A Sanctuary for cancer cells: Microenvironment in T-cell acute lymphoblastic leukemia survival and drug resistance

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Abstract

T-cell acute lymphoblastic leukemia (T-ALL) is a heterogeneous malignancy associated with a high risk of treatment failure. Efforts to improve outcomes have focused on underlying genetic defects. However, strong evidence suggests that leukemic cells prime a maladapted niche that in turn provides signals capable of sustaining the dormancy of leukemia initiating cells and protects them from toxic chemotherapeutic agents. Here, we aim to describe how key components of the bone marrow microenvironment are essential for leukemia initiation and progression. Although many mechanisms have been recently discovered, further studies are required to fully dissect the molecular mechanisms governing the bidirectional interactions between tumor and host cells. We predict that these new discoveries will pave the way for the implementation of novel therapeutic strategies and will eventually lead to the eradication of the drug-resistant cells, substantially and ultimately enhancing cure rates for T-ALL patients.

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive and highly heterogeneous group of neoplasms, originated from T-cell progenitors. Despite intensive chemotherapy and stem cell transplantation based therapies, most T-ALL patients experience recurrences within 2 years after diagnosis with very dismal survival perspectives [1,2]. Although cure rates have improved to approximately 75% in children and 50% in adults, poor prognosis and high disease burden remain for relapsed/refractory subsets [1]. Recent efforts have focused on understanding the genomic background associated with naive and refractory/relapse phenotypes, which will lead to the discovery of driving defects promoting tumor progression. The most prominent cell-intrinsic aberrations in T-cell leukemia/lymphoma include activating mutations of Notch, deletion of tumor suppressor genes and translocations with consequent aberrant expression of transcription factor oncogenes [1,3]. Furthermore, a high incidence of overlapping mutations in the JAK/STAT as well as PI3K/Akt/mTOR pathways was frequently found in refractory/relapsed patients [4]. These latter data correspond with the tumorigenic role of these lesions and their association with poor clinical outcome makes them valuable clinical biomarkers.

Besides these pathogenic events, increasing evidence suggests that host-mediated pro-tumorigenic signals play a critical role as well. Indeed, the marrow microenvironment acts as sanctuary for leukemic cells, promoting their survival/dormancy and protecting them from chemotherapeutic stress, thus fostering tumor refractory or relapsed phenotypes [5,6]. Recent studies have argued that rare stem-like leukemic cells, capable of recreating the entire tumor, are responsible not only for T-ALL initiation but also for propagation [7]. These rare “leukemia initiating cells” (LICs) share common features with normal hematopoietic stem cells (HSCs), such as multi-potency, dormancy and self-renewal [8,9]. This implies that leukemia stem cell-like cells have features that make them less responsive to therapy and can lead to cancer relapse. Therefore, elucidating the molecular and cellular properties that promote this phenotype and thus overcoming chemoresistance remains an unmet medical need.

In this review we discuss the extrinsic factors that are known to influence the survival of leukemia initiating cells.

HSC niche: a peaceful community

Strong evidence suggests that the mechanisms that define the relationship between healthy HSCs and microenvironment closely mimic those adopted by leukemic cells to escape chemotherapy.

Normal hematopoietic cells are organized in a hierarchy headed by a pool of quiescent and pluripotent stem cells bearing self-renewal capacity. By dividing and differentiating committed progenitors, they can generate mature blood cells [10,11]. It is evident that normal hematopoiesis requires multiple coordinated mechanisms. Two specialized regions of the BM microenvironment - the osteoblastic niche and the vascular niche - work in concert to provide distinct signals in the form of secreted factors and cell surface molecules for HSC maintenance and regulation of normal hematopoiesis [12]. The osteoblastic niche, comprised of osteoblasts, nerve cells and specialized macrophages, contributes to the maintenance of stem cell dormancy and self-renewal. Moreover, the osteoblastic niche plays an essential role as a sanctuary for leukemia initiating cells.

