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REVIEW

Renegade homeostatic cytokine responses in T1D: Drivers of regulatory/effector T cell imbalance

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Abstract Homeostatic cytokines contribute to the balance between regulatory and effector T cells (Tregs and Teffs respectively) and are necessary to maintain peripheral tolerance. These cytokines include IL-2 that supports Treg and IL-7 and IL-15 that drive Teff. In overt settings of lost tolerance (i.e. graft rejection), IL-2 Treg signatures are decreased while IL-7 and IL-15 Teff signatures are often enhanced. Similar cytokine profile imbalances also occur in some autoimmune diseases. In type 1 diabetes (T1D), there are underlying defects in the IL-2 pathway and Teff cytokine blockade can prevent and treat diabetes in NOD mice. In this review, we summarize evidence of IL-2, IL-7 and IL-15 genetic and cellular alterations in T1D patients. We then discuss how the combined effect of these cytokine profiles may together contribute to altered Treg/Teff ratios and functions in T1D. Implications for combination therapies and suggestions for integrated cytokine and Treg/Teff biomarker development are then proposed.

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Abbreviations: Tregs, regulatory T cells; Teffs, effector T cells; T1D, type 1 diabetes; NOD, non-obese diabetic mice; IL2Rα, IL-2 receptor alpha; IL7Rα, IL-7 receptor alpha; IL-15Rα, IL-15 receptor alpha.

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1. Introduction

Peripheral tolerance requires signals that selectively contribute to the preservation of regulatory T cells (Tregs) while restraining signals that perpetuate effector T cells (Teffs). Cytokines deliver many of these signals. For example, the homeostatic cytokine IL-2 supports Treg while IL-7 and IL-15 support Teff cell proliferation and survival. Consistent with the functions of these cytokines, therapies that augment IL-2 or block IL-7 or IL-15 can restore a beneficial Treg/Teff ratio in animal models of lost tolerance. In many autoimmune diseases, there are inherent defects in homeostatic cytokine pathways including IL-2, IL-7 and IL-15 [19]. Thus, we suggest that signatures of IL-2, IL-7 and IL-15 may also be biomarkers of disease progression in autoimmunity and cytokine-based therapies may be used to manipulate these responses.

Type 1 diabetes (T1D) is an autoimmune disease in which one's own immune system destroys the pancreatic beta islet cells resulting in a life-long dependence on exogenous insulin therapy. Changes in both Teff and Treg contribute to T1D progression and pathology. This is highlighted by the fact that immune-modulatory monotherapies have had underwhelming or transient efficacy to date [23] suggesting a need for combination therapy that both inhibits Teff and amplifies Treg for effective and durable treatment [48]. As a major genetic factor in T1D, HLA contributes to the selection and activation of autoreactive T cells [54]. However, the simple presence of autoreactive Teff does not lead to disease [13]. Instead, expansion and maintenance of autoreactive Teff and trafficking to the pancreas lead to disease progression. Importantly, homeostatic cytokines drive many of these processes. In this review, we discuss how dysregulation of the homeostatic T cell cytokines IL-2, IL-7 and IL-15 may alone or in combination impact the Teff/Treg balance in T1D and further discuss integration of cytokine signatures and Treg/Teff ratios as a biomarker of T1D progression and response to therapy.

2. Introduction to homeostatic IL-2, IL-7 and IL-15 cytokine responses in T1D

IL-2, IL-7 and IL-15 are all members of the common gamma chain cytokine family. Each cytokine is produced by different cell types; IL-2 is primarily produced by activated T cells and dendritic cells, IL-7 is primarily produced by stromal cells and IL-15 is produced by multiple cell types including bone marrow and activated antigen presenting cells. Common to IL-2, IL-7 and IL-15 is expression of their receptors on T cells. Selective expression of each unique cytokine receptor determines the magnitude and persistence of the cytokine response. Treg and activated Teff express the high affinity IL-2 receptor alpha (IL2Rα, or CD25) that pairs with the low affinity IL-2 receptor beta (IL2Rβ, or CD122) and the common gamma chain. Naïve and resting Teff cells express the highest level of the high affinity IL-7 receptor alpha (IL7Rα, or CD127). Activated T cells express high levels of the IL-15 receptor alpha (IL15Rα) that pairs with the IL2Rβ and the common gamma chain. However, the majority of IL-15 signaling occurs through cross-presentation of IL-15 by IL-15Rα to T cells expressing the low affinity IL-2Rβ. Differential expression of IL-2, IL-7 and IL-15 receptors on T cell subsets leads to selective IL-2-driven expansion of Treg and selective IL-7 and IL-15-driven expansion of distinct Teff subsets. The basic biology of each cytokine and its receptor has been well reviewed by others [10,45,60]. In Section 2, we discuss alterations of these cytokine pathways in T1D and the functional implications (Table 1).

2.1. IL-2

IL-2 plays a crucial role in Treg fitness and function. However, IL-2 also promotes Teff activation and differentiation. In particular, strong IL-2 signals favor differentiation of CD8 effector memory cells while weak IL-2 signals favor Th17 and T follicular helper cell differentiation [45]. Alterations in IL-2 and IL-2R signaling have clearly been linked to T1D [27]. Non-obese diabetic (NOD) mice produce lower amounts of IL-2 resulting in reduced Treg numbers [67]. In many T1D subjects, there is increased soluble IL-2Rα [17] and a reproducible decrease in response to IL-2 as measured by phosphorylation of STAT5 in both Treg and memory CD4 T cells [41]. This decreased response to IL-2 is evident in several independent down-stream cellular phenotypes: IL-2-mediated maintenance of FOXP3 expression in Treg of T1D subjects is impaired [41], Treg survival is reduced in recent onset T1D subjects due to IL-2 deprivation [28] and Th17 cells, a cell type that differentiates in the absence of IL-2, are increased [46]. Together these finding strongly suggest that reduced IL-2 and IL-2 response are characteristics of diabetes.

Genetic variation underlies much of the diminished IL-2 response in T1D. In genome wide association studies (GWAS), multiple T1D-associated variants have been identified in *IL2* itself, *IL2RA*, *IL2RB*, and the protein tyrosine phosphatase N2 (*PTPN2*) gene, a phosphatase in multiple signaling pathways including the IL-2R signaling pathway (reviewed in [38]). All of these SNPs are non-coding suggesting subtle changes in regulation of expression, not altered protein structure. The molecular mechanisms underlying the phenotypes associated with *IL2RA* risk variants appear to be at least two-fold involving decreased transcription of IL2Rα in memory T cells and increased production of sIL-2Rα, both leading to differences in the surface expression of CD25 and response to IL-2 [11,14,44]. Similarly, the T1D-associated variant in *PTPN2* is also associated with changes in gene expression and reduced IL-2 responsiveness [42]. Together, multiple variants in at least four genes encoding unique proteins involved in the IL-2 pathway strongly argue that there is a genetic component to reduced IL-2 response in T1D subjects [27].