# Changes in induced regulatory T cells by interleukin 35 during atopic dermatitis*

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It was with great interest that I read the recently published, brief communication by Roesner *et al.*, which analyzed the circulation frequency of forkhead box P3 (Foxp3)$^+$ regulatory T cells (Tregs) in adult patients with atopic dermatitis (AD).[1] The study found a positive correlation between these cells and disease severity. Recently, several researchers have focused on the relatively newly identified Tregs, which are induced by interleukin (IL)-35 and suppress effector T cell function. This type of Treg was primarily described by Collison *et al.* in 2010 and termed iTr35.[2] Unfortunately, despite the critical roles of iTr35 in regulating immune responses, its role in different autoimmune diseases like AD remains largely unknown. It was reported that iTr35 cells are phenotypically and functionally distinct from previously identified Tregs, including Foxp3$^+$ and Tr1 Tregs. These cells mediate suppression of effector T cells in an IL-10 and TGF-β independent manner. Additionally, it was shown that iTr35 can suppress T helper (Th)2 cell differentiation, which benefits AD patients suffering from Th2 dominancy. Furthermore, iTr35 produces IL-35 in an autocrine manner. Indeed, through the promotion of iTr35, a positive feedback loop of IL-35 production and iTr35 development could be established. Because the functions of autoantibody-producing B cells are strongly dependent on T cells, it seems that suppression of autoreactive T cell functions, especially Th2 cells via iTr35, may impair autoreactive B cell production. Although this type of cell plays a critical role in AD theoretically, no study measured frequency of iTr35 in patients with this disease. Given the crucial role of IL-35 in differentiating these cells, it is suggested that determining IL-35 levels could also assist in addressing the question of how iTr35 Tregs change during AD. Understanding this issue will help to provide a new therapeutic approach toward the inhibition of aggressive responses from immune systems. It seems that this new subset of Tregs may decrease during AD. However, further studies are needed to confirm this hypothesis. Recently, it was revealed that IL-35 can also induce a new subset of regulatory B cells (Bregs).[3] These newly emerged Bregs may be a critical factor in various autoimmune diseases, including AD.[4] By analyzing the populations of these Bregs, in addition to their functions, a new biological treatment based on inducing the cells may be initiated. In AD patients, it can be speculated that IL-35$^+$ Bregs may decrease and that dysfunction may be observed. If so, induction of IL-35 could be used to remit severe AD patients. In our recent studies, we examined the increased IL-4 levels in pemphigus patients and the inhibition of this cytokine with a newly emerged drug for moderate to severe AD; dupilumab was suggested.[5,6] For future studies, we recommend measuring iTr35 and IL-35$^+$ Bregs as well as IL-35 levels in AD patients. This could help to establish a new biological treatment for AD patients.❑

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