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Key words: T-ALL, microenvironment, leukemic niche

Received: April 14, 2017; Accepted: May 15, 2017; Published: May 17, 2017
over the long-term [13-15]. Adhesion molecules expressed by both stem cells and stromal cells work by regulating the bidirectional network and governing both HSCs dormancy and cell renewal/proliferation. These include N-cadherin, CD44 and VLA4 [16]. VLA-4 expressed by HSCs interacts with VCAM-1 on osteoblasts promoting homing and retention of HSCs within the niche [17,18]. Angiopoietin-1 secreted by osteoblasts interacts with Tie-2, a tyrosine kinase receptor on the surface of HSCs cells, leading to upregulation of N-cadherin expression and consequently enhancing HSC-osteoblast adhesion and promoting the quiescence of HSCs [19]. Additionally, osteoblasts negatively regulate the number of HSCs in the bone marrow through the secretion of osteopontin, resulting in the inhibition of proliferation and induction of apoptosis of HSCs [20,21]. Conversely, myoexpression represses N-cadherin, inducing exit from the niche and HSC cycling [22]. The ligand jagged-1, secreted by osteoblasts, also binds to Notch and fires a signaling cascade in the HSCs, promoting self-renewal and clonal expansion [15].

Glia non-myelinated Schwann cells of the sympathetic nerves provide an additional layer of regulation contributing to the endosteal niche. These cells are in contact with a substantial number of HSCs and regulate their dormant state through transforming growth factor-beta (TGF-b)/Smad signaling [23].

At the same time, the components of the vascular niche, such as endothelial cells (EC), mesenchymal stromal cells (MSC) and megakaryocytes (Meg) support HSC maintenance, proliferation, differentiation and mobilization [14,24]. Stromal cell-derived factor-1 (also called CXCL12) is a critical factor in homing, retention and mobilization of HSCs. It is mainly secreted by endothelial cells and in part by osteoblasts during homeostasis or tissue injuries [25]. CXCL12 is a homeostatic chemokine that binds the CXCR4 receptor on the surface of HSCs, inducing homing, chemotaxis and adhesion of HSCs. CXCL12 also leads to the activation of VLA-4 on HSCs, promoting the VLA-4/VCAM-1 signaling pathway and potentiating HSC adhesion to the endothelial cells followed by their trans-endothelial migration [26].

Growth factors, such as the Granulocyte colony-stimulating factor (G-CSF) decrease the levels of CXCL12 in the marrow and increase the expression of CXCR4 on the HSCs surface. As consequence, HSCs are free to mobilize in the peripheral blood [27,28]. Additionally, G-CSF induces the secretion of proteolytic enzymes such as matrix metalloproteinases (MMPs) that disrupts the cell-cell anchors between HSCs and stromal cells, promoting mobilization of HSCs [29]. Lastly, endothelial cells also express Notch and c-Kit ligands as well as a specific set of angiogenic factors (FGF, Ang-1, IGFBP2), promoting HSC self-renewal and proliferation.

**Leukemia march to the marrow: a new landlord**

There is ample evidence supporting the hypothesis that the same extrinsic factors provided by the bone marrow niche responsible for maintaining the quiescence of HSCs may also facilitate LICs survival. LICs themselves alter the architecture of the BM microenvironment, triggering a maladapted niche that supports neoplastic phenotypes and progression [30,31]. Emerging evidence indicate that leukemic cells can "educate" the neighboring stroma to block the interactions between normal niche and residing HSCs, paving the way for a new pathological niche. Using four-dimensional imaging, Hawkins et al. pointed out how T-ALL cells invade the bone marrow and lead to rapid remodeling of the endosteal niche, with a total loss of mature osteoblasts. Similarly, using a mouse model of Notch-driven T-ALL, Wang et al. [32] showed that leukemic cells affect the homing of healthy

HSCs, compete for the occupancy of perivascular areas and suppress the number of osteoblasts, disrupting the normal hematopoiesis. The authors demonstrated the key role of Notch pathway in these processes, since Notch blockade recovered the osteoblasts and fostered HSCs proliferation in vivo. Interestingly, Enciso et al. [33] developed a dynamic Boolean network and proposed that up-regulation of NF-kB signaling contributes to ALL progression in concomitance to normal hematopoietic failure through disruption of CXCL12/CXCR4 and VLA4/VCAM-1 axes.

