activity is expected. The failure of F(ab')2 fragments to bind is unexpected, pointing to a critical role for the Fc portion of the IgG molecule in stabilising antibody interaction. The Fc portion can contribute to anti-DNA by inducing a conformational change in the binding sites; contacting DNA; or forming Fc:Fc interactions to increase valency. This binding pattern can be called Fc-dependent monogamous bivalency. The findings suggest that agents that affect the Fc portion may be useful to therapeutically inhibit anti-DNA interactions.

AI-17 BAFF PROMOTES SYSTEMIC AUTOIMMUNITY VIA TACI-DEPENDENT ACTIVATION OF TRANSITIONAL B CELLS

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10.1136/lupus-2016-000179.17

Background Although excess levels of B cell activating factor of the TNF family (BAFF, also known as BLyS) have been implicated in the pathogenesis of SLE, how excess BAFF promotes breaks in B cell tolerance is not completely understood. Transgenic mice (Tg) overexpressing BAFF develop an autoimmune disease resembling human SLE. BAFF binds to distinct receptors expressed on B cells, the BAFF receptor (BAFF-R) and transmembrane activator and CAML interactor (TACI). Since BAFF-R deletion results in loss of mature B cells, BAFF-R-dependent signals are presumed to explain BAFF-mediated autoimmunity. However, potential important roles for TACI in lupus pathogenesis have not been addressed.

Materials and methods After crossing BAFF-Tg and *Taci*$^{-/-}$ mice, we used standard immunologic techniques to test the impact of TACI on BAFF-driven autoimmunity.

Results Despite prior evidence of a negative role for TACI in B cell activation, we discovered that TACI deletion resulted in a striking loss of class-switched serum autoantibodies. Loss of serum autoantibodies also correlated with protection from immune-complex glomerulonephritis in *Taci*$^{-/-}$.BAFF-Tg mice. Importantly, lack of autoimmunity was not explained by alterations in peripheral B cell development, since both BAFF-Tg and *Taci*$^{-/-}$.BAFF-Tg mice exhibited similar B cell hyperplasia, with equivalent expansion of the follicular (FM) and marginal zone (MZ) compartments. Rather, whereas surface TACI expression is usually limited to mature B cells, we discovered that excess BAFF integrates with dual B cell receptor (BCR)- and MyD88-dependent signals to promote TACI upregulation on transitional B cells. The novel TACI^{hi} subset of transitional B cells from BAFF-Tg mice are characterised by an activated, cycling phenotype and expressed activation-induced cytidine deaminase (AID) and T-bet. Single-cell cloning of B cell receptors from TACI^{hi} vs TACI^{lo} transitional B cells demonstrated that the TACI^{hi} cell subset is specifically enriched for autoreactivity and exhibits evidence of somatic hypermutation. Finally, consistent with a direct role in autoimmune pathogenesis, TACI^{hi} transitional B cells from BAFF-Tg mice spontaneously produce class-switched autoantibodies *ex vivo*.

Conclusion Our combined findings highlight a novel mechanism whereby BAFF promotes humoral autoimmunity via TACI-dependent activation of transitional B cells. In addition to SLE and other autoimmune disorders characterised by elevated BAFF, dysregulated transitional B cell activation is likely to be relevant a range of other clinical scenarios, including: autoimmune disease relapse after treatment with B cell-depletion therapies; *de novo* humoral autoimmunity following stem cell transplantation; and, rapid IgM- and IgG-mediated antibody responses during pathogen challenges.

Acknowledgements This work was supported by the National Institutes of Health (NIH) under award numbers: R01HL075453 (DJR), R01AI084457 (DJR), R01AI071163 (DJR), DP3DK097672 (DJR) and K08AI112993 (SWJ). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional support provided by the Benaroya Family Gift Fund (DJR); by the ACR REF Rheumatology Scientist Development Award (SWJ); and by the Arnold Lee Smith Endowed Professorship for Research Faculty Development (SWJ).

AI-18 B CELL IFN-γ RECEPTOR SIGNALLING PROMOTES AUTOIMMUNE GERMINAL CENTRESVIA CELL-INTRINSIC INDUCTION OF BCL-6

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10.1136/lupus-2016-000179.18

Background Dysregulated germinal centrecenter (GC) responses are implicated in the pathogenesis of human autoimmune diseases, including systemic lupus erythematosus (SLE). Although type 1 interferons (IFNs) are most frequently associated with lupus pathogenesis, type 2 interferon (IFN-γ) has also been shown to promote SLE. However, the respective impacts of these cytokines in promoting B cell activation during humoral autoimmunity have not been addressed.

Materials and methods We recently developed a chimeric murine lupus model in which Wiskott-Aldrich syndrome protein (WAS)-deficient B cells promote spontaneous humoral autoimmunity (Jackson, *et al*. *J Immunol* 2014). An important advantage of the WAS chimaera model is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we contrast the impact B cell-intrinsic type 1 IFN vs. IFN-γ signals on autoimmune GC formation and the pathogenesis of SLE.

Results Although type 1 IFN prominently enhanced B cell responses *in vitro*, B cell-intrinsic IFNAR deletion exerted surprisingly minimal impacts on class-switched autoantibody titers and spontaneous GC formation *in vivo*. This finding suggested that other cytokines promote B cell activation in the WAS chimaera model. Notably, B cells directly initiated CD4^{+} T cell activation and T follicular helper cell formation via MHC Class II (MHC-II)-dependent antigen presentation. In addition, activated T cells exhibited prominent IFN-γ production that was lost following B cell-intrinsic MHC-II deletion, suggesting a direct role for IFN-γ in promoting autoimmune GC formation. Strikingly, B cell-intrinsic deletion of the IFN-γ receptor was sufficient to abrogate spontaneous GCs, class-switched autoantibodies and systemic autoimmunity. Mechanistically, although IFN-γ receptor signals increased B cell T-bet expression, B cell-intrinsic deletion of T-bet exerted an isolated impact on class-switch recombination to pathogenic IgG2c autoantibody subclasses without impacting GC development. Rather, in both murine and human B cells, IFN-γ synergized with BCR, TLR and/or CD40 activation signals to promote cell-intrinsic BCL-6 expression. Finally, IFN-γ driven BCL-6 expression in B cells was blocked using clinically-relevant Janus kinase inhibitors, ruxolitinib and tofacitinib.