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IL-7R-mediated signaling in T-cell acute lymphoblastic leukemia: An update

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ABSTRACT

Interleukin 7 (IL-7) and its receptor (IL-7R, a heterodimer of IL-7Rα and γc) are essential for normal lymphoid development. In their absence, severe combined immunodeficiency occurs. By contrast, excessive IL-7/IL-7R-mediated signaling can drive lymphoid leukemia development, disease acceleration and resistance to chemotherapy. IL-7 and IL-7R activate three main pathways: STAT5, PI3K/Akt/mTOR and MEK/Erk, ultimately leading to the promotion of leukemia cell viability, cell cycle progression and growth. However, the contribution of each of these pathways towards particular functional outcomes is still not completely known and appears to differ between normal and malignant states. For example, IL-7 upregulates Bcl-2 in a PI3K/Akt/mTOR-dependent and STAT5-independent manner in T-ALL cells. This is a 'symmetric image' of what apparently happens in normal lymphoid cells, where PI3K/Akt/mTOR does not impact on Bcl-2 and regulates proliferation rather than survival. In this review, we provide an updated summary of the knowledge on IL-7/IL-7R-mediated signaling in the context of cancer, focusing mainly on T-cell acute lymphoblastic leukemia, where this axis has been more extensively studied.

1. Introduction

Interleukin 7 (IL-7), a cytokine produced by stromal cells in the bone marrow, thymus and a range of other organs, and its receptor (IL-7R), expressed mainly in lymphoid cells, are absolutely required for normal T-cell development and homeostasis of mature T-cells. For years, it has been known that, in both mice and humans, inactivation of any of the elements that constitute the IL-7/IL-7R signaling machinery would lead to immunodeficiency. On the other hand, numerous studies have reported the association of this axis with, and involvement in, different autoimmune and chronic inflammatory conditions, such as diabetes, multiple sclerosis or rheumatoid arthritis. However, the most striking evidence for the fundamental need to maintain this axis under tight physiological regulation comes from more recent knowledge that driver gain-of-function mutations in *IL7R* exist in a subset of patients with acute lymphoblastic leukemia (ALL) of T- and B-cell origin. We previously reviewed the importance of IL-7 and IL-7R for normal T-cell development and homeostasis, the role of IL-7 as an anti-cancer agent, and the involvement of IL-7/IL-7R-mediated signaling in T-ALL (Ribeiro et al., 2013). In the following sections we provide a brief recall on these topics and then focus mainly on updating the knowledge on the participation of IL-7 and IL-7R in T-ALL, with a glimpse on therapeutic implications and opportunities.

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2. The good… IL-7/IL-7R in normal T-cell biology and clinical potential of IL-7 administration

IL-7, a four helix-bundle cytokine, is produced in different organs, including the thymus, bone marrow and liver (Jiang et al., 2005; Oliveira et al., 2017; Ribeiro et al., 2013). The IL-7 receptor (IL-7R) is expressed essentially in hematopoietic cells, namely of the lymphoid lineage, and is constituted by the 'specific' IL-7Rα (CD127) subunit (which is actually shared by the receptor for another cytokine - TSLP) and the common gamma chain (γc; CD132), which is shared by the receptors for IL-2, -4, -9, -15 and −21. A few years after it was first cloned - 3 decades ago (Namen et al., 1988) - IL-7 and its receptor were found to be essential for normal lymphoid development in mice (Boyman et al., 2008; Peschon et al., 1994; von Freeden-Jeffry et al., 1995). In humans, IL-7R inactivating mutations result in severe T-cell lymphopenia with normal, yet non functional, numbers of B-cells (Noguchi et al., 1993; Puel et al., 1998). Additionally, IL-7 is involved on the homeostasis, differentiation and functioning of mature T-cells (Azevedo et al., 2009; Lenz et al., 2004; Pellegrini et al., 2011; Prlic et al., 2002; Schluns et al., 2000; Seddon et al., 2003; Soares et al., 1998; Swainson et al., 2007). In fact, the importance of IL-7 availability for T-cells is hinted from studies showing that IL-7-mediated signaling leads to IL-7Rα rapid internalization (Henriques et al., 2010) and subsequent transcriptional downregulation (Fry et al., 2003; Park et al., 2004), in what may be a biological strategy that has been selected to maximize the number of T-cells that gain access to this vital resource (Fry et al., 2003; Mazzucchelli and Durum, 2007; Park et al., 2004).

