Biomarker of Neuroinflammation in Parkinson's Disease

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Contributor: Tsai Wei Liu, Chiung-Mei Chen, Kuo-Hsuan Chang

Parkinson's disease is caused by an abnormal accumulation of alfa-synuclein in dopaminergic neurons of the substantial nigra, which subsequently causes motor symptoms. Neuroinflammation plays a vital role in the pathogenesis of neurodegeneration in PD. This neuroinflammatory neurodegeneration involves the activation of microglia, upregulation of proinflammatory factors, and gut microbiota.

Keywords: Parkinson's disease ; Neuroinflammation

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease characterized by the loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc). Its main symptoms include resting tremors, rigidity, shuffling gait, and bradykinesia. The pathogenesis of neurodegeneration in PD is driven by the abnormal accumulation of misfolded α-synuclein in the central nervous system (CNS) [1]. The subsequent neurotoxic cascades involving genetic [2][3], environmental [4], and immunological factors [5] can further enhance the neurotoxicity of misfolded α-synuclein, causing neurodegeneration in the neighboring brain regions. Genome-wide association studies have identified many genetic variants associated with PD. Studies of animal models, neuroimages, and postmortem pathology have also provided substantial insights into the involvement of neuroinflammation in PD pathogenesis [6][7][8], and indicate that cytokine-induced inflammatory responses may play a vital role.

At present, no effective treatment exists to halt PD progression. Sensitive and practical biomarkers of PD are urgently required, and their efficacy for diagnosing PD in early or presymptomatic stages should be validated in clinical trials. Various molecules in the cerebrospinal fluid (CSF), such as α-synuclein, DJ-1, amyloid-β, tau, and lysosomal enzymes, may be biomarkers of PD [9][10]. Positron emission tomography, single-photon emission computed tomography, and magnetic resonance imaging are important imaging tools that reveal DAergic nerve projections in SN. Recently, studies involving neuroimaging, neuropathology, and cell and animal models further indicated an important interaction between neuroinflammation and neurodegeneration of DAergic neurons in PD [6][7][8].

2. Role of Neuroinflammation in PD

In the early 1980s, McGeer observed activated microglial infiltrations in the SN of the postmortem PD brain [6]. Numerous studies have since been conducted on the neuroinflammation associated with PD pathogenesis, such as increased proinflammatory cytokines in the blood [11] or CSF [10][12]. Activated microglia secrete several proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 [11][13][14][15][16]. They also express major histocompatibility complex (MHC) class II, and are associated with damaged neurons in patients with PD [17]. Furthermore, neuroimaging studies have used radiotracers specific to microglial activation to demonstrate ongoing neuroinflammation in PD [18][19]. A well-known example is [11C](R)PK11195 binding to several brain regions in patients with PD [7].

The aggregation of the abnormal, insoluble form of α-synuclein plays a key role in PD pathogenesis [20]. Misfolded α-synuclein is involved in the pathogen-associated molecular pattern- or damage-associated molecular patterns (DAMP)-mediated dysregulation of microglial toll-like receptor (TLR)2 or TLR4-mediated signaling pathway, which ultimately activates myeloid differentiation primary response 88 (MyD88) and nuclear factor kappa B (NFκB), triggering TNF-α and IL-1β production [21]. The treatment of BV2 mouse microglial cells or primary microglia with aggregated α-synuclein upregulates the production of TNF-α, IL-1β, monocyte chemoattractant protein (MCP)-1, and interferon (IFN)-γ [22][23][24]. Panicker et al. demonstrated that aggregated α-synuclein binds to the microglial surface cell membrane receptors TLR2 and CD36, then recruits Fyn kinase, thereby activating and subsequently phosphorylating protein kinase C-delta (PKCδ);

this leads to increased PKCδ-dependent activation of the NFκB pathway, followed by increased IL-1β production [25]. Knockout of *TLR2* reduces the uptake of α-synuclein in mouse microglia [26]. The activation of the TLR-4–NFκB pathway mediates the incorporation of α-synuclein into autophagosomes [27][28]. A functional block of TLR4 in BV2 mouse microglia or *TLR4*-knockout primary mouse microglia inhibits the uptake of α-synuclein and prevents TNF-α and IL-6 production [29]. α-Synuclein also increases the microglial expression of IFN-γ, thereby inducing neuronal MHC-I expression; thus, the neurons can be selectively targeted by CD8+ T cells [30]. α-Synuclein is encoded by *SNCA*. SNCA overexpression in rat SN decreases fiber density in DAergic neurons and increases the number of MHC-II+ microglial cells [31]. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, T cells from mice immunized to nitrated α-synuclein potentiate neurodegeneration in response to MPTP [22]. Both proinflammatory type 1 T helper (Th1) and type 17 T helper (Th17) subtypes can enhance MPTP-induced neurodegeneration, whereas the regulator T cell (Treg) subtype is protective against it [32]. These results support the role of T cell subsets activated by α-synuclein-induced immune responses in the pathogenesis of DAergic neurodegeneration.

