical spectrum and symptomatology of PD (Braak and Braak, 2000; Chaudhuri et al., 2006; Halliday et al., 2011). Other neurotransmitter systems, including noradrenalin, acetylcholine and serotonin have been shown to be involved in various non-motor systems that are experienced by most of the PD patients (Braak and Braak, 2000; Jellinger, 2011; Dickson et al., 2009; Bohnen and Albin, 2011; Evans et al., 2011). Hence, both in terms of predictive value and disease development (Shulman et al., 2001; Global Parkinson's Disease Survey Steering Committee, 2002), a proper understanding of the pathological correlates of the full spectrum of PD symptoms is critical.

Another important recent development in the field is that the traditional view of PD, i.e. a movement disorder largely caused by nigrostriatal dopamine deficiency, is being replaced by concepts that consider PD primarily as a proteinopathy. Lewy bodies (LBs), the neuropathological hallmark of PD, contain aggregates that primarily consist of the presynaptic protein alpha-synuclein (α-syn). LBs are found throughout various brain areas, including the substantia nigra (SN) but also in several brain regions involved in the regulation of non-motor functions (Braak et al., 2003).

Moreover, prominent neuroinflammatory changes have been implicated in PD etiology. These are largely characterized by microglial activation throughout several regions of the PD brain. Within the local brain microenvironment, glial cells play critical roles in the homeostatic mechanisms that support neuronal survival. Microglial cells in particular have a specialized role in immune surveillance and mediate innate immune responses to invading pathogens. They can secrete a myriad of factors including cytokines, prostaglandins, reactive oxygen species and growth factors, and are involved in the phagocytosis and clearance of cellular debris. Although prior studies suggested that neuroinflammation has mainly detrimental consequences, more recent results demonstrate that distinct aspects of the inflammatory response can in fact also be beneficial for central nervous system (CNS) function and several studies have now convincingly implicated microglia in processes like neuroprotection, the mobilization of neural precursors for repair, remyelination and in axonal regeneration (Walter and Neumann, 2009; Welser et al., 2010; Zhu et al., 2008; Ekdahl et al., 2003; Antony et al., 2011; Czeh et al., 2011).

Aberrant regulation of microglial responses has also been implicated in other neurodegenerative disorders like Alzheimer's disease (AD) (Qian et al., 2010; Lull and Block, 2010; McGeer and McGeer, 2008; Orr et al., 2002; Block and Hong, 2005). Furthermore, activated microglial cells and increased levels of pro-inflammatory mediators, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and -6 (IL-6) and others have been found in the striatum and SN of PD brain, where they are tightly interrelated with PD pathology and dopaminergic cell death. Importantly, α-syn mediated neurotoxicity can be enhanced by