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Review

Cellular phenotypes as inflammatory mediators in Parkinson's disease: Interventional targets and role of natural products

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ABSTRACT

Pathogenesis of Parkinson's disease (PD) is undoubtedly a multifactorial phenomenon, with diverse etiological agents. Pro-inflammatory mediators act as a skew that directs disease progression during neurodegenerative diseases. Understanding the dynamics of inflammation and inflammatory mediators in preventing or reducing disease progression has recently gained much attention. Inflammatory neuro-degeneration is regulated via cytokines, chemokines, lipid mediators and immune cell subsets; however, individual cellular phenotypes in the Central Nervous System (CNS) acts in diverse ways whose persistent activation leads to unresolving inflammation often causing unfavorable outcomes in neurodegenerative disease like PD. Specifically, activation of cellular phenotypes like astrocytes, microglia, activation of peripheral immune cells requires different activation signals and agents like (cytokines, misfolded protein aggregates, infectious agents, pesticides like organophosphates, etc.,). However, what is unknown is how the different cellular phenotypes respond uniquely and the role of the factors they secrete alters the signal cascades in the complex neuron-microglial connections in the CNS. Hence, understanding the role of cellular phenotypes and the inflammatory mediators, the cross talk among the signals and their receptors can help us to identify the potential therapeutic target using natural products. In this review we have tried to put together the role of cellular phenotypes as a skew that favors PD progression and we have also discussed how the lack of experimental approaches and challenges that affects understanding the cellular targets that can be used against natural derivatives in alleviating PD pathophysiology. Together, this review will provide the better insights into the role of cellular phenotypes of neuroinflammation, inflammatory mediators and the orchestrating factors of inflammation and how they can be targeted in a more specific way that can be used in the clinical management of PD.

1. Introduction

Parkinson's disease (PD) is, after Alzheimer's disease, the second most common neurodegenerative disorder clinically represented by slowness of movements, tremor, rigidity, and postural instability whose pathogenesis is associated with progressive loss of substantia nigra pars compacta (SNpc) dopaminergic (DA) neurons [1]. However, the exact mechanisms underlying pathogenesis of PD has not yet been fully explained. Though researchers postulate a number of possible pathogenic mechanisms over the years, including role of toxic oxygen free radicals during enzymatic dopamine catabolism, loss of mitochondrial function and trophical support, dyshomeostasis of kinase activity and intracellular calcium, abnormal protein degradation and neuroinflammation, the pathogenesis of PD and their potential therapeutic

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targets remains challenging [2]. Furthermore, the current drugs for PD have largely met with failure due to lack of efficacy and lack of target of specificity in context with cellular phenomenon such as protein and gene metabolism. Also, there is much evidence that denotes the role of individual genes and proteins in brain parenchymal cells might act as double-edged sword in contributing to cellular component dysfunction and pathogenesis of PD [3].

Classical knowledge on the role of events associated with inflammatory and non-inflammatory targets will highly serve in identifying early therapeutic options and will set pace for progressive treatment to those who are in greater demand for better cure against this debilitating neurodegenerative disorder PD [4]. In this review, we have briefly addressed how the role of inflammation associated neuro-degeneration and the cellular phenotypes associated with inflammation in PD can be used a potential therapeutic target for neuro-protection. Based on a review of recent and previous literatures about therapeutic targets in pathogenic mechanisms of PD, strategies that aim and target inflammation and associated events are highly regarded as potential targets PD treatment. To support our notion, there is lot of recent findings that denotes the possible involvement of immune mechanism as pathogenic mediator of NDDs. In various diseases like Alzheimer's (AD), Hungtinton's (HD), multiple sclerosis (MS) presence of inflammatory mechanisms were strongly documented with experimental and clinical research studies. Such studies denote that presence of an inflammatory niche could act as an initial trigger that may eventually cause cell death or as a result of secondary response to neuronal or brain parenchymal cellular injury [5].

Nature has gifted us with enormous benefits in the form of medicinal plants, dietary components (fruits and vegetables) that has been considered and shown to exert protection against PD's while their exact mechanism of actions are unknown. Hence, studies and literatures that covers the importance of such natural products and their use on specific cellular targets like inflammation and the cellular phenotypes of inflammation associated with pathobiology of PD's will pave new avenues for an enhancing the therapeutic/clinical management of PD's patients life. Given the information that naturally existing plant components are well known not only for their anti-oxidative, anti-inflammatory activities and but also their inhibitory roles on iron accumulation, protein misfolding and maintenance of proteasomal degradation, mitochondrial homeostasis that are reported in PD's pathogenesis, here we have reviewed the present understandings of neuroinflammatory events and the associated cellular phenotypes, underlying molecular players and their role in PD's pathogenesis and how they can be targeted using natural products for protecting against PD's [6–8].

