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Review

Interleukin-7: Fuel for the autoimmune attack

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ABSTRACT

Interleukin-7 (IL-7) is a critical survival factor for lymphocytes and recent studies suggest targeting the IL-7/IL-7Rα pathway holds promise for the treatment of autoimmune diseases. Several lines of evidence, genetic as well as functional, indicate an important role for this cytokine in autoimmune inflammation: polymorphisms in the IL-7Rα have been associated with increased risk for autoimmune disease and blocking IL-7/IL-7Rα with antibodies showed therapeutic efficacy in several autoimmune mouse models. Insights are starting to emerge about the mechanisms underlying IL-7's role in autoimmunity and tolerance, revealing surprising novel functions beyond its traditional activity as a T cell survival factor. In the first part of this review, the functions of IL-7 in the immune system are concisely described, providing a basis for understanding their potential role in promoting autoimmune responses. In the second part, current knowledge about the role of IL-7 in various autoimmune conditions is reviewed.

1. Introduction

Autoimmune diseases typically develop over a prolonged period of time as a consequence of the integration of several genetic, immunological and environmental events. Central to the paradigm, however, is that one or more self-antigens inappropriately activate tissue-specific immune cells that then initiate destruction of the target tissue. However, the spectrum of autoimmune diseases is not solely determined by the origin of the self-antigens, but also by the types of immune cells involved. Autoimmune diseases can be T- or B-cell dependent and, within the T cell group, the nature of the response (Th1, Th2, Th17) is an important factor in the etiology of specific diseases. The cytokine environment, the conditions of antigen presentation and T cell – intrinsic properties all contribute in determining the differentiation of various T cell subsets. While approaches to specifically tolerize the cells responsible for initial tissue recognition and/or subsequent destruction are considered the holy grail in therapy of autoimmune diseases, these have proven difficult [1]. Not only is the nature of the causative antigen often not clear, epitope spreading further challenges the feasibility of antigen-specific therapies. On the other hand, interfering with cytokines that play critical roles in the initiation and/or effector phases of the autoimmune attack represents a strategy that has shown success. Several drugs (e.g. etanercept, infliximab, adalimumab) to block TNFα, a major pro-inflammatory mediator, are on the market for the treatment of rheumatoid arthritis, psoriasis and Crohn's disease. Many more members of the TNF family are currently being targeted in clinical trials for a host of indications (for overview see Ref. [2]). Blocking IL-1 and IL-6 activity is also being used for treating rheumatic diseases and many other cytokine targets are in clinical trials or under development. Promising results have been obtained with blocking IL-17 in psoriasis, a Th17 dependent disease [3], underscoring the potential of targeting cytokines involved in T cell function for therapy. Such an approach may also have the added benefit of keeping innate immunity largely intact to fight opportunistic infections. In addition, reinforcing cytokine pathways that bolster immune regulation have also garnered a lot of interest in recent years. Using IL-2, which is critical for regulatory T cells (Tregs), is an attractive candidate for Type 1 Diabetes (T1D) for example [4]. One candidate meriting further research in the context of autoimmune disease is IL-7. In recent years, interest in IL-7 as a factor contributing to the autoimmune response has grown. While initially described as a broadly active T cell survival factor that is important for T cell development in the thymus and peripheral maintenance of naïve and memory cells, recent studies point to a more complex set of functions of this cytokine in T cell biology.

2. Interleukin-7: functions relevant for autoimmunity

Throughout their life, T cells depend on integrated signals from TCR-mediated recognition of antigen and cytokines to survive, proliferate and differentiate [5,6]. TCR stimulation is required to select and maintain the diversity of the TCR repertoire and

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guarantee the specificity of the T cell response to pathogens. Cytokines determine to a large extent the magnitude and type of this response. Many of the cytokines regulating the various phases of T cell life belong to the common γ chain (γc) family, which shares a receptor component (γc) for signaling. Specificity for each cytokine is accomplished by combining this chain with a cytokine-specific second and, in some cases, third chain: IL-2 is critical to maintain effector and regulatory T cells [7–10], IL-4 stimulates proliferation and differentiation of Th2 cells [11–14], IL-9 supports Th17 proliferation [15] and IL-15 [16,17] and IL-21 [18,19] are critical for the survival and function of $CD4^+$ and $CD8^+$ effector/memory T cells. IL-7 uses the γc chain together with IL-7Rα for signaling and this dimeric complex activates the PI3K and STAT5 signaling pathways [20]. It is important to keep in mind that IL-7Rα is also used as part of the Thymic Stromal Lymphopoietin (TSLP) receptor, since this may have consequences for anti-IL-7Rα blocking studies in vivo [21]. In this section, I will review the activities of IL-7 in T cell biology and indicate how they may contribute to pathogenic autoimmune T cell responses.

