C-X-C Chemokine Receptor 4 in Diffuse Large B Cell Lymphoma: Achievements and Challenges

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Keywords

Diffuse large B cell lymphoma · C-X-C chemokine receptor 4 · CXCL12/CXCR4 axis · Functional mechanism · Therapeutic applications

Abstract

Diffuse large B cell lymphoma (DLBCL), an aggressive cancer of the B cells, is the most common subtype of non-Hodgkin lymphoma (NHL) worldwide. In China, the cases of DLBCL increase yearly. C-X-C chemokine receptor 4 (CXCR4) has been implicated in the migration and trafficking of malignant B cells in several hematological malignancies, and only a few reports have been published on the role of CXCR4 in the metastasis of DLBCL. This review summarizes the relevant perspectives on the functional mechanism, prognostic significance, and therapeutic applications of the CXCL12/CXCR4 axis in DLBCL, in particular DLBCL with bone marrow involvement.

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Introduction

Diffuse large B cell lymphoma (DLBCL) is a clinically, morphologically, and molecularly heterogeneous disease with an unknown etiology, and it accounts for approxi-

mately 30% of adult non-Hodgkin lymphoma (NHL) cases [1–5]. It presents with rapid tumor growth as a nodal or extranodal mass. Approximately 70% of DLBCL patients have at least 1 extranodal site and 30% of patients have multiple sites [6]. Overall survival (OS) has improved significantly since the new therapy anti-CD20 monoclonal antibody (rituximab), in combination with CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) chemotherapy, has been in use [7]. Nevertheless, one-third of patients are still refractory or experience a relapse, and most of these patients have poor long-term outcomes [8, 9]. Therefore, it is necessary to identify the patient groups at diagnosis.

According to the cell of origin, gene expression profiling (GEP) divides DLBCL into activated B cell (ABC) and germinal-center B-like (GCB) subtypes, with approximately 10–20% of cases being unclassifiable [10]. The prognosis for the GCB subtype is better than for the non-GCB subtype. Because GEP is not widely available, immunohistochemistry (IHC) is used as a substitute to predict the cell of origin. At least 5 IHC-based algorithms are available in daily diagnostic practice [11]. The Hans algorithm, consisting of CD10, BCL-6, and MUM-1 (IRF4), is most commonly used. The GCB tumor cells are CD10⁺ or CD10[−]/BCL-6⁺/MUM-1[−], and non-GCB tumor cells are CD10[−]/MUM-1⁺ [12]. In the newly revised WHO classification, the adequate IHC panel consists of CD20, CD10,

BCL-6, and MUM-1. The modifications also state that the expression of CD5 and double expressor (MYC and BCL-2) in DLBCL appear to have adverse prognostic value [13]. Schmitz et al. [14] studied 574 DLBCL biopsy samples and extended these findings. They uncovered 4 subtypes of DLBCL, termed MCD (based on the co-occurrence of MYD88L265P and CD79B mutations), BN2 (based on BCL6 fusions and NOTCH2 mutations), N1 (based on NOTCH1 mutations), and EZB (based on EZH2 mutations and BCL2 translocations). These subtypes with distinct genotypic, epigenetic, and clinical characteristics provided a potential nosology for precision-medicine strategies in DLBCL. The BN2 and EZB subtypes have favorable survival and the MCD and N1 subtypes own the inferior outcomes.

Since the International Prognostic Index (IPI) was developed as a predictive model almost 20 years ago, it has been widely used to predict the outcomes of DLBCL patients [15]. The IPI mainly emphasizes clinical and biological characteristics, such as patient age and tumor stage, but provides little insight into the underlying biologic behavior associated with genetic and molecular variation. Novel biological biomarkers involved in cell signaling and trafficking are necessary [16].

Chemokines surrounding the tumor microenvironment play crucial roles in tumor development by binding to corresponding receptors. They control lymphoid cell development, differentiation, and migration; support B cell development, growth, and survival; and adjust the balance between subsets of T cells [17, 18]. The chemokines participate in organogenesis and immune responses, function as cellular growth factors, and facilitate angiogenesis [19]. In addition, they can activate adhesion molecules, which promote the trafficking of lymphocytes into and within tissues [20, 21]. C-X-C chemokine receptor 4 (CXCR4) is a receptor specific to stromal-derived factor-1 (SDF-1, also CXCL12) [22]. The CXCL12/CXCR4 axis regulates the migration of T lymphocytes and other immune cells expressing CXCR4, the retention of B cell precursors in bone marrow (BM), and the homing of B lymphocytes to lymph nodes [23]. Abnormal CXCR4 expression has been shown to be critical for metastasis to organs with a high expression of CXCL12, such as the BM, lymph nodes, and bones [24], and it has prognostic significance in some solid cancers, such as lung [25], renal [26], prostate [27], breast [28], colorectal [29], and hepatocellular [30] cancers. CXCR4 may also be an indicator of metastasis in several hematological malignancies [31]. CXCR4 overexpression has been associated with poor prognosis and contributes to therapeutic resis-

tance in acute myelogenous leukemia (AML) [32–35], acute lymphoblastic leukemia (ALL) [36, 37], myelodysplastic syndrome (MDS) [38], lymphoplasmacytic lymphoma [39], chronic lymphocytic leukemia (CLL) [40], and other B cell NHLs [41, 42]. For example, CXCR4 can protect leukemic cells from chemotherapy-induced apoptosis by giving leukemic blasts a higher capacity to seed into BM niches [24, 32, 34, 39, 43].