Given what we have just summarized, it is not surprising that IL-7 can have an important role in boosting the immune system. This is especially relevant in the context of cancer, since chemotherapy and radiotherapy frequently induce long-lasting lymphopenia (Mackall et al., 2011). Consequently, recombinant human IL-7 (rhIL7) has been tested in patients with refractory cancer, with results indicating that treatment with rhIL7 promoted sustained peripheral $CD4^+$ and $CD8^+$ T-cell expansion, and increased T-cell survival and diversity of the TCR repertoire, independently of the age of the subject (Sportes et al., 2010). Although the clinical evidence is still limited, the use of IL-7 in the context of anti-cancer therapies seems promising, in the least as a booster of T-cell numbers and consequent improvement of immune reconstitution. Moreover, creative ways of exploring the beneficial impact of IL-7 on T-cells may lead to new therapeutic developments. For example, in a recent study chimeric antigen receptor (CAR)-T cells were engineered to express IL-7 and CCL19. These cells showed superior anti-tumor activity compared to conventional CAR-T cells, with improved immune cell infiltration and CAR-T cell survival in mouse pre-established solid tumors. These enhanced features ultimately resulted in complete tumor regression and extended survival of the mice (Adachi et al., 2018).

3. The bad … IL-7 and IL-7R in autoimmunity, chronic inflammation and cancer

The knowledge that absent IL-7/IL-7R-mediated signaling results in lymphopenia stresses the importance of maintaining the levels of IL-7 and IL-7R above a certain physiological threshold. Below this, T-cell development and homeostasis are severely compromised. One may then ask whether an upper limit exists as well, above which excessive signaling may lead to T-cell hyper-proliferation and/or excessive activation. In line with this possibility, deregulation of the IL-7/IL-7R axis has been implicated in autoimmune diseases such as diabetes and multiple sclerosis (Lee et al., 2012; Mazzucchelli et al., 2012; Monti and Bonifacio, 2014), and chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (Churchman and Ponchel, 2008; Krzystek-Korpacka et al., 2017; Nemoto et al., 2013). The link between chronic inflammation and cancer is well established and, in agreement, elevated IL-7 levels can be found not only in patients with Crohn's disease and ulcerative colitis but also in those with metastatic colorectal cancer (Krzystek-Korpacka et al., 2017). The potential contribution of IL-7/IL-7R-mediated signaling extends to other solid cancers, including breast, lung, melanoma, bladder and colon cancer (Al-Rawi et al., 2003, 2004; Boesch et al., 2018; Cosenza et al., 2002; Li et al., 2014; Park et al., 2014; Suzuki et al., 2013; Yang et al., 2014), and different lymphoid malignancies, ranging from Hodgkin's lymphoma to chronic lymphocytic leukemia (Adachi et al., 2015; Bachireddy et al., 2015; Brown et al., 2003; Cattaruzza et al., 2009; Digel et al., 1991; Foss et al., 1994; Frishman et al., 1993; Long et al., 1995; Sasson et al., 2010). The exact mechanisms by which IL-7/IL-7R may contribute to cancer progression remain poorly explored but may be multiple, including indirect effects on the immune system or on cells from the cancer microenvironment (such as endothelial cells or fibroblasts) and direct effects on cancer cells themselves, which in some cases appear to ectopically express the IL-7R.

4. The ugly… IL-7 and IL-7R in T-ALL

Whereas reports of participation of the IL-7/IL-7R signaling axis in other cancers are still limited and often restricted to mere associations or studies *in vitro* with cell lines, there is compelling evidence of its involvement in ALL. In the remainder of this review, we will highlight mainly the knowledge on T-ALL, for which the most convincing findings exist of the tumorigenic potential of the IL-7/IL-7R axis.

