IL-7 Contributes to the Progression of Human T-cell Acute Lymphoblastic Leukemias

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Abstract

The importance of microenvironmental factors for driving progression in leukemia has been debated. Previous evidence has pointed to interleukin-7 (IL-7), a fundamental cytokine to normal T-cell development and homeostasis, as an important determinant of the viability and proliferation of T-cell acute lymphoblastic leukemia (T-ALL) cells in vitro. In this study, we report that IL-7 is also a critical determinant of T-ALL progression. T-ALL cell lines and primary T-ALL samples initiated leukemia more slowly when engrafted to immunocompromised Rag2−/−Il2rg−/− mice lacking IL-7. This effect was not related to reduced engraftment or homing of transplanted cells to the bone marrow. Instead, IL-7 deficiency diminished expansion of leukemia cells in the bone marrow and delayed leukemia-associated death of transplanted mice. Moreover, infiltration of different organs by T-ALL cells, which characterizes patients with advanced disease, was more heterogeneous and generally less efficient in IL-7−/−deficient mice. Leukemia progression was associated with increased Bcl-2 expression and cell viability, reduced p27Kip1 expression, and decreased cell-cycle progression. Clinical measurements of IL-7 plasma levels and IL-7 receptor (IL-7R) expression in T-ALL patients versus healthy controls confirmed that IL-7 stimulates human leukemia cells. Our results establish that IL-7 contributes to the progression of human T-cell leukemia, and they offer preclinical validation of the concept that targeting IL-7/IL-7R signaling in the tumor microenvironment could elicit therapeutic effects in T-ALL. Cancer Res; 71(14): 4780–9. ©2011 AACR.

Introduction

Interleukin-7 (IL-7) is essential for normal T-cell development and homeostasis. Paradoxically, several lines of evidence indicate that the IL-7/IL-7 receptor (IL-7R) axis may also play a significant role in promoting leukemogenesis. IL-7 can act as an oncogene in vivo, as IL-7 transgenic mice develop B- and T-cell lymphomas (1, 2), and murine thymocytes spontaneously overexpressing IL-7R have a selective advantage that contributes to proliferation and leukemogenesis (3). IL-7 is produced by bone marrow and thymic stroma (4–7), suggesting that IL-7 is present in the microenvironments where leukemia cells develop, thus having the potential to directly modulate leukemia growth. In vitro studies have shown that thymic epithelium and bone marrow stromal cells promote survival of T-cell acute lymphoblastic leukemia (T-ALL) cells via production of IL-7 (8, 9). Importantly, IL-7 induces in vitro proliferation of the majority (>70%) of primary T-ALL samples (10, 11). IL-7 promotes cell-cycle progression and viability of T-ALL cells via activation of the phosphoinositide-3-kinase (PI3K)/protein kinase B (PKB)/Akt signaling pathway (12), resulting in downregulation of the cdk inhibitor p27^Kip1 and upregulation of Bcl-2 (13). Remarkably, IL-7 may contribute to resistance to treatment with rapamycin in ALL in general (14) and to imatinib in Bcr/Abl−/− ALL (15, 16). However, these observations are counterweighted by the understanding that most malignant cells proliferate independently of external cues. Furthermore, although IL-7 may have a significant impact on some primary T-ALL cells cultured in vitro under conditions of growth factor paucity, it is possible that IL-7 has only a redundant effect on leukemia expansion in vivo, given the diversity of other survival and proliferative signals present in the tumor milieu.

In the present study, we sought to clarify the importance of IL-7 for the progression of human T-ALL in vivo, using a combination of xenotransplant mouse models of human leukemia and analysis of primary T-ALL specimens collected directly from patients. Our results indicate that IL-7 is consumed by and stimulates human T-ALL cells in vivo. IL-7 induces p27^Kip1 downregulation and Bcl-2 upregulation in T-ALL cells, promotes their viability and proliferation, and
contributes to leukemia progression. Our data support the notion that microenvironmental cues, produced in a nonautocrine fashion, can partake in leukemia development.

Material and Methods

Cells

Primary T-ALL cells were collected from peripheral blood or bone marrow of patients at diagnosis as described previously (17). Normal thymocytes were isolated from thymic tissue obtained from children undergoing cardiac surgery. Informed consent and Institutional Review Board approval were obtained for all primary leukemia and thymic sample collections. The IL-7–dependent T-ALL cell line TAIL7 was established by our group, and it is regularly tested by flow cytometry and PCR (18). TAIL7 cells share significant similarities with primary leukemic cells; minus sign indicates <30% positive cells, except for IL-7Rα, where minus sign indicates <3% positive cells.

