Deciphering Variability in The Role of Interleukin-1β in Parkinson's disease

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Abstract

Although the role of inflammation in neurodegeneration has been well-acknowledged, less is pored over the issue of each cytokine in specific neurodegenerative diseases. In this review, we will present evidence elucidating that the interleukin-1 beta (IL-1β) has a multi-faceted character in pathogenies of Parkinson's disease, which is a progressive neurodegenerative disorder. Increased levels of IL-1β were found in PD patients. Besides, in addition to the observation of PD symptoms in IL-1β wild-type, but not deficient, animals suggest that IL-1β may be either propagator or progenitor in dopaminergic degeneration (PLEASE REWRITE THIS SENTENCE, IT IS NOT CLEAR). On the other hand, decreased levels of IL-1β suggest that IL-1β may be either a postponer or prohibitor in dopaminergic degeneration.(NOT CLEAR). Presumably, the broad range of IL-1β rol is due to its interaction with both upstream and downstream mediators. Differences in IL-1β levels could be owing to glia population (i.e. microglia and astrocytes), MAPK and NF-κB signaling pathways, and several mediators (including cyclooxygenase, neurotrophic factors, reactive oxygen species, caspases, Heme oxygenase-1, and matrix metalloproteinases). Although far from practice at this point, unraveling theoretical therapeutic targets based on the Up-Down IL-1β neuroweb could facilitate the development of strategies which are likely to be used for pharmaceutical designs of anti-neurodegenerative drugs of the future.

Key words: Cytokines, Inflammation, Interleukin-1β, Neurodegeneration, Neurodegenerative diseases, Parkinson’s disease, Proinflammatory cytokines.

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1. Introduction

Parkinson's disease (PD) is considered one of the most common neurodegenerative disease after Alzheimer's disease and is characterized by progressive loss of dopaminergic cells in the striatum. Clinical signs and/or symptoms cover a broad spectrum of motor and non-motor manifestations. However PD patients often present manifestations such as rest tremor, bradykinesia, rigidity, and loss of postural reflexes [1]. Very few PD are related to genetic mutations (almost 10%), however, many of PD cases are classified as sporadic PD. However, the aethiology of PD has not been established yet, some possible mechanisms of pathogenesis are excitotoxicity [2], genetics [3], oxidative stress [4], and inflammation [5](THIS IS NOT CLEAR, I WOULD ERASE IT).

Inflammation is known to be implicated in many pathological events. However, it remains unknown whether it is a cause or a consequence of those events. Angiogenesis [6], atrial fibrillation [7], neurodegeneration [8], and thromboembolism [9] are considered as such events (THIS IS NOT CLEAR). The role of inflammation in both initiation and progression of neurodegenerative disease has been studied over the past decade [1, 2], but the importance of cytokine has been overlooked.

Among the inflammatory elements, we decide to focus on the role of Interleukin (IL)-1 family which plays a role in the regulation of the immune responses [12]. The IL-1 family comprises at least three monumental members interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), and interleukin-1 receptor antagonist (IL-1Ra). While IL-1α and IL-1β are pro-inflammatory cytokines, IL-1Ra acts as an anti-inflammatory cytokine. Amino acid and nucleotide sequences of IL-1α and IL-1β are respectively homologous

with 26% and 45%, however each one has been linked to specific mechanism of expression, localization, maturation, synthesis and secretion. Meanwhile, IL-1Ra has structurally similarity of 18% and 26% with IL-1α and IL-1β respectively [13]. (VERY CONFUSE THIS SENTENCE AND HAS NO RELATIONSHIP WITH THE PREVIOUS SENTENCE, I WOULD DELETE IT)

The IL-1β plays the important role in different neurobiological process processes, such as neuroinflammation, neurotoxicity and host defense, therefore, this cytokine has been linked to both acute and chronic neurodegenerative conditions [14-16]. The IL-1β exerts its effects via the expression and secretion of a wide variety of neurotoxic proteins, transcription factors, and inflammatory mediators and signaling pathways (e.g. cytokines, matrix metalloproteinase (MMP), cyclo-oxygenase-2 (COX-2), prostaglandin E2 (PGE2), plasminogen activator inhibitor type-1, ceruloplasmin, complement component C3, nitric oxide (NO), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), CCAAT/enhancer-binding proteins (C/EBPs), the activator protein 1 (AP-1), the interferon regulatory factor 1 (IRF-1), and protein kinase C (PKC)) [17-21]. Additionally, IL-1β interferes with the function of neurotrophic factors, e.g. brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and thereby could be involved in neurodegeneration [22, 23]. It is thus expected that IL-1Ra administration to the hippocampus of rats prior to the social isolation (that leads to the upregulation of IL-1β) could prevent the downregulation of BDNF and related memory impairment [24]. (NOT CLEAR, I WOULD DELETE IT)

The IL-1β converting enzyme (ICE or caspase-1), also known as a member of B-cell lymphoma 2 (bcl-2) family, is involved in apoptotic processes and expressed by neurons,

endothelial cells, astrocytes and activated macrophages and microglia [25, 26]. The inactive precursor of IL-1β (pro-IL-1β) requires cleavage by ICE, which explains the beneficial effect of ICE inhibitors in ischemic infarction and excitotoxic neuronal damage [25, 27-30]. . In addition both acute and chronic neurodegenerative conditions have been considerably improved by IL-1Ra-based therapeutic approaches [34, 35]. Taken together, the role of IL-1β in inflammation-related neurodegeneration is indisputable [36, 37]. However, it was described the role of IL-1β in various neurodegenerative scenarios. Elevated concentrations of IL-1β (E-IL-1β) lead to either promoting or preventing the progression of neurodegenerative diseases (NDDs). Third, which are the main upstream inducers and respective pathways of E-IL-1β in NDDs? (I DON'T UNDERSTAND). Microglia activation could be the upstream event dealing with the overproduction of IL-1β (REFERENCE). The expression of IL-1β on glial cells in the substantia nigra (SN) of PD patients was substantially greater than control patients [38]. Thus, it could be hypothesized that there is another upstream source, except microglia cells, inducing the expression of IL-1β during the pathogenesis of AD, particularly in the late-stages(I don't understand this conclusion). Herein, a comparative study is required to review the role of IL-1β and study its role in neurodegenerative diseases. The aim of the review is intended to describe the role of IL-1β in dopaminergic cells degeneration.