T-cell precursors undergoing malignant transformation are exposed to, and likely compete for, IL-7 in their microenvironment, since they are believed to originate from the thymus and subsequently home to the bone marrow. This means that IL-7 should have the potential to modulate leukemogenesis. In agreement, IL-7 transgenic mice display accelerated mortality due to T- and B-cell lymphoma development (Abraham et al., 2005; Osborne et al., 2010; Rich et al., 1993). However, this constitutes a peculiar model, in that IL-7 is ectopically expressed in lymphoid cells (rather than in stromal cells), thus generating an IL-7 autocrine loop that appears to be a rare event at least in human T-ALL. On the other hand, AKR/J mice, which naturally overexpress IL-7Rα, tend to spontaneously develop thymic T-cell lymphomas. Overexpression of IL-7Rα in thymocytes from AKR/J mice associates with increased survival and selective advantage in competitive transplantation assays (Laouar et al., 2004). This suggests that T-cell precursors that have higher levels of IL-7R, and somehow 'break the rule' (mentioned above) that IL-7 stimulation must lead to transcriptional

downregulation of *IL7R*, will outcompete those with lower levels of the receptor, with the increased capacity to respond to IL-7 potentially degenerating into lymphoma development. These observations are in line with the knowledge that T-ALL cells transplanted into Rag2$^{-/-}$ IL2rg$^{-/-}$ mice lacking IL-7 develop disease significantly slower than those transplanted into Rag2$^{-/-}$ IL2rg$^{-/-}$ control mice (Silva et al., 2011a). Moreover, NOTCH1, one of the most commonly mutated genes in T-ALL, is known to transcriptionally upregulate *IL7R* (Weng et al., 2004), and IL-7Rα appears to be involved in Notch-mediated leukemia cell maintenance (Gonzalez-Garcia et al., 2009). Also, R98S mutation in ribosomal protein L10 (RPL10-R98S), which is found in 8% of pediatric T-ALL cases, promotes the expression of IL-7Rα and elements of downstream signaling, as well as IL-7R signaling pathway activation upon IL-7 stimulation (Girardi et al., 2018).

Malignant cells collected from human T-ALL patients at diagnosis frequently express IL-7Rα and IL-7 promotes the survival and proliferation of leukemia cells (Barata et al., 2001, 2004a; Digel et al., 1991; Eder et al., 1990; Karawajew et al., 2000; Scupoli et al., 2007; Silva et al., 2011b; Touw et al., 1990) in a majority of T-ALL cases (more than 70%), independently of their developmental stage (Barata et al., 2001, 2004a; Touw et al., 1990). Importantly, thymic epithelial cells and bone marrow stromal cells cultured *in vitro* also promote T-ALL cell survival by producing IL-7 (Scupoli et al., 2003, 2007)), and chimeric fetal thymus organ cultures provide evidence that IL-7 produced in the thymus contributes to T-ALL cell proliferation (Barata et al., 2006).

5. And the really ugly… IL-7R mutational activation in T-ALL

The most striking and direct evidence for the involvement of IL-7R signaling in T-ALL stems from the identification, in 2011, of somatic gain-of-function mutations in IL-7Rα, which lead to constitutive activation of the receptor promoting cell transformation *in vitro* and tumor formation *in vivo* (Bains et al., 2012; Porcu et al., 2012; Shochat et al., 2011; Zenatti et al., 2011; Zhang et al., 2012). The mutations are all located in exon 6, and the majority originates an unpaired cysteine in the extracellular juxtamembrane-transmembrane portion of IL-7Rα, leading to disulfide bond-dependent receptor homodimerization of two mutant α chains and constitutive, ligand-independent signaling. The few exceptions to this 'rule' insert other residues within the transmembrane region closer to the cytosolic domain, including a tryptophan residue, an SxxxG related motif, both of which have been implicated in facilitating homo- or heterodimer formation of other receptors (Ridder et al., 2005; Russ and Engelman, 2000), or other residues that can also lead to ligand-independent IL-7Rα homodimerization (Shochat et al., 2014). Finally, some non-cysteine mutations may not promote homodimerization but instead increase responsiveness to IL-7 (Cante-Barrett et al., 2016).