In vivo bioluminescence imaging

Mice were intraperitoneally (i.p.) injected with 150 μg luciferin/g, anaesthetized, and scanned with an IVIS Lumina bioluminescence imaging device (Caliper Life Sciences). Mice were imaged after 7 minutes and total flux (photons per second) was calculated using Living Image software (Caliper Life Sciences).

Blood and organ analysis

For flow cytometric analysis, collected blood was depleted of erythrocytes by using red blood cell lysis buffer (BD Pharmingen). Bone marrow was extracted by flushing off bones. Spleen, liver, and kidneys were mechanically disintegrated into single-cell suspensions, which were then washed in PBS, stained for 45 minutes at 4°C with monoclonal antibody for human CD2 or CD5 (Becton Dickson), and analyzed using a FACSCalibur flow cytometer (Becton Dickinson) and FlowJo software (Tree Star). For histology analysis, small representative portions of the collected organs (spleen, liver, and kidneys) and at least 1 complete femur were preserved in formalin at 4°C for 24 to 48 hours with hematoxylin/eosin staining.

Xenotransplantation

Protocols and studies involving animals were conducted in accordance with the UK Home Office regulation and local guidelines. Rag2<−/−, Il2rg<−/−, and Il7<−/− strains were obtained from The Jackson Laboratory and intercrossed to generate compound knockouts required for this study. Il7<−/− Il2rg<−/− Rag2<−/− and Il7<−/− Rag2<−/− strains were both on C57Bl6/j background. Strains were bred in specific pathogen-free facilities at the National Institute for Medical Research (London, UK), Instituto Gulbenkian de Ciência (Oeiras, Portugal), and Instituto de Medicina Molecular (Lisbon, Portugal). HPB-ALL, Luc.GFP, TAIL7, P12, and primary T-ALL cells (5 × 10^6 to 2 × 10^7 cells) were injected i.v. in a final volume of 250 μL per injection. Mice were sacrificed when moribund or at the indicated time points. Organs were collected for postmortem analysis. Mice were classified as leukemic when T-ALL cells represented more than 20% of the bone marrow cellularity, according to the clinical definition of human leukemia (23). We further classified mice as preleukemic (<20% and >0.1% malignant cells in the bone marrow) and nonleukemic (>0.1%).

Table 1. Immunophenotype and maturation stage of primary T-ALL samples and cell lines

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<th>CD5</th>
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<td>Pt#2</td>
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NOTE: Maturation stages were defined according to the EGIL criteria (see Materials and Methods). Plus sign indicates >30% positive cells; minus sign indicates <30% positive cells, except for IL-7Rα, where minus sign indicates <3% positive cells. Abbreviations: cCD3, cytoplasmic CD3; Pt, patient.
stained for 30 minutes at 4°C with anti-Bcl-2-FITC antibody (Dako), anti-ki-67-PE antibody (Becton-Dickinson), or with irrelevant isotype-matched antibody. For viability analysis, bone marrow cells were surface stained for human CD5-FITC, washed and resuspended in 1× binding buffer, and stained with Annexin V–phycoerythrin (PE). Samples were washed and analyzed by flow cytometry. Results were expressed as the percentage of positive cells in comparison with the negative control and as specific mean intensity of fluorescence (MIF).

**Immunoblotting**

Cell lysates were resolved by 10% SDS-PAGE, transferred onto nitrocellulose membranes, and immunoblotted with antibodies against ZAP-70 (Upstate) or p27<sup>kip1</sup> (Santa Cruz Biotechnology). Immunodetection was carried out by incubation with horseradish peroxidase–conjugated anti-rabbit IgG (Promega) and developed by enhanced chemiluminescence (Amersham-Pharmacia).

**Quantitative reverse transcriptase PCR**

Total RNA (1 μg) was reverse transcribed using the ImProm II Reverse Transcriptase enzyme (Promega) and random hexamers. The quantitative assessment of IL7R transcriptions was made by SYBR green-based quantitative reverse transcriptase PCR (qRT-PCR) on an ABI PRISM 7500 (Applied Biosystems) with the following primers: ABL, TGGAGATAACACTCTAAG-ATGTCATCCACCCT (exon 8). Standard curves were obtained with the following primers: ABL, TGGAGATAACACTCTAAG-ATGTCATCCACCCT (exon 8). Standard curves were obtained and constituted a model for primary IL-7-dependent <i>in vitro</i> and constitute a model for primary T-ALL (18). First, we transplanted CFSE-labeled TAIL7 cells into IL-7 WT and IL-7 KO mice and evaluated engraftment 6 hours after i.v. injection. Analysis of the bone marrow revealed the presence of very few leukemia cells, and no difference between IL-7 WT (36.5 ± 26.7) and IL-7 KO (31.6 ± 16.7) mice (Supplementary Fig. S1). Spleen and several nonlymphoid organs (lung, liver, and kidney) were also analyzed and all presented very few cells with no differences between the 2 mouse strains (data not shown). Our data indicate that IL-7 did not affect the engraftment and initial homing capacity of T-ALL cells.

