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LETTER

Bcl-xL affects the development of functional CD4 Tregs

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See related research by Haque *et al.*, http://arthritis-research.com/content/12/2/R66

We read with great interest the article by Haque and colleagues [1] in a recent issue of *Arthritis Research & Therapy*. They hypothesized that co-transduction of $CD4^+$ T cells with both forkhead box P3 transcription factor (FoxP3) and Bcl-xL will generate highly reactive regulatory T cells (Tregs) that can be used to prevent autoimmune disease. The authors showed that the accumulation, persistence, and efficient function of Tregs were attributable to the expression of Bcl-xL in CD4 Tregs.

Indications for a potential role of Bcl-xL in the development of functional Tregs were first described by our group, and the results of studies supporting this notion were published in numerous journals (for example, [2-5]). Because this information was not mentioned in the article by Haque and colleagues [1] and because the results presented in their article confirm our previous studies [2-5], we think that it is important, scientifically and ethically, to acknowledge these data.

Our group has been studying systemic lupus erythematosus (SLE) and developed a tolerogenic peptide, namely hCDR1, shown to ameliorate manifestations of the disease through several mechanisms of action, including the induction of CD4 Tregs [2]. We showed that Bcl-xL was upregulated in CD4 Tregs of SLE-affected (NZBxNZW)F1 mice following treatment with the tolerogenic peptide [3]. Bcl-xL played a suppressive role in the tolerized mice, as it inhibited the activation of T and B cells, and mediated the downregulating effects of hCDR1 on the production of the pathogenic cytokines interferon-gamma and interleukin-10 and the upregulating effects on the immunosuppressive cytokine transforming growth factor-beta (TGF-β). Furthermore, CD4 Tregs of the tolerized mice elicited the expression of Bcl-xL in the effector CD4 cells, thus contributing to the amelioration of SLE manifestations [3]. Although CD8 Tregs could not trigger the expression of Bcl-xL in effector CD4 cells, the former cells were essential for the optimal inhibitory function of CD4 Tregs [4]. Finally, we demonstrated that Bcl-xL played a role in inducing the regulatory/inhibitory molecules FoxP3, cytotoxic T lymphocyte antigen 4 (CTLA-4), and TGF-β and in repressing PD-1 (programmed death 1) [5]. We showed that Bcl-xL also mediated the induction of CTLA-4 and TGF-β in effector CD4 cells by CD4 Tregs of the tolerized mice, thus explaining the inhibition of proliferation and the decreased activation of effector CD4 cells [5]. These newly described roles of Bcl-xL may provide a novel mechanism of induction of CD4 Tregs. All together, our data [2-5], supported by those presented by Haque and colleagues [1], suggest that immunomodulation of Bcl-xL expression in T cells might be valuable for controlling and treating diseases that are affected by CD4 Tregs.

Abbreviations

CTLA-4, cytotoxic T lymphocyte antigen 4; FoxP3, forkhead box P3 transcription factor; SLE, systemic lupus erythematosus; TGF-β, transforming growth factor-beta; Treg, regulatory T cell.

Competing interests

The authors declare that they have no competing interests.

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