Importantly, it should be noted that gain-of-function mutations occur not only in IL-7Rα itself (although not, curiously, in γc) but also in downstream effectors of IL-7/IL-7R-mediated signaling, namely in elements of JAK/STAT, PI3K/Akt/mTOR and RAS/MEK/Erk pathways, which are found in 30–50% of T-ALL cases (Cante-Barrett et al., 2016; Li et al., 2016; Oliveira et al., 2017; Ribeiro et al., 2013). IL-7R pathway mutations were reported to be enriched in patients overexpressing *HOXA* and *TLX* (Cante-Barrett et al., 2016; Liu et al., 2017; Vicente et al., 2015; Zenatti et al., 2011) or with early T-cell precursor ALL (ETP-ALL) (Goossens et al., 2015; Zhang et al., 2012), and to negatively associate with the *TAL-LMO* subgroup (Zenatti et al., 2011). In line with the latter, TAL1 ChIP-seq data indicate that TAL1 may directly repress *IL7R* (Bornschein et al., 2018), and overexpression of TAL1 combined with *Pten* deletion (which commonly co-occur in T-ALL) in a mouse pro-T-cell *ex vivo* culture system led to the downregulation of the IL-7R/JAK/STAT signaling cascade, compensated by activation of Akt and expression of E2f and Myc gene clusters (Bornschein et al., 2018). Mutations in *IL7R*, *JAK1* and *JAK3* were also shown to associate with genetic lesions in *WT1*, *PRC2* or *PHF6* epigenetic regulators (Vicente et al., 2015). This notwithstanding, *IL7R* mutations may actually occur in all subtypes of T-ALL (Liu et al., 2017).

In vivo studies on the impact of mutant *IL7R* in hematopoietic precursors highlight its leukemogenic potential, although the effects observed depend on the differentiation stage at which the mutation is expressed (Barata, 2013; Treanor et al., 2014; Yokoyama et al., 2013). Yokoyama and colleagues found that ectopic expression of mutant IL-7Rα alone in primary hematopoietic stem and progenitor cells induces oligoclonal myeloproliferation. However, when the same mutation was expressed in combination with a constitutively active form of intracellular Notch1 (ICN1), it accelerated ICN1-induced T-ALL. Furthermore, forced expression of the *IL7R* mutant in common lymphoid progenitors caused mature B-cell acute leukemia/lymphoma that, curiously, did not really recapitulate the B-cell precursor phenotype that is observed in *IL7R* mutant B-ALL patients (Roberts et al., 2012; Shochat et al., 2011). The most unexpected observation, however, came with the expression of the mutant in T-cell precursors, which did not originate T-cell leukemia or lymphoproliferation. This is possibly due to more stringent mechanisms of *IL7R* regulation in T- than in B-cell precursors, and may suggest the need for longer latency periods in *IL7R* mutant-derived T-ALL because of the requirement of additional transforming events (Barata, 2013; Yokoyama et al., 2013). In line with this possibility, Treanor et al. showed that mutant *IL7R* overexpression in CD4/CD8 double-negative T-cell progenitors with inactivation of the *Ink4/Arf* tumor suppressor locus (from *Arf*$^{-/-}$ mice), induced a block in thymocyte development (at a stage that retains both myeloid and T-cell differentiation potential), and induced monoclonal leukemia that resembled human ETP-ALL (Treanor et al., 2014).