The CXCL12/CXCR4 Axis and DLBCL

Cellular Localization of CXCR4

Lemma et al. [44] and Jahnke et al. [45] found that expression of CXCR4 was localized to the nucleus or cytoplasm of lymphoma cells in primary central nervous system lymphoma samples. Strong nuclear expression of CXCR4 is most strongly associated with nodal DLBCL.

Prognostic Significance of the CXCL12/CXCR4 Axis

The prognostic significance and functional mechanism of CXCR4 expression in malignant lymphomas is not fully understood. Compared to other types of tumors, primary lymphomas have differing gradients of CXCL12 expression [46]. Few studies have been done on the role of CXCR4 in DLBCL. Some studies determined that the key role of CXCR4 is the dissemination of DLBCL. For example, CXCR4 expression was associated with disease progression in 12 cases of primary testicular DLBCL [47] and 94 cases of DLBCL treated with rituximab-containing regimens [48]. Recently, high CXCR4 expression was reported to be associated with a lower survival rate in mice injected intravenously with DLBCL cells [48]. Another important study showed poorer progression-free survival in a training/validation cohort of 468/275 GCB-DLBCL patients due to CXCR4-related chemotaxis [49]. However, in 1 Asian study, CXCR4 was not associated with the survival of DLBCL patients [50].

CXCL12/CXCR4 Axis and BM Infiltration

Early on, scientists recognized that activated B cells likely home to the BM via CXCR4-dependent pathways during the humoral immune response [51]. CXCR4 expression was found to be linked to BM infiltration in some B cell neoplasms [52]. A positive correlation between a significant decrease in CXCR4 mRNA expression in the BM after treatment and better prognosis was found in 20 NHL patients [53]. The CXCL12/CXCR4 axis directs CXCR4-positive lymphoma cells to reside in the BM through concentration gradients of CXCL12 and underlies de-

Fig. 1. Schematic diagram of the SDF-1/CXCR4 axis affecting major signaling pathways. SDF-1 (CXCL12) binding to CXCR4 can (1) activate GRK and downstream molecule β -arrestin, subsequently mediating MAPK signaling promoting cell migration; (2) trigger intracellular calcium mobilization through the activation of the PLC/IP3 signaling pathway; (3) affect the PI3K/AKT signaling pathway. AKT is a central node in signaling cascades that can activate mTOR and NF- κ B regulating cell survival and proliferation;

(4) activate JAK/STAT pathway mediating transcription. GRK, G-protein-coupled receptor kinase; MAPK, mitogen-activated protein kinase; BTK, Bruton tyrosine kinase; PLC, phospholipase C; PIP2, phosphatidylinositol 4,5-bisphosphate; IP3, inositol 1,4,5 trisphosphate; PI3K, phosphoinositide-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor- κ B; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

creased chemosensitivity and disease progression. Chen et al. [49] found an inverse correlation between CXCR4 and CXCL12 mRNA expression in the stromal cells of patients without BM involvement. They speculated that this abnormal condition (high CXCR4/low CXCL12) at the primary sites led to the metastasis of CXCR4-positive lymphoma cells to other organs with a higher expression of CXCL12, which directly resulted in the disease progression of DLBCL. Additionally, they found that CXCR4 expression had a significant prognostic effect in nodal but not in extranodal DLBCL.

Functional Mechanisms of CXCR4

Migration of CXCR4-positive hematopoietic cells is promoted by a CXCL12 gradient produced by stromal cells [54]. Inhibiting the interaction of CXCR4 with

CXCL12 can reverse the tumor-promoting signals of stromal cells, which results in tumor cells being more susceptible to chemotherapy and having an increased rate of apoptosis [55, 56]. The progression of B-NHL depends partly on interactions with the tumor microenvironment, which are adjusted by integrins, chemokines, and chemokine receptors [57]. There is a feedback loop between CXCL12/CXCR4 and the signaling pathways mediating tumorigenicity. The CXCL12/CXCR4 axis can activate various intracellular signaling transduction pathways and downstream effectors, such as integrin, tyrosine kinases, G-proteins, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (MAPK) pathways, and mammalian target of rapamycin (mTOR) (Fig. 1) [23, 24, 40, 58–61]. Previous studies have confirmed that abnormal activation of the PI3K/Akt/mTOR

signaling pathway increases tumor proliferation and is associated with the poorer prognosis of patients with DLBCL [62, 63]. Signaling molecules, physiological stimuli, and cotranslational modifications effect the expression of CXCR4 [49]. CXCR4 expression is positively regulated by nuclear factor (NF)- κ B, CD63, interleukin (IL)-21, PI3K/Akt, hypoxia-inducible factor 1 α , CREB3, PAX3-FKHR, Wnt, Notch, and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways [49, 64, 65]. In contrast, CXCR4 expression is negatively affected by p53, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and ubiquitination [24, 58, 66–68].

