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Therapeutic utility of the newly discovered properties of interleukin-21

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ABSTRACT

Since its discovery in 2000, interleukin-21 (**IL-21**) has been shown to display a broad spectrum of pleiotropic actions including the regulation of development, differentiation and function of lymphoid-myeloid cells. More specifically, IL-21 modulates the effector functions of T, B and NK cells, which not only have key roles in antitumoral and antiviral immunity but also in exerting major effects on inflammatory responses promoting the development of autoimmune diseases. Recent studies have unveiled an unexpected role for IL-21 in immune regulation and *de novo* T-cell development. While highlighting its critical role in immunity, this review will mainly focus on recent advances in IL-21 biology and how such newly discovered properties could potentially be exploited therapeutically in the establishment of future clinical trials.

1. Introduction

One of the key functions of the immune system consists in producing cytokines as a mean to regulate immune cell activity [1]. More specifically, cytokines can drive the expansion and effector function of myeloid and lymphoid cells as well as the down-regulation of immune responses once the non-self agent or invading pathogen have been eradicated [1]. Much attention has been paid over the past decades on the role of cytokines in modulating immunity as understanding their mechanisms of action is central for designing novel strategies aimed at disease control. Of all the 60 cytokines identified so far, some members of the type I four-α-helical-bundle cytokine family have been widely studied due to their importance in immune cell development and function as illustrated by the X-linked severe combined immunodeficiency [2,3]. This disease is characterized by mutations in the *IL2RG, which* encodes the common gamma chain (**γc**) commonly used by the dimeric or trimeric receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [2,3]. Under such context, the host becomes extremely susceptible to infections due to the near-absence of T and NK cells as well as impaired B-cell functions [2,3]. Of all members of the γc cytokine family, IL-21 stands out due to its broad spectrum of effects (Fig. 1). Initially, IL-21 was known for its capacity to trigger the proliferation of B and T cells as well as to generate highly lytic NK cells [4–7]. These initial reports not only provided meaningful leads into the biology of the IL-21/IL-21 receptor (**IL-21R**) axis, but formed the groundwork for many subsequent studies highlighting its critical role as a central antitumoral and antiviral agent [8–14].

2. IL-21 Ligand/receptor expression and signaling

IL-21 is primarily secreted by $CD4^+$, NKT cells, and T helper (**Th**) 17 cells (Fig. 1) with distinct gene expression regulation compared to other γc cytokines [14]. For instance, the IL-21 gene is located adjacent to the IL-2 gene. Although, TCR stimulation of $CD4^+$ T cells triggers secretion of both cytokines, IL-21 expression can be induced by a calcium signal alone, whereas IL-2 induction requires both a calcium signal and protein kinase C [15]. Furthermore, nuclear factor of activated T cells can bind the IL-21 promoter and regulate its transcription [15,16]. Interestingly, mycobacterial antigens have also been reported to enhance IL-21 levels in mouse and human NKT cells suggesting a role for innate immune signals in stimulating IL-21 production [17].

The expression of the IL-21R, on the other hand, is restricted to the lympho-hematopoietic system. It is detected on the surface of $CD4^+$ and $CD8^+$ T cells, B cells, NK cells, dendritic cells (**DCs**),

Abbreviations: APC, antigen-presenting cell; BCR, B-cell receptor; BIM, BH3-only protein; BM, bone marrow; B10, IL-10-producing B cells; Breg, B regulator cell; DC, dendritic cells; DEX, dexamethasone; DN, double-negative; DP, double-positive; GFP, green fluorescent protein; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IL-21R, IL-21 receptor; JAK, Janus kinase; RTE, recent thymic emigrant; SP, single-positive; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; Th, T-helper; Tr1, T regulatory 1; Treg, T regulatory cell; WT, wild-type; γc, common gamma chain.

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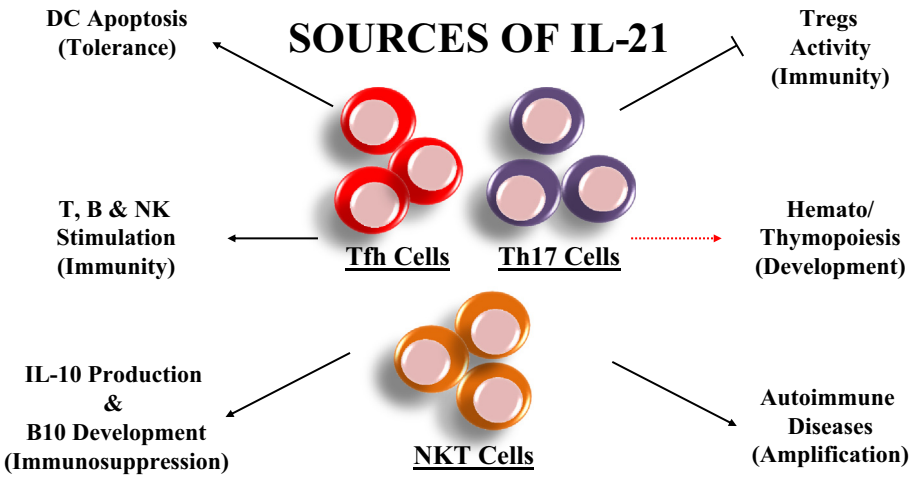