6. The good, the bad and the ugly dissected… peculiarities of IL-7/IL-7R-mediated signaling in normal T cell precursors and T-ALL cells

IL-7/IL-7R-mediated binding is initiated by binding of IL-7 to the receptor and the formation of a trimeric complex between the cytokine, IL-7Rα and γc (Gonnord et al., 2018; McElroy et al., 2012), leading to JAK1 and JAK3 activation, trans-phosphorylation and subsequent phosphorylation of tyrosine residues in the cytoplasmic tail of IL-7Rα that constitute docking sites for effector molecules such as PI3K and STAT5 (reviewed in (Kittipatarin and Khaled, 2007; Mazzucchelli and Durum, 2007; Ribeiro et al., 2013)). At least three main pathways are then activated: STAT, MEK/Erk and PI3K/Akt/mTOR in both T-ALL and normal T-cells (Barata et al., 2005;

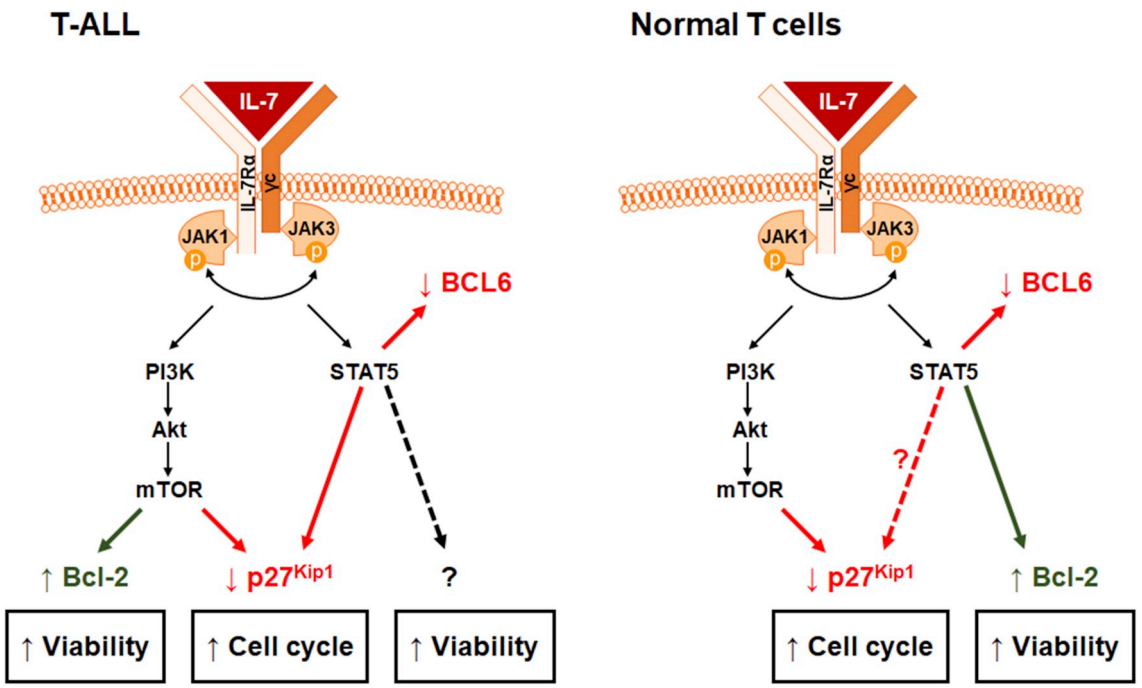

Fig. 1. Differences in the functional impact of IL-7/IL-7R-mediated signaling in T-ALL cells and their normal counterparts. In T-ALL cells, Bcl-2 is upregulated by IL-7 via PI3K/Akt/mTOR pathway, which also regulates cell cycle progression. STAT5 is also required for IL-7-mediated cell cycle progression and viability. However, STAT5 does not upregulate Bcl-2 downstream from IL-7. By contrast, IL-7 recruits PI3K/Akt/mTOR pathway strictly for cell cycle progression in normal T-cells, whereas STAT5 appears to transcriptionally activate Bcl-2 and upregulate viability.

