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

1F Mackay*, 1University of Melbourne, School of Biomedical Sciences, University of Melbourne, Australia

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 and also crossed BAFF Tg mice onto TACI-/- mice. 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.

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-/- 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.

THE CONTRIBUTION OF INTERFERON LAMBDA TO SLE

1C Macle* 1ES Pang, 1Posley, 2K Radford, 3M O’Keeffe. 1Monash University, Biochemistry and Molecular Biology, Clayton, Australia; 2Mater Research-UQ, TRI, Brisbane, Australia

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

- to identify the DC subsets producing IFN-λ.
- to investigate the role of IFN-λ in DC functions.
- to investigate the role of IFN-λ in SLE.

Methods
- Mouse and human DC subsets were stimulated ex vivo and the IFN-λ expression was measured.
- The maturation and the capacity of DC to cross-prime T cells was compared in WT and IFN-AR-/- mice. T cell cross-priming by human DCs was measured ex vivo in the presence of exogenous IFN-λ.
- Serum levels of IFN-λ 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+ DC highly secrete IFN-λ. In humans, the CD141+ DC are the major IFN-λ producers.
- IFN-λ enhances the capacities of mouse and human DCs to mature and to cross-prime T cells.
- High serum levels of IFN-λ 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+ DCs (producing IFN-λ).

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