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EDITORIAL

Interleukin-7 signaling as a therapeutic target in acute lymphoblastic leukemia

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1. Introduction

Acute lymphoblastic leukemia (ALL) is a disease characterized by clonal growth of lymphoid precursors caused by somatic genetic and epigenetic aberrations that disrupt normal lymphoid development. These aberrations include activation of proliferative and survival signals in lymphoid precursors and silencing of signals promoting lymphoid differentiation.

Interleukin-7 (IL-7) is critical for induction of lymphopoiesis. Its elimination in mice results in a depletion of both B and T cells, while congenital mutations in IL-7 receptor alpha (*IL-7R*) in humans result in severe combined immunodeficiency (SCID) characterized by a complete absence of T cells with preservation of (inactive) B cells [1,2]. It is thus not surprising that activation of IL-7 signaling is seen in the majority of T-ALLs and in some of the B cell precursor ALL (BCP-ALL) [3,4].

In this editorial, we shortly review the mechanisms of activation of IL-7 signaling in ALL, focusing mainly on T-ALL and the promises and challenges in therapeutic targeting of this pathway. For more comprehensive information, the readers are referred to recent reviews [5,6].

2. Pattern of activation of IL-7 signaling in ALL

The receptor to IL-7 is formed by a dimer of IL-7Rα (CD127) and the common γ chain (γc; CD132) which is shared by the receptors for IL-2,-4,-9,-15, and-21. Upon binding of the ligand, IL-7, intracellular signaling is generated by phosphorylation of JAK1 (bound to IL-7Rα) and JAK3 (bound to γc) and consequent phosphorylation and activation of STAT proteins, mainly STAT5. Phosphorylated STAT proteins translocate into the nucleus, bind to DNA and activate transcription of pro-survival and proliferation proteins. The mTOR and MAPK pathways may be also activated. IL-7Rα can also heterodimerize with *CRLF2*, forming the receptor for thymic stromal lymphopoietin (TSLP). This receptor signals through JAK1 and JAK2 binding to IL-7Rα and CRLF2, respectively.

Aberrant activation of IL-7 signaling occurs in multiple ways in ALL. The receptor to IL-7 is upregulated in about 50% of T-ALL through mutational activation of its upstream regulator NOTCH1. In BCP-ALL, aberrant expression of the receptor to TSLP is caused by genomic rearrangements leading to overexpression of CRLF2. Somatic mutations in IL-7Rα that cause its abnormal homodimerization and constitutive activation of JAK1 are observed in about 10% of T-ALLs and more rarely in BCP-ALL [7,8]. The JAK-STAT pathway is also commonly activated by gain-of-function mutations in downstream signaling components such as JAK1 (T- and BCP-ALL), JAK2 (BCP-ALL), JAK3 (T-ALL), and STAT5B (T-ALL) or by loss of function mutations of negative regulators (SH2B3, PTPN2). The leukemogenic roles of activated JAK2 and JAK3 in BCP-ALL and T-ALL, respectively, have been recently shown in transgenic mice [9,10]. These genomic aberrations dramatically increase the sensitivity of cells to either IL-7 or to TSLP.

3. Targeting IL-7 signaling in ALL – the promises

Consistent with the absolute requirement of IL-7 to human T cell development, most T-ALLs have been shown to respond to IL-7 [4]. Thus targeting IL-7 signaling might be a reasonable general approach for treatment of T-ALL, regardless the presence of activating mutations. Although the role of IL-7 in human B cell development is unclear, it is conceivable that BCP-ALL with mutational activation of this pathway may also be sensitive to its targeting.

There are three general approaches for targeting IL-7 signaling:

(a) Targeting the upstream regulators. For example, one of potential multiple antileukemic effects of NOTCH1 antagonists could be the reduction of transcription of IL-7Rα. Similarly, reduction of the cytokine levels, for example by anti-TSLP antibodies (developed for therapy of allergy induced asthma [11]) for CRLF2-positive BCP-ALL, neutralizing anti-IL-7 antibodies are other potential approaches that have still not been tried for antileukemia therapy.
(b) Targeting the receptors. Anti-CRLF2 CAR-T cells have shown dramatic effects against CRLF2 expressing BCP-ALL in a preclinical in vivo model [12]. This approach may also be useful for the recently described T-ALLs with increased expression of the TSLP receptor, although it is unclear if the low level of expression is sufficient for immunologic recognition [13]. Anti-CRLF2 antibodies are also in preclinical development [14]. Antibodies against IL-7Rα have shown dramatic therapeutic effects in preclinical mouse models of multiple

