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Expression and Function of TNF and IL-1 Receptors on Human Regulatory T Cells

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Abstract

Regulatory T cells (Tregs) suppress immune activation and are critical in preventing autoimmune diseases. While the ability of Tregs to inhibit proliferation of other T cells is well established, it is not yet clear whether Tregs also modulate inflammatory cytokines during an immune response. Here, we show that the expression of inflammatory cytokine receptors IL-1R1 and TNFR2 were higher on resting mature Tregs compared to naïve or memory T cells. While upon activation through the T cell receptor (TCR), expression of IL-1R1 and TNFR2 were upregulated on all T cell subsets, IL-1R1 maintained significantly higher expression on activated Tregs as compared to other T cell subsets. The decoy receptor for IL-1 (IL-1R2) was not expressed by any of the resting T cells but was rapidly upregulated and preferentially expressed upon TCR-stimulation on Tregs. In addition, we found that Tregs also expressed high levels of mRNA for IL-1 antagonist, IL-1RA. TCR-stimulation of naïve T cells in the presence of TGFβ, which induces FOXP3 expression, however did not result in upregulation of IL-1R1 or IL-1R2. In addition, ectopic expression of FOXP3 in non-Tregs, while causing significant upregulation of IL-1R1 and IL-1R2, did not achieve the levels seen in *bona fide* Tregs. We also determined that resting human Tregs expressing IL-1R1 did not have higher suppressive capacity compared to IL-1R1- Tregs, suggesting that IL-1R1 does not discriminate suppressive resting Tregs in healthy individuals. Functionally, activated human Tregs displayed a capacity to neutralize IL-1β, which suggests a physiological significance for the expression of IL-1 decoy receptor on Tregs. In conclusion, our findings that human Tregs preferentially express receptors for TNF and IL-1 suggest a potential function in sensing and dampening local inflammation.

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Introduction

Regulatory T cells (Treg) are characterized by the ability to suppress immune activation [1]. Tregs are a subset of CD4+ cells and are typically identified based on CD25 and FOXP3 expression [1]. The latter is a transcription factor also necessary for their development and function [1]. While it is well established that Tregs are highly potent in inhibiting the activation and proliferation of other T cell subsets *in vitro* and *in vivo*, the exact mechanisms of this suppression are not fully understood [2]. However, evidence from mouse models suggests that Tregs may have other anti-inflammatory properties in addition to suppressing T cell activation [1,3]. For example, Tregs have been shown to prevent T cell independant intestinal inflammation [4]. Little is known on how Tregs mediate T cell-independent suppressive mechanisms and whether the inflammatory milieu may have modulatotry effects on the function of Tregs.

Recently, IL-1R1 and IL-1R2 were shown to be expressed on *in vitro* expanded human Tregs [5] and TNFR2 was shown to be expressed on murine and human Tregs [6]. IL-1R1 is a signaling receptor for IL-1, which mediates its function [7]. IL-1R2, instead neutralizes IL-1 either as a surface decoy receptor or in a cleaved and secreted form [7,8,9]. TNFR2 is an inducible receptor for TNF, that can trigger both cell survival and inflammatory signals [10].

In humans, Tregs comprise 2–5% of total CD4+ cells and similar to mouse Tregs, are crucial for proper immune function, as their absence results in massive autoimmunity [11]. The canonical murine Treg markers, FOXP3 and CD25, do not selectively define human Tregs, since these markers can be induced on other human T cells upon activation, especially in the presence of TGFβ [12,13]. It was recently shown that IL-1R1 and IL-1R2 can be useful markers to purify Tregs from *in vitro* expanded cultures [5]. However, the expression pattern and function of these receptors on human Tregs is not yet fully characterized. Here, we show that IL-1R1 and TNFR2 are preferentially expressed on resting *ex vivo* isolated Tregs. However, upon activation both of these receptors are upregulated on other T cells subsets, although IL-1R1 maintains preferential expression on Tregs. We also found that Tregs have the capacity to neutralize IL-1β activity, suggesting that preferential expression of IL-1β decoys by these cells has a functional consequence of possibly suppressing the inflammatory cytokine milieu.

Results

Human Tregs preferentially express IL-1 and TNF receptors and decoys of IL-1

In order to identify new effector molecules that may contribute to Treg function, we had performed differential gene expression