Humoral adaptive immunity is also involved in PD pathogenesis. Numerous autoantibodies target CNS-specific proteins, such as tau, S100B, glial fibrillar acidic protein (GFAP) [33][34][35], neurofilament [36][37], GM1 [38], and neuronal calcium channels [39]; moreover, autoantibodies to α-synuclein [40][41] have also been discovered. Blood levels of anti-melanin antibody are elevated in the early stages of PD [42]. Together, these findings indicate that both innate and adaptive immune systems are activated in PD.

In addition to the brain, α-synuclein aggregation has also been discovered in the enteric nervous system (ENS) [43]. The expression of α-synuclein in enteric neurites is positively correlated with the degree of intestinal wall inflammation [44][45]. The expression of TNF-α, IFN-γ, IL-6, and IL-1β is upregulated in colon biopsy samples of patients with PD [46]. IL-1 and IL-8 are also elevated in stool specimens of patients with PD [47]. Altered gut metabolites and microbiomes are also involved in intestinal inflammation in patients with PD [48][49][50]. Notably, specific gut metabolites may increase neurodegeneration in PD. In *SNCA* transgenic mice, short-chain fatty acids produced by the intestinal microbiome lead to a higher degree of α-synuclein aggregation in the basal ganglia and SN, potentiating motor deficits [47]. Fecal microbiota transplantation in 11 PD patients with constipation increased the abundance of *Blautia* and *Prevotella* in feces and improved motor and nonmotor symptoms [51]. Therefore, PD pathogenesis likely involves an interplay among gut microbiota, metabolites, and cytokines.

3. Candidate Biomarkers of Inflammation in PDs

The clinical diagnosis of PD is made mostly based on clinical symptoms, which may appear only in advanced disease stages, thus precluding therapeutic intervention in early stages. Biomarkers are important for detecting PD in the early stage as well as for monitoring disease progression and treatment responses. Among molecular biomarkers of PD, α-synuclein, tau, and Aβ42 in the CSF, blood, and other body fluids have attracted considerable research interest [10][52][53][54][55][56][57]. Inflammatory molecules can be used as potential biomarkers to reflect the neuroinflammatory pathogenesis of PD [10][15][58]. Because obtaining live human neurons from patients with PD is challenging, the CSF is an acceptable source and can be used to detect molecular changes underlying the neurodegenerative pathogenesis. The leakage of inflammatory factors from degenerated brain regions can also be detected in the peripheral blood. The alterations of inflammatory biomarkers in the blood of patients with PD also indicate the peripheral involvement of PD pathogenesis, such as the gut–brain axis. Recent studies have described IL-1β, IL-2, IL-6, IL-10, high-sensitivity C-reactive protein (hsCRP), TNF-α/soluble TNF-receptors (sTNFRs), and regulated upon activation, normal T cell expressed and presumably secreted (RANTES), as potential peripheral biomarkers.

3.1. IL-1β

IL-1β is a proinflammatory cytokine with pleiotropic biological actions in the peripheral blood and brain. Sustained IL-1β expression in the striatum causes DAergic neuronal death and motor disabilities in rats [59]. IL-1β levels are elevated in the striatum of patients with PD [60][61]. IL-1β levels in the CSF are elevated in patients with PD, particularly those with probable REM sleep behavior disorder (PRBD) [62]. Serum IL-1β levels are significantly elevated in patients with PD, and those who also exhibit high titers of antibodies against common pathogens [63][64]. A large multicenter study demonstrated higher serum IL-1β levels in patients with PD compared with control participants [11]. However, other studies did not observe alterations in IL-1β levels in the serum [65] and CSF [66] samples of patients with PD. A 2016 meta-analysis including six studies (623 patients) concluded that blood IL-1β levels are elevated in patients with PD [15].

3.2. IL-2

The gut microbiome composition may alter cytokine profiles and affect inflammatory processes in PD [67], whereas IL-2 can suppress chronic inflammation in the gastrointestinal tract [68][69][70]. IL-2 plays a critical role in T cell proliferation, Treg cell expansion, and mediation of inflammation-induced cell death [71]. Decreased blood IL-2 levels reduce the number and function of Treg cells, leading to lymphoproliferation and autoimmunity [71]. IL-2 levels are elevated in the striatum of patients with PD [72]. Patients with PD have higher serum IL-2 levels than control participants [11][73][74]; the higher serum IL-2 levels can be reduced by treatment with antiparkinsonian medications [74]. In addition, high serum levels of soluble IL-2 receptors (sIL-2R) are associated with severe symptoms of anxiety or depression in patients with PD [75]. The meta-analysis in 2016 including three studies (282 patients) revealed the elevation of IL-2 in the blood of patients with PD [15].

