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Top Reads

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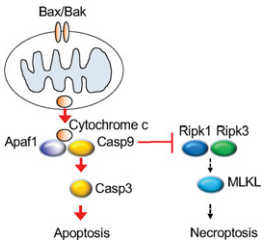
TRIMming Up the IFN Response

In this Top Read, Hoffpauir et al. (p. 153) demonstrate that tripartite motif-containing protein 14 (TRIM14) is critical for the induction of type 1 IFN and resolution of *Mycobacterium tuberculosis* infection in macrophages. Infection upregulated TRIM14, which bound to the kinase TBK1, leading to phosphorylation of STAT3 at S727 and its subsequent translocation into the nucleus. In macrophages lacking TRIM14 (*Trim14*$^{-/-}$), STAT3 phosphorylation shifted to the inhibitory S754 position, resulting in decreased STAT3 translocation and a defect in *Socs3* induction. Because *Socs3* is a negative regulator of IFN, *Trim14*-deficient macrophages produced more IFN-β than wild type macrophages. In addition to an enhanced IFN response, *Trim14*-deficient macrophages also produced higher levels of inducible NO, which inhibited replication of *M. tuberculosis* within macrophages. Together, these data support an important role for TRIM14 in the IFN response to *M. tuberculosis* infection of macrophages.

Improving MHC Class II Prediction

To date, tools predicting and/or identifying MHC class II (MHC-II) binding peptides are impaired by a high false positive rate. In this Top Read, Osterbye et al. (p. 290) report a novel method to generate large amounts of peptide binding data for specific MHC-II molecules that were used to train artificial neural networks (ANNs), which generate predictive models for binding peptide epitopes. The authors investigated the binding of recombinant HLA-DRB1*01:01 and HLA-DRB1*03:01 to high-density microarrays containing 70,000 random peptides in triplicate. ANN training with the peptide microarray datasets returned prediction models with a very high internal correlation and indicated that the respective HLA-DR molecules contain distinct and recognizable patterns extracted by the algorithm. A direct comparison of the prediction scores between the peptide microarray–driven models and those derived from conventional binding assays revealed comparable performance, suggesting that high-density peptide microarrays can be used to generate relevant peptide–HLA-II binding data. Thus, this approach represents an improved method to generate large amounts of peptide–MHC-II binding data that can improve prediction models.

Inhibition of Necroptosis by Caspase-9 in B Cells



In this Top Read, Zhang et al. (p. 113) show that caspase-9 protects germinal center (GC) B cells and Ab responses by inhibiting necroptosis. IgG1^{+} GC B cells displayed activated caspase-9 in both naive and 4-hydroxy-3-nitrophenylacetyl–keyhole limpet hemocyanin (NP-KLH)–immunized mice. Naive mice with a B cell–specific deletion of caspase-9 (B/*Casp9*$^{-/-}$) displayed normal B cell development. However, B/*Casp9*$^{-/-}$ mice immunized with NP-KLH showed reductions in the number of NP^{+} IgG1^{+} GC B cells and the number of Ag-specific CD138^{+} plasma cells, suggesting that caspase-9 is important for maintaining Ab responses after immunization. Consistent with previous observations, caspase-9 deficiency in B cells decreased apoptosis and promoted necroptosis, which was also evidenced by increased phosphorylation of Ripk3. Congruently, deletion of both Ripk3 and caspase-9 in B cells decreased cell death in naive animals and restored Ab responses in NP-KLM–immunized mice. Together, these data reveal an important role for caspase-9 in maintaining a balance between apoptosis and necroptosis to protect the homeostasis of GC B cells in Ab responses.

Tracing BCR Self-Reactivity

Although studies of transgenic mice expressing self-reactive BCRs defined mechanisms of immunological tolerance, they are limited due to restricted diversity of the quasi-clonal B cell populations. In this Top Read, Nojima et al. (p. 90) used single B cell cultures, which do not support V(D)J mutation and therefore represent the BCR expressed by each founder B cell, to trace the natural dynamics of autoreactive BCR repertoires in normal mice. In contrast to knock-in models, the absolute frequencies of DNA-reactive B cells in normal mice did not significantly change during B cell development and maturation. Rather, B cells most avid for DNA were lost in the transition from small pre-B to immature and transitional-1 (immature/T1) B cells, revealing the first tolerance checkpoint. DNA reactivity did not significantly change when immature/T1 B cells developed into mature follicular (MF) B cells, suggesting that the second tolerance checkpoint is negligible in removing autoreactive BCRs. Autoreactivity was enriched in the transitional-3 (T3) and CD93^{+} IgM$^{-/lo}$IgD^{hi} anergic B cells and a CD93^{-} anergic subset in the spleen. Whereas splenic T3 and CD93^{+} anergic B cells are short-lived, CD93^{-} IgM$^{-/lo}$IgD^{hi} B cells had half-lives comparable to MF B cells. B cell–specific deletion of proapoptotic genes *Bak* and *Bax* resulted in increased CD93^{-} IgM$^{-/lo}$IgD^{hi} B cells but not T3 B cell numbers, suggesting that apoptosis differently regulates persistent and short-lived autoreactive B cells. Thus, a persistent, self-reactive compartment may be the origin of systemic autoimmunity and a potential target for therapeutic intervention.