Editorial

Investigating lymphocyte populations in patients with Parkinson's disease

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Parkinson's disease (PD) is a globally prevalent age-related neurodegenerative movement disorder. With an average age of onset of 60–70 years, symptoms of PD include muscle rigidity, tremor, bradykinesia, hyposmia, sleep disorders and gastrointestinal dysfunction. PD symptomology is associated with the progressive degeneration of dopamine producing neurons in the midbrain, in conjunction with the spread and pathological accumulation of α-synuclein protein in many brain regions (1). PD is progressively disabling and often culminates in dementia and a reduced quality of life in later years. The motor features of PD can be symptomatically treated with dopamine replacement therapy, and for a subset of eligible patients that can tolerate a more invasive approach, deep brain stimulation. However, current therapies do not alleviate non-motor symptoms and they do not slow down or prevent disease progression.

The current lack of disease modifying therapies for PD largely stems from the incomplete understanding of the biology underlying disease pathogenesis. Indeed, by the time PD is clinically diagnosed, approximately 40–60% of dopamine neurons have already irreversibly degenerated. Estimates based on the extrapolation of brain pathology suggest that PD may commence up to 20 years prior to motor symptoms manifesting and subsequent clinical diagnosis (2). PD symptomology is also heterogenous, confounding both diagnosis and prognosis and suggesting a disease of complex etiology (1). This is supported by genetic studies that collectively suggest a dynamic interplay between genes and the environment may modulate both PD risk and disease progression [for review see (3)]. As a main interface between the body and the environment, there is increasing interest in the role of the immune system in PD.

Intriguingly, the earliest PD symptoms and earliest signs of α-synuclein pathology appear not in the brain, but rather in the periphery (4). Although challenging to measure, pathological α-synuclein deposits have been observed in the gastrointestinal tract (5), submandibular gland (6) and skin (7) of prodromal PD patients and/or asymptomatic patients at high risk of developing PD, such as patients with idiopathic REM sleep behaviour disorder (8). Accumulation of α-synuclein in the gastrointestinal tract may underlie enteric nervous system dysfunction and subsequent common prodromal PD symptoms such as constipation (9). Moreover, pathological forms of α-synuclein have been shown to activate innate immune inflammatory pathways (10) and modulate T cell responses (11), ostensibly linking the immune system to PD pathology. Despite this link, determining the extent of immune dysfunction in PD has remained challenging. A number of studies have reported higher levels of inflammatory cytokines in PD patient blood samples, but this is not always observed, and like the clinical symptoms of PD results show considerable heterogeneity [for review see (12)]. A number of studies have also assessed the extent to which circulating immune cell populations in PD patients may underlie inflammatory phenotypes. In general PD is associated with a decrease

in T lymphocytes, but study outcomes are variable and interpretation complicated by the diversity of lymphocyte subsets and how they are phenotyped [for review see (13)]. Further complicating is that, in line with a slow progressing age related disorder, immune phenotypes in PD patients are subtle, requiring robust sample sizes and careful analysis of the data. Moreover, it is possible that only distinct subsets of patients may display altered lymphocyte populations and this may relate to the heterogenous progression of PD.

To further explore peripheral immune cell populations in the context of PD and its symptomology, Sun and colleagues used flow cytometry to measure the percentage of different lymphocyte populations in blood samples obtained from 127 PD patients and 148 well matched healthy control participants. In comparison to the control cohort, they found a significant increase in natural killer (NK) cells combined with a significant decrease in CD4 T cells in the PD patients. Both of these findings are in agreement with a meta-analysis of prior studies investigating lymphocyte populations in PD (14). However, an intriguing observation was that the percentages of measured lymphocyte populations had a markedly increased range in the PD patients. The large sample size studied allowed the authors to determine a normal reference range for the measured lymphocyte populations in their specific cohort. Approximately 30% of PD patients differed from the normal reference range for all lymphocyte populations measured. In all instances, this was significantly higher than the ~10% of control participants that differed from the normal reference range. Statistical modelling suggested that deviation of NK and CD4 T cells from the reference range was associated with increased PD risk, and patients with a divergent population of CD8 T cells had worse PD motor symptoms compared to patients in the normal range. These results add to evidence that alterations in the peripheral immune system can influence disease onset and progression, at least in a subset of individuals.

These findings are of interest and certainly raise a number of questions. First is how might altered T cell populations modulate disease progression? The PD patients that deviate from the normal reference range presumably include members with both abnormally high, and abnormally low percentages of T cells, thus a direct relationship between lymphocyte numbers and disease progression seems unclear. The authors plausibly suggest, that as has been observed in animal models (15), increased infiltration of T cells into the brain may promote neuroinflammation and dopamine neuron degeneration. However, this is difficult to prove in a clinical population. It is also possible that factors secreted from immune cells, that more readily cross the blood brain barrier than the immune cells themselves, may influence neuroinflammation and PD progression. At least one example of such a result was recently observed for mice with the PD implicated LRRK2 G2019S mutation (16). Whether there are any phenotypic differences that functionally link the response of the altered immune cell populations to environmental stimuli would be interesting to determine. There is also the question of when do immune cell populations become altered in PD? The authors propose that the increased PD risk associated with divergence of certain immune cell populations from the normal range infers potential causality. However, the study of a manifesting clinical PD population always raises questions about cause or consequence. It would certainly be of interest to determine if the same immune cell alterations are observed in *de novo* PD patients. In particular, it would be of interest to determine if the same results are observed in cohorts at high risk for developing PD in the future, such as carriers of GBA or LRRK2 missense mutations, or patients diagnosed with idiopathic REM sleep behaviour disorder. Complicating such studies though is the relatively lower available sample size, and as the authors explain, the normal reference range for each cohort may be influenced by age, gender, ethnicity, geographical location and experimental methodology. Potentially even more important is longitudinal assessment. Are altered immune cell populations transient, potentially reflecting an acute change to environmental stimuli, or are these stable adaptations with utility as biomarkers and how do the populations change dynamically with time or disease progression? That not all PD patients exhibit the altered immune cell population phenotype also suggests that this is not a singular cause of PD, but rather modulates risk and progression in a distinct subgroup and may contribute to the heterogeneity of PD symptomology. Finally, in agreement with the authors, is that the characterisation of the immune cell populations is potentially only the starting point. For example, within the lymphocyte population is the divergence from the reference range mediated by particular immune cell subsets such as regulatory T or B cells? Are the results indicating defects in immune cell differentiation and/or can differences be detected at the level of progenitor cells? Are any defects intrinsic to lymphocytes or potentially mediated by other cells such as myeloid cells? Whether myeloid cells show the same phenotype in PD patients would seem important to assess, given the reports of monocyte dysfunction in PD (17), the role of monocytes in mediating the activation and recruitment of lymphocytes and that

monocytes are highly enriched in PD implicated genes (18).

In conclusion, the work of Sun and colleagues provides impetus for continued studies into the role of the peripheral immune system in PD, and the potential use of immune readouts for much needed PD biomarkers. As for all clinical studies, the extent to which the results are replicated and how applicable they are across divergent cohorts will be important to determine.

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Footnote

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