**Leukemic niche: guilty of aiding and abetting**

The first crucial step in leukemia-stroma interaction is the homing and adhesion of LICs to protective niches. This is orchestrated by chemokines produced by the microenvironment, that interact with specific receptors on the surface of LICs inducing the production of integrin and adhesion molecules. One of these key mediators is CXCL12, known to play a critical role in hematological malignancies as well as in solid tumors. Specifically, CXCL12 regulates invasion and controls metastatic capacity. Activated CXCR4 induces migration, adhesion, survival and proliferation of leukemic cells through the activation of multiple signaling pathways, including Jak/STAT, MAPK, PI3K/Akt and PKC. Of note, the deregulation of these pathways is also known to cause drug-resistance in ALL cells [34,35]. Using dynamic in vivo confocal imaging Sipkins et al. [36] have recently showed that when leukemic cells are injected in mice, they selectively localize in specific areas of marrow vasculature expressing high levels of E-selectin and CXCL12. The role of E-selectin has been proven using knock-out mice in which leukemic cell homing is considerably compromised. This is also in line with the data generated by small molecules that inhibit CXCL12-CXCR4 interactions. Indeed, the treatment of mice with AMD3100 dramatically affected leukemic homing, providing direct evidence that CXCR4 is necessary for this process and for retention of cancer cells into the marrow spaces [3]. Similarly, the work of Pitt et al. [6] has showed that direct contact of T-ALL with CXCL12-producing vascular endothelial cells allows for the creation of protecting leukemic niches. Collectively, these findings strongly support the potential of CXCR4 inhibitors in the treatment of T-ALL.

Interleukins also play an important function in the interplay between tumor and stroma elements. Relapsed B-ALL and stromal cells from leukemic BM niches have been shown to express higher levels of interleukins and their receptors, as compared to the levels observed in normal samples, thereby suggesting the existence of complex autocrine/paracrine loops regulating leukemic cell functions [37]. Toward this end, in vitro experiments proved that marrow-released CXCL12 increases IL-8 production in T-ALL cells through NF-kB and c-Jun phosphorylation [38]. A recent study has demonstrated that the inhibition of IL-18 pathway in T-ALL cells is associated with a delay of leukemia progression in xenograft models [39]. Moreover, Chiaretti et al. [40] have shown, by gene expression analysis, that IL-18 is highly expressed in refractory T-ALL patients compared to responders. An other critical lymphokine is Interleukin-6 (IL-6), which appears to be a promising factor to further study the interplay between T-ALL and microenvironment. This cytokine is a strong activator of the Jak/STAT pathway and induces cell proliferation and inhibits apoptosis via cyclins, c-myc and bcl-2. Notably, in bone marrow of ALL patients IL-6 is increased and its levels correlate with the severity of disease [41].

In addition to the cytokines, a prominent role is played also by growth factors. Triplett et al [42] have shown that dendritic cells (DCs) from the tumor microenvironment promote T-ALL growth.
and facilitate leukemia survival in both primary thymic and metastatic tumor sites. Using gene expression profiling, they found the up-regulation of both PDGFRB and IGFR1 on T-ALL cells and their cognate ligands by tumor-associated DCs.

Considering the importance of Notch signaling, its role in the crosstalk with stroma has been the object of extensive investigation. Of note, the over-expression of Notch3 ligand DLL-4 by bone marrow vascular endothelium promoted T-ALL survival and its inhibition delayed leukemia-initiating activity in xenograft models [43,44]. In addition to T-ALL, B-ALL also shows high expression levels of both Notch 3 and 4 receptors. Their activation, controlled by DLL-1 or Jagged-1 ligands expressed by BM-mesenchimal cells, sustains primary B-ALL survival and promotes chemoresistance to hydrocortisone in co-culture experiments [45].

Moreover, several adhesion molecules have been proven to regulate the activation of intracellular signals, promoting the survival of T-ALL via BM stroma-mediated engagement. LFA-1/ICAM-1 adhesive interactions as well as VCAM-1 and E-selectine molecules are also necessary for the survival of T-ALL cell lines and patient-derived T-ALL cells on BM stroma in vitro [46]. Lastly, B-ALL of relapsed patients have been shown to express high levels of VLA-4, which interacts with VCAM-1 on the stromal cells leading to the differential expression of a battery of genes involved in PI3K/mTOR, Wnt and NFkB signaling pathways [47,48].