2. Search Strategy

The main medial database, PubMed, was searched for articles relevant to the topic of the present review published until January, 2014. We searched without activating the language filter and our search terms were "interleukin-1 beta" and "Parkinson's disease".

3. The Contents of IL-1β in Parkinson' Disease

I. Increased levels of IL-1β suggest that IL-1β could be either propagator or progenitor in dopaminergic degeneration (What is the meaning of progenitor in this sentences??

Investigations in PD patients revealed that IL-1β levels wereincreased in the striatum and in the CSF of patients.(reference). A possible explanation could be the genetic background, as it has been demonstrated the IL-1β-511 variants are associated with the risk and age at onset of PD in various ethnic populations e.g. German, American, British, Turkish, and Japanese populations [40-50]. (this sentence make no sense in this paragraph, I would delete it). Further, stimulated concentrations of IL-1β in PBMCs were found to be elevated in PD patients compared to controls [51, 52]. Additional, evidences were also obtained from animals models. LPS induced PD symptoms by stimulating IL-1β in wild type animals but not in IL-1b deficient animals [35, 53, 54]. Additionally, it was described that a single high-dose of IL-1β induced akinesia and dopaminergic cell death in the substantia nigra (SN)similar to human PD-like symptoms [55, 56]. Altogether, these data revealed a detrimental role of IL-1β in the context of PD, which could contribute to dopaminergic degeneration.

II. Decreased levels of IL-1β suggest that IL-1β could be either a postponer or prohibitor in dopaminergic degeneration (It is not clear the meaning of postponer and prohibitor in this sentence)

Perhaps an introductory sentence explaining the contents of the item should be better

On the contrary to the previous paragraphs, it was described that IL-1 levels in PBMCs (Peripheral blood mononuclear cells) and plasma were significantly reduced among PD

patients compared to controls (26). A negative association between LPS-induced IL-1β levels and the disability scores of PD patients were describe (references). In addition, the older age at onset of PD in those who had higher levels of IL-1β production suggests a beneficial role for IL-1β in PD [47, 49, 57](THIS SENTENCES IT IS VERY CONFUSE, I DON'T UNDERSTAND). The IL-1β-511 T-carrying genotype was proved to protect the aged Taiwanese population against PD [58]. Interestingly, people carrying the IL-1β-511-CC genotype, associated with earlier age at onset of PD, had lower concentrations of IL-1β [47].

III. Unaltered levels of IL-1β suggest that IL-1β has no clear role in dopaminergic degeneration

Recently it was published that there is no significant association between IL-1β-511 variant and PD risk [59, 60]. Further, lack of correlation between non-motor PD symptoms and serum content of IL-1β and no evidence of increased level of IL-1β in the hippocampus of Parkinson patients and in the striatum and substantia nigra of young mice overexpressing human wild-type alpha-synuclein raise serious doubts that if IL-1β has a significant role in the progression of PD(TOO LONG AND CONFUSE SENTENCE) [61-63].

The role of IL-1β in PD has been illustrated in the figure 1.

4. IL-1β as a Mediator of Dopaminergic Degeneration Induced by SEVERAL Stimulants

I. α-Syn → IL-1β → Dopaminergic Degeneration (the reviewer clear said that he doesn't like this kind of sentences, I would rewrite it)

Neuroinflammation is recognized as one of the main mechanisms underlying pathogenesis of synuleinopathies. Accumulation of α-synuclein (αSyn) protein leading to

the formation of Lewy bodies is commonly described as a pathological hallmark of PD (for review see [65])...

The inflammatory response, via both production and maturation of inactive IL-1β, relies on activation of microglia cells and NLRP3 inflammasome, respectively [66, 67]. The increased IL-1β concentration is considered as an antecedent of dopaminergic degeneration, according to the rat model of AAV α-synucleinopathy [68]. It has been demonstrated that chronic exposure to IL-1β directly contributes to the expression of α-SYN protein, indeed, IL-1Ra, seriously impeded the expression of α-SYN [69]. As it will be discussed in detail in subsequent sections, increased production of IL-1β by α-SYN-induced microglia is regulated by MMPs and subsequent stimulation of PAR-1 [67]. The monomeric form of α-SYN, but no the aggregate one, induces production of IL-1β [67]. As well, this cytokine had a hand in the production of α-SYN protein from sAPP (Secreted forms of the beta-amyloid precursor protein (APP))-activated microglia; due to that the receptor antagonist (e.g IL-1Ra) seriously impeded the expression of α-SYN [69](confuse sentence).

II. LPS → IL-1β → Dopaminergic Degeneration

LPS-induced neurodegeneration could be a consequence of microglia activation and IL-1β production, although, the injection of IL-1β did not induce neurodegeneration [53, 70, 71].

III. MPTP → IL-1β → Dopaminergic Degeneration

MPTP injection in the striatum was related to increasing levels of IL-1β. The expression of mRNA IL-1β was observed 6 hours after MPTP injection [72]. Increased levels of IL-

1β was observed only in chronic regimen of MPTP-induced dopaminergic degeneration model, but not in acute or subacute ones [73].

