

### 345 DELETION OF THE BAFF RECEPTOR TACI FULLY PROTECTS AGAINST SLE WITHOUT REDUCTION OF B CELL NUMBERS AND FUNCTION

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**Background and aims** B cell-activating factor of the TNF family (BAFF) is an essential B cell survival factor. However, high levels of BAFF promote systemic lupus erythematosus (SLE) in mice and humans. Belimumab (anti-human BAFF) limits B cell survival and is approved for use in patients with SLE. Surprisingly, the efficacy of rituximab in SLE remains controversial, despite depleting B cells more potently than belimumab. This raises the question of whether B cell depletion is really the mechanism of action of belimumab. In BAFF transgenic (BAFF-Tg) mice, SLE development is T cell-independent but relies on innate activation of B cells in cooperation with the BAFF receptor TACI. Therefore, in this study we tested whether TACI, a BAFF receptor dispensable for B cell survival may have a role in the pathogenesis of SLE.

**Methods** To test the role of TACI in driving BAFF-mediated autoimmunity, we reconstituted BAFF Tg mice with a TACI-deficient bone marrow and also crossed BAFF Tg mice onto TACI<sup>-/-</sup> mice.

**Results** We show that loss of TACI on B cells protected against BAFF-mediated autoimmune manifestations while preserving B cells, suggesting that loss of BAFF signalling through TACI, rather than loss of B cells, may underpin the effect of belimumab in the clinic. Moreover, a multimeric form of BAFF, is very effective at activating TACI, suggesting that this abnormal form of BAFF may also be a pathogenic factor in SLE.

**Conclusions** B cell-sparing blockade of TACI may offer a more specific and safer therapeutic alternative to broad B cell depletion in SLE.

### 346 THE CONTRIBUTION OF INTERFERON LAMBDA TO SLE

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**Background and aims** Interferon lambda (IFN- $\lambda$ ) is a novel type of interferon produced by dendritic cells (DC). Despite its binding to a different receptor, IFN- $\lambda$  shares functional similarities with type I IFN (IFN-I) by upregulating the expression of IFN-stimulated genes. The role of IFN- $\lambda$  in DC biology and in autoimmunity remains unknown.

- to identify the DC subsets producing IFN- $\lambda$ .
- to investigate the role of IFN- $\lambda$  in DC functions.
- to investigate the role of IFN- $\lambda$  in SLE.

#### Methods

- Mouse and human DC subsets were stimulated *ex vivo* and the IFN- $\lambda$  expression was measured.
- The maturation and the capacity of DC to cross-prime T cells was compared in WT and IFN- $\lambda$ R<sup>-/-</sup> mice. T cell cross-priming by human DCs was measured *ex vivo* in the presence of exogenous IFN- $\lambda$ .

- Serum levels of IFN- $\lambda$  was measured in lupus-prone mice and in SLE patients. The phenotype of the blood DC subsets from SLE patients was also characterised.

#### Results

- Mouse plasmacytoid DC (pDC) and CD8<sup>+</sup> DC highly secrete IFN- $\lambda$ . In humans, the CD141<sup>+</sup> DC are the major IFN- $\lambda$  producers.
- IFN- $\lambda$  enhances the capacities of mouse and human DCs to mature and to cross-prime T cells.
- High serum levels of IFN- $\lambda$  were detected in lupus-prone mice and in some SLE patients. SLE patients display increased activation of the IFN-producing DC subsets: the pDCs (producing IFN-I) and the CD141<sup>+</sup> DCs (producing IFN- $\lambda$ ).

**Conclusions** IFN- $\lambda$  is produced by some DC subsets and enhances their functions. Furthermore, IFN- $\lambda$  is expressed during SLE, suggesting a potential role of the cytokine in the aetiology of SLE.

### 347 IMPACT OF CD200-FC ON DENDRITIC CELLS IN LUPUS-PRONE NZB/WF1 MICE

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**Background and aims** Abnormal expression of CD200/CD200R1 may contribute to the immunologic abnormalities in patients with systemic lupus erythematosus (SLE). This study aimed to assess the function of CD200/CD200R1 and impact of CD200-Fc on dendritic cells in lupus-prone NZB/WF1 mice.

**Methods** Female NZB/WF1 mice were treated with CD200-Fc or control for 4 weeks. Plasma samples were collected to measure autoantibody levels. The expression levels of CD200/CD200R1 in peripheral blood mononuclear cells (PBMCs) and splenocytes were examined.

**Results** The percentage of CD200/CD200R1-positive cells in splenocytes from NZB/WF1 mice was lower than that of C57BL/6 mice ( $p < 0.05$ ). The plasma level of anti-dsDNA was significantly higher in NZB/WF1 mice than C57BL/6 mice ( $p < 0.001$ ). However, the anti-dsDNA levels decreased ( $p = 0.047$ ) after CD200-Fc treatment. Finally, CD200-Fc reduced the levels of IL-6 ( $p = 0.017$ ) and IL-10 ( $p = 0.03$ ) in the dendritic cell culture supernatant.

**Conclusions** The immunosuppressive CD200/CD200R1 signalling pathway might be involved in the immunopathology of NZB/WF1 mice; the present results merit further exploration of agents that can modulate the CD200/CD200FR1 pathway as a therapy for human lupus

### 348 DECTIN-1 ON MONOCYTIC CELLS MEDIATES ABERRANT INNATE AND ADAPTIVE IMMUNE RESPONSES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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