We next evaluated the effect of IL-7 on disease progression. The percentage of TAIL7 cells circulating in the peripheral blood increased with time and was consistently higher in IL-7 WT mice at all time points analyzed (Fig. 1B). These differences may have resulted from compromised leukemia expansion in the bone marrow of IL-7-deficient mice. To test this possibility, mice were sacrificed 84 days posttransplantation, before disease symptoms were apparent. All IL-7 WT animals (<i>n</i> = 9) presented clear bone marrow involvement. Most mice (6 of 9; 67%) displayed overt leukemia according to the clinical definition (23), presenting more than 20% leukemia cells in the bone marrow. All the remaining IL-7 WT mice showed detectable disease in the bone marrow and were thus considered preleukemic (3 of 9; 33%), as defined in Materials and Methods (Fig. 1C). In contrast, only 4 of 10 (40%) IL-7 KO mice were leukemic and 2 of 10 preleukemic (20%; Fig. 1C). The remaining 4 IL-7 KO mice did not show detectable signs of bone marrow involvement at this time point or displayed extremely low leukemia cellularity (<0.1%). All IL-7 WT and most IL-7 KO mice, except those without signs of leukemia, displayed splenomegaly (data not shown) due to infiltration
Figure 1. IL-7 accelerates leukemia expansion and leukemia-related death in mice xenotransplanted with human T-ALL cell lines. A, Rag2−/− Il2rg−/− mice, either Il7−/− (IL-7 WT; n = 3) or Il7+/+ (IL-7 KO; n = 3), were injected i.v. with 10⁷ HPB-ALL:Luc:GFP cells and analyzed 5 weeks posttransplantation. Animals were injected i.p. with 150 μg luciferin/g 7 minutes before imaging and ventrally scanned for total-body luminescence (total flux), with a medium binning 3-minute exposure, using IVIS Lumina and Living Image software. Images on the left are overlays of the luciferase signal with photographs of each animal. Corresponding bioluminescence values are represented as mean ± SEM in the graph on the right (P = 0.0245; Student t test). B–E, IL-7 WT (black; n = 9) or IL-7 KO (red; n = 10) mice were injected i.v. with 10⁷ TAIL7 cells. B, human leukemia cells were monitored in the blood through time by flow cytometric analysis with an anti-human CD2 antibody. Differences between IL-7 WT and IL-7 KO groups were statistically significant (P = 0.0047; 2-way ANOVA). C, animals were sacrificed 84 days posttransplantation, and bone marrow infiltration of TAIL7 cells was evaluated as described in the Materials and Methods. Animals were classified as leukemic if presenting more than 20% T-ALL cells in the bone marrow, preleukemic if 20% or less, and nonleukemic if less than 0.1%. D, infiltration of TAIL7 cells in the spleen was analyzed at the same time point (P = 0.0782; Mann–Whitney test). Lines indicate median values of each group. E, survival of TAIL7-transplanted IL-7 WT (n = 8) and IL-7 KO mice (n = 14) was compared. Kaplan–Meier survival curves are indicated. Disease progression was significantly accelerated in IL-7 WT mice (P = 0.0023; log-rank test). Experiments in A and E were carried out once. Results in B–D are representative of 3 independent experiments.
with malignant blasts (Fig. 1D). The nonlymphoid organs analyzed (liver, kidney, and lungs) also presented leukemia infiltration (Supplementary Fig. S2). However, IL-7 KO mice consistently displayed a more heterogeneous distribution and lower median values of malignant infiltration in all lymphoid and nonlymphoid organs analyzed (Fig. 1C and D; Supplementary Fig. S2). Importantly, we found that the median survival of TAIL7-transplanted IL-7 WT mice (97 days) was significantly shorter than that of IL-7 KO mice (138 days; P = 0.0023; log-rank test; Fig. 1E). Postmortem analysis showed that all animals died of leukemia with multiple organ infiltration (Supplementary Fig. S3). Hence, although our data...
with actin to confirm equal loading. Patient 1, lanes 1, 2, 6, and 7; patient 2, lanes 3 to 5 and 8 to 11; total lysates of TAIL7 cells were used as a positive control. Right, corresponding densitometric analysis of p27kip1 levels, normalized to actin loading control and expressed in arbitrary units (a.u.), in IL-7 KO and IL-7 WT mice (P = 0.0260). D, Ki-67 protein levels were assessed by flow cytometry after intracellular staining of primary T-ALL cells with PE-conjugated anti-Ki-67 antibody. Left, a representative histogram overlay is shown. Right, percentage of Ki-67-positive T-ALL cells collected from IL-7 WT and IL-7 KO mice (P = 0.0121). Results represent a pool from the 2 different patient samples for a total of 4 IL-7 WT and 6 IL-7 KO mice.
indicate that lack of IL-7 is not sufficient to prevent leukemia progression and leukemia-related death. IL-7 clearly contributed significantly to leukemia acceleration in vivo. Both IL-7 KO and IL-7 WT mice lack γ-chain, which is essential for efficient IL-7–mediated signaling by forming the IL-7R together with IL-7Rα (26, 27). Thus, the differences observed in leukemia expansion should largely reflect the direct impact of IL-7 on T-ALL cells, which display both IL-7Rα and γ-chain (11, 28). For confirmation, we transplanted growth factor–independent, IL-7Rα–negative P12 T-ALL cells and analyzed IL-7 KO and WT mice at 4 weeks. Both strains showed similar signs of leukemia (Supplementary Fig. S4).