Accordingly, a mass of evidence in the experimental models of PD suggested that the successful anti-neurodegenerative strategies, either pharmacological or non-pharmacological, are based on the theory that the expression of IL-1β triggers inflammatory cycles [53, 74-106]. α-SYN protein, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro pyridine (MPTP) or MPP^+, 6-OHDA (6-hydroxydopamine), LPS (Lipopolysaccharide), manganese chloride ($MnCl_2$), maneb, paraquat, and chronic cerebral hypoperfusion have been used to induce human PD-like symptoms (REFERENCES). Therapeutic strategies include a cytokine combination of GM-CSF and IL-3, 7-hydroxy-6-methoxy-2-propionyl-1,2,3,4-tetrahydroisoquinoline (PTIQ), minocycline, nimodipine, naloxone, bioflavonoid compound, ycnogenol (PYC), caffeine or caffeic acid, aminoguanidine, pyrrolidine dithiocarbamate (PDTC), genistein or SB202190, piperine, quercetin, sesamin, tenuigenin (TEN), paroxetine, chrysanthemum indicum Linn (CI), doxycycline, ganoderma lucidum (GL), dexamethasone, angiotensin type 1 receptor antagonist candesartan (Angiotensin type 1 receptor antagonist), ghrelin, resveratrol, exendin-4 and ketogenic diet (KD), triptolide, tellurium immunomodulating compound ammonium trichloro (dioxoethylene-O,O'-) tellurate (AS101), Acorus gramineus Solander (Acoraceae, AG) and PARP inhibitor 3-Aminobenzamide (AB) (REFERENCES). Others non-pharmacological strategies to experimentally inhibit IL-1 expression includes, knockout of IFN-γ, IL-1α, and IL-1β genes, noninvasive delivery of mesenchymal stem cells (MSCs), Ad-HO-1 (adenovirus containing human HO-1 gene), AAV2-hIL-10 (Vector containing cDNA for human interleukin 10), myelin

oligodendrocyte glycoprotein (MOG) immunization, osmotic pump infusion of IL-10, and exercise [53, 78, 89, 90, 102-104].

5. Microglia and IL-1β

Microglia cells are the CNS (Central nervous system)-resident macrophages that act as a sensor system to detect pathological changes in the CNS [107]. The overwhelming activation of microglia results in the excessive release of detrimental molecules. There is, however, a broad range of microglia-produced molecules, including cytokines, chemokines, arachidonic acid (the main precursor of PGs), reactive oxygen and nitrogen species (85). The crosstalks from activated microglial cells to activated astrocytes are believed to manage substantially by pro-inflammatory mediators (see review in [108]), because of a) stimulating high expression of proinflammatory cytokines by activated microglia, b) eliciting the dual function of Cx43 by treatment with the pro-inflammatory mixture contains IL-1β, and c) blocking of this inflammation induced dual function of Cx43 by anti-inflammatory treatments [109].(this sentence makes no sense here, because is item microglia and is very confuse if you start talking about astroglia)(I would delete it)

Neurotoxins, such as… (please give examples) act in three different modes, direct, mixed and indirect (see review in [8]). Direct neurotoxins lead to neurotoxicity without activating microglial cells, such as MPTP and 6-OHDA. Indirect neurotoxins e.g. LPS eventuate in neurotoxicity, depending on activation of microglial cells. HIV gp120 (Envelope glycoprotein gp120 of human immunodeficiency virus), Aβ (Amyloid beta), prion and rotenone are examples of neurotoxins, which can cause neurotoxicity via either

direct or indirect ways, assigned to the mixed mode category [8]. The possible pathway from activated microglia to neurotoxicity is hold by pro-inflammatory agents such as IL-1β, oxidative stress products and prostaglandins (PG) [8]. It was well expected that amplifying the systemic or peripheral inflammatory response by administration of LPS, 6-OHDA, AdIL-1, TNF-α, and IL-1β, and other inflammatory agents exacerbates the insult in animal models of chronic neurodegenerative disease, increases neurodegeneration,inducedisruption of blood brain barrier (BBB), and aggravates the cognitive, behavioral and PD-like symptoms (for review see [110, 111] and [34, 35, 94, 112-117]). Interestingly, a transient systemic inflammatory condition (e.g. by CFA: complete Freund's adjuvant) can act asa preconditioner and make microglia defensive against the threat of neuronal death afterwards; whereas that chronic inflammatory condition (e.g. by IL-1β and TNF-α) can act as an unpleasant preconditioner and exert, in itself, human PD-like symptoms, particularly dopaminergic degeneration and α-SYN aggregation(very confuse sentence) [55, 69, 118, 119]. However, both of them (either transient or chronic) are potential propagators of the neurodegenerative status. In addition, neurotoxic activation of microglia with pro-inflammatory phenotype is restricted to aged mice(this sentence is not clear) [120].

LPS, MPTP or MPP^+-induced morphological activation of microglial cells and induce IL-1β production and subsequent neurotoxicity, which could beimpeded by anti-neuroinflammatory agents e.g. glucocorticoid treatment, fiestin, m-chlorophenylpiperazine (m-CPP), honey flavonoid extract (HFE), diphenyliodonium (an inhibitor of the NADPH oxidase), Schisandrin B (Sch B), Agrimoniae Herba, resolvin D1 (RvD1), naloxone, Cerebrolysin, KL-1037, K252a pyridylimidazole compound KR-

31360, and specific IL-1 inhibition [34, 121-132]. Microglia activation and subsequent microglia-induced IL-1β expression are strongly impressed by microglia-expressed NADPH oxidase (NOX) activity and subsequent superoxide content, especially phagocytic oxidase (PHOX), and opioid factors(I don't understand what do you mean) [125, 128, 133, 134]. Accordingly, activated microglial cells potenciate the inflammatory scenario by inducing several pro-inflammatory agents, includingIL-1β, and its receptors, and alsodifferent signaling pathways.

6. IL-1β and Astrocytes

IL-1β influences on the major functions of astrocytes, including secretion(which molecules?), gene transcription, and proliferation (of what?) [135-138]. Although it is not fully understood how it works, it has been demonstrated that complement component C3, ceruloplasmin, and plasminogen activator inhibitor type-1 are altered under the influence of IL-1β [135, 136]. Also, the TaqMan Human Inflammation Assay has demonstrated dramatic variations (at least two-fold) in the expression of 29/92 human inflammatory genes in IL-1β-pretreated human astrocytes [138]. However, both neurodegenerative and neuroprotective roles of IL-1β were apparently determined by its receptor due to findings as follows; a) a significant increase in both mRNA and protein levels of IL-1β and its receptor IL-1R1 in the SN and striatum of MPTP-induced PD mice models, b) inhibition of dopaminergic degeneration following blockade of IL-1R1 in the LPS-induced PD rat model, and c) inhibition of IL-1β-mediated neuroprotection by IL-1Ra pretreatment in the NMDA (N-Methyl-D-aspartate)-induced neurotoxicity model [103, 115, 136, 139, 140].