**Breaking the alliance**

Clinically, T-ALL patients are most commonly treated by high-dose multiagent chemotherapy protocols, frequently followed by bone marrow stem cell transplantation, once a molecular remission is achieved with a curate intent. Despite the introduction of such aggressive treatments, more than 20% of children and 40% of adults unfortunately become resistant to chemotherapy and eventually relapse [1,2]. Several preclinical studies have shown some degree of efficacy for a variety of inhibitors that specifically target multiple intrinsic alterations, often in combination with lower dose of chemotherapeutic agents. Despite these novel attempts, only minimal results have been achieved and effective therapeutic protocols remain an unmet medical need.

The deregulated activation of the JAK/STAT signaling pathway has been recognized in many refractory/relapsed T-ALL cases. Unchecked P13K/Akt signals enhance resistance to apoptosis, promoting tumor development and progression. Additionally, PTEN, that physiologically acts as a negative regulator of the pathway, is deleted and/or defective in many T-ALL patients; a phenomenon linked to the maintenance of leukemia stem cell phenotype and tumor progression. The Notch and Wnt signaling pathways are well known as key regulators of LICs self-renewal activity, and are both activators of c-myc expression [49-52]. In addition, the HIF1α pathway modulates the self-renewal activity and differentiation of both normal and leukemic cells in hypoxic conditions [53,54]. A subset of LICs with active Wnt signaling has proven to reside preferentially within hypoxic niches in a mouse model of Notch-driven T-ALL. In particular, HIF1a pathway regulates the expression of β-catenin at the transcriptional level, which in turn potentiates Wnt signaling [55,56]. Targeting these key signaling cascades represents an attractive strategy. The γ-secretase inhibitors (GSIs), which block the proteolytic cleavage of the Notch receptors and preclude the release of activated Notch1 (ICN1) from the membrane, have been proposed as potential targeted therapy in T-ALL. Despite the promising results in preclinical in vitro and in vivo models, the effects of GSIs are transitory and the treated mice eventually undergo tumor progression followed by death.

The non-competitive and reversible agent, PF-03084014, selectively inhibits γ-secretase and has proven to lead a full hematological recovery in T-ALL patients with acceptable toxicity [57]. Similar results have been achieved in a single patient treated with GSI BMS-906024 [58].

Interestingly, the association of GSI with the mTOR inhibitor rapamycin has proven to be effective in increasing apoptosis, decreasing tumor burden and prolonging the overall survival in leukemic mice [59]. Similarly, GSI and PI3K or c-myc inhibitors synergistically decrease human T-ALL in vitro [60,61]. These data suggest that combination therapies may be needed to improve GSI efficacy and improve the treatment of T-ALL patients. Using a high-throughput drug screening approach, Roti et al. [62] identified the sarco/endoplasmic reticulum calcium ATPase (SERCA) channels as targets in Notch1-driven T-ALL. Indeed, a small molecule SERCA inhibitor thapsigargin selectively interfered with Notch signaling and proved to have anti-leukemic activity in both in vitro and in vivo models.

The treatment with the mTOR inhibitor rapamycin increases the response to the chemotherapeutic agent dexamethasone in T-ALL cells [63]. Similarly, the dual PI3K/mTOR inhibitor NVP-BEZ235 induced apoptosis and showed strong synergistic activity when administered with conventional chemotherapeutic agents in T-ALL cell lines and in primary patients lymphoblasts [64]. Since JAK/STAT pathway deregulation was found to be a key hallmark of immature leukemias harboring IL7R, JAK1, JAK3 or STAT5 alterations, specific small molecule inhibitors represent appealing agents for the treatment of this subset of T-ALL. Notably, the in vivo treatment with the JAK1/2 inhibitor ruxolitinib showed strong antitumoral effects in ETP-ALL patient-derived xenografts[65]. ETP-ALL is bcl-2 dependent and is very sensitive to in vitro and in vivo treatment with ABT-199, a drug well tolerated in clinical trials [66]. It is important to note that bcl-2 is highly expressed in early T-cell precursors and gradually decreases during normal T-cell differentiation. The response to ABT-199 has also proven effective in preclinical xenograft models of immature T-ALL and its combination with conventional chemotherapy displayed higher synergism providing a rationale for including this compound in clinical arenas [67]. Various small inhibitors as well as blocking antibodies against Wnt ligands or receptors have been synthesized and tested with promising anti-tumor activity [68-70].

