

activity is expected. The failure of F(ab')<sub>2</sub> 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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**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*<sup>-/-</sup> 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*<sup>-/-</sup>.BAFF-Tg mice. Importantly, lack of autoimmunity was not explained by alterations in peripheral B cell development, since both BAFF-Tg and *Taci*<sup>-/-</sup>.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<sup>hi</sup> 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<sup>hi</sup> vs TACI<sup>lo</sup> transitional B cells demonstrated that the TACI<sup>hi</sup> cell subset is specifically enriched for autoreactivity and exhibits evidence of somatic hypermutation. Finally, consistent with a direct role in autoimmune pathogenesis, TACI<sup>hi</sup> 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.

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

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**Background** Dysregulated germinal center (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<sup>+</sup> 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.