S100B (S100 calcium binding protein B), secreted by IL-1β-induced astrocytes, is a key molecule in the relationship between IL-1β and NF-kB and MAPK (Mitogen-activated protein kinase) signaling pathways [141].

7. IL-1β and Signaling Pathways

The signaling pathways of activated microglia occur via MAPK and NF-κB pathway (REFERENCES).

I. MAPK Pathway

MAPKs including ERKs (Extracellular signal-regulated kinase), JNKs and p38 are required for cell division, transcription and inflammation, respectively [142]. All of the subfamilies of MAPKs were found to be upregulated under rotenone treatment, whereas LPS selectively evoked ERKs and p38 in microglia cells [143, 144]. Moreover, both ERKs and p38 were activated in IL-1b treated astrocytes and to a lesser extent with LPS [143]. The beneficial effect of 3-AB (PARP inhibitor 3-Aminobenzamide) on the expression of the tight junction-associated proteins in the LPS-induced PD rat model was accompanied by decreased expression of IL-1β and p-ERK1/2 and increased expression of p-p38 [77]. KCa3.1 (this protein is encoded by potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4 (KCNN4).) channels are largely responsible for neurotoxicity-associated behavior of activated microglial cells, particularly nitric oxide-dependent neurodegeneration. Further, they may play a role in the inflammatory event following microglia activation via the selective stimulation of p38 MAPK (but not NF-κB) [145] (not clear). Apoptotic neurons will boost the

production of MMP-3, which has been shown to activate microglia mostly through selective engagement of ERK, but not p38 and JNK substrates, which might explain the increased production of IL-1β and its receptor, IL-1Ra (I DON'T UNDERSTAND THE RELANTIONSHIP BETWEEN mmp-3 AND il-1) [146]. The IL-1β-induced α-APP depends on MAPK pathway, as the inhibitors of MEK1/2 and JNK significantly hindered its production in neuroglioma U251 cells [147].(THIS SENTENCES HAS NOTHING TO DO INTHIS PARAGRAPH)

Knock down of LRRK2 (Leucine-rich repeat kinase 2) gene, which has been associated with PD (also known as PARK8), was found to decrease the phosphorylation of p38 following LPS administration in murine microglia cells. Interestingly, the expression of both p38 and JNK was upregulated in LPS-induced cells overexpressing the human LRRK2 pathologic, kinase-active mutant G2019S, but not in WT and other mutant models (i.e R1441C and G2385) [148]. These experiments demonstrate the effect of the LRRK2 gene expression in changing the function of MAPK signaling pathway based on the genetic background. Alpha-SYN has been shown to make a widespread impression on activation of more than 81 phosphorylation-sites, favourably all three MAPK subfamilies(PLEASE, EXPLAIN BETTER). Also MAPK has been demonstrated to activate the expression of MMPs (including MMP-1, -3, -8, and -9) and proinflammatory cytokines (e.g. IL-1β and TNF-α) in microglia [67, 149]. Both production of proinflammatory cytokines and the activity of MAPK were diminished by the inhibition of MMP-3 or -9. However, a PAR-1–specific inhibitor and a PAR-1 antagonist (of which molecule??) were, as well, able to abate the production of proinflammatory cytokines [67]. Mutations in the PINK1 gene have been associated with autosomal recessive early-

onset PD. The PINK1-deficient mice models established that the activity of JNK is increased as a primary effect of PINK1 deficiency, leading towards increased dopamine turnover and reduced levels of dopamine [150]. Thrombin has been shown to activate all three MAPK subfamilies in microglia cells. As expected, each one of three MAPK inhibitors was able to improve the dopaminergic degeneration induced by thrombin [151, 152]. Meanwhile, IFN-γ (Interferon gamma) deficiency has been demonstrated to inhibit selectively p38 MAPK and JNK (c-Jun amino-terminal kinase) substrates [89].

II. NF-κB Pathway

IL-1β in chronic neurodegenerative disease could be related to: a: activation of microglia, b: induction of more IL-1β, and neurotoxicity and neurodegeneration, as a consequence induction of neuroinflammation,. It was been demonstrated that microglia activation, directly involves the NF-κB signaling pathway [144, 153]. As mentioned before, rotenone, known as a mitochondrial complex 1,leads to neurotoxicity through microglia NF-κB activation and subsequent the microglia-induced expression of IL-1β. So, the microglial pathway of NF-κB activation-induced IL-1β expression has great potential as therapeutic target, as it was demonstrated using RvD1, Sch B, PDTC and AG [80, 129, 131].

There is evidence that loss-of-function mutations in the parkin gene are associated with familial PD in an autosomal recessive inheritance manner [154, 155]. Deficient parkin gene leads to significantly higher sensitivity to pro-inflammatory cytokines e.g. IL-1β and their expression on LPS-induced macrophages, which, in turn, enacts the scenario of neuroinflammation(very confuse) [156, 157]. Further, the PINK1 and PARK7 (Parkinson protein 7 that is also known as DJ-1) genes protect cells against stress-induced

mitochondrial dysfunction, whereas their mutated forms have been linked to autosomal recessive early-onset PD (http://www.ncbi.nlm.nih.gov/gene). Down regulation of DJ-1 gene leads to increase in the expression of IL-1β and dopaminergic neurotoxicity in the MPTP model [158, 159]. The peripheral LPS-induced increased expression of IL-1β in the striatum was significantly higher in deficient-PINK1 compared to wild-type mice [150]. The mechanism of action of the aforementioned genetic deficiencies underpinning the pathogenesis of PD might operates via stimulation of NF-κB pathway because of positive regulation TRAF6 (TNF receptor-associated factor 6, E3 ubiquitin protein ligase) and TAK1 (Transforming growth factor beta-activated kinase 1) or degradation of IκB (inhibitor of kappa B), and subsequent overexpression of proinflammatory cytokine, IL-1β [150, 156, 157, 160, 161]. By contrast, the deficiency of the LRRK2 has been proven to act as a negative regulator (this means that in inhibit NF-kb???) of NF-κB signaling pathway and IL-1β in LPS-induced murine microglia model(I don't understand this part) [148].

