

## **Timing is everything: the T-cell response to alpha-synuclein is maximal in early Parkinson's**

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Accumulating evidence suggests significant involvement of the immune system in Parkinson's disease, both in the brain and systemic circulation.<sup>1</sup> Whilst multiple immune elements are likely to contribute, T-cells have been strongly implicated in both animal and human studies. Genetic association has been established between PD risk and the Human Leucocyte Antigen (HLA) locus,<sup>2</sup> which encodes proteins vital to antigen presentation and recognition by T-cells. Sulzer and colleagues have recently reported an alpha-synuclein-specific T-cell response in PD, associated with possession of known PD risk alleles at the HLA locus,<sup>3</sup> suggesting a potential mechanistic pathway for immune activation in PD. These researchers have now extended this work to investigate how the alpha-synuclein-specific T-cell response differs according to disease duration.<sup>4</sup> This is a critical question to help us better understand its relevance to disease onset and/or progression.

In their new study,<sup>4</sup> Lindestam Arlehamn and colleagues describe a PD case study for whom cryopreserved peripheral blood mononuclear cells (PBMCs) were available longitudinally over 20 years (pre- and post-diagnosis). PBMCs were stimulated with alpha-synuclein epitopes, and cytokine responses evaluated using Fluorospot assays and intracellular cytokine staining. CD4<sup>+</sup> T-cell reactivity against alpha-synuclein was detectable 10 years before diagnosis, and declined following diagnosis. Similar methodology was used in a cross-sectional study including PBMCs from 96 PD cases (disease duration 0-27 years), and 67 controls. The magnitude of the alpha-

synuclein-specific T-cell response was higher in PD than controls, and highest in PD cases close to diagnosis: T-cells from 40% with disease duration <10 years responded, versus only 8.6% with disease duration 10-27 years. Alpha-synuclein T-cell reactivity was correlated with increased age (in keeping with increased autoimmunity in the elderly), and lower levodopa dose (possibly a proxy of earlier disease stage).

The cross-sectional study robustly demonstrates that alpha-synuclein-specific T-cell reactivity is most prominent in the earliest stages of PD, which is in keeping with similar observations regarding alpha-synuclein auto-antibody responses.<sup>5</sup> Whilst the alpha-synuclein T-cell response 10 years before diagnosis in the case study is intriguing, its relevance is unclear, given that similar responses were observed in some controls and Alzheimer's cases. Another important question is why only 40% of early PD cases are responders. This implies that either immune factors are only relevant in a subgroup, or other antigens drive the response in many cases. Further longitudinal characterisation of the immune response and its antigen specificity in PD and controls is needed to help guide targeted immune therapies and their optimal timing.

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3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

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