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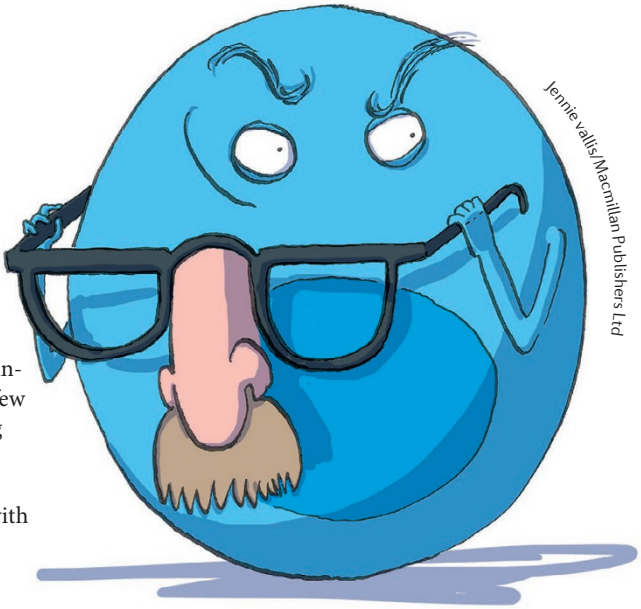
NEUROIMMUNOLOGY

Mistaken identity



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People with Parkinson disease (PD) show specific neuropathology, including neurodegeneration in the substantia nigra (SN) and intracellular accumulation of α-synuclein (α-syn)-containing Lewy bodies. The drivers of this neuropathology are not known, but recent evidence that T cells infiltrate the SN in PD suggests that the acquired immune system might play a part. Here, Sulzer, Sette and colleagues show that fragments of α-syn expressed on cells of the SN induce a form of autoimmunity that could result in the SN neurodegeneration observed in PD.

Activation of the acquired immune system requires recognition of 'foreign' antigens bound to major histocompatibility complex (MHC) family proteins by T cells expressing a receptor that corresponds to the antigen being presented. T cell receptor–antigen binding triggers T cell proliferation and differentiation into $CD4^+$ T helper cells and cytotoxic $CD8^+$ T cells, which generate an immune response that can lead to cell death.

To investigate the relationship between the acquired immune responses and PD, the authors tested the response to α-syn-derived peptides of isolated peripheral blood mononuclear cells (PBMCs), which include T cells, from patients with PD and healthy controls. The cells from patients with PD that responded were mostly interleukin-5-producing $CD4^+$ T cells and a few $CD8^+$ cytotoxic T cells producing interferon-γ.

The authors identified two α-syn-derived peptide regions with antigenic activity. One included the Y39 region of α-syn, which was presented by class II MHC proteins, and the other included the S129 region of α-syn, which required phosphorylation at amino acid residue S129 to activate T cells; phosphorylated S129 is a modification present at high levels in Lewy bodies of patients with PD.

A binding assay of human leukocyte antigen (HLA) class II variants found that peptides including S129, both in phosphorylated and in unphosphorylated forms, bound to several HLA class II variants with varying affinity. Moreover, α-syn fragments containing Y39 bound with high affinity to HLA class II β-chain variants DRB1*15:01 and DRB5*01:01; both of these variants occurred twice as often in people with PD compared with healthy controls. Y39-containing epitopes also bound to MHC class II variant DQB1*03.04 and to an MHC class I variant, A*11.01, which had not been previously associated with PD. Indeed, all the individuals with PD whose PBMCs responded to the Y39 epitope carried one of these four MHC variants. Furthermore, both native α-syn and protofibrils of α-syn, which are associated with PD, induced responses in T cells from patients with PD. Together, these findings show that specific HLA alleles associated with PD encode MHC variants that bind to α-syn epitopes and thus can result in T cell activation and cytokine release.

Overall, these findings demonstrate a functional link between HLA-DRB alleles that are associated with PD and activation of the acquired immune system, and could partly explain the selective vulnerability of SN neurons in neurodegeneration.

Sian Lewis

ORIGINAL ARTICLE Sulzer, D. *et al.* T cells from patients with Parkinson's disease recognize α-synuclein peptides. *Nature* **546**, 656–661 (2017)

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