IL-7 accelerates leukemia expansion in mice xenotransplanted with human primary T-ALL cells

To ask whether the influence of IL-7 was a more general feature of T-ALL and not restricted only to leukemia cell lines, we xenotransplanted primary T-ALL cells collected from 2 patients at diagnosis, which differed in their developmental maturation block (Table 1). According to the EGIL criteria (22), the samples were arrested at the cortical (patient 1) and mature (patient 2) thymocyte stage, whereas TAIL7 cells are pre-T and HPB-ALL are cortical but differ from patient 1 in the expression of CD3 (Table 1). Similar to the cell lines, we observed a longitudinal increase in the percentage of circulating T-ALL cells, with systematically higher levels in the presence of IL-7 (Fig. 2A). In addition, IL-7 WT mice culled 112 days posttransplantation presented significantly higher leukemia incidence in the bone marrow than IL-7 KO animals (Fig. 2B). Furthermore, absence of IL-7 clearly impaired infiltration of organs such as spleen, liver, kidney, and lungs (Fig. 2C).

IL-7 promotes p27kip1 downregulation, Bcl-2 upregulation, proliferation, and viability of xenotransplanted human primary T-ALL cells

We previously showed that IL-7 promotes survival and cell-cycle progression of T-ALL cells in vitro via Bcl-2 upregulation and p27kip1 downregulation (12, 13). We sought to understand whether the same mechanisms and functional effects were responsible for the accelerated leukemia progression in the presence of IL-7 in vivo. We collected T-ALL cells from the bone marrow of mice sacrificed at 112 days and analyzed them for viability and Bcl-2 expression. Primary leukemia cells collected from IL-7 WT animals displayed significantly higher Bcl-2 levels (Fig. 3A) and increased percentage of viable cells (Fig. 3B), in agreement with the observation that IL-7 transgenic mice present upregulation of Bcl-2 protein (29). Conversely, p27kip1 levels were downregulated in T-ALL cells recovered from IL-7 WT mice (Fig. 3C), which presented higher Ki-67 expression, indicative of increased in vivo proliferation (Fig. 3D).

Leukemia cells in T-ALL patients appear to respond to and consume IL-7

IL-7 circulating levels are regulated by consumption (30) and IL-7 signaling leads to the transcriptional downregulation of IL-7Rα (31). Although cancer cells may grow independently of external stimuli, our data argue that a significant fraction of human T-ALL cells respond to and benefit significantly from the presence of IL-7 in vivo. We collected evidence directly from patient specimens at diagnosis supporting this notion. We found that T-ALL cells had significantly lower IL7RA mRNA levels than normal T-cell precursors (Fig. 4A) and that IL-7 levels were decreased in the plasma of T-ALL patients as compared with healthy age-matched controls (Fig. 4B), suggesting that T-ALL cells consume IL-7 and thereby downregulate IL-7Rα. In support of this notion, we found that 4 of 6 patient samples cultured ex vivo in medium without IL-7 showed upregulation of IL-7Rα surface expression, which was prevented by the addition of IL-7 (Fig. 4C). Taking into account that more than 70% of T-ALL patient samples respond to IL-7 ex vivo and express functional IL-7Rs (11, 28), our current observations suggest that human T-ALL cells from a majority of patients might be sensitive to IL-7 signaling in vivo in the actual disease setting.