Considering the fact that leukemia cells within maladapted niches can effectively evade therapy, treatments designed to de-bulk leukemic cells are likely to fail to eradicate cancer cells. Thus, it is anticipated that combination strategies targeting both intrinsic and extrinsic mechanisms will be necessary. Nevertheless, the disruption of the pro-survival signals from the host remains highly challenging. Currently, a variety of approaches have been tested, often designed to disrupt self-renewal pathways induced by stromal cells. Drugs against cytokines and chemokines driving the leukemic cells, as well as adhesion molecules and growth factors controlling tumor-cell interactions represent valuable approaches to break the connection between T-ALL cells and stromal/host cells. In particular, in acute myeloid leukemia, most of the progresses have been achieved by development of CXCR4 inhibitors [71]. As discussed, these compounds can be used to disrupt the pro-survival pathways activated by CXCL12/CXCR4 axis, blocking downstream targets that include PI3K/Akt signals. This hypothesis is supported by prolonged remission of leukemic CXCR4-mice [6]. Furthermore, treatment with a CXCR4 antagonist (AMD3465) dramatically suppresses human T-ALL and prolongs the survival of xenograft mouse models. Toward this end, Passaro et al. [5] have also
demonstrated that the transduction of human T-ALL with shCXCR4 vectors negatively affects the ability of T-ALL cells to migrate into the bone marrow spaces and slows disease initiation. This strongly supports the clinical potential for CXCR4 inhibition in the treatment of T-ALL. Meanwhile, CXCR4 inhibitors activate and mobilize leukemic cells out of niches to the peripheral blood where they are susceptible to co-administered chemotherapy [6,16]. Thus, different studies are currently investigating the combination of chemotherapy with CXCR4 antagonist for the treatment of hematological malignancies, including ALL [72].

Additional strategies focus on blocking growth factor signaling pathways, via either inhibitors that directly target growth factor receptors on the surface of T-ALL cells or molecules that compete with their ligands provided by stromal cells. Of note, the inhibition of IGF1R, using both specific inhibitors and siRNA, resulted in a relevant reduction in T-ALL survival and proliferation. On the same line, Cao et al. [73] have recently shown that angiomodulin effectively inhibits the IGFR-1 receptor on tumor cells and delays the growth of cancer cells, suggesting its putative usage in the treatment of hematological disorders and many other human neoplasms addicted to IGF-1 signaling. In the case of T-ALL, the aberrant activation of Notch signaling enhances the expression of IGFR1 signaling, making them highly responsive to IGF-1 provided by microenvironment [74]. Using specific inhibitors or genetic deletion of IGFR1, Medyouf et al. showed a significant reduction in the growth and viability of T-ALL cells in vitro and in a compromised tumor-initiating activity in transplanted mice.

In both normal and malignant BM microenvironment, restricted oxygen conditions regulate the self-renewal capacity and differentiation of stem cell subsets through the transcriptional activity of hypoxia inducible factors. In this context, novel HIF-1α inhibitors, capable of blocking HIF-1α DNA binding or disrupting its interaction with transcriptional co-activators have moved into the clinical arena [75,76]. As HIF-1α interacts with the chaperone HSP90, heat shock inhibitors can effectively induce HIF-1α degradation [77]. Similarly, the topoisomerase inhibitors were shown to reduce HIF-1α expression with consequent inhibition of angiogenesis and tumor growth in xenograft models [78]. These studies are also in line with findings observed in a mouse model of bcr-abl positive chronic myeloid leukemia in which the HIF1-a deletion was associated with reduced tumor initiation in secondary transplanted mice [79].

Conclusions

Despite improvements, substantial efforts are required to improve the understanding of the molecular and biological mechanisms dictating the mutual dependency of leukemic cells with their surrounding microenvironment. This is will eventually open new avenues to test and validate more effective strategies targeting both compartments and hopefully improve the outcome of leukemic patients.

Financial support

This work was partially supported by funds from the Leukemia Lymphoma Society, (SCOR grant) to G.I. and the AIRC 5xMille (Genetics-driven targeted management of lymphoid malignancies) to G.I.

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