At pathological level, aggregated α-SYN could activate microglia NF-κB signaling pathway in a time-dependent manner [162]. IL-1β induce astroglial CXCL10, via microglia NF-κB activation, however, α-SYN aggregation alone was not able to induce astrocytes to express CXCL10, [163]. α-SYN aggregation could act as an amplifier of the effect of IL-1β via an increasing in the stability of CXCL10(this phrase make no sense with the previous one) [163]. , NF-κB signaling pathway can be triggered by severalpathologic hallmarks of PD (i.e. α-SYN), some PD-associated genetic deficiencies (e.g. the transcription factor Nrf2 (Nuclear factor erythroid 2–related factor 2), PARK2 (Parkin RBR E3 ubiquitin protein ligase) and PINK1 (PTEN induced putative kinase 1)),

and as well by PD-related environmental neurotoxins (e.g. paraquat)(this phrase is very confuse) [67, 89, 156, 160-162]. Accordingly, the use of inhibitors of the NF-κB pathway, such as chrysanthemum indicum Linn (CI), MMP-3 and MMP-9 inhibitors, has been proved to provide a protective effect for PD.[67, 91, 146].

8. Main Mediators of IL-1β in Parkinson's Disease

I. IL-1β and Cyclooxygenase

The prostaglandins (PGs) are produced in response to many stimuli, mainly inflammation and trauma [164]. The first precursor of PGs is a 20 carbon fatty acid (mainly arachidonic acid), which is converted by cyclooxygenase enzime (COX-1 or COX-2) into PGH_2, producing several PG types according to the cell type (see review in [165]). This pathway is important because the anti-inflammatory action of non-steroidal anti-inflammatory drugs (NSAIDs) might selectively inhibit the COX-2 enzyme [165]. However, the hypothesis of considering COX-2 as a target to inhibit neuroinflammation could be controversial because of the dual function of COX-2. The induction of COX-2 was found to being closely correlated with IL-1β content in a hind paw-inflammation model [166]. The IL-1β-induced COX-2 expression prompted the PGE2 synthesis, which could be significantly reduced by an ICE inhibitor [166]. Further, the injection of PGEs, contributing to the IL-1β-induced IL-6 mRNA expression in human astrocytoma cells, appeared to lead to postural disturbance in animal model(I would delete this phrase) [167, 168]. Human primary astrocytes pretreated with IL-1β induce COX2 expression, which has been shown to be largely and partly dependent on activity of p38 MAPK and C\EBPβ (CCAAT (cytosine-cytosine-adenosine-adenosine-thymidine)/enhancer binding protein

(C/EBP), beta), respectively [138]. In this regard, the inhibition of p38 MAPK and ERK1/2 induce either blockage or increment of IL-1β-pretreated astrocytes-induced COX-2 expression, respectively [138].(Please, explain better)

The MPTP model shows increment of COX-2 enzyme expression in ventral mid-brain dopaminergic neurons [169]. The contribution of COX-2 enzyme to PDprogression is not restricted to the MPTP-induced PD in animal models, because it was also observed in postmortem PD samples [169]. However, a direct conflict has arisen from evidence indicating the possible correlation between microglia activation and MPTP-induced COX-2(Don't understand this phrase) [169, 170]. The activation of JNK-2 and JNK-3-induced COX-2 pathways were involved in neurodegeneration, and as well no synergic effect was seen between JNK blockage and COX-2 deprivation in induced neuroprotection in an MPTP model. COX-2 deficient mice were appeared to be more resistance to MPTP-induced dopaminergic cell death (DCD), the JNK blockage inhibited the MPTP-induced COX-2 upregulation (rewrite, I don't undersand what it means)[169, 171]. However, the NF-kB pathway was not involved in COX-2 induction, because not differences could be found in MPTP-induced COX-2 expression between p50-deficient (explain this mice clearly) and wild-type mice [171]. However, COX-2, being an inducible enzyme conditional to inflammation, exerts its neuroprotective effect in the MPTP mice model amelioratingthe production of oxidant species dopamine-quinone (I don't understand, what do you mean with dopamine-quinone???), instead to limit microglia-provoked inflammatory response [169]. The increased mRNA expression of COX-2 hit its (do you mean that induce neurodegeneration??) peak at 4 hours after

intranigral thrombin injection, and as well the COX-2 inhibitor (DuP-697) ameliorate thrombin-induced dopaminergic loss [152].

Several animal PD models have clearly demonstrated a significant increase in production of COX-2 and subsequent PGE2, which could be reduced by a range of treatments include caffeic acid, nimodipine, DuP-697 (a COX-2 inhibitor), doxycycline, chrysanthemum indicum Linn (CI) and IFN-γ knockout [87, 89, 91, 97, 100, 152].

II. IL-1β and BDNF

Brain-derived neurotrophic factor (BDNF) contributes to neuroprotection through activation of intracellular pathways, which includes PI3-K and ERK pathways. IL-1β acts as an antagonist of NF-induced neuronal survival, which probably operates via the PI3-k/Akt pathway, suppressing Akt, and stimulating ceramide generation [22].

Lower serum concentrations of BDNF was measured in patients at early PD stages compared to PD patients at later stages explaining the presence of compensatory mechanism during the PD progression [172].

Genetic polymorphisms of BDNF have been frequently associated with motor performance and cognitive functions in both patients with neurologic/psychiatric disorders and healthy individuals What to mean? Thera are no differences between patiens and healthy individuals??). For example, BDNF val66met polymorphism could be correlated with cognitive impairment in PD patients [173]. Various animal models of PD have clearly indicated a significant decrease in production of BDNF, which could be enhanced by a range of treatments (explain which kind of treatments) include caffeic acid, Ad-Ho-1 (Adenovirus containing human HO-1 gene), and IFN-γ knockout [87, 89, 101]. It has been defined a clearly positive role for BDNF in differentiation of NPCs

(Neuronal progenitor cells) towards dopaminergic phenotype [174]. Hence, it is of crucial importance to design a multi-faceted therapeutic architecture, i.e. simultaneous aiming at decreasing the IL-1β production and at increasing the BDNF production.