Discussion

There is mounting evidence that microenvironmental factors can contribute to tumor progression. IL-7 is produced in the thymus and bone marrow, the microenvironments where T-ALL develops and expands. Interestingly, IL-7 has been shown to have oncogenic potential in vivo. Transgenic mice expressing IL-7 in lymphocytes develop B- and T-cell lymphomas (1) as a consequence of an autocrine loop involving IL-7 stimulation via IL-7R (2). However, there is no evidence that human T-ALL cells express IL-7, largely excluding the existence in this malignancy of an IL-7–dependent autocrine loop that has been suggested to play a role in other hematologic cancers (32, 33). Thus, in the present study, we explored the alternative hypothesis that IL-7 produced by the microenvironment may promote human T-ALL expansion in vivo.

Our data indicate that IL-7 does not affect the engraftment and initial homing capacity of T-ALL cells to the bone marrow or other organs. However, it remains to be evaluated whether the late differences between IL-7–deficient and IL-replete mice regarding leukemia infiltration into organs such as spleen and liver reflect modulation of leukemia cell trafficking from the bone marrow to these organs and/or of malignant cell proliferation within each infiltrated organ.

We found that lack of IL-7 is not sufficient to prevent leukemia progression and leukemia-related death, such that all animals died of leukemia irrespective of IL-7. This may reflect the acquisition of growth factor independence or the effect of other microenvironmental stimuli (e.g., γc–signaling cytokines (11), Notch ligands (34), or chemokines such as CCL25 and CXCL13 (35, 36) that may provide T-ALL cells with alternative growth signals in the absence of IL-7. This notwithstanding, IL-7 clearly contributes significantly to leukemia acceleration in vivo. Curiously, despite the evidence that mouse and human IL-7 have similar in vitro bioactivity toward human lymphocytes (24, 25), including T-ALL cells (25), it was recently shown that in vivo IL-7–present in the mouse is less active on human cells (37). This suggests that the effect of IL-7 on human leukemia progression in the RAG KO xenotransplant models we used may constitute an underestimation of
Disease progression is especially remarkable. The related because cancer cells are generally viewed as nonreliant on the impact of IL-7 on human T-ALL patients. Moreover, the impact of IL-7 on human T-ALL patients. Moreover, because cancer cells are generally viewed as nonreliant on growth factor signals (38), the fact that IL-7 accelerated disease progression is especially remarkable. The related questions of whether IL-7 promotes survival of a putative leukemia stem cell population and participates in T-ALL initiation remain to be scrutinized.

At the molecular level, we found that IL-7–related disease progression was associated with decreased p27\(^{kip1}\) expression and upregulated Bcl-2. Given our previous demonstration that regulation of p27\(^{kip1}\) and Bcl-2 is mandatory for IL-7–mediated antiapoptotic and proliferative effects on T-ALL cells in vitro (13), it is reasonable to infer that the same mechanisms underlie T-ALL expansion in vivo in response to IL-7. In support of this possibility, it is noteworthy that T-ALL patient samples frequently display p27\(^{kip1}\) downregulation (39) and Bcl-2 upregulation (40). Moreover, most primary T-ALL samples show PI3K pathway activation (17), which may be the consequence not only of cell autonomous mechanisms (17, 41, 42) but also of microenvironmental stimuli such as IL-7 (12). The importance of IL-7/IL-7R signaling is further illustrated by the observations that in vitro IL-7 responsiveness (28) and IL7RA gene expression (43) appear to have prognostic value in T-ALL. Notably, our studies indicate that the in vivo impact of IL-7 on T-ALL cells is not restricted to a particular maturation stage or CD4/CD8 immunophenotype (Table 1). These observations are reminiscent of our in vitro findings, in that T-ALL patient samples proliferated in response to IL-7 irrespective of the stage at which they were developmentally blocked (11).

Altogether, our data provide the first clear evidence that human T-ALL cells utilize the IL-7/IL-7R axis for expansion in vivo, providing experimental support to the hypothesis that responsiveness to a γc-signaling cytokine contributes to T-ALL development in vivo (5, 44). Because the majority of T-ALL cases are known to respond to IL-7 in vitro (11) and thus possibly benefit from IL-7 stimulation in vivo, therapeutic protocols may prove beneficial for the treatment of T-ALL. In addition, our observations confirm the need for caution when administering IL-7 in the context of cancer immunotherapy (45) and suggest that the promise that IL-7 holds as an immunorestorative (46, 47) and in enhancing immunologic responses against cancer (48, 49) should be further evaluated strictly in patients suffering from cancers that are well characterized as refractory to the cytokine.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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