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Involvement of Innate and Adaptive Immunity in Parkinson's Disease

Abstract

Central nervous system (CNS) was considered as an "immunologically privileged site". However, accumulating evidence supports a role for neuro inflammation in progress in Parkinson's disease (PD). Not only the activated resident microglia in brains, cytokine levels in CNS and blood, the presence of auto antibodies, and the infiltration of T-cell in CNS also contribute disease progression. The interplay between innate and adaptive immunity in the pathobiology of PD will be focused on this article.

Mini Review

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Innate immunity in PD

The presence of HLA-DR (human MHC class II cell surface receptor) positive activated microgliain Parkinson's disease (PD) patients'brain including Substantia Nigras (SNs) has been described [1-3]. In vivo imaging using positron emission tomography (PET) suggests widespread activated microglia in PD patients [4]. Moreover, HLA-DQ as well as HLA-DR, both expressed by monocytes in the CSF and peripheral blood of PD patients are significantly higher compared with controls [5]. More recently, genome-wide association studies (GWASs) of PD patients [6-10], including a meta-analysis of the GWASs, [11] verified an increased relative risk for PD and expression of HLA-DR or HLA-DQ MHC II molecules, leading to the designation of HLA-DRA as PARK18, a genetic marker recently found to be associated with susceptibility to PD [6]. Activated microglia and monocytes in PD brains secrete proinflammatory neurotoxic cytokines. Indeed, levels of IL-1β, IL-6, and TNF-α are elevated in the CFS of PD patients [11,12]. Increased expression of NFκB (nuclear factor κB) in the SN of PD patients is found in CD11b+ microglia and also in affected neurons [13]. These data support the hypothesis that activation of cells of the innate immune system, such as microglia and monocytes, directly contribute to the pathobiology of PD.

It is likely that α-synuclein (αSyn) associated pathology modulates the microglia response as αSyn deposition correlates with the presence of MHC II expressing microglia [14]. Nitrated αSyn within Lewy bodies, released from dying or dead dopaminergic neurons, was reported to induced microglia activation [15]. In addition, αSyninduced microglia activation was mediated through PRRs binding [16]. Although αSynis a typical cytosolic protein, it has also been found not only in CSF but also blood. Changes in the levels and characteristics of extracellular αSyn are associated with the disease and extracellular αSyn has been shown to be taken up by cultured microglia as well as neuron [17]. Moreover, presence of abnormal αSyn expression in cells surrounding neuroinflammatory lesions was reported within the brains of patients with multiple sclerosis [18]. Therefore, neurotoxicity related to accumulation of in PD may occur through an excessive microglia stimulation.

A harmful role of reactive microglia has also found in several PD animal models. Behavial changes or dopaminergic neurodegeneration, which are caused by neurotoxins MPTP and 6-OHDA, are associated with microglial activation and increased production of proinflammatory cytokines in the SNc [19-22]. MPTP treated mice showed behavioral dysfunction, activated microglia, and increased the levels of IL-10, IL-12(p40) IL-13, IFN-γ, and MCP-1 in CSF [22]. Moreover, both peripheral and intranigral administration of lipopolysaccharide (LPS), a potent microglial activator and a ligand of TLR-4, induces a rapid microglial response and increased levels of pro-inflammatory cytokines and free radicals in the brain, which is followed only at a later time by dopaminergic degeneration [23-27]. Finally, several studies have demonstrated a clear relationship between pro-inflammatory cytokines and nigral degeneration; over expression of TNF-a via virus delivery system causes dopaminergic cell death, while deficiency of TNF-a receptor is neuroprotective against MPTP toxicity[28-29] and IL1-b over expression exacerbates LPS or 6-OHDA-induced neurodegeneration [30-31].

Adaptive Immunity in Parkinson Disease

Today, accumulating evidence suggested the adaptive immune system also involve PD pathology. Both patients and animal models showed exacerbation of the neurodegenerative process after a peripheral inflammatory stimulus [32]. Increasing inflammation and breakdown of the blood–brain barrier (BBB) forces increased communication between the CNS and peripheral immune systems as evidenced in several neurodegenerative diseases with increased leukocyte migration within the brain parenchyma [33].

Along with activated microglia and astrocytes, T cells may also comprise components of PD pathobiology. More recently, both CD4+ and CD8+ T cells have been discovered within the SN of PD patients and MPTP treated mice [33]. Intercellular

adhesion molecule-1 (ICAM-1) is known to play a key role in T-cell mediated host defense mechanisms and ICAM1-positive glia are also increased in the SN of PD brains and MPTP treated monkey brain [34], as well as association with lesioned areas of Alzheimer disease, amyotrophic lateral sclerosis, Pick's disease and progressive supranuclear palsy [35].

Although several autoantibodies for dopamine neuron antigens are reported in sera and CSF of PD patients [36,37], the role of the adaptive immune system has only recently begun to be investigated in depth. IgG from PD patients (PD-IgG) activated microglia via the Fcgamma receptor (FcR) and induce dopaminergic cell injury, while PD IgG injection in FcR -/- mice resulted in no significant increase of microglia and no loss of TH-positive cells in the SNpc [38]. Accumulating evidence suggested that PD patients showed brain-associated autoantibodies including those directed against, GM1, S100B, glial fibrillar acidic protein (GFAP), NGF, neurofilament, myelin basic protein, tau, Aβ, and neuronal calcium channels, as well as α-syn and its modified and fibriliary forms [38-45]. Immunohistochemical staining of tissues from PD patients show that Lewy bodies were strongly immunolabelled with IgG. [47]In MPTP-intoxicated mice, α-syn drains to cervical lymph nodes where it activates antigen-presenting cells and T cells [48]. Moreover, antibodies to α-syn and catecholamine-derived melanin (neuromelanin) are increased in PD patients with antineuromelanin immunoglobulin binding shown to be more active in early disease [49]. Indeed, these data suggest that endogenous antibodies of unknown specificity have the capacity to cross the BBB and bind cognate antigens expressed by dopaminergic neurons.

Conclusion

I have reviewed here the overwhelming evidence that supports a role for neuroinflammation in PD. The number of activated microglia in brains, cytokine levels in CNS and blood, the presence of autoantibodies, and the infiltration of T-cell in CNS suggest that not only the local immune system but the peripheral immune system involve disease progression. However, more evidence is necessary for immunomodulatory strategies in PD treatment.

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