III. IL-1β and NO

The physiologically production of nitric oxide (NO) is deemed to be crucial for neurophysiological functions include cognitive function, synaptic plasticity and neurosecretion especially in the stress axis, and neuronal survival via influencing on kinase Akt, transcription factor CREB and heme oxygenase 1 (HO-1) [175]. Nonetheless the overexpression of nitric oxide (NO), generated from amino acid L-arginine by inducible nitric oxide synthase (iNOS), results in nitrosative stress (elevated NO-induced oxidative stress), mitochondrial damage, disturbed Ca^{2+} homeostasis, transcriptional changes and p53 activation, which , in turn, can end in apoptosis via activation of Bax/Bak and caspase proteins and TNF/FAS receptors [176]. The inducible pathway concern to cell death, via either apoptosis or necrosis, is prominently triggered by the NO metabolite, peroxynitrite ($ONOO^-$) in AD and PD (see review in [176]). The elevation of NO content can be stemmed from both activated microglia and astrocytes and regulated by p38 MAPK, instituting NO-dependent neurodegeneration [143, 145]..

An apparent increase in the NO production and ensuing neurotoxicity were manifested on IL-1β-treated primary human astrocyte cultures, which could be, as well-expected, greatly hampered by interleukin-1 receptor agonist (IRAP) [177]. In contrast, IL-1b was not only enough to enforce iNOS production in microglia, but the combination of IL-1b and IFN-γ empowers both microglia cells and astrocytes to produce, respectively, iNOS and NO [143, 177]. Similar to this, IL-1β together with IFN-γ could amplify the effect of

IFN-γ on expression of CD23 in cultures of glial cells, whereas IL-1β itself was insufficient to induce this effect [38]. The number of CD-23 positive cells, either astrocytes or microglia, in the SN of patients with PD was higher than that of normal [38]. The antibody-mediated CD23 ligation led to induce the mRNA and protein expressions of iNOS and subsequently the production of NO in the IFN-γ-treated astrocytoma cells [38]. IL-1β induces neurodegenerative damage partly via, overproduction of NO (references). The NOX activity arisen from activated microglia cells, which increase the extracellular ROS, leads to degeneration of dopaminergic neurons in the MPTP-induced PD model. Meanwhile, the NOX activity deteriorate the LPS-induced dopaminergic neurodegeneration via inducing expression of proinflammatory genes [134, 178]. Higher expression of iNOS could be consider as the molecule involve in the dopaminergic degeneration in animal models of PD, including α-SYN protein and deficient genes e.g parkin and IFN-γ models [67, 89, 157]. The mRNA expression of iNOS reached its peak at 12 and 24 hours after thrombin and MPTP injection, respectively [72, 152]. It seems that iNOS is not involved in dopaminergic degeneration induced by LPS injection, because LPS inhibition cause no alteration in LPS-induced neurotoxicity (it make no sense, LPS degeneration is not inhibit by the inhibition of LPS??, what is the effect of iNOS???) [71]. Interestingly, although there was no significant difference between two monomer and aggregated forms of α-SYN protein on the amount of NO production, the monomer form was shown to be more capable of inducing IL-1β.(explain better). overproduction of iNOS, neuronal NOS and NO are key features of everal animal PD models[67, 87, 89, 95-98, 100, 152].

IV. IL-1β and HO-1

The overexpression of HO led to a decreased IL-1β production, increased dopaminergic neuronal survival and decreased levels of dopamine in MPP^+-induced PD model [101]. On the other hand, accumulation of HO-1 has been observed in the formation of neuronal Lewy bodies in SN of PD patients [179]. Taken together, it could be possible that high expression of HO-1 can act as a compensatory mechanism to avoid dopaminergic loss in the early stages, and organize Lewis body formation in the late stages.

V. IL-1β and MMPs

α-SYN protein induced mRNA expression of both MMP-1 and MMP-8 [67]. MMP-3 and MMP-9 are involved in microglia activation and subsequent IL-1 and IL-1Ra production. [67, 146]. So, this pathway (MMPs-induced microglia-induced IL-1β-neurodegeneration) could be considered as a potential therapeutic targets to ameliorate dopaminergic degeneration, [97, 98] (it is a risky conclusion).

VI. IL-1β and Caspases

Apoptosis has two regulatory checkpoints, Bcl-2 family and IL-1β converted enzyme (ICE) (reviewed in [180]). ICE, known as caspase-1, converting pro-IL-1β to the biologically active form of IL-1β, was described in developing ischemic brain injury. [28]. Estrogen has been shown to exert its neuroprotective effect by an increase in the BCL-x level and also a decrease in the ICE level, leading to significantly diminish the apoptosis ratio on MPP^+-induced PD model [181]. In addition, increasing IL-1β levels correlates with diminishing in the Bcl-2 expression in the LPS-induced PD model [104]. There have been evidenced increased activities of ICE and caspase-3 in the SN of post-mortem brains from parkinsonian patients compared to controls, whereas no significant

differencewere found in the striatum [182]. However both caspases and calpains appeared to conduce to neurodegeneration, the inhibition of caspase proteins, unlike calpains, has been clearly shown to be neuroprotective against ceramide exposure-induced cell death in CAD cells [183](very confuse). The evidence have pointed out the role of both caspase-1 and -3 in neurodegeneration of SN of PD models, which could be ameliorated by osmotic pump infusion of IL-10 and AS101 [104, 105]. However, this advantageous role of both caspase-1 and -3 inhibitors has been solely attributed to improvement of dopaminergic maturation, not to overall survival of these neurons, in the model of E14 rat ventral mesencephalon-derived dopaminergic neurons [184].

9. Consequences of Current Therapeutic Protocols in PD

This paragraph need an introductory sentence. The lack of teripeptide glutathione (GSH), which mediates the oxidant homeostasis in the nigra of PD patients, establishes a chain of events of oxidative degradation of L-DOPA and dopamine and generation of ROSs leading up to the cellular damages [185, 186]. Hereon, L-DOPA is prescribed for a perfect proportion of patients with PD and its early intervention is associated with the improvement of motor symptoms [187]. Surprisingly, patients with PD receiving L-DOPA for a long time had to face up with the abnormal involuntary movements (AIMs). The L-DOPA-induced dyskinesia (LID) in the hemi-parkinsonian rat are correlated with an increased level of IL-1β in the lesion side and a decreased level of LID after IL-1Ra injection [188].

