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Review

Lymphopenia and autoimmunity: A double-edged sword

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ABSTRACT

Lymphopenia is strongly associated with autoimmune diseases. The molecular mechanisms that link both phenomena are still unclear, but certain key pathways have been described. Central tolerance is as important as peripheral. In the earlier, epithelial and dendritic cells play a crucial role in the selection of clones. In the latter, regulatory T cells (Tregs) rise as inductors of anergy in order to prevent the development of autoimmune pathology. In lymphopenic conditions, T cells develop the process of lymphopenia-induced proliferation (LIP). A complex interaction between the major histocompatibility complex (MHC) and the T cell receptor (TCR) makes this process possible. Furthermore, IL-7 can act synergistically or in an independent manner to promote LIP. A lack of Transforming Growth Factor-β (TGF-β) was recently described as the second hit needed to develop autoimmunity in a lymphopenic microenvironment, given its actions in Tregs and its interaction with CTLA-4. Regarding autoimmune clinical scenarios, lymphopenia is related to both, systemic and organ-specific diseases. Thus, the molecular study of such patients has been limited and needs to be widened to the pathways shown here to be involved in the development of lymphopenia and autoimmunity.

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1. Introduction

Lymphopenia is a phenomenon associated with multiple pathologic conditions, including autoimmune disease, which has been both widely studied and poorly understood. The molecular mechanisms involved in the role lymphopenia plays in the development of autoimmunity are varied, and had been studied in an isolated manner, up until recently when they were linked to a more specific process: lymphopenia-induced proliferation (LIP). In this work, we intend to review the role of lymphopenia in the development of autoimmunity, along with the molecular mechanisms involved in this process by making a final remark on systemic and organ-specific autoimmune diseases, we aim to contribute to a better understanding of their pathophysiology, which could lead, in a not too distant future, to a more specific and targeted treatment.

2. Immunological tolerance: keeping track of the autoreactive cells

The mechanisms involved in immunological tolerance have proven to be complex and interrelated. Classically, immunological tolerance is divided into central and peripheral. However, deeper knowledge in the matter has made evident that this division is becoming less accurate, because of the shared pathways.

2.1. Central and peripheral tolerance: a common pathway towards autoimmunity

The thymus is the organ where T cells learn self-tolerance. The mechanism by which T cells are differentiated consists of two main steps, positive and negative selection. Whilst positive selection allows for a great number of T cells to continue the differentiation pathway, including self-reactive ones, negative selection ensures the elimination of high-affinity self-reactive clones. Dendritic cells (DCs) play a crucial role in the induction of tolerance. Using human peripheral blood mononuclear cells and thymuses, it was shown that dendritic cells positively select regulatory T cells in the thymus. Also, the thymic epithelium plays a role as an activator of dendritic cells, mainly through the secretion of thymic stromal lymphopoietin (TSLP) [1].

Since not all self-antigens are present in the thymus, peripheral tolerance is also relevant in avoiding self-reactivity. The main pathways to achieve it are clonal deletion and anergy. Regulatory T cells (Tregs; $CD4^+CD25^+Foxp3^+$) and DCs are among the most important peripheral elements to prevent the development of pathogenic autoimmune responses (see Fig. 1).

Different groups have proved that it is the interaction between DCs and Tregs what makes self-tolerance possible in the periphery. DCs have been shown to induce $FoxP3^+$ Tregs in the periphery in steady-state conditions [2–4]. On the other hand, through the use of DIETER and DEREG/DIETER mice (whose Tregs are depleted by means of injecting diphtheria toxin), Schildknecht et al. showed that steady-state DCs are unable to induce tolerance in the absence of $Foxp3^+$ T cells, concluding the crucial role of these cells' interaction in the prevention of autoimmunity [5].

2.2. AIRE: the link between central and peripheral tolerance

Aire (autoimmune regulator) has been associated with the development of autoimmunity, and its role in the induction of central tolerance is complex and diverse, as made evident by the multiple phenotypes shown by the Aire-deficient mouse models [6,7]. A recent model for the study of Aire confirmed its role in thymic negative selection, based on the indirect presentation of tissue antigens from thymic epithelial cells to dendritic cells, regardless of the antigen expression level [8]. Although it is mainly associated with central tolerance, Aire has also been found in peripheral lymphoid organs, both in mice and humans [9,10], and has been shown to promote tolerance through the interaction of extra-thymic Aire-expressing cells (eTACs) with T cells [9]. Specifically, it was recently shown that the peripheral expression of Aire is sufficient to prevent autoimmunity in a lymphopenic environment. Using an Aire-deficient mouse model, in which they transferred PBMCs to lymphopenic hosts, Kekäläinen et al. showed that a peripheral Aire-rich environment is able to prevent autoimmunity in the setting of LIP, even after the central loss of Aire [11]. This highlights the crucial role of Aire in the maintenance of tolerance.

3. IL-7: the master cytokine takes the lead

3.1. Major anti-apoptotic signaling pathways

IL-7 has been described as a growth factor for both B and T cells. Alongside IL-2, IL-9, IL-15 and IL-21, IL-7 is part of the cytokine family that shares the common γ-chain to signal. It is required to interact with a membrane specific IL-7 receptor (IL-7Rα/CD127) to activate the diverse intracellular pathways involved in IL-7 signaling. Jak1 and Jak3 have been shown to be phosphorylated and brought together by the action of IL-7. This interaction leads to the phosphorylation of STAT5, which enhances its DNA binding activity, triggering the transcription of several anti-apoptotic genes such as Bcl-2 [12–14]. The transcription of anti-apoptotic genes has been considered one of the most important mechanisms implicated in the pro-survival effects of IL-7 signaling.

The PI3-Kinase pathways are also regulated by IL-7 [15]. The activation of the p85α subunit of the PI3K pathway together with STAT5 leads to the regulation of Akt, which is involved in the transcription of Glut-1 (a major glucose transporter), p27-kip1 (a cyclin-dependent kinase inhibitor) and Bcl-2 (an antiapoptotic protein) [16,17]. With these data, it could be said that IL-7 participates in the regulation of cell metabolism, cell cycle and survival.

3.2. IL-7 and regulatory T cells: from development to function

Tregs work in the periphery as suppressors of auto-reactive T cells. Several studies show that Tregs are directly related to the prevention and/or development of autoimmunity [18,19]. IL-2 is well known for its role in the development and maintenance of peripheral homeostasis of regulatory T cells. A function for IL-7R in this subset of T cells has been shown to be primarily in their thymic development, where IL-7 plays a major role in IL-2Rβ$^{-/-}$ mouse models [20]. Controversy surrounding the role of IL-7 in Treg function arises from the evidence supporting a low expression