AUTOIMMUNITY

Monocytes take centre stage

DOI:
10.1038/nri2166

New research published in *Nature Medicine* reports that a subset of monocytes has been shown to have a pivotal role in T-cell-mediated attenuation of autoimmune disease in the central nervous system (CNS). These results were obtained in mice with experimental autoimmune encephalomyelitis (EAE) that had been treated with glatiramer acetate (GA; Copaxone; Teva Pharmaceutical Industries Ltd.), a drug approved for the treatment of patients with the relapsing–remitting form of multiple sclerosis.

GA is a synthetic random copolymer made up of four amino acids that resembles myelin basic protein. Its mechanism of action has not been fully elucidated, although most studies have focused on its influence on the adaptive immune response. There have been reports, however, that GA might also act on antigen-presenting cells (APCs).

In this study, Weber *et al.* confirmed that GA prevents and reverses established EAE in mice, and promotes a bias towards the T helper 2 (T_H2)-type for myelin-reactive T cells and induces the expansion of forkhead box P3 (FOXP3)$^+$CD4$^+$CD25$^+$ regulatory T (T_{Reg}) cells. Interestingly, they observed that the beneficial clinical effects of treatment with GA were associated with the development of type II, or anti-inflammatory, monocytes. These monocytes secreted less pro-inflammatory (tumour-necrosis factor (TNF) and interleukin-12 (IL-12)) and more anti-inflammatory (IL-10 and transforming growth factor-β (TGFβ)) cytokines compared with monocytes from control-treated mice, and also showed reduced signal transducer and activator of transcription 1 (STAT1) signalling. STAT1 augments pro-inflammatory cytokine production while repressing anti-inflammatory cytokine production.

Antigen-specific T-cell lines generated from GA-treated patients with multiple sclerosis show T_H2-cell polarization, and there have been some reports that GA treatment of multiple sclerosis can restore the number and function of T_{Reg} cells. The authors therefore investigated whether type II monocytes from GA-treated mice could direct T-cell-mediated immune modulation, and showed that they promoted the differentiation of both T_H2 cells and T_{Reg} cells *in vitro* independent of T-cell antigen specificity. Previous studies suggest that the beneficial effects of T_{Reg} cells induced by GA treatment are due to their cross-reactivity with myelin antigen, but here, the authors showed that foreign-antigen-specific T_{Reg} cells induced by type II monocytes ameliorated EAE, suggesting that neither GA specificity nor recognition of self antigen is required for the therapeutic effects of GA-induced T_{Reg} cells.

But how do type II monocytes from GA-treated mice behave *in vivo*? The authors adoptively transferred GA-induced type II monocytes into recipient mice with established EAE, and this was shown to ameliorate the disease. The proliferation and secretion of T_H1-type cytokines by myelin-reactive T cells were reduced, whereas T_H2-type cytokine secretion was increased. Development of pro-inflammatory T_H17 cells was suppressed, and the attenuation of EAE was shown to require the induction of MHC-class-II-restricted host T_{Reg} cells.

Type II monocytes, therefore, have a key role in T-cell-mediated immune modulation of autoimmunity *in vivo* following GA treatment, and could be an important therapeutic target to consider for the development of treatments for autoimmune diseases.

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ORIGINAL RESEARCH PAPER
Weber, M. S. *et al.* Type II monocytes modulate T cell-mediated central nervous system autoimmune disease. *Nature Med.* **13**, 935–943 (2007)