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The functional insufficiency of human CD4^{+}CD25^{high} T regulatory cells in allergic asthma is subjected to TNF-α modulation

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Allergic asthma is characterized by a systemic, exacerbate Th2 cytokine immune response to environmental allergens that leads to airflow obstruction, airway hyper-responsiveness (AHR), and ongoing active airway inflammation (1). Despite recent progress in the understanding of the role of Th2 and inflammatory cytokines, such as TNF-α•(2), in the pathogenesis of the disease, the mechanism underlying the development of allergen sensitization, and more importantly, the role of the regulatory pathway in the control of allergic diseases remains unknown. Although there is extensive evidence that regulatory T cells (Treg) play a major role in controlling immune responses (3), studies exploring the role of CD4^{+} Treg cells in allergic diseases have primarily focused on antigen-induced IL-10 producing Treg cells (i.e. inducible Treg) (4, 5).
Thymus-derived naturally occurring regulatory T cells (nTreg) are CD4^{+}CD25^{+} T cells, functionally distinguished by their capacity to limit CD4^{+}CD25^{-} T cell proliferation and Th1/Th2 cytokines production (6, 7). Only few studies have focused on the role of nTreg in common allergic diseases. For example, children who had outgrown their cow's milk sensitivity had significantly higher levels of CD4^{+}CD25^{+} T cells in their peripheral blood and were less responsive to stimulation with β-lactoglobulin *in vitro* than those who maintained a clinically active allergy (8). Natural Tregs have also been shown to suppress allergic responses to inhaled antigens such as grass or birch pollen (9-11). In contrast, animal studies on the role of nTregs in allergic asthma have yielded conflicting data. Although the development of AHR is unaffected by altering the number of CD4^{+} CD25^{+} Treg cells (12, 13), the development of eosinophilic airway inflammation is reported to be both increased (12), and paradoxically decreased (14), after depletion of naturally occurring CD4^{+} CD25^{+} Treg cells. This discrepancy may be due to the different genetic backgrounds of the mice studied. However, the factors that influence the functional capacity in Treg cell-mediated suppression of allergen–specific immune responses have not been delineated in allergic asthmatic patients.

Herein, we have demonstrated that the expression of Foxp3 and cell-induced suppressive activity in CD4^{+}CD25^{high} regulatory T cells were significantly decreased in allergic asthmatic patients (Fig.1).

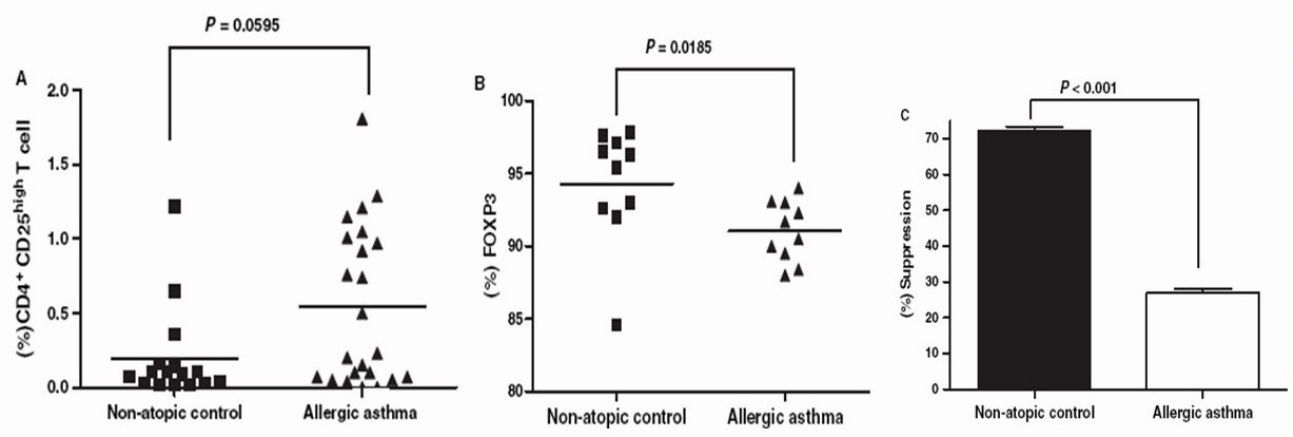

Figure 1.

