The role of T-bet in B cells

To the editor:

We read with interest the recent paper by Liu *et al.* describing the observation that immunostimulatory CpG oligonucleotides induce the transcription factor T-bet in B cells, apparently leading to the suppression of immunoglobulin G1 (IgG1) and IgE isotype switching[1]. We were particularly interested in the potential implications of this observation to the pathogenesis of humoral autoimmunity, which seems to involve critical interactions between CpG sequences, Toll-like receptor 9 (TLR9) and T-bet[2–4].

The authors and commentators conclude that CpG oligonucleotides suppress IgE and IgG1 through T-bet[4]. T-bet, however, is entirely dispensable for the ability of CpG oligonucleotides to suppress IgE and IgG1 *in vitro*, although it is essential for the production of IgG2a (**Fig. 1** and data not shown). Indeed, the strongest evidence for T-bet seems to be in the promotion IgG2a class switching[3]. As such, the data of Liu *et al.* raise even more intriguing issues, as it would seem that T-bet mediates only one of the class-switching effects induced by TLR9 activation, and its expression, at least in the present context, reflects simply a marker of redirection to the IgG2a isotype. We propose that another transcriptional repressor, perhaps Bcl-6 (ref. 5) or Id2 (ref. 6), independently of T-bet, mediates the suppression of IL-4-related isotypes by CpG.

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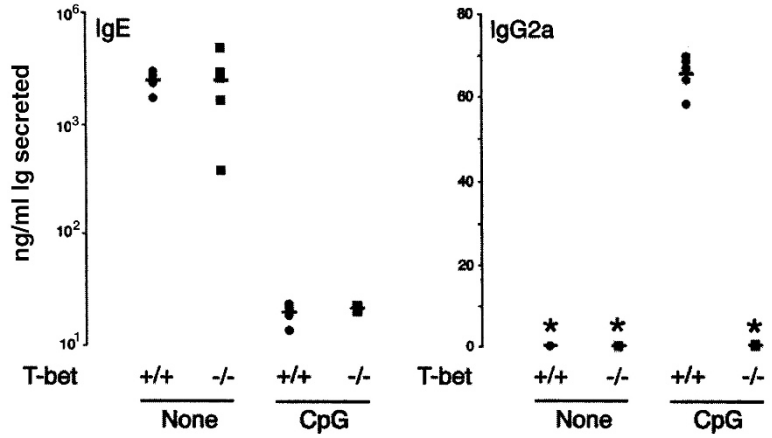

Figure 1 Immunoglobulin response to CpG oligonucleotides. B cells from T-bet-deficient (squares) or T-bet-sufficient (circles) C57BL/6 mice were incubated in culture for 10 d in the presence of antibody to CD40 and recombinant murine IL-4, in the presence (CpG) or absence (None) of stimulatory CpG oligonucleotides. Secreted IgE or IgG2a titers were determined by enzyme-linked immunosorbent assay. Results for IgG1 (data not shown) were analogous to those of IgE, presented here. *, titers below the limit of the assay (2.5 ng/ml). Each data point represents B cells isolated from one individual mouse; data are representative of three experiments, reflecting five to seven mice per genotype.

Liu replies:

We appreciate seeing the data promptly generated by Peng *et al.* As we were unable to obtain T-bet-deficient mice, we concluded[1] that the CpG-induced up-regulation of T-bet correlated with the induction of IgG2a and the inhibition of IgE and IgG1. The data of Peng *et al.* confirmed our results and further clarified the T-bet-dependent IgG2a induction and T-bet-independent inhibition of IgE, directing the course of CpG-regulated humoral immunity to two scenarios.

The issue raised, then, is how CpG inhibits IL-4-induced IgE switching. It is not likely to be due to interference with tyrosine phosphorylation of STAT6 by Janus kinases[1]. Many possibilities still need to be tested, however. For example, serine phosphorylation of STAT6 prevents its binding to DNA, and the transcription factors NF-κB, AP-1, E2A, C/EBP, Bcl6 and Id2 also regulate IL-4-induced IgE switching[2]. Indeed, in an attempt to understand TLR9-mediated gene programming in B cells on a genomic scale, we found that CpG-TLR9 regulated a distinct set of transcription factors (data not shown). Notably, in many cases it results in transcriptional suppression through either down-regulation of transactivators or induction of transcriptional repressors. Identification of the molecules responsible for the CpG-mediated inhibition of IgE switching must await the results of biochemical and functional analyses.

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