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Can we treat cancer by targeting Treg subset without causing autoimmune disease?

The regulatory T cells (Tregs), are a type of $CD4^+$ T cells that suppress the potentially adverse effect of the immune system and prevent autoimmune disease. Although they play a central role in maintaining self-tolerance, Tregs also represent a major barrier for the antitumor immunity. Targeting Tregs is an effective approach to treating cancer, however, they could also lead to life-threatening autoimmune problems. Thus, there is a clear need to develop more selective approaches to limit tumor-related Treg cell function without impacting peripheral immune homeostasis.

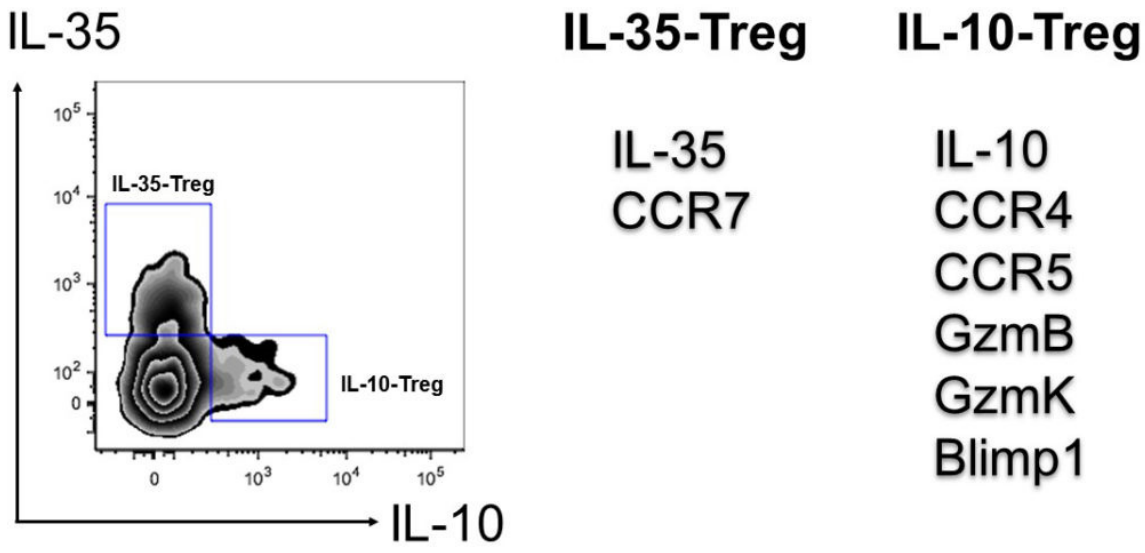

Fig. 1. Two distinct effector Treg subsets.

Similar to effector T cells, Treg cells undergo an activation process to gain increased inhibitory activity and eventually differentiate into effector Tregs, which can produce various soluble inhibitory cytokines and surface molecules to suppress the immune response. Effector Tregs can exert their functions through multiple suppressive mechanisms: 1) inhibitory cytokines release, in which Tregs secrete inhibitory cytokines such IL10, TGF-β, and IL35 to prevent prolonged inflammatory reactions; 2)cytolysis, which is similar to the cytotoxic T lymphocyte (CTL) granzyme-dependent pathway used to kill target cells;3) metabolic disruption; and 4) modulation of APC function, in which Tregs downregulate surface levels of CD80/CD86, CD40, MHC-I, and MHC-II on APCs, thus blocking the stimulation of effector T cells by APCs. Although these specific mechanisms have been well defined, it is uncertain how Tregs exactly employ these mechanisms and if a single effector Treg utilizes all of those suppressive mechanisms or multiple distinct Treg effectors cooperate together.

We seek to address this question by looking at inhibitory cytokines producing Treg subsets. Aside from the well known inhibitory cytokines such as TGF-β and IL-10, the new immunosuppressive cytokine IL-35 has

been implicated in Treg cell function through a combination of bystander suppression and infectious tolerance. Therefore, we generated an IL-35 reporter mouse (Ebi3-Dre-Thy1.1) in which the surface expression of Thy1.1 reflects intracellular IL-35 secretion. Using this transgenic mouse, we found effector Tregs can be divided into two functionally distinct subsets based on their suppressive cytokine induction: IL-35-Tregs are IL-35 producers and express intermediate levels of ICOS and CCR7, preferentially localizing in the T cell zone; and IL-10-Tregs express high levels of IL-10, ICOS, granzymes, and multiple chemokine receptors responsible for migrating to peripheral non-lymphoid tissues. The IL-35-Tregs were distinguished from IL-10-Tregs, not only by their distinct expression signatures but also in their developmental dependency on a distinct transcriptional factor. Terminal effector transcription factor, Blimp1 was only crucial for IL-10 production but not for IL35, whereas Foxp3 determined the expression of IL-35 in Treg but not IL-10. Those two distinct Treg effector subsets, play complementary roles in the maintenance of immune tolerance.

Interestingly, although depletion of IL-35-Tregs did not affect IL-10 secretion by Foxp3+ Treg cells, nor caused any obvious immune activation, targeting IL35-Tregs indeed induced a better anti-tumor immune response in controlling tumor lung metastases. Thus, targeting IL-35^{+} Treg cells via antibody-mediated depletion could potentially push the immune system to detect and kill cancer cells without causing significant adverse events, such as general inflammation and autoimmune complications. We believe this finding might have important implication for future clinic therapy.

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Publication

Reciprocal Expression of IL-35 and IL-10 Defines Two Distinct Effector Treg Subsets that Are Required for Maintenance of Immune Tolerance.
Wei X, Zhang J, Gu Q, Huang M, Zhang W, Guo J, Zhou X
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