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IL-10 Responsiveness in Autoimmune Monocytes Shapes the Induction of Tolerogenic Dendritic Cells

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Interleukin 10 (IL-10) is a central anti-inflammatory cytokine that plays a pivotal role in the establishment and maintenance of peripheral immune tolerance. IL-10 imprinting on human monocytes drives the differentiation of a subset of tolerogenic dendritic cells (tolDC), known as DC-10. Our previous studies demonstrated that monocytes from patients with multiple sclerosis exhibit a reduced capacity to differentiate into functional DC-10 compared with those from healthy controls, suggesting disease-associated intrinsic or extrinsic defects. For investigating this aspect, we characterize the ability of circulating monocytes from patients with different autoimmune diseases, including Type 1 Diabetes (T1D), Rheumatoid arthritis (RA), and Neuromyelitis Optica (NMO), to respond to IL-10. As control, monocytes from age-matched healthy subjects (HD) were used. Upon LPS stimulation, autoimmune monocytes produced higher levels of TNFα and IL-6 than HD monocytes; however, they maintained the ability to properly respond to IL-10. Consistent with this, autoimmune monocytes successfully differentiated into functional DC-10, capable of inhibiting allogeneic CD4+ T cell activation, proliferation, and IFN-g production, and inducing Type 1 T Regulatory (Tr1, CD4+CD45RA-CD49b+LAG3+) cells at levels comparable to DC-10 generated from HD monocytes. We next evaluated the ability of autoimmune monocytes to be engineered with a lentiviral vector encoding for IL-10 and disease-associated antigen. Engineered DC generated from monocytes of T1D and NMO patients produced supra-physiological levels of IL-10 and effectively inhibited autologous antigen-specific $CD4^+$ T cell responses *in vitro*. These findings demonstrate that, despite their pro-inflammatory profile, monocytes from patients with autoimmune diseases retain the capacity to respond to IL-10 and can be successfully differentiated or engineered into functional tolDCs, supporting their use as a platform for personalized cell therapies to restore tolerance.