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Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism

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Abstract

Inflammation, a common denominator among the diverse list of neurodegenerative diseases, has recently been implicated as a critical mechanism responsible for the progressive nature of neurodegeneration. Microglia are the resident innate immune cells in the central nervous system and produce a barrage of factors (IL-1, TNFα, NO, PGE_2, superoxide) that are toxic to neurons. Evidence supports that the unregulated activation of microglia in response to environmental toxins, endogenous proteins, and neuronal death results in the production of toxic factors that propagate neuronal injury. In the following review, we discuss the common thread of microglial activation across numerous neurodegenerative diseases, define current perceptions of how microglia are damaging neurons, and explain how the microglial response to neuronal damage results in a self-propelling cycle of neuron death.

Contents

Abbreviations: DEP, diesel exhaust particles; PM, particulate matter; PD, Parkinson's disease; AD, Alzheimer's disease; ROS, reactive oxygen species; NO, nitric oxide; TNFα, tumor necrosis factor-alpha; TH, tyrosine hydroxylase; Aβ, beta-amyloid; LPS, lipopolysacharide; HIV, human immunodeficiency virus; MS, multiple sclerosis; AIDS, acquired immune deficiency syndrome; HAD, HIV associated dementia; PHOX; phagocytic oxidase; PGE_2, prostaglandin E2; IR, immuno-reactive; SN, substantia nigra; VTA, ventral tegmental area; FTD, frontotemporal dementias; 6-OHDA, 6-hydroxydopamine; DA, dopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP+, 1-methyl-4-phenylpyridinium ion; NSAID, non-steroidal anti-inflammatory drug; CNS, central nervous system; IR, immunoreactive; NADPH, nicotinamide adenine dinucleotide phosphate; MMP-3, matrix metalloproteinase-3; ECM, extracellular matrix; NFκB, nuclear factor-κB; iNOS, inducible nitric oxide synthase; IL-1β, interleukin-1 beta

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1. Introduction

Inflammation occurs in multiple neurodegenerative diseases, where each disease has unique pathology and symptoms. There is an extensive list of specific triggers of neuronal damage, where each environmental toxin or genetic mutation is specific for a selected disease. However, the gradual accumulation of neuronal death and the increase in disease severity across time is a unifying theme across the diverse classifications of neurodegenerative disease. Previously, inflammation was viewed as only a passive response to neuronal damage. However, increasing reports demonstrate that inflammation is capable of actively causing neuronal death and damage, which then fuels a self-propelling cycle of neuronal death. Thus, while the triggers of various neurodegenerative diseases are diverse, inflammation may be a basic mechanism driving the progressive nature of multiple neurodegenerative diseases. Several cell types have been listed as contributors to inflammation-mediated neurodegeneration, but microglia are implicated as critical components of the immunological insult to neurons. In the following review, we discuss the role of microglia in neuronal death and describe the evidence implicating microglia as a critical mechanism driving the self-propelling nature of neurodegenerative disease.

2. Glial cells are inflammatory mediators of neurodegenerative disease

Early reports described the brain as an immune privileged organ, due to its compartmentalization and separation from the peripheral blood system, as provided by the blood–brain-barrier. However, most neurodegenerative diseases are characterized by both local inflammation from resident cell types in the brain and by the infiltration of leucocytes from the periphery (Kurkowska-Jastrzebska et al., 1999; McGeer et al., 1989). While infiltrating peripheral immune cells can be significantly toxic to neurons (Freude et al., 2002; Wu and Proia, 2004), leukocyte infiltration is not always associated with neurotoxicity (Boztug et al., 2002; Trifilo and Lane, 2003), indicating a critical role for the local glial cells (astroglia and microglia) in the inflammatory response associated with neurodegeneration.

2.1. Astroglia

In the normal brain, astroglia play essential roles in providing glia-neuron contact, maintaining ionic homeostasis, buffering excess neurotransmitters, secreting neurotrophic factors, and serving as a critical component of the blood–brain barrier (Aloisi, 1999; Hansson and Ronnback, 1995; Vernadakis, 1988). Although the pro-inflammatory function of astroglia is not as prominent as that of microglia (Barde, 1989; Lindsay, 1994; Streit et al., 1999), astroglia become activated in response to immunologic challenges or brain injuries (Aloisi, 1999; Tacconi, 1998). Astroglia also produce a host of trophic factors (Friedman et al., 1990; Lindsay, 1994), which are crucial for the survival of neurons. However, activated astroglia become hypertrophic, exhibit increased production of glial fibrillary acidic protein, and form glial scars, which hinder axonal regeneration. While there is a clear relationship between astroglia and microglia in both resting and activated conditions (Kahn MA et al., 1995; Rezaie et al., 2002), efforts to understand the detailed mechanisms of this complex association are ongoing.

2.2. Microglia

Microglia were originally described by del Rio-Hortega (1932) as a unique cell type differing in morphology from other glia and neurons, comprising approximately 12% of the brain. While the precise origin of microglia in the brain is