We also find that TNF-α, a pleiotropic cytokine, plays a critical role in bridging innate and adaptive immunity in chronic inflammatory disease, is increased in Der p-stimulated PBMCs of allergic asthmatics, and impairs the regulatory activity of natural Treg cells via the TNF-α receptor 2 (TNFR2) signaling pathway to down-modulate Foxp3 expression (Figure 2 and 3)

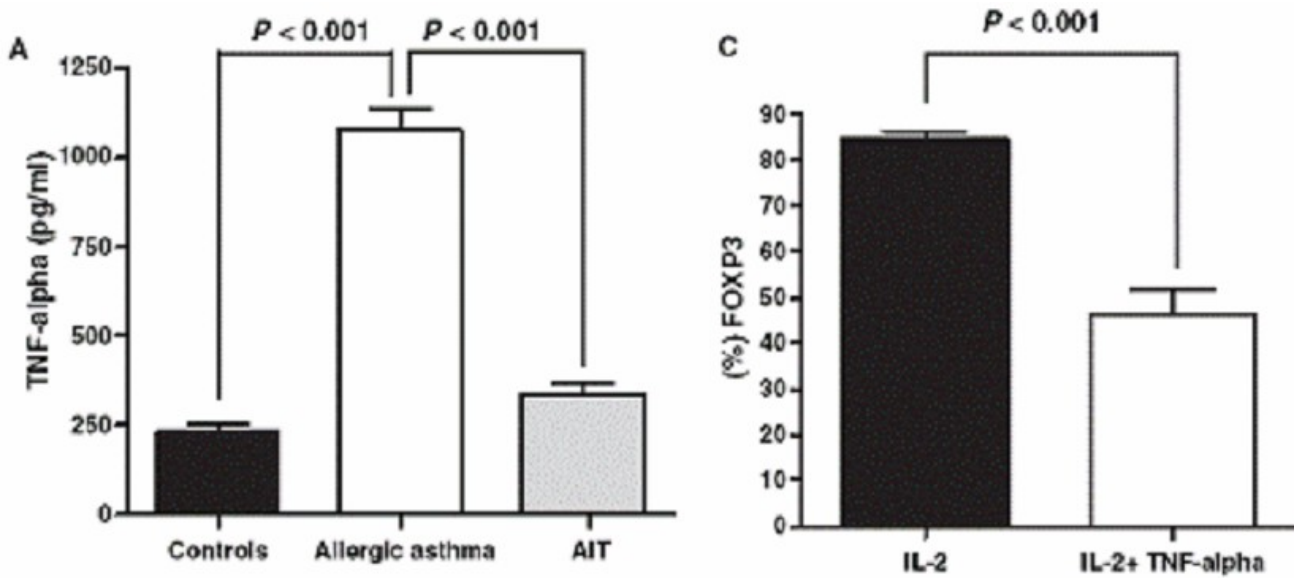

Figure 2.