2.1. T cell development

Unlike other γc cytokines, IL-7 is not produced by T cells themselves but by non-immune stromal cells, fibroblastic reticular cells, keratinocytes as well as certain DCs and macrophages [20,22,23]. The bone-marrow and thymus are premier sites of IL-7 production and the cytokine plays a critical role in T (and B) cell development. IL-7- and IL-7Rα-deficient mice show a dramatic reduction in cellularity of the thymus [24]. On immature thymocytes, IL-7Rα is initially expressed on $CD4^-CD8^-$ double negative (DN) cells at the DN2 and DN3 stages. IL-7 provides survival and proliferation signals at these stages and genetic deletion of IL-7/IL-7Rα results in a developmental block at DN3. At DN4, IL-7Rα expression is downregulated and becomes completely extinguished at the double positive (DP) stage when αβ TCRs are being expressed and their engagement regulates life/death decisions for maturing thymocytes [25,26]. DP cells receiving an appropriate TCR signal resulting in expression of the anti-apoptotic protein Bcl-2 will survive, while absence of a matching TCR ligand will result in death. Hence, absence of IL-7Rα in this phase is critical to ensure the proper execution of the positive selection process. IL-7Rα is re-expressed after positive selection and IL-7 provides pro-survival signals and guides T cell lineage differentiation [27]. Once lineage commitment has finalized and T cells enter the periphery, they become dependent on IL-7 for life during the steady-state. While it seems feasible that dysregulation of IL-7/IL-7Rα expression in the thymus may lead to defects in T cell development and negative and/or positive selection processes, there is no robust evidence that this leads to the release of autoreactive T cells in the periphery. Hence, transgenic mice overexpressing either IL-7 or IL-7Rα show aberrant thymocyte numbers leading to increased T cells in the periphery and sometimes lymphoma/leukemia development, but observations of autoimmunity are limited [28–31]. These models don't necessarily recapitulate subtle changes in thymic IL-7 signaling that might occur in individuals at-risk for autoimmunity, but a role for IL-7 in overcoming central tolerance remains speculative at this time. Finally, IL-7 is also indispensable for B cell lymphopoiesis [32,33]. IL-7- and IL-7Rα-deficient mice show arrested B cell development in the bone marrow but cells that escape this block and appear in the periphery are activated plasma cells, causing a 3–5 fold increase in serum IgM & IgG [34–36].

2.2. T cell survival

Perhaps the best characterized function of IL-7 is to provide survival signals to lymphocytes (Fig. 1). Naïve T cells, once they leave the thymus and enter the periphery, need signals to induce pro-survival members of the Bcl-2 family [6]. The balance of these anti-apoptotic proteins with pro-apoptotic members of the family determines whether a cell will persist. Two main signals have

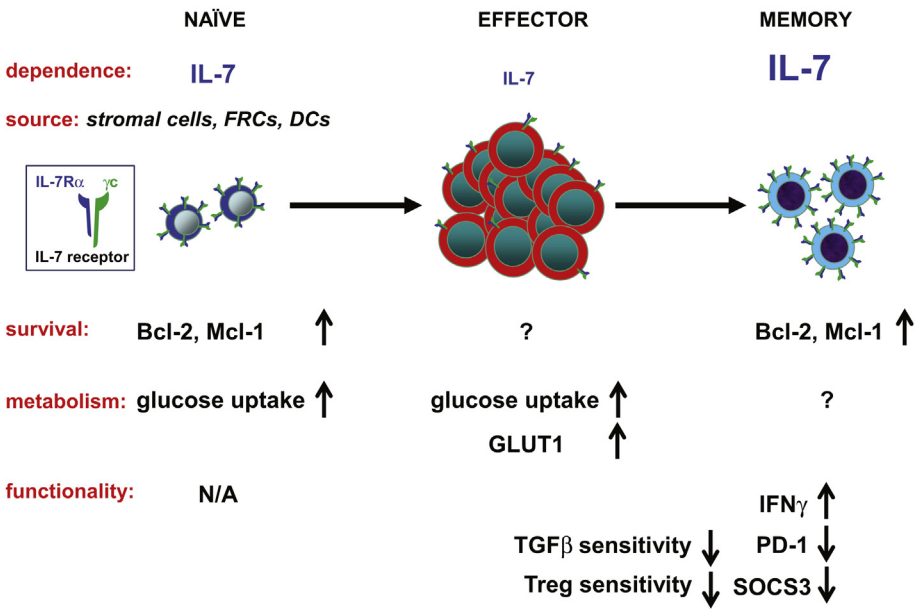

Fig. 1. Role of IL-7 in peripheral T cells. After emigration from the thymus, naïve T cells become dependent on IL-7 (and self/MHC) for their survival. IL-7 induces expression of anti-apoptotic members of the Bcl-2 family and regulates metabolism of these cells, which express high levels of the IL-7Rα. When T cells get activated by their cognate antigen, they downregulate IL-7Rα expression and become largely independent of the cytokine for survival signals. Activated T cells differentiate into effector cells and, in the later stages of the response, IL-7 facilitates the transition to memory T cells. In situations of chronic effector/memory responses, IL-7 has the capacity to increase T cell effector functions such as IFNγ production by suppressing various inhibitory mechanisms (whether such IL-7 effects act on effector and/or bona fide memory T cells is currently not clear). Long-lived memory T cells re-express IL-7Rα at very high levels and need IL-7 signals for their maintenance.

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