12 MICE LACKING FLT3L ARE PROTECTED FROM COLLAGEN-INDUCED ARTHRITIS: IMPAIRED T CELL FUNCTION?

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Background and objectives Autoimmune diseases often result from inappropriate or unregulated activation of autoreactive T cells. The induction and maintenance of T cell tolerance to tissue antigens is essential to prevent autoimmunity. Combinations of central and peripheral mechanisms act in parallel to inactivate, eliminate or control autoreactive T cells. A key requirement for tolerance is the presentation of antigens in a correct context. Dendritic cells (DCs) are the central antigen-presenting cells (APCs) for the initiation of T cell responses. In this context, stimulation of the Flt3 via Flt3L is known to drive expansion and differentiation of DCs. Traditional approaches to treatment of autoimmune diseases through immunosuppression have focused on direct inhibition of T cells. In the present study, the authors examined the targeted inhibition of APCs as a mean to downregulate /prevent autoimmune disease in a mouse model for rheumatoid arthritis.

Materials and methods Collagen-induced arthritis (CIA) was induced in mice lacking Flt3L (Flt3L^{-/-}) and WT littermates (C57/BL6 background, 9–10 weeks old). The severity of the arthritis was assessed using an established semiquantitative scoring system (0–4). After 60 days (chronic phase) phenotypical and functional analysis of spleen and lymph nodes was performed: T and B cell markers, FoxP3 expression, activation markers, co-stimulatory markers and cytokine production.

Results In steady-state, Flt3L^{-/-} mice show reduced cellularity in both spleen (p=0.007) and lymph nodes (p=0.01) and reduced T and B cell numbers compared with WT. In CIA abrogation of Flt3 signaling led to decreased disease incidence and severity. As shown for steady-state conditions, in CIA Flt3L^{-/-} mice showed reduced spleen and lymph node cellularity (p<0.0001) but also reduced percentage of CD4⁺CD25⁺ T cells compared with WT (p=0.03). Flt3L^{-/-} CD4⁺ T cells also produce significantly less IL-17 (p=0.016) and tumour necrosis factor α (p=0.010), and CD8⁺ T cells less interferon (IFN γ) (p=0.029) compared to WT.

Conclusions Mice lacking Flt3L are protected from collagen-induced arthritis. The authors observed that Flt3L deletion influences the magnitude (cell numbers) and quality (CD25 expression) of T cell responses. Stimulation of lymphocytes by different types of DC, DC at different stages of maturity and producing and responding to different growth factors might contribute for this change in T cell numbers and/or effector functions in Flt3L^{-/-} mice. Targeting this signalling pathway might be considered as a good therapeutic strategy in RA.