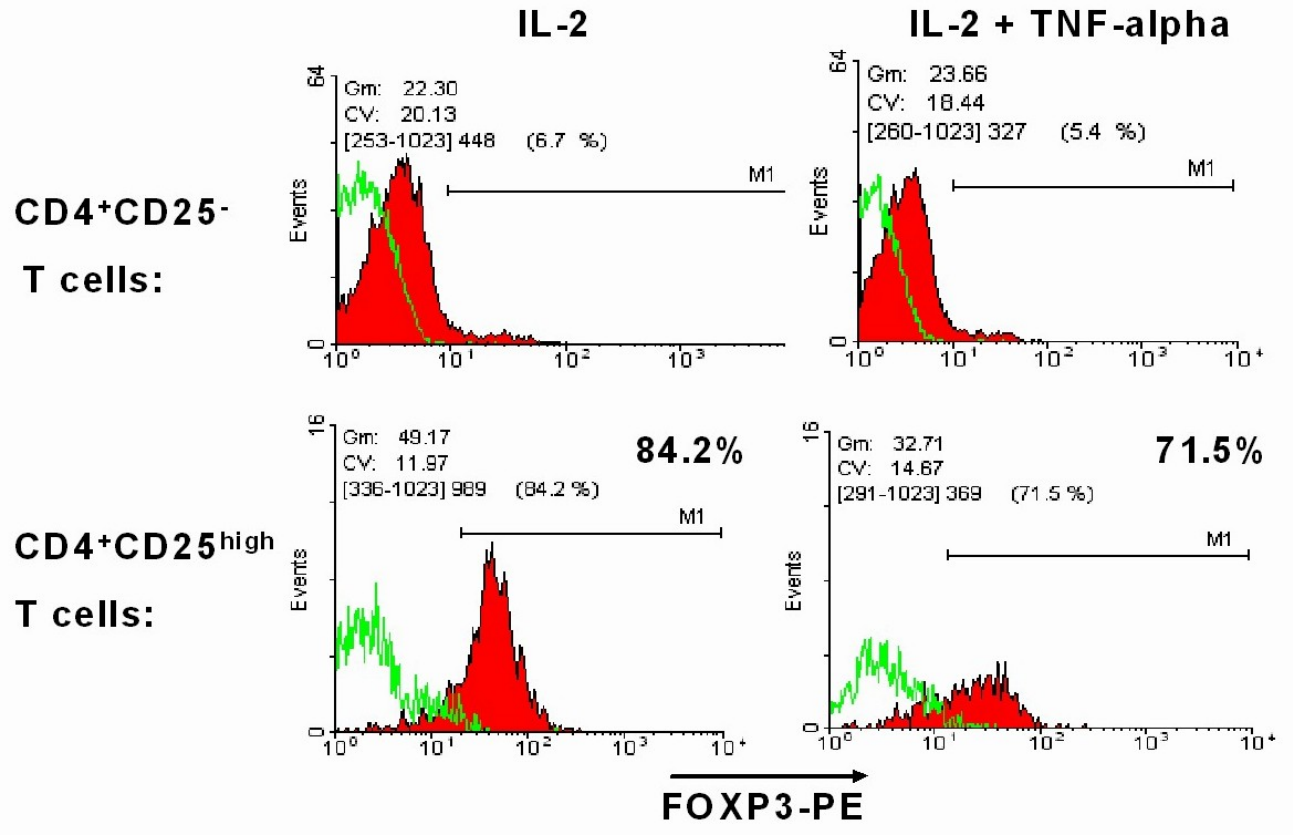

Figure 3.

The addition of the soluble TNF-α receptor-IgG_1Fc fusion protein, etanercept, reversed the expression of Foxp3 and the loss of inhibitory activity of Treg cells in allergic asthmatics, which may explain, at least in part, the mechanism of functional insufficiency of natural regulatory T cells in allergic asthma (Figure 4).

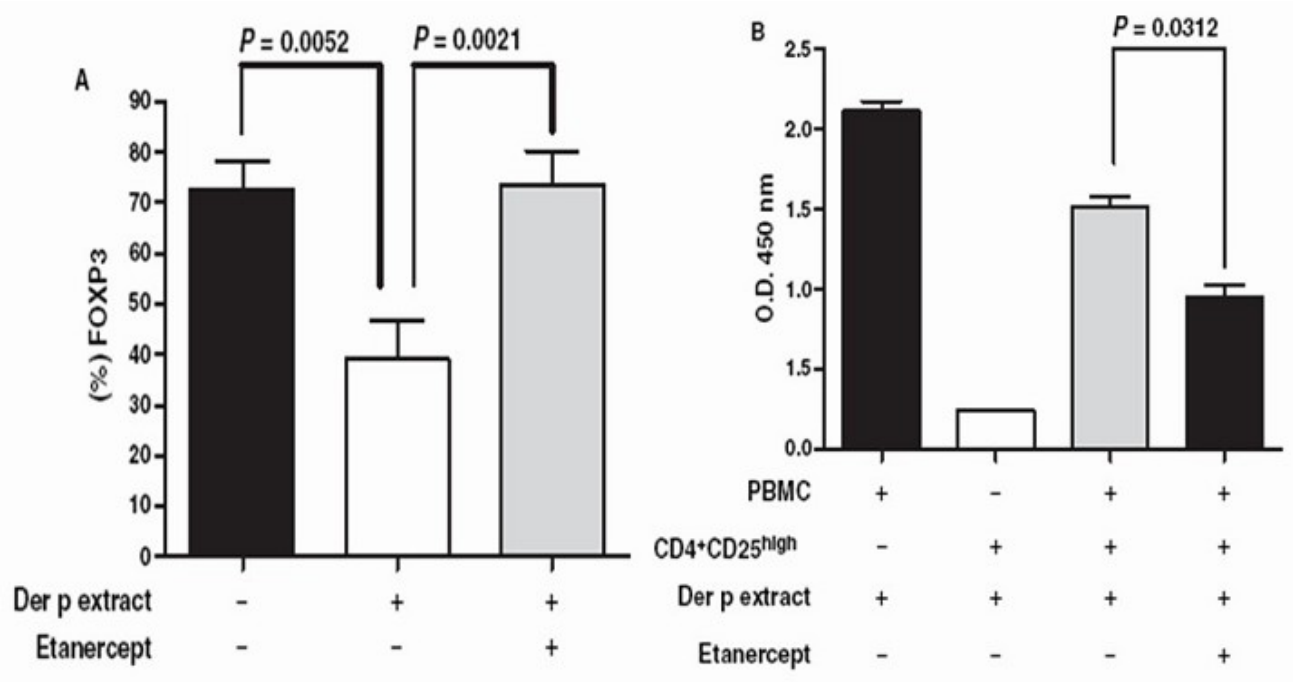

Figure 4.

In summary, we have found that functional insufficiency of natural Tregs in allergic asthma may be

related to the enhanced production of TNF-α and its effect on the Foxp3 expression in Treg cells. These results may provide a new therapeutic modality in the treatment of allergic asthma.

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