3.3. IL-6

IL-6 is a multifunctional cytokine mainly secreted by neurons and glial cells, and it plays a vital role in neuronal development and differentiation [76]. It triggers neuronal survival after injury but also causes neuronal death in neurodegenerative diseases [77]. IL-6 levels are elevated in the striatum, CSF, and serum of patients with PD [64][73][75][78][79][80][81][82][83]. Higher serum IL-6 levels are correlated with infection in patients with PD [63]. Serum IL-6 levels are inversely correlated with clinical parameters, including functional mobility, gait speed, and Mini-Mental Status Examination scores, in patients with PD [84][85]. Scalzo et al. reported that serum IL-6 levels cannot reflect PD severity because serum IL-6 levels were not correlated with the scores of Unified Parkinson's Disease Rating Scale (UPDRS) part III and H&Y stage [84]. However, regarding the nonmotor symptoms of PD evaluated using UPDRS part I, plasma IL-6 levels were correlated with the severity of depression [85]. Another study reported no correlation of serum IL-6 levels with H&Y stages, disease duration, and UPDRS scores [81]. Elevated serum IL-6 levels are also associated with death in patients with PD [86]. The scores of the activity daily living scale in patients with PD are negatively correlated with serum IL-6 levels [13]. However, some studies have not detected an elevation of serum IL-6 levels in patients with PD [11][64][66][74], although a 2016 meta-analysis including 13 studies (898 patients) revealed higher peripheral IL-6 levels in patients with PD [15].

3.4. IL-10

IL-10 is an anti-inflammatory cytokine produced by lymphocytes and microglia [87]. It has neuroprotective effects against LPS-induced cell death [88]. Serum IL-10 levels are increased in patients with PD compared with control participants [11][73][89]. However, two studies have not indicated any changes in serum and CSF IL-10 levels in patients with PD [66][90], whereas the meta-analysis in 2016 including five studies (376 patients) demonstrated higher peripheral IL-10 levels in patients with PD [15].

3.5. TNF-α/sTNFRs

TNF-α is a proinflammatory cytokine that plays a key role in host defense [91]. TNF-α binds to sTNFR and regulates sTNFR expression; sTNFR expression may be an indicator of TNF-α activity [92]. TNF-α activates microglia to induce the progressive loss of DAergic neurons in the SN [93][94][95]. TNF-α is upregulated in the SN of patients with PD [96]. TNF-α levels in the CSF are elevated in PD patients [94], particularly those with PRBD [62]. Serum TNF-α levels are also elevated in patients with PD [11][66][73][75][82][83] and those with atypical parkinsonism [73]. Elevated plasma sTNFR1 is associated with poor executive function in patients with PD [97]. Plasma TNF-α levels are positively correlated with cognitive impairment, depression, and disability in patients with PD [75][98]. Serum TNF-α levels are not significantly elevated in PD patients with infectious burdens [63]. The meta-analysis in 2016 including nine studies (809 patients) demonstrated higher peripheral TNF-α levels in patients with PD [15].

3.6. RANTES

RANTES is a proinflammatory chemokine involved in the regulation of immunoreactions and the recruitment of immune cells such as monocytes, granulocytes, and T cells to sites of inflammation [99]. A study reported that serum RANTES levels in patients with PD were higher than those in control participants [100]. Serum RANTES levels are positively correlated with H&Y stages and disease duration [82][101], but are not associated with UPDRS scores [82]. However, Gangemi et al. noted that serum RANTES levels were comparable in patients with PD and control participants [102], whereas the meta-analysis in 2016 including five studies (171 patients) demonstrated higher blood RANTES levels in patients with PD [15].

3.7. High-Sensitivity C-Reactive Protein (hsCRP)

The circulating hsCRP level is a useful marker of ongoing inflammation or tissue damage [103]. hsCRP has potential as a marker of neuroinflammation in PD [104]. Elevated plasma hsCRP levels are present in patients with PD who underwent levodopa treatment [105]. Serum hsCRP levels are also higher in patients with PD than in control participants [106][107]. However, these elevations of hsCRP have not been recapitulated by other studies [11][75][108]. The meta-analysis in 2016 including six studies (696 patients) demonstrated higher blood hsCRP levels in patients with PD [15].

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