Jiang et al., 2005). However, the manner in which they appear to be wired is not identical in healthy and malignant cells. PI3K/Akt/mTOR signaling is essential for IL-7-mediated proliferation and survival of T-ALL cells by promoting $p27^{kip1}$ downregulation and Bcl-2 upregulation (Barata et al., 2001, 2004b; Silva et al., 2011b). By contrast, in healthy T-cells, PI3K signaling activation by IL-7 induces cell cycle progression (Swainson et al., 2007) without impacting on cell survival or Bcl-2 expression (Rathmell et al., 2001). These differences should be highlighted, since they may constitute a therapeutic 'window of opportunity' in that PI3K/Akt/mTOR pathway inhibitors should preferentially and selectively eliminate IL-7-dependent leukemia cells while being merely cytostatic to their normal counterparts. Extending these observations to the JAK/STAT pathway, we have recently shown that STAT5 is required for increased T-ALL cell viability, growth and cell cycle progression induced by IL-7. However, contrary to what happens in normal T-cells, we found that IL-7-mediated upregulation of Bcl-2 in T-ALL is independent of STAT5 activity. Interestingly, we also observed that, in response to IL-7 stimulation, STAT5 directly downregulates *BCL6* in T-ALL cells and promotes the expression of *PIM1*, which in turn plays a role in mediating the proliferative effects of IL-7 (Ribeiro et al., 2018). These results are in line with the fact that *PIM1* expression levels are higher in cases with IL-7R pathway mutations and in the $HOXA^+$ T-ALL patient subgroup, as well as with studies on mouse T-ALL cells indicating PIM1 as a JAK-STAT pathway target downstream from IL-7 (de Bock et al., 2018). In short, normal and malignant T-cells activate the same signaling pathways downstream from IL-7/IL-7R, but appear to utilize them to achieve a certain functional outcome in different ways (Fig. 1). More IL-7/IL-7R-mediated signaling peculiarities of normal versus malignant T-cell precursors can be found in our previous review on this topic (Ribeiro et al., 2013).

7. A promise… targeting IL-7R-mediated signaling in T-ALL for therapeutic purposes

Given the high frequency of T-ALL patients (around 70% of the cases) whose blasts express the IL-7R and respond to IL-7, on top of which around 10% display *IL7R* gain-of-function mutations, which associate with very high risk in relapsed patients (Richter-Pechanska et al., 2017), there is strong basis to try and therapeutically target the IL-7/IL-7R pathway in T-ALL. This can be done in multiple ways.

An obvious strategy is to use small molecules to inhibit specific downstream signaling elements. We and others have generated *in vitro* and *in vivo* preclinical data in this direction by showing that clinical-stage JAK small molecule inhibitors are able to kill *IL7R*-mutant (Senkevitch et al., 2018; Shochat et al., 2011; Zenatti et al., 2011) and IL-7-dependent (Barata et al., 2004b; Melao et al., 2016) cells. Moreover, studies with a limited number of ETP-ALL patient samples showed that they were highly sensitive to IL-7 stimulation *in vitro* and mouse xenograft models using those samples demonstrated that the JAK1/2 inhibitor ruxolitinib could delay disease progression *in vivo* (Maude et al., 2015). Anti-leukemia effects of ruxolitinib treatment *in* vivo had been previously reported, albeit with more heterogenous, less pronounced effects, using a murine IL-7R mutant-induced ETP-ALL model mentioned above (Treanor et al., 2014). Notably, it was recently shown that a subset of glucocorticoid-resistant T-ALL cells display strong induction of

JAK/STAT signaling in response to IL-7 and that IL-7 removal or treatment with ruxolitinib sensitizes the leukemia cells to glucocorticoids (Delgado-Martin et al., 2017). These observations are in line with previous studies showing that cysteine mutations in *IL7R*, or mutations in downstream signaling elements (such as *JAK1* and *KRAS*), confer glucocorticoid resistance and poor clinical outcome in childhood T-ALL, working as biomarkers of reduced steroid response (Li et al., 2016). Steroid resistance was partially explained by strong activation of RAS/MEK/Erk and/or PI3K/Akt signaling pathways, which resulted in reduction of steroid-induced cell death and powerful leukemia cell survival responses. Therefore, resistance could be possibly overcome by therapeutic combinations with MEK/Erk or PI3K/Akt/mTOR signaling-specific inhibitors (Cante-Barrett et al., 2016; Li et al., 2016), the latter having demonstrated clear potential against T-ALL in pre-clinical studies (Chiarini et al., 2010; Evangelisti et al., 2011; Grimaldi et al., 2012; Hall et al., 2016; Simioni et al., 2012).

