Editorial

Linking Immune Activation and Parkinson's Disease

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The potential etiologies and pathogenetic mechanisms of Parkinson's disease (PD) have been investigated extensively. Several epidemiologic studies have highlighted the contributions of various genetic mutations/variations, lifestyle and environmental factors [1]. With the exception of a few rare inherited forms of PD, post mortem studies reveal pathologic hallmarks comprising alpha-synuclein positive inclusions (termed Lewy bodies and Lewy neurites), with dopaminergic cell loss in the substantia nigra and degenerative changes in other brain regions. In affected brain regions, evidence of oxidative stress, mitochondrial and endolysosomal dysfunction, impaired proteosomal function, and protein misfolding have been well documented, and disease models from experimental laboratories have added further mechanistic insight [1]. Notably, post mortem brains reveal inflammatory changes in the substantia nigra and limbic system in PD, suggesting that neuroinflammation may play a role in disease susceptibility and/or progression [1].

The cause and effect relationship between neuroinflammation and neurodegeneration in PD is difficult to determine as the initiating event(s) likely occur many years before neuronal loss and clinical manifestations arise. PD is influenced by many factors including a mix of immunogenetics and the environment, such as infection history [2]. In recent years, increasing evidence suggests an association with autoimmune conditions, with involvement of the immune system or its aberrant responses in patients and various experimental models [1, 3–20]. In this special issue, a series of articles highlight the latest research breakthroughs on the links between immune activation and neuroinflammation and PD, and discuss the challenges and novel therapeutic strategies targeting the immune system, all of which hope to reduce or reverse neurodegeneration. Here, we briefly mention some of the key take aways from these state of the art reviews.

Observations from several population-based cohort studies have found an association between inflammatory bowel disease and other autoimmune diseases and PD risk, where some have shown an apparent protective effect, possibly conferred by immunosuppressant medications [3]. Interestingly,

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variants in genes involved in immune system regulation have been similarly found in both PD and autoimmune conditions. Bioinformatic analysis utilizing gene expression and protein data have further corroborated shared genetic risk variants and molecular pathways [3]. Glucocerebrosidase (GBA) mutations, which – depending on the specific population that is studied – are found in 5-20% of PD patients worldwide, have been implicated in aberrant immune responses (such as microglia-mediated antioxidant and protective response in neurons) [4]. Some data suggest neuroinflammation and peripheral immune changes in patients with isolated REM sleep behaviour disorder and asymptomatic carriers of GBA or LRRK2 gene mutations [5].

The immune system comprises innate (first line of defense against pathogens without prior encounter) and adaptive (dependent on antigen presentation and activation) immunity. T cells, neutrophils, monocytes, dendritic cells, and natural killer (NK) cells form the cellular immunity, while humoral immunity involves antibodies and complement proteins. Several clinical studies using blood and cerebrospinal fluid (CSF) from PD patients have suggested involvement of both cellular and humoral immunity with evidence of changes in pro-inflammatory and anti-inflammatory mediators [6]. B lymphocytes (especially regulatory subset) are decreased in PD, although the relative temporal changes in peripheral and CSF B cells over time in patients still need to be evaluated further [7]. T lymphocyte subsets are altered, with a shift towards pro-inflammatory Th1 and Th17 cells in PD, and with an attenuation of age-related senescent changes in CD8+ T-cells [8]. Furthermore, T lymphocytes with specificity for alpha-synuclein peptides are found in higher numbers in PD cases versus controls [9]. T lymphocytes enter the brain in PD and there is evidence that neurons in the substantia nigra and locus coeruleus express MHC Class I molecules. Recent results suggest that CD8+ T lymphocyte recognition of the antigen/MHC Class I complexes on neuronal membranes promotes cytotoxic cell damage [10]. Changes in NK cells (innate lymphocytes involved in antimicrobial defense) and their receptor expression have been reported in PD patients [11].

Microglia are the innate immune cells in the brain. By helping to clear waste and toxic products, they have a protective role in maintaining homeostasis in the brain. Activated microglia have been described in brains of PD patients, and they might interact with pathological alpha-synuclein assemblies by affecting clearance and spreading of protein aggregates. Activated microglia can present autoantigens to T cells through MHC class I and II molecules, thereby activating the adaptive immune system. They have also been suggested to play a role in the conversion of astrocytes into neurotoxic phenotypes [12].

Understanding how neurons respond to the early stages of inflammation will provide crucial clues for potential early intervention. In this context, the demonstration of inflammasome activation in the brain suggest that these multi-protein intracellular signaling complexes (part of the innate immune system) play an important role in neuroinflammatory responses to pathogens and toxic insults [13]. It is interesting to note that chronic NLRP3 (NLR Family Pyrin Domain Containing 3) inflammasome activation is facilitated by pathogenic misfolded alpha-synuclein aggregates, while targeting NLRP3 inflammasome activation is protective in experimental animal models [14].

There is increasing interest in gut-derived inflammation. Several groups have shown that microbiota in the gut are linked to inflammatory processes in both clinical and experimental models. PD patients appear to have different gut microbiota compared to controls (albeit that the pattern is not consistent across different studies), and the use of microbiota from PD patients promoted neuroinflammation and motor phenotype in an alpha-synuclein overexpression mouse model [15]. Whether altering commensal microbiota, e.g. via the use of probiotics, can protect against the development of PD (when applied during the prodromal disease phase) or slow down disease progression (in those with manifest PD) still needs to be investigated.

In summary, multiple independent studies in clinical and pre-clinical models have provided corroborative evidence of the involvement of central and peripheral immune and inflammatory processes in PD [1, 3–20]. Our knowledge of how the immune system contributes to PD pathogenesis is constantly evolving, with increasing evidence for a role of several genes and susceptibility loci [1, 3]. A major challenge is to use these data and knowledge to identify specific targets within the immune system or to target major pathogenic proteins involved in aberrant immune responses [19]. In this light, clinical trials targeting alpha-synuclein have already commenced and both clinical or experimental trials focusing on different immune components are ongoing. However, considerable research is still needed to determine the individual and collective roles of the individual

immune cells (and their subsets), and how they interact with each other within the neurovascular units and with alpha-synuclein and other key proteins, particularly in the early phase of inflammasome activation and neurodegeneration. From the clinical perspective, longitudinal studies using molecular imaging that measures microglial activation in the brain, and detailed blood and CSF immune function tests and phenotyping in at risk subjects or prodromal PD may identify crucial clues on the temporal cause-effect relationship between neuroinflammation and PD. These studies can potentially identify subsets of patients who are more likely to respond to immune modulatory therapies.

CONFLICTS OF INTEREST

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