2. Limitations of therapeutic approaches in Parkinson's disease

Clinically PD patients develop several complications that impair their survival in terms of motor and non-motor complications, including dyskinesia, unpredicted response to drugs, dementia hallucinations, sleep disorders, depression and psychosis [6]. Drugs like mono amine oxidase B (MAO-B) inhibitors (Causes hypertension, cardiac arrhythmia), dopamine agonists (DA) (Causes nausea, vomiting, nasal congestion, head ache, sudden sleep attack), Catechol-O-methyl transferase (COMT) (causing involuntary muscle movements, cramps, nausea, vomiting, insomnia, headache, diarrhea etc.,) NMDA antagonists (amantadine) and anti-cholinergics (like amantadine causing swollen ankles and mottled skin, visual hallucinations etc.,). However, none of the above drugs can completely reduce or inhibit the various PD pathological pathologies as its etiology remains complex and hence a greater understanding of its pathobiology will pave way for better therapeutic avenues [6,7].

Also recently drugs that were successfully marketed for PD, for example, $D_{2/3}$ receptor agonists (D-152, ropinirole) [8], safinamide [9,10], and Opicapone [11] also exerts adverse side effects, while few drugs like rasagiline and exenatide (under testing for clinical applications), a glucagon-like peptide-1 (GLP-1) receptor agonist were found to be protechave beneficial effects. For example, D2/3 agonists exerts protections during early-stage PD's, while it is less effective in later disease stages and does not regulate / inhibit disease progression, while safinamide, APO controls motor function abnormalities in advanced PD conditions and improves quality of life but does not completely prevents PD's symptoms [8,10]. Similarly, opicapone, a new COMT inhibitor developed is found to increase the on-time without troublesome dyskinesia while reducing the off-time, however is not exempted from side effects like dyskinesia or in having drawback of providing complete cure against PD [11].

3. Inflammation and neuro-degeneration in Parkinson's disease

Right from the first report on PD in 1817, the pathobiology of PD remains uncertain while recent studies suggest neuroinflammation and microglia, the major resident brain parenchyma plays crucial role in its pathogenesis. To date, the most important question is whether protein aggregates cause the selective loss of dopaminergic neurons causing clinical symptoms and associated neuroinflammation is a cause or consequence of neuronal cell loss in substantia nigra [12–16]. Moreover, increasing evidence denotes neuroinflammation may be a likely contributor to PD development, progression and the genetic mutations of PD's might incline PD subjects to increased neuroinflammation. Interestingly reports denotes that inflammatory niche prevailing in this chronic degenerative disorder is unusual because CNS is considered to be an immune privileged area [17], which evolved over many years. We consider here the key targets of immune response associated with PD and the associated cellular and molecular phenotypes that can be used as therapeutic targets with a view to develop as a clinically potential agent for the disease control. Furthermore, inflammation is also speculated to be a convergence point for genetic and environmental factors that promote PD pathogenesis. Factors like viral, bacterial infections, neuronal injury, other factors inducing chronic inflammatory syndromes (rheumatoid arthritis, atherosclerosis, diabetes, crohns disease, multiple sclerosis), environmental toxins (pesticides, particulate matter), gastrointestinal inflammation and infections etc., [14,15]. Further, the role of peripheral immune cells in inflammatory response in PD has not been extensively investigated, based on the merits of recent reports it is known that inflammation in CNS of PD is highly contributed via infiltration of peripheral immune cells from circulation, favored by dysfunctional blood brain barrier (BBB). For instance, presence of CD4 + and CD8 + T cells populations are observed in SNpc of PD patients and in MPTP-intoxicated mice [18]. To add presence of CD4 + /CD25 − effector T cells and CD4 + /CD25 + regulatory T cells (Tregs) were also found to be involved in PD inflammation progression. Based on the above information's it is known that not only resident macrophage but also adaptive immune system contributes to the pathogenesis of PD via modulation of several effector cells which we has been described below in detail in sections "cellular Phenotypes and inflammation in PD. Hence, a comprehensive review on the role of effectors of immune mediators in PD will shed light on identifying novel targets to deliver neuroprotective agents and the use of the naturally products like plant derivatives and their components will be of greater boon to regulate or inhibit disease progression.

3.1. Cellular phenotypes and inflammation in Parkinson's disease

Epidemiological, genetic studies and post-mortem studies support a role of neuroinflammation in the pathophysiology of PD via involvement of innate and adaptive immunity in the affected brain regions of PD [19] Indeed reports denotes the role of diverse cellular phenotypes in the SNpc of patients with increased inflammation in PD. Presence of activated microglial cells, reactive astrocytes in the parenchyma (neurons, astrocytes and endothelial cells) of CNS, along with direct involvement of adaptive and innate immune systems, enhanced