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Brain Research

Review

The role of the immune system in neurodegenerative disorders: Adaptive or maladaptive?

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ARTICLE INFO

Article history:
Accepted 2 September 2014
Available online 8 September 2014

Keywords:
Central nervous system
Neuroimmunology
Neuroinflammation
Alzheimer's disease
Parkinson's disease
Amyotrophic lateral sclerosis

ABSTRACT

Neurodegenerative diseases share common features, including catastrophic neuronal loss that leads to cognitive or motor dysfunction. Neuronal injury occurs in an inflammatory milieu that is populated by resident and sometimes, infiltrating, immune cells – all of which participate in a complex interplay between secreted inflammatory modulators and activated immune cell surface receptors. The importance of these immunomodulators is highlighted by the number of immune factors that have been associated with increased risk of neurodegeneration in recent genome-wide association studies. One of the more difficult tasks for designing therapeutic strategies for immune modulation against neurodegenerative diseases is teasing apart beneficial from harmful signals. In this regard, learning more about the immune components of these diseases has yielded common themes. These unifying concepts should eventually enable immune-based therapeutics for

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ApoE, apolipoprotein E; AP-1, activator protein-1; β-APP, β-amyloid precursor protein; ATF, activating transcription factor; ATP, adenosine triphosphate; BBB, blood brain barrier; BCSFB, blood–cerebrospinal fluid barrier; BSCB, blood–spinal cord barrier; c/EBP, CCAAT/enhancer binding protein; CCL, chemokine ligand; CCR, C-C chemokine receptor; CNS, central nervous system; COX, Cyclooxygenase; CR, complement receptor; CREB, C-AMP response element-binding protein; CSF, cerebrospinal fluid; CTLs, cytotoxic T lymphocytes; CX3CR, CX3C chemokine receptor; CXCL, chemokine (C-X-C motif) ligand; DAMPs, danger associated molecular patterns; GSH, glutathione; HLA-DR, human leukocyte antigen-DR; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; iNOS, inducible nitric oxide synthase; IRAK, interleukin-1 receptor-associated kinase; IRF, interferon regulatory factor; LFA-1, lymphocyte function-associated antigen-1; LOAD, late-onset AD; LRRK, leucine-rich repeat kinase; MAPKs, mitogen-activated protein kinases; MHC, major histocompatibility complex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappaB; NFR, nuclear factor erythroid 2-related factor; NK, natural killer; NLRP3, NOD-like receptor family, pyrin domain containing 3; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NRF, nuclear factor erythroid 2 related factor; OS, oxidative stress; PAMPs, pathogen associated molecular patterns; PD, Parkinson's disease; PRRs, pattern recognition receptors; PS, presenilin; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta; SOCS, suppressor of cytokine signaling; SOD, superoxide dismutase; TIR, toll-interleukin receptor; TIRAP, toll-interleukin receptor domain-containing adapter protein; TGF-β, transforming growth factor-beta; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-alpha; TREM, triggering receptor expressed on myeloid cells; TRIF, TIR-domain-containing adapter-inducing interferon-β; TYROBP, TYRO protein tyrosine kinase-binding protein; UTP, uridine triphosphate

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http://dx.doi.org/10.1016/j.brainres.2014.09.008

treatment of Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis. Targeted immune modulation should be possible to temper maladaptive factors, enabling beneficial immune responses in the context of neurodegenerative diseases.

This article is part of a Special Issue entitled SI: Neuroimmunology in Health And Disease.

Contents

1. Introduction

1.1. *The immune system in neurodegenerative disorders*

Neurodegenerative disorders are associated with age-dependent deposition of aggregated and misfolded proteins, cognitive disturbance, locomotive dysfunction, and neuronal loss (Forman et al., 2004). Importantly, evolution of these diseases occurs against a dysregulated neuroinflammatory backdrop (Glass et al., 2010). It has become clear in genetically modified animal models and from longitudinal patient studies that neuroinflammation and immune activation in the CNS develop early in the course of disease, likely prior to large-scale neuronal loss. Activated microglia, the CNS-resident macrophage population, are present in nearly all neurodegenerative disorders (Long-Smith et al., 2009; Prokop et al., 2013; Sargsyan et al., 2005). In addition to microglia, activated astrocytes and peripheral monocytes or lymphocytes can be detected in the diseased CNS under certain conditions. Studies linking immune activation to poor prognosis in patients are raising a major question: are all neuroinflammatory pathways detrimental to CNS health?

A broad view would argue that inflammation in the CNS creates a neurotoxic environment, and must be sanctioned in order to prevent disease and to support recovery. In contrast to this 'inflammation is strictly damaging' view of neurodegeneration, several studies in animal models have revealed that inhibition of anti-inflammatory factors or expression of pro-inflammatory molecules can improve disease-relevant outcomes. This dichotomy supports the notion that broad-based manipulation of the immune system should likely be switched in favor of targeted immunomodulation of key effectors. This review will focus on current models of immune modulators, cytokines, chemokines, and receptors that are thought to drive immune responses within the CNS. It is becoming clear that all neurodegenerative diseases have a dominant inflammatory phenotype, and we will pay particular attention to advances in understanding immune-based mechanisms of Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). It is particularly striking that recent mechanistic studies into these debilitating diseases have provided common nodes of innate immune cell dysfunction, yielding important insight into immune modulation therapeutic strategies.