A less obvious approach may involve targeting the hedgehog signaling pathway, whose activation occurs in around 22% of T-ALL cases, with a strong positive correlation with JAK3 levels (Dagklis et al., 2015, 2016; Vicente et al., 2015). The link to the IL-7/IL-7R axis stems essentially from the fact that activation of hedgehog pathway in the T-ALL cells stimulates thymic epithelial cells to produce T-cell stimulatory molecules, such as IL-7, to promote leukemia cell survival and proliferation. Primary T-ALL patient samples presenting high expression levels of the transcription factor GLI1, a downstream effector of hedgehog pathway, were shown to be sensitive to specific inhibitors of the pathway, such as GANT61 or vismodegib. Moreover, patient-derived xenograft mouse models confirmed the potential of those inhibitors to delay *in vivo* disease progression. The same inhibitors were also able to increase the sensitivity of T-ALL cells to conventional chemotherapy (Dagklis et al., 2016).

Also perhaps not evident from a superficial standpoint but potentially promising strategy may involve targeting the cell cycle checkpoint kinase 1 (CHK1), which, in an apparent paradox, is overexpressed in T- and B-ALL cells (Iacobucci et al., 2015; Sarmento and Barata, 2016; Sarmento et al., 2015). It so happens that CHK1 increased expression in ALL cells is essential for preventing apoptosis arising from the high replication stress levels within leukemia cells (Sarmento and Barata, 2016; Sarmento et al., 2015). As such, CHK1 and/or ATR inhibitors are particularly appealing therapeutic options for highly proliferative T-ALL cases, including those that are responsive to IL-7 stimulation. In fact, we have shown that PF-004777736, a clinical-grade CHK1 inhibitor, efficiently promotes T-ALL cell death even in the presence of IL-7 (Sarmento et al., 2015).

Another potential target is the serine/threonine protein kinase CK2, which is a posttranslational activator of constitutive PI3K/Akt signaling in T-ALL cells by inhibiting PTEN (Silva et al., 2008). CK2 was shown to play a key role in promoting the proliferation of ALL cells of both B and T cell origin (Gomes et al., 2014; Gowda et al., 2017a, 2017b; Silva et al., 2008) and was recently shown to be required for optimal IL-7-mediated signaling, and consequent IL-7-dependent T-ALL cell cycle progression and viability (Melao et al., 2016). CK2 was also required for the viability of mutant IL-7R-expressing leukemia T-cells. Of potential clinical interest, CX-4945 (silmitasertib), a clinical-grade CK2-specific pharmacological inhibitor, synergized with ruxolitinib in promoting the death of both IL-7-dependent and mutant IL7R-expressing T-ALL cells (Melao et al., 2016).

Because IL-7/IL-7R-triggered signaling leads to the upregulation of Bcl-2, which is required for IL-7-mediated T-ALL cell survival (Barata et al., 2001), the use of Bcl-2 pharmacological inhibitors, whose preclinical efficacy has already been shown, constitutes also an appealing strategy to obviate leukemia expansion. In this regard, it is interesting to mention that JAK3 mutant T-ALL cells, whose phosphoproteomic profiling showed regulation of PI3K/Akt, RAS/MAPK and apoptotic signaling pathways downstream of the mutation, displayed increased sensitivity, both *in vitro* and *in vivo*, to combined treatment with the JAK1/3 inhibitor tofacitinib plus the Bcl-2 inhibitor venetoclax than to each inhibitor alone (Degryse et al., 2018), and that mutant *IL7R*-expressing mouse T-cells showed similar results for ruxolitinib and venetoclax (Senkevitch et al., 2018). Notably, the efficacy of venetoclax as a single agent has been demonstrated in immature T-ALL patients presenting high levels of Bcl-2 (Peirs et al., 2014). Still in the context of JAK3 mutant T-ALL cells, having present that PIM1 is a downstream target of the JAK/STAT pathway and that the majority of JAK3 mutants are strongly dependent on JAK1 to transform cells (Degryse et al., 2014), a recent study highlighted the therapeutic benefit of targeting both JAK1 and PIM1 with ruxolitinib and AZD1208, respectively (de Bock et al., 2018).