Fig. 1. Schematic representation of the pleiotropic action of IL-21 on various components of the immune system. IL-21 is secreted by three cell populations: activated $CD4^+$ T cells, NKT cells and Th17 cells. Depending on the context it is found in, IL-21 can either support antiviral or antitumoral immunity by stimulating T, B and NK cells as well as by inhibiting Tregs activity or suppress ongoing immunity by triggering DCs apoptosis, IL-10 production by $CD4^+$ T cells and B10 differentiation. In addition, IL-21 has been largely linked to promoting autoimmune disorders. A new function for IL-21 has been lately unveiled in thymopoiesis, which could be exploited to tailor novel IL-21-based strategies to improve T-cell functions in the elderly as a mean to efficiently control viral infections and cancer.

macrophages, keratinocytes as well as hematopoietic progenitors [14]. This dimeric receptor is composed of the IL-21Rα (ensuring proper receptor specificity with no intrinsic signaling capabilities), and the common γc chain (involved in signal transmission) [18]. In terms of expression intensity, IL-21R is highly expressed on B cells at steady states [19–21]. In contrast, its expression levels are low on resting T cells but increase significantly following T-cell receptor (**TCR**) stimulation [7]. With respect to signaling pathways, IL-21 leads to the activation of the Janus kinase (**JAK**)-signal transducer and activator of transcription (**STAT**), the mitogen-activated protein kinase and the phosphoinositide 3-kinase signalling pathways. Like other $_c$ cytokines, IL-21 mainly activates JAK1 and JAK3, which subsequently trigger the phosphorylation of STAT1, STAT3, and both STAT5a and STAT5b [18]. However, the activation of Stat5a and Stat5b is relatively weak and transient in comparison to STAT3, which is mostly sustained [18].

In terms of immune development, studies conducted in IL-$21R^{-/-}$ mice clearly showed that IL-21 has no major role in primitive hematopoiesis. This is however surprising as IL-21R is detected in bone marrow (**BM**) progenitor cells of wild-type (**WT**) mice, which end-up expanding both *in vitro* and *in vivo* if treated with IL-21 [5,22]. Within the T-cell lineage, IL-21R expression is induced as thymocytes differentiate from the double-negative (**DN**; $CD4^-$-$CD8^-$) to the double-positive (**DP**; $CD4^+CD8^+$) stage [5]. Akin to the situation with BM progenitors, IL-21 does not seem to be essential for intrathymic T-cell differentiation due to normal thymopoiesis in IL-$21R^{-/-}$ mice as well [5]. Its role is however more pronounced within the B-cell lineage as IL-21R is expressed at low levels at the pre-B cell stage of development with a noticeable increase in expression at the second transitional stage [23]. Mature follicular B cells, on the other hand, express higher basal levels of IL-21R than other B-cell populations, and these levels are further increased by signals triggered either through the B-cell receptor (**BCR**) or CD40 [24]. Marginal zone B cells respond to IL-21 but have lower IL-21R expression than do follicular B cells whereas the terminally differentiated plasma cells have no detectable IL-21R cell surface expression [25].

3. Brief overview of the pleiotropic effects of IL-21

At the functional level, IL-21 can potently regulate both innate and adaptive immune responses in addition to its linked roles in autoimmune disorders and allergies [14]. Given such breadth of immunomodulatory targets and pleiotropic actions (Fig. 1), the IL-21/IL-21R axis became an attractive target for therapeutic manipulation. For instance, IL-21 is itself under evaluation in Phase I and II clinical trials for its anticancer activity, whereas blocking IL-21 has been evaluated in Phase I clinical trials for rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease [26]. As several reviews describing IL-21 antitumoral and antiviral functions have been published, the herein review will summarise the most recent advances in IL-21 biology with emphasise on its unconventional but critical roles in immune-regulation and intrathymic T-cell development.

4. Regulating the regulators of immunity

4.1. IL-21 and DC differentiation

Although IL-21 is known for its potent stimulatory activity on both innate and adaptive immunity, it can nevertheless exert negative regulatory effects on lympho-myeloid cells [14]. For instance, IL-21 can lead to: (i) the differentiation of DCs with altered functions such as reduced capacity to prime T-cell activation, or (ii) inhibit the activation and maturation of granulocyte–macrophage colony-stimulating factor (**GM-CSF**)-induced DCs maturation by triggering their apoptosis in a STAT3- and BIM-dependent manner [27,28]. The mechanism behind the latter described effect is based on the fact that GM-CSF normally activates STAT5 inhibiting therefore the induction of the pro-apoptotic molecule BIM and thus, DCs apoptosis [28]. Therefore, by reverting the balance towards STAT3 activation, IL-21 triggers increased BIM expression consequently blocking the GM-CSF-induced survival effect. The fact that IL-21 can regulate the number of conventional DCs and thereby the magnitude of immune responses highlights a central role for this cytokine in maintaining tolerance.

4.2. IL-21 and immunosuppression by $CD4^{\pm}$ T cells

In addition to its inhibitory effect on antigen-presenting cells (**APCs**), IL-21 can block regulatory T-cell (**Tregs**) development as both IL-$6^{-/-}$ and IL-$21^{-/-}$ mice display increased numbers of FOXP3-expressing Tregs [29]. Elegant studies further demonstrated that IL-21 impedes Tregs generation and viability *in vitro* in an indirect