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Review article

Impact of aging immune system on neurodegeneration and potential immunotherapies

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ABSTRACT

The interaction between the nervous and immune systems during aging is an area of avid interest, but many aspects remain unclear. This is due, not only to the complexity of the aging process, but also to a mutual dependency and reciprocal causation of alterations and diseases between both the nervous and immune systems. Aging of the brain drives whole body systemic aging, including aging-related changes of the immune system. In turn, the immune system aging, particularly immunosenescence and T cell aging initiated by thymic involution that are sources of chronic inflammation in the elderly (termed inflammaging), potentially induces brain aging and memory loss in a reciprocal manner. Therefore, immunotherapeutics including modulation of inflammation, vaccination, cellular immune therapies and "protective autoimmunity" provide promising approaches to rejuvenate neuroinflammatory disorders and repair brain injury. In this review, we summarize recent discoveries linking the aging immune system with the development of neurodegeneration. Additionally, we discuss potential rejuvenation strategies, focusing aimed at targeting the aging immune system in an effort to prevent acute brain injury and chronic neurodegeneration during aging.

Contents

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; ADCC, antibody dependent cell-mediated cytotoxicity; ALS, amyotrophic lateral sclerosis; APCs, antigen presenting cells; APOE, apolipoprotein E; APP, amyloid precursor protein; APP/PS1, amyloid precursor protein and presenilin; α-Syn, α-synuclein protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; C/EBP, CCAAT/enhancer binding protein; CMV, cytomegalovirus; CNS, central nervous system; COX, cyclooxygenase CP choroid plexus; CRP, C-reactive protein; CSEF, circulating systemic environmental factor; CSF, cerebrospinal fluid; CTFs, C-terminal fragments; CTL, Cytotoxic T Lymphocytes; EAE, experimental autoimmune encephalomyelitis; GM-CSF, granulocyte-macrophage colony-stimulating factor; GCs, glucocorticoids; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; HIV, human immunodeficiency virus; IFN, interferon; IL-β, interleukin-β; i.p., intraperitoneal; i.v., intravenous; LPS, lipopolysaccharides; LTP, long-term potentiation; $M_{ø}$, macrophage; MBL, mannan-binding lectin; MBP, myelin basic protein; MCAO, middle cerebral artery occlusion; MHC, major histocompatibility complex; miR, microRNAs; MOG, myelin oligodendrocyte glycoprotein; MS, Multiple sclerosis; mTOR, mechanistic target of rapamycin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFT, neurofibrillary tangles; NLRP3, nod-like receptor protein 3; NOS2, nitric oxide synthase; NSAIDs, non-steroidal anti-inflammatory drugs; NSCs, neuron stem cells; NT-3, neurotrophin-3; PD, Parkinson's disease; POCD, postoperative cognitive dysfunction; ROS, reactive oxygen species; RRMS, relapse-remission multiple sclerosis; SA-βGal, senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; TCR, T cell receptor; TCV, T-cell vaccine; TGF-β, transforming growth factor-beta; Th1/2/17, T helper cell 1/2/17; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; TREM2, triggering receptor expressed on myeloid cells 2; WT, wild-type.

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1. Introduction

The mutual interactions and dependency of nervous and immune systems have been recognized for long and recently cause more and more attentions (McAllister and van de Water, 2009; Trakhtenberg and Goldberg, 2011). This is simply because the nervous and immune systems interact and crosstalk each other over many physiological processes, like development, homeostasis, pathogenesis, and aging. The immune system has both detrimental and beneficial effects on the nervous system. The autoimmune demyelinating disease multiple sclerosis (MS) is a typical example of an abnormal immunity-induced pathological damage in nervous system (Naegele and Martin, 2014). The central nervous system (CNS) in turn induces immunological changes via the neuro-endocrine network (Procaccini et al., 2014; Rosas-Ballina and Tracey, 2009; Tanriverdi et al., 2003). Stroke-induced global immunosuppressant effect is a well-known example (Meisel and Meisel, 2011). However, the beneficial effects of the immune system on the nervous system have only recently and gradually been recognized (Schwartz et al., 2013). For example, the immune cells and inflammation have been demonstrated to be required for brain healing (Raposo et al., 2014; Ziv et al., 2006a). Even autoimmunity can play both detrimental and beneficial effects to the CNS. While autoimmunity induced neuroinflammation and neurodegeneration (Bhat and Steinman, 2009), brain antigen-induced "autoimmunity" (so-called "protective autoimmunity") may be involved in the maintenance of CNS functional integrity (Moalem et al., 1999).

The interaction and mutual dependency between the nervous and immune systems lead to reciprocal affects on both systems during aging process. It is a question that which system goes first during neurodegeneration. As we know, cellular immune system aging, particularly of the T cell system resulting from age-related thymic involution which typically starts as early as in adolescence (Gui et al., 2012), takes place far before brain aging. Therefore, the significant age-related alterations of the immune system should causally influence nervous system homeostasis and regeneration. It is recognized that natural aging bring about immune activation and cell infiltration into the brain (Lucin and Wyss-Coray, 2009), which is probably due to aging-induced inflammatory conditions. This aging-relevant condition possibly promoted by pro-inflammatory cytokines produced by glial cells and senescent cells in other tissues would significantly increase the permeabilization of the blood-brain barrier (BBB), and recruit more immune cells to the CNS (Deverman and Patterson, 2009). Immunosenescence is believed to be directly associated with brain aging and memory loss (Di Benedetto et al., 2017; Ron-Harel and Schwartz, 2009). On the other hand, age-related neurodegeneration and the subsequent