Targeting the IL-7R itself is another valid therapeutic option. Since most T-ALL-related *IL7R* mutations lead to constitutive signaling via aberrant disulfide bond formation between the IL-7Rα-mutated chains, antioxidants may also represent an interesting therapeutic strategy. The reducing agent N-acetylcysteine (NAC), although not selective, has been used to disrupt IL-7Rα homodimerization, inhibiting downstream signaling and thus promoting apoptosis of IL-7Rα mutant cells *in vitro*, and decreasing leukemia progression *in vivo* (Mansour et al., 2015).

In alternative, other ways of targeting IL-7R-expressing T-ALL cells may rely on the administration of chimeric antigen receptors (CAR T-cells) against IL-7Rα or the use of anti- IL-7Rα antibodies (Cramer et al., 2016). While there are no reports as yet on the former, the latter strategy has led already to promising results. It has been very recently shown that high IL-7Rα expression directly correlated with central nervous system involvement in B-ALL patients. The authors then used a commercially available monoclonal anti-IL7Rα antibody to abrogate leukemia development in xenografted mice, which outperformed ruxolitinib (Alsadeq et al., 2018). In another study, glucocorticoid resistance in T-ALL was tackled by using a murine anti-IL-7Rα antibody conjugated to a cytotoxic agent. Although this antibody is clinically inconsequential, results highlight the potential of targeting IL-7R using monoclonal antibodies (Yasunaga et al., 2017). Following similar lines, we have generated a fully human antibody against IL-7Rα using phage display with the ability to inhibit IL-7/IL-7R-dependent signaling and anti-tumor potential against IL-7R-expressing T-ALL cells both *in vitro* and *in vivo* (Akkapeddi et al., unpublished data).

8. The not so bad… IL-7 and IL-7R as tumor suppressors?

The studies we highlighted above indicate that over-activation of the IL-7/IL-7R signaling axis can contribute to leukemia/

lymphoma establishment and progression; however, there is also some evidence pointing out to the contrary. For example, restraining IL-7R-mediated signaling can accelerate T-cell lymphomagenesis in the context of p53 deficiency (Kibe et al., 2012), due to the ability of the IL-7/IL-7Rα axis to maintain telomere integrity via POT1 expression during T-cell development. *Il7r −/− p53 −/−* mice displayed a marked reduction of apoptosis in T-cell precursors and increased thymic lymphomagenesis, with telomere erosions and exacerbated chromosomal abnormalities, including chromosome duplications, breaks, and translocations. IL-7/IL-7Rα signaling withdrawal led to telomere erosion and activation of the p53 pathway (Kibe et al., 2012). Obviously, in the absence of p53 this did not drive apoptosis and thus likely potentiated the formation of T-cell tumors via genomic instability. Another example of potential (although not formally tested) anti-tumor effects of IL-7-mediated signaling come from the demonstration that IL-7R-mediated signaling in pre-B cells serves as a safeguard against premature activation of AID, preventing concomitant activation of AID and RAGs - which in turn are required for B-ALL development (Swaminathan et al., 2015). This feature may, however, be counterbalanced by the fact that IL-7 contributes to the survival and proliferation of B-cell precursors (Corfe and Paige, 2012), which may also justify why *IL7R* mutations have been identified in high-risk B-ALL cases (Roberts et al., 2012, 2014), and the IL-7/IL-7R signaling axis has been shown to contribute to the proliferation and/or survival of B-ALL cells, to steroid resistance and poor outcome in B-ALL (Brown et al., 2003; Li et al., 2016; Morishita et al., 2012; Mullighan, 2013; Roberts and Mullighan, 2015; Touw et al., 1990; van der Plas et al., 1996), and, as mentioned above, to associate with central nervous system infiltration and relapse (Alsadeq et al., 2018).

Conflicts of interest

The authors have no conflict of interest to declare. Funding agencies, mentioned in the Acknowledgements section, did not have any influence on the planning, execution or writing of the manuscript.

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