The role of IL-1β has been proved advantageous in differentiation of NPCs towards the dopaminergic phenotype in vitro [174]. However, the resultant promotion of motor and

cerebellum functions justifying the transplant treatment by MSCs and adipose-derived stem cell (ADSC) were accompanied by a reduction in the IL-1β expression [90, 189]. Meanwhile, the survival of dopaminergic (DA) neurons was independent of both exogenous IL-1β and IL-1Ra expression [190].

10. Factors that Affected on the Concentration of IL-1β (this title is not appropriate) IL-1 and depression could be better

A considerable proportion of PD patients suffers from depression disorder [191]. As mentioned before, patients with PD represented an increase in the level of IL-1β and a decrease in IL-1Ra levels [192]. However, no association was found between the fatigue scale and the circulating concentration of IL-1Ra in PD patients [192]. This finding is consistent with positive correlations between depression and the concentrations of IL-1β and IL-1Ra [193]. Depression disorder is widely anticipated to be coinciding with PD; then there is a special need to design a prophylactic setting with anti-inflammatory purposes specific to patients with PD.

11. Role of Protease-Activated Receptors (PARs) in PD

IL-1β production could be inhibited by PAR-1 inhibitor cathepsin G and PAR-1 antagonist (SCH-79797), elucidating the point that this receptor and probably other members of PAR family play a leading role in the α-SYN-induced microglia-induced IL-1β play(very confuse) [67]. However, it has been shown that the overexpression of PAR-1 on astrocytes and neurons but not on microglia cells led to the release of glutathione peroxidase, which is known to be a brain' compensatory mechanism in the attempt to

protect dopaminergic neurons against degeneration [194]. These lines of evidence suggest that the role of PAR family should be regarded as double-edged sword.

12. IL-1β in the Neuronal Survival

The dual function of IL-1β in neurodegeneration is due to its leading role in the neuroprotection against NMDA-induced excitotoxicity, neurite outgrowth of brain slices, hippocampus-dependent working memory, and as well in the differentiation of human neuronal progenitor cells (NPCs) towards the dopaminergic phenotype in vitro [137, 139, 174, 195, 196]. Interestingly, this neuroprotective mechanism of action of IL-1β was detected following acute administration of IL-1β in hippocampus, but not following subacute one, stressing the importance of time for intervention [196]. Nevertheless, the nerve growth factor (NGF), contrary to IL-1β, influenced significantly the neurite outgrowth inspinal cord. , The similarity between the roles of IL-1β and NGF on neuronal survival was described, where that IL-1β strived to a: protect neurons against NMDA-induced neurotoxicity and also b: to promote neurite growth and cell survival of rat superior cervical ganglion (SCG) grafts, largely depending on the NGF contribution [139, 195, 197] Very confuse. As it was widely anticipated that the neuroprotective effect of IL-1β Ra, the IL-1β-induced neuroprotection was effectively restrained by IL-1Ra in NMDA-induced excitotoxicity in the mouse cortical neuronal cultures [139].

The beneficial aspect of the role of IL-1β in preventing neuronal damage/death is mediated through its influence on neurotropic factors. The overexpression of IL-1β results in the astrocytes-specific expression of glial cell line-derived neurotrophic factor (GDNF), which is clearly recognized as the potential promoter of survival/differentiation

of dopaminergic neurons in embryonic midbrain cultures [199, 200]. It is certain that GDNF should be considered as an important therapeutic target architectures of PD and as a matter of fact, treatments including caffeic acid, Ad-Ho-1, AS101 (Tellurium immunomodulating compound ammonium trichloro (dioxoethylene-O,O'-) tellurate), thrombin, and MOG immunization could achieve to the increased level of GDNF and subsequent neuroprotection in the injured areas(I don't understand what do you mena) [87, 99, 101, 105, 194]. As well it was expected that some of the aforementioned treatments, for example complete Freund's adjuvant (CFA) pretreatment, increased the GDNG level accompanied with the overexpression of IL-1β [118].

13. Concluding Remarks

It is now well understood that neurodegeneration and immune system-derived mechanisms are intimately intertwined. A quick scan of the evidence reveals the character of anti- and pro-inflammatory cytokines as hero and anti-hero in the scenario of neurodegeneration. In deep, the literature fires several question marks concerning the mechanism of action of each neurodegenerative process thatinvolve immune responses and cytokines. Excellent reviews were written on the role of inflammation in neurodegeneration as a whole; however, less is pored over the issue of each cytokine in the context of neurodegeneration. Here we presented evidence elucidating that the interleukin-1 beta (IL-1β) has a multi-faceted character in pathogenies of Parkinson's disease. Increased levels of IL-1β in P and the involment of IL_1b in several animal modelssuggest that IL-1β may be either propagator or progenitor in dopaminergic degeneration I still don understand propagator and progenitor). On the other hand, decreased levels of IL-1β suggest that IL-1β may be either a postponer or prohibitor (these are very confuse terms) in dopaminergic degeneration. As well, unaltered levels of IL-1β suggest that IL-1β has no clear role in dopaminergic degeneration(what it means??). Altogether human and experimental studies suggest the full spectrum of findings about the role of IL-1β in PD patients It make no sense human and animal

models and then PD patients. Presumably the broad range of IL-1β roles is due to its interaction with two vast arrays of upstream inducers and downstream mediators. This Up-Down (explain better) IL-1β neuroweb is held principally by glia population (i.e. microglia and astrocytes), MAPK and NF-κB signaling pathways, and various mediators (including cyclooxygenase, neurotrophic factors, reactive oxygen species, caspases, Heme oxygenase-1, and matrix metalloproteinases).Our review evidences adual mechanism of action of IL-1β in Parkinson's disease. The overproduction of IL-1β induced by microglia could be an involved in dopaminergic neurodegeneration, but, on the other side, the expression of neurotrophic factors,. Induced by IL-1b,, reveal a a double-edged roleof both IL-1β and glial population during chronic neurodegenerative diseases. Accordingly, the simplest therapeutic protocol should include an efficient inhibitor of IL-1β and favors to the most important neurotrophic factors. However, it is mandatory to design strategies based on the selective regulation of all identified molecules or cells as upstream inducers and/or downstream mediators of cytokines, such as IL-1β.

