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Editorial Open Access

Possible Antigen-Specific Cellular Immunotherapy Using Tr1 Cells for Atopic Diseases

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Regulatory T cells (Treg cells) are important players in the regulation of tolerance to self and foreign antigens. There have been accumulated evidences indicating that Treg cells play crucial roles in prevention of allograft rejection [1]. In addition, it has been demonstrated that Treg cells function to maintain immune homeostasis against self-antigen: Pathogenesis of autoimmune diseases such as rheumatoid arthritis are controlled by endogenous Treg cells [2].

Treg cells can be classified into 2 classes: naturally occurring Treg cells (nTreg cells) [3,4] and inducible Treg cells (iTreg cells) [5,6]. nTreg cells are $CD4^+$ $CD25^+$T cells, which constitutively express a transcription factor, Foxp3, and exert their immunomodulatory actions through production of an immunosuppressive cytokine, interleukin (IL)-10. nTreg cells emerge directly from the thymus, and antigen specificity of nTreg cells has been unknown. Efficacy of adoptive transfer of nTreg cells on autoimmune diseases has also been reported in animal models [7].

On the other hand, representative iTreg cells are Tr1 cells, which can be induced by an IL-10-dependent process in vivo and in vitro, and exert their immunosuppressive actions through production of IL-10 and transforming growth factor (TGF)-β. Tr1 cells have been found to be $CD4^+$ T cells, but negative for the transcription factor, Foxp3 [8]. Regarding cytokine profile, Tr1 cells produce a large amount of IL-10, but no IL-4 and low level of interferon (IFN)-γ [9], so that Tr1 cells could be distinguished from Th1 and Th2 cells. However, no specific cellular marker of Tr1 cells has been identified. One report demonstrated that repressor of GATA-3 (ROG) was expressed in Tr1 cells but not in nTreg cells [10], whereas ROG is expressed in activated Th cells also.

Probably different from features of nTregs, Tr1 cells can be induced by foreign (environmental) antigens through activation of T-cell receptor (TCR) [7]. I and colleagues have also demonstrated that multiple intratracheal administration of a protein antigen induced IL-10-producing $CD4^+$T cells *in vivo* in a murine model of asthma, and that the cells did not express Foxp3, suggesting that the cells can be a class of Tr1 cells [11]. Additionally, we demonstrated that neutralization of IL-10 function by anti-IL-10 receptor antibody augmented allergic airway inflammation [11]. Thus, Tr1 cells differentiated by the multiple antigen challenges could respond to the specific antigen to produce IL-10, which exerted anti-inflammatory actions in the asthma pathogenesis.

From these observations, Tr1 cells can be utilized for an antigen-specific cellular immunotherapy for atopic diseases. A literature reported by Chen et al. [12] documented that adoptive transfer of iTreg cells prevented allergic airway inflammation in a murine model of asthma. However, efficacy of Tr1 cells/iTreg cells on allergic diseases has never been well demonstrated. Recent murine studies have revealed efficient methodologies for Tr1 cell differentiation, in which Tr1 cells can be differentiated in the presence of IL-21, IL-27 and TGF-β [13-15]. Future studies may establish efficient ways to obtain a large number of Tr1 cells that respond to a specific antigen.

Although further basic researches on Tr1 cells are required for application of the cells to clinical immunotherapy, advantages of Tr1 cells for immunotherapy can be summarized as follows: (1) Tr1 cells have a nature to be activated in an antigen-specific manner, suggesting that the immunotherapy using Tr1 cells may not exert redundant immunosuppressive actions in comparison with nTreg cells, and (2) immunotherapy using antigen-specific Tr1 cells can be logically applicable to various atopic diseases, not only asthma but also atopic dermatitis and pollenosis, in which specific antigenic proteins have been identified.

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