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sclerosis and thus could be developed as a general approach for treatment of T-ALL [15]. A specific approach against the 10% of T-ALL with activating mutations in IL-7Rα has been proposed by Mansour et al. [16]. These mutations insert cysteine into the extracellular domain of IL-7Rα causing dimerization through the formation of S–S bonds. *N*-Acetylcysteine (NAC), a generic reducing agent approved for human use, reverses these bonds and blocks the leukemogenic signaling of mutated IL-7R [16].

(c) Targeting the downstream signaling. The most straightforward approach is blocking the activity of the JAK-STAT pathway, specifically either JAK1 or JAK3 or both. Ruxolitinib, a dual JAK1/JAK2 inhibitor, has shown dramatic effects against xenografts of T-ALL [17]. Two clinical trials with ruxolitinb against CRLF2/JAK-mutated BCP-ALLs have been recently opened (NCT02723994 and NCT02420717). However, given the general requirement of IL-7 for survival of T-cells and the dramatic results in the preclinical model, extension of these trials to T-ALL is warranted. JAK3 is probably a major player in IL-7 signaling in T-ALL. It would be interesting to see if the JAK3 inhibitors recently approved for treatment of rheumatic disorders (e.g. tofacitinib) may prove useful for treatment of T-ALL. Second generation of allosteric JAK inhibitors [18], less prone for resistance, may be also promising. Development of dual JAK1/JAK3 inhibitors could prove ideal for blocking T-cell activity in autoimmune disorders and for treatment of T-ALL. Targeting STAT proteins has been more challenging; however, recent small RNA-based therapies may prove successful [19].

4. Targeting IL-7 signaling in ALL – challenges and culprits

(a) Eliminating normal T cells. Perhaps the major recent breakthroughs in treatment of malignant B cell diseases have been the development of anti-CD19 immunotherapies. While such therapies result in complete elimination of normal B cells, this can be compensated by Immunoglobulin replacement therapy. However, as exemplified by the congenital SCID caused by mutations in IL-7Rα, a successful block of IL-7 signaling (e.g. by anti-IL-7Rα antibodies or anti-IL-7Rα CAR-T or CAR-NK cells) may be associated with irreversible severe immunodeficiency. Such effective approach may be useful however for elimination of T-ALL as a 'bridge to transplant'.

(b) The importance of other downstream signaling pathways. IL-7 signaling induces mTOR and MAPK intracellular cascade in addition to the JAK-STAT pathway [6]. A preclinical study with CRLF2/IL-7R-driven BCP-ALL have demonstrated the effectivity of mTOR inhibitors [20]. Moreover, genomic studies have revealed the presence of multiple subclones in every case of ALL. Thus treatment with JAK inhibitors is likely to cause the emergence of subclones with activating RAS pathway mutations, recently shown to be common in both relapsed T- and B-ALLs [21]. It would be logical therefore to combine MAPK and JAK inhibitors in treatment of IL-7-driven ALLs. Beyond the serious problem of costs of therapy combining two new propriety drugs, dramatic increase of toxicity may be observed by 'blanket blocking' of multiple essential signaling pathways. It may be essential to alternate therapeutic blocks with specific signaling inhibitors.

(c) Combining IL-7 inhibition with anti-BCL-2 therapies. One of the key role of IL-7 is to protect lymphoid precursor cells from apoptosis due to DNA damage response to ongoing rearrangements of the immune receptors [5]. This is achieved through activation of the antiapoptotic protein BCL-2 [22,23]. Newly developed anti-BCL-2 drugs have shown promising activity in hematopoietic malignancies including in preclinical models of T-ALL [24,25]. Interestingly, elimination of chronic myeloid leukemia stem cells was achieved by combination therapy of BCL-2 inhibitors with thyrosine kinase inhibitors [26]. Thus it is reasonable to speculate that a combination of a JAK1 inhibitor (e.g. ruxolitinib) or JAK3 inhibitor (e.g. tofacitinib) with a BCL-2 inhibitor could prove extremely useful for T-ALL. Given the extremely poor prognosis of relapse T-ALL, there is an urgent need for such targeted therapies.

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Declaration of interest

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