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Abbreviations used throughout the manuscript

6-OHDA: 6-hydroxydopamine

AAV2-hIL-10: Vector containing cDNA for human interleukin 10

3-AB: PARP inhibitor 3-Aminobenzamide

Aβ: Amyloid beta

Acoraceae/AG: Acorus gramineus Solander

Ad-HO-1: Adenovirus containing human HO-1 gene

AdIL-1: Adenovirus expressing interleukin 1

ADSC: Adipose-derived stem cell

AS101: Tellurium immunomodulating compound ammonium trichloro (dioxoethylene-O,O'-) tellurate

BCR: B-cell receptor

bFGF: Basic fibroblast growth factor

Candesartan: Angiotensin type 1 receptor antagonist

C\EBPβ: CCAAT (cytosine-cytosine-adenosine-adenosine-thymidine)/enhancer binding protein (C/EBP), beta

CFA: Complete Freund's adjuvant

CI: Chrysanthemum indicum Linn

CNS: Central nervous system

CSF: Cerebrospinal fluid

Diphenyliodonium: An inhibitor of the NADPH oxidase

ERK: Extracellular signal-regulated kinase

GDNF: Glial cell line-derived neurotrophic factor

GL: Ganoderma lucidum

HFE: Honey flavonoid extract

HIV gp120: Envelope glycoprotein gp120 of human immunodeficiency virus

ICE: Caspase 1

IFN-γ: Interferon gamma

IL-1α: Interleukin-1 alpha

JNK: c-Jun amino-terminal kinase

KCa3.1: This protein is encoded by potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4 (KCNN4).

KR-31360: K252a pyridylimidazole compound

LPS: Lipopolysaccharide

LRRK2: Leucine-rich repeat kinase 2

m-CPP: m-chlorophenylpiperazine

MAPK: Mitogen-activated protein kinase

MMP: Matrix metalloproteinase

MOG: Myelin oligodendrocyte glycoprotein

MSCs: Mesenchymal stem cells

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

NGF: Nerve growth factor

NMDA: N-Methyl-D-aspartate

NPCs: Neuronal progenitor cells

Nrf2: Nuclear factor erythroid 2–related factor 2

NSAIDs: Non-steroidal anti-inflammatory drugs

PARs: Protease-activated receptors

PARK2: Parkin RBR E3 ubiquitin protein ligase

PARK7: Parkinson protein 7

PBMCs: Peripheral blood mononuclear cells

PDTC: Pyrrolidine dithiocarbamate

PINK1: PTEN induced putative kinase 1

PTIQ: 7-hydroxy-6-methoxy-2-propionyl-1,2,3,4-tetrahydroisoquinoline

PYC: Bioflavonoid compound Pycnogenol

RvD1: Resolvin D1

S100B: S100 calcium binding protein B

sAPP: Secreted forms of the beta-amyloid precursor protein (APP)

Sch B: Schisandrin B

TAK1: Transforming growth factor beta-activated kinase 1

TEN: Tenuigenin

TNF-α: Tumor necrosis factor alpha

TRAF6: TNF receptor-associated factor 6, E3 ubiquitin protein ligase

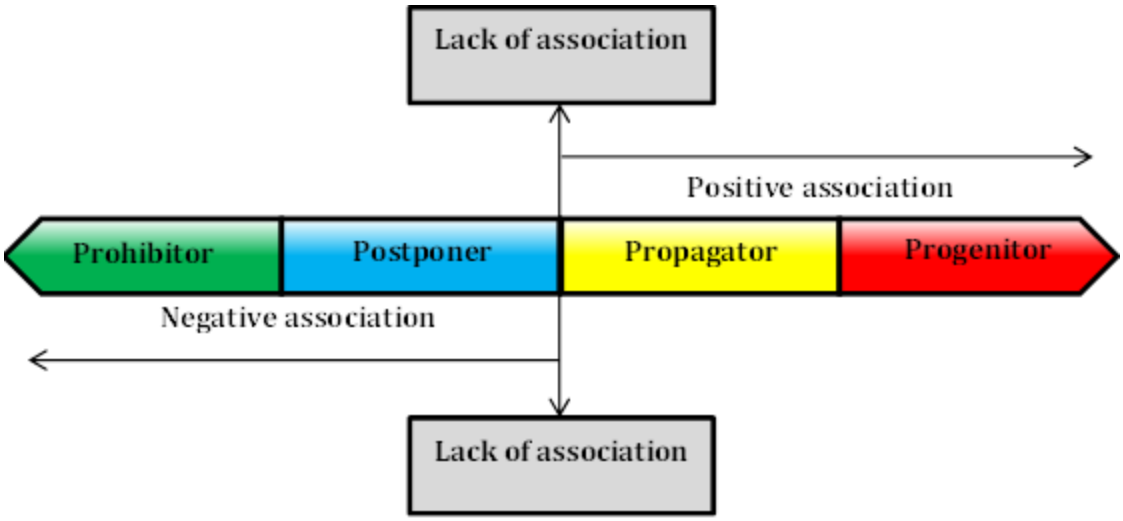

Figure 1. The role of IL-1β in Parkinson's disease. This figure represent a very double-edged remark about the broad range of IL-1β rols in Parkinson's disease. The figure shows that the IL-1β has a multi-faceted character in the pathogenies of Parkinson's disease. Increased levels of IL-1β in PD patients and in animal experimental models suggest that the IL-1β may be either propagator or progenitor in dopaminergic degeneration. On the other hand, decreased levels of IL-1β suggest that IL-1β may be either a postponer or prohibitor in dopaminergic degeneration. As well, unaltered levels of IL-1β suggest that IL-1β has no clear role in dopaminergic degeneration.

You dont explain what means negative or positive association in the caption. An arrow indicating decreasing or increasing levels of association could be very self explanatory