Th17 Cells in Parkinson’s Disease: The Bane of the Midbrain

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Emerging data implicate potential roles for T cells in Parkinson’s disease (PD); however, direct evidence for human T cells in PD-associated neurodegeneration has been lacking. In this issue of Cell Stem Cell, Sommer et al. (2018) demonstrate that IL-17-producing T cells from sporadic PD patients promote cell death of patient iPSC-derived midbrain neurons.

Parkinson’s disease (PD) is a debilitating neurological disorder caused by degeneration of dopaminergic neurons in the substantia nigra pars compacta. Although the exact etiology of PD remains poorly understood, there has been mounting speculation that aberrant immune responses contribute to disease progression. The link between immune dysregulation and PD in humans is supported by data demonstrating that PD is associated with peripheral immune cell infiltration into the central nervous system (CNS), chronic neuroinflammation, and mutations in immune-related genes (Hamza et al., 2010; Kannarkat et al., 2013). Furthermore, the recent identification of autoreactive T cells directed against alpha-synuclein (α-syn), a protein whose aggregation is a hallmark of PD-associated neuropathology, in PD patients has conjured debate about potential autoimmune origins of the disease (Sulzer et al., 2017). Studies in animal models of PD have largely corroborated many of the immune phenotypes reported in patients and have further extended these findings to show that modulation of immune dysfunction can limit PD-associated neurodegeneration (Brochard et al., 2009; Harms et al., 2013). While these collective studies point toward roles for immune dysfunction in PD, the field has been in search of further proof that patient-derived immune cells can directly promote death of autologous neurons in order to further substantiate the involvement of the neuroimmune axis in PD.

In this issue of Cell Stem Cell, Sommer et al. (2018) report that IL-17-producing T cells are drivers of PD-associated neurodegeneration. To interrogate whether PD patient-derived T cells are capable of promoting neuronal cell death, they established an autologous cell co-culture system composed of human induced pluripotent stem cell (hiPSC)-derived midbrain neurons paired with peripheral blood T cells. In their experimental setup, fibroblasts and peripheral T cells were collected from sporadic PD patients and age-matched controls, and then fibroblasts were reprogrammed into hiPSCs followed by differentiation of hiPSCs into midbrain neurons. They then paired these hiPSC-derived midbrain neurons with autologous T cells. Leveraging this innovative hiPSC-based approach, they demonstrate that PD patient-derived T cells cause cell death of midbrain neurons in their culture conditions, whereas T cells isolated from healthy controls were not found to negatively impact survival of hiPSC-derived midbrain neurons.

In their assessment of circulating T cell effector responses in PD, the authors observed elevated production of IL-17 by CD4+ T cells (commonly referred to as T helper 17 cells or Th17 cells) in the PD population in comparison to healthy controls. To ascertain whether IL-17 production could underlie T cell-mediated neuronal cell death, co-cultures were treated with IL-17 or IL-17 receptor (IL-17R) neutralizing antibodies to abrogate the effects of IL-17. In these studies, ablation of IL-17 signaling fully rescued T cell-mediated neuronal cell death in PD co-cultures (Figure 1), which indicates a critical role for human IL-17-producing T cells in neuronal cell death. The involvement of CD4+ T cells in PD-associated neurodegeneration proposed by Sommer et al. in this issue is further supported by recent studies in mouse models of PD (Brochard et al., 2009; Harms et al., 2013; Liu et al., 2017). In one such study, CD4+ T cells were shown to be major culprits of dopaminergic cell death in the MPTP model of PD (Brochard et al., 2009). Likewise, mice lacking CD4+ T cells were also found to be protected against neurodegeneration in a PD mouse model driven by α-syn overexpression (Harms et al., 2013).

Through this study and others, it is clear that T cells can instigate dopaminergic neuron cell death, both through the effects of CD8+ cytotoxic T cell killing of neurons and via T cell-mediated IL-17 production (Figure 1) (Cebrián et al., 2014). While the findings presented by Sommer et al. (2018) in this issue break new ground in our understanding of how human T cell responses can contribute to neurodegeneration in PD, a number of important questions still remain. For example, it will be important to explore how glial cells and other infiltrating immune cells influence the neurodegenerative properties of Th17 cells in the brain. Adding hiPSC-derived microglia into the co-culture system would be a logical next step as recent studies demonstrate that activated microglia promote the upregulation of antigen presentation on neurons and that this leads to cytolytic CD8+ T cell-mediated killing of neurons (Cebrián et al., 2014). This work suggests that microglia are prominent modulators...
Figure 1. Mechanisms Underlying T Cell-Mediated Neurodegeneration in Parkinson’s Disease

(A) IL-17-producing CD4+ T cells (Th17 cells) isolated from Parkinson’s disease patients provoke midbrain neurons to undergo cell death. Engagement of the IL-17 receptor (IL-17R) on neurons causes altered NF-κB activation and subsequent neurodegeneration. The ability of microglia and astrocytes to modify Th17 cell-induced neuronal cell death requires further investigation.

(B) IFN-γ production and secreted factors produced by activated microglia promote aberrant upregulation of MHC class I expression by catecholaminergic neurons. This induction of antigen presentation by MHC class I on neurons can trigger activation of cytotoxic CD8+ T cells capable of killing neurons.

of adaptive immune responses in PD; however, whether microglia influence CD4+ T cell effector responses in PD has yet to be studied in great detail.

The antigen specificity of the IL-17-producing T cells identified in PD patients by Sommer et al. (2018) also requires further investigation. In their studies, they relied on activators of polyclonal T cell responses to conclude that IL-17 production by T cells is elevated in the PD population compared to healthy controls. A recent study reported that CD4+ T cells isolated from PD patients do not produce appreciable levels of IL-17 in response to a-syn-derived peptides (Sulzer et al., 2017). Instead, these a-syn-specific T cells were shown to produce IFN-γ and IL-5 (Sulzer et al., 2017). Taken together, this implicates that the Th17 responses identified by Sommer et al. (2018) in PD are likely directed against antigens other than a-syn. Determining whether IL-17-producing T cells in PD target other CNS-specific antigens will be an important area of future investigation. The intestinal microbiome has emerged as an important inducer and also regulator of Th17 responses (Ivanov et al., 2009). Therefore, the potential exists that the Th17 responses identified in PD patients are microbiota specific. Interestingly, there has been increasing evidence linking gut microbiota to PD (Sampson et al., 2016), and it is possible that the induction of commensal-specific Th17 responses might provide a mechanistic explanation as to how microbiota dysbiosis can contribute to PD.

The clinical implications stemming from this study are promising, as treatment with the already FDA-approved drug seckinumab could potentially be used to slow disease progression in PD patients. This avenue of treatment could prolong the time before dopamine replacement drugs are required and greatly improve quality of life. However, further in vivo testing must be done to clarify the relevance of this model in a more complex cellular environment. Clinically, this study not only provides a plausible mechanism behind the dopaminergic cell death but also implicates PD into the broader category of inflammatory and potentially even autoimmune diseases.

REFERENCES


