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Review article

Microglial phenotypes in Parkinson's disease and animal models of the disease

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ABSTRACT

Over the last decade the important concept has emerged that microglia, similar to other tissue macrophages, assume different phenotypes and serve several effector functions, generating the theory that activated microglia can be organized by their pro-inflammatory or anti-inflammatory and repairing functions. Importantly, microglia exist in a heterogenous population and their phenotypes are not permanently polarized into two categories; they exist along a continuum where they acquire different profiles based on their local environment. In Parkinson's disease (PD), neuroinflammation and microglia activation are considered neuropathological hallmarks, however their precise role in relation to disease progression is not clear, yet represent a critical challenge in the search of disease-modifying strategies. This review will critically address current knowledge on the activation states of microglia as well as microglial phenotypes found in PD and in animal models of PD, focusing on the expression of surface molecules as well as pro-inflammatory and anti-inflammatory cytokine production during the disease process. While human studies have reported an elevation of both pro- or anti-inflammatory markers in the serum and CSF of PD patients, animal models have provided insights on dynamic changes of microglia phenotypes in relation to disease progression especially prior to the development of motor deficits. We also review recent evidence of malfunction at multiple steps of NFκB signaling that may have a causal interrelationship with pathological microglia activation in animal models of PD. Finally, we discuss the immune-modifying strategies that have been explored regarding mechanisms of chronic microglial activation.

Contents

Abbreviations: BBB, blood-brain barrier; CSF, cerebral spinal fluid; COX1, cyclo-oxygenase 1; COX2, cyclo-oxygenase 2; CRP, C reactive protein; DA, dopamine; EGF, Epidermal growth factor; FACIT, functional assessment of chronic illness therapy; FcγRII, Fc gamma receptor II; HADS, hospital anxiety and depression scale; IFN-γ, interferon-gamma; IL-1, βinterleukin-1 beta; IL-6, interleukin-6; IL-12, interleukin-12; IP-10, interferon gamma-induced protein-10; LRRK2, leucine-rich repeat kinase 2; LPS, lipopolysaccharide; MHC-II, major histocompatibility complex-II; MCP-1, monocyte chemotactic protein-1; MIP-1β, macrophage inflammatory protein-1β; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NFκB, nuclear factor kappa beta; NT-proCNP, N-terminal Pro-C-type natriuretic peptide; PET, positron emission tomography; RNF11, Ring Finger Protein 11; SN, substantia nigra; TGF-β, transforming growth factor β; TNF, tumor necrosis factor; TLR, toll-like receptor; 6-OHDA, 6-hydroxydopamine.

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1. Introduction

The pathological hallmarks of Parkinson's disease (PD) are a loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SN) and the presence of proteinaceous inclusions termed Lewy bodies and neurites. In addition, numerous studies have highlighted a potential role for neuroinflammation in PD, the hallmark of which is microgliosis (Tansey and Goldberg, 2010). Microglia are the resident immune cells in the brain derived from progenitors originating in the yolk sac during embryogenesis (Alliot et al., 1999). They serve various functions that include eliminating and remodeling synapses during development, surveying the environment to maintain homeostasis, and responding to injury to limit tissue damage, initiate repair processes, and promote neuronal survival. On the other hand, in response to an insult or in various neurodegenerative disorders microglia can proliferate, display morphological changes, alter their gene expression and surface markers to those that are characteristic of chronic activation. Together this response is termed microgliosis, yet it is not clear if microglia play a beneficial or detrimental role in the neurodegenerative process. Similarly, it is not well understood if microglia solely contribute to PD as a pathogenic response that facilitates disease or as a disease-initiating component. Although microglia are the primary cell in the brain responsible for immune surveillance, under pathological conditions, peripheral macrophages and other immune cells can traffic across a disrupted blood brain barrier (BBB) and most likely contribute to the role of neuroinflammation in PD. A new and growing area of PD research is now focused on understanding whether microglia exert a protective function via production of neurotrophic factors, or contribute to neuronal death by producing inflammatory factors that are toxic to DA and other vulnerable neurons. In order to address the impact of microglia on neurodegeneration in PD, whether protective or deleterious, we must better understand the behavior of microglia during disease progression. We posit that the microglial phenotypes in the aging brain become further altered in PD giving rise to a prevalence of pro-inflammatory microglia, which likely contribute to progressive neuronal loss (Fig. 1). To support our view we will discuss the complex microglial phenotypes found in PD and in animal models of PD and the immune-modifying strategies that have been explored regarding mechanisms of chronic microglial activation.

1.1. Microglia activation states: complex and heterogeneous phenotypes

Over the last decade the important concept has emerged that microglia, similar to other tissue macrophages, assume different phenotypes and perform specific effector functions depending on the precise nature of the stimulus, its intensity and duration (Olah et al., 2011; Perry et al., 2007; Tansey and Goldberg, 2010). Activation of microglia through various pattern recognition receptors such as toll-like receptors (TLRs) leads to the synthesis of a range of different cytokines, inflammatory mediators, growth factors and cell surface molecules. These secondary effects of microglial activation have been used to classify them as either pro- or anti-inflammatory. However it is crucial to understand that activated microglia exist in a heterogenous population and that their phenotypes are not necessarily polarized into two categories, either pro- or anti-inflammatory, but instead exist along a continuum where they acquire different profiles based on their local environment. And as the brain ages, a progressive pro-inflammatory status also referred to as inflammaging manifests increasing the risk of age-related disorders and leading to microglial priming that may increase the propensity to develop neurodegenerative diseases such as PD (Perry and Holmes, 2014).

Microglia undergo morphological changes when they shift from a quiescent to an activated state. Morphologically, resting, quiescent microglia have long ramified processes with small cell bodies *in vivo*, while activated microglia take on an amoeboid shape with shorter processes and larger cell bodies. Functionally, one way that microglia remain in a quiescent state is via the interaction between the glycoprotein CD200 located on surrounding neurons and the receptor CD200R located on microglia (Hoek et al., 2000). There are multiple other ligand-receptor pairs that make up an important system for cross-talk between neurons and microglia including CD45-CD22 and fractalkine-CX3CR1. Recent evidence suggests that morphological changes should not be interpreted as a sign of activation but instead that the microglia are impaired and can no longer efficiently perform their intrinsic functions (Heppner et al., 2015). Microglia Aβ-binding scavenger receptors that are largely involved in Aβ plaque clearance were downregulated in aged Alzheimer's disease mice (Hickman et al., 2008), suggesting alterations in microglial receptors may be a process that coincides with a shift in morphology. Furthermore, in a mouse model of Alzheimer's disease, the phagocytic capacity of microglia was reduced and inversely correlated to the Aβ plaque

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