CONNECTIVE TISSUE DISEASES

ICOS sustains pathogenic T-cell survival in SLE mouse model

Inducible T cell co-stimulator (ICOS) supports follicular T-cell differentiation and is a known promoter of organ inflammation in mouse models of systemic lupus erythematosus (SLE). In a new report published in *Immunity*, ICOS ligand (ICOSL) expression by CD11c⁺ (also known as integrin α -X, encoded by *Itgax*) myeloid cells was associated with enhanced T-cell survival in the kidneys of lupus-prone mice.

“...results suggest an autoantibody-independent role for ICOS in self-reactive T-cell survival in target organs...”

Expression of ICOS by T cells has been implicated in the disease process in lupus-prone mice, but the involvement of CD11c⁺ dendritic cells (DCs), a major type of antigen-presenting cell (APC), in this process was unclear. In the study, lupus-prone MRL.*Fas*^{lpr} mice in which the gene encoding ICOSL (*Icosl*) was

specifically deleted in CD11c⁺ cells (*Itgax-Icosl*^Δ mice) had reduced proteinuria, interstitial nephritis and infiltrate size compared with *Icosl*-sufficient controls. Inflammation of the lung, but not of the skin, was also decreased in *Itgax-Icosl*^Δ mice, but no substantial differences in T-cell accumulation in lymphoid tissues were detected between the two groups.

Previous reports have shown that complete *Icos* deletion in MRL.*Fas*^{lpr} mice leads to disease amelioration and reduced numbers of T extrafollicular helper (T_{EFH}) cells, which express Bcl6, produce IL-21, and are thought to support autoantibody generation and provide B-cell help. In the present study, *Itgax-Icosl*^Δ mice had a 28% lower frequency of splenic T_{EFH} cells among CD4⁺ T cells when compared with *Icosl*-sufficient controls. Unexpectedly, only a modest decrease in antinucleosome antibodies was observed in *Itgax-Icosl*^Δ mice, but, in agreement with the reduction in infiltrate size observed by histological analysis, the numbers of CD4⁺ and CD8⁺ T cells in the kidneys of *Itgax-Icosl*^Δ

mice were reduced by 38.0% and 50.2%, respectively. T_{EFH} cells from *Itgax-Icosl*^Δ mice showed normal expression of Bcl6 and IL-21, but had increase levels of apoptosis in kidney sections compared with control mice (8.8-fold increase in TUNEL⁺ cells per mm²). This increase in apoptotic T_{EFH} cells was associated with reduced phosphorylation and activity of the Akt survival pathway.

These results suggest an autoantibody-independent role for ICOS in self-reactive T-cell survival in target organs of lupus-like disease. According to corresponding author Lino Teichmann, “the study represents a critical piece of the puzzle in understanding the relative roles of two major types of APCs—B cells and DCs/macrophages—in promoting systemic autoimmunity”.

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Original article Teichmann, L. L. et al. Local triggering of the ICOS coreceptor by CD11c⁺ myeloid cells drives organ inflammation in lupus. *Immunity* 42, 552–565 (2015)