Let us review the relationship between CXCR4 and NF- κ B further. Okera et al. [69] suggested that CXCR4 expression is associated with the activities of IL-8, matrix metalloproteinase (MMP)-9, and vascular endothelial growth factor (VEGF), which are often regulated by NF- κ B. In a recent study, Shin et al. [50] reported coexpression of NF- κ B and CXCR4 in DLBCL patients. In ABC-DLBCL, the NF- κ B signaling pathway is activated due to mutations in the genes encoding pathway members upstream of NF- κ B [70]. As a central transcription factor, NF- κ B can induce the transcription of CXCR4, and activity of the CXCR4 pathway leads to nuclear accumulation of NF- κ B [24, 71]. Given the associations between the expression of CXCR4 and NF- κ B, plerixafor, a CXCR4 antagonist, could possibly counterbalance NF- κ B signaling pathway deregulation.

Furthermore, due to oncogenic elements such as dysregulated TNF cytokines, MYC overexpression, or the secondary event of BCL2 translocation in the germinal center, abnormal reduction in CXCL12 expression in lymph nodes can initiate tumorigenesis [49]. Decreased expression of CXCL12 also leads to the dissemination of CXCR4-positive tumor cells to distant organs with higher CXCL12 levels [46, 72]. Therefore, the levels of CXCL12 and CXCR4 may be highly relevant for both lymphomagenesis and the progression of lymphoma.

Therapeutic Applications

Since the microenvironment provides growth and survival stimuli for both normal [73] and neoplastic lymphocytes [74–76], understanding the environmental niches of the neoplastic cells in B-NHL can lead to new therapeutic approaches. Some drugs, such as ibrutinib (a Bruton tyrosine kinase inhibitor) and idelalisib (a PI3K inhibitor), have been successfully used in the treatment of lymphoma [77–79]. These drugs inhibit the kinases involved in B cell receptor signaling and displace B-NHL cells from their protective residencies by block-

ing chemokine-induced adhesion signals [80]. In a similar way, inhibitors of CXCR4 have been shown to enhance the efficacy of rituximab in the B-NHL mouse model [81].

Inhibiting the interactions of CXCL12 and CXCR4 can disrupt metastasis, promote apoptosis, and increase the chemosensitivity of a variety of cancers [82–84]. Therapeutic regimens containing a CXCR4 antagonist can increase the rate of cell death in lymphoma models [85]. The effects of CXCR4 antagonists, in combination with traditional antineoplastic agents, are being evaluated in clinical trials for the treatment of hematological malignancies [86]. For example, the CXCR4 antagonist plerixafor has been found to enhance the effect of rituximab in Burkitt's lymphoma [87, 88]. Plerixafor, a bicyclic reversible inhibitor, blocks the binding of CXCL12 to CXCR4 by combining with an extracellular binding pocket [86]. It can prevent tumor cell homing to BM and mobilize the cells to the peripheral blood, which may cause the tumor cells with CXCR4 overexpression to be more susceptible to treatment with rituximab [89]. The effect of plerixafor occurs via receptor blockade or by disrupting the tumor-stromal cell mutual effect, thereby preventing stroma-induced CXCR4 expression. O'Callaghan et al. [87] found that combining plerixafor with rituximab in vivo significantly prolonged the survival time of mice with Burkitt's lymphoma and CLL. In contrast, low doses (10 μ M) of plerixafor did not significantly increase the survival of Burkitt's lymphoma cells in vitro. As such, the effect of plerixafor on the proliferating tumor cells is believed to be greatly dependent on the drug concentration. Other studies found that plerixafor can significantly enhance the effect of rituximab at most drug concentrations [90]. From these findings, a synergistic interaction between rituximab and plerixafor can be inferred. Cell-penetrating lipopeptide pepducins and the CXCR4 antagonist BKT140 have an enhancing effect on rituximab efficacy as well [81]. BKT140 can reverse rituximab-induced cellular arrest in Burkitt's lymphoma by increasing the activation of the apoptotic caspase 3 pathway. CXCR4 antagonists have also been shown to enhance the effect of other drugs in the R-CHOP regimen. Lee et al. [91] verified a synergistic drug interaction of the CXCR4 antagonist T22 and cyclophosphamide in vivo. In ALL, the survival time of engrafted mice was extended with a combination of the drugs plerixafor and vincristine [92]. Adding a CXCR4 antagonist to the therapeutic schedule can reduce the cycles of chemotherapy that a patient must receive, which may increase the curative effect or lower the drug-induced toxicity [93].

Conclusion and Perspectives

The expression of CXCR4 plays a crucial role in the oncogenesis and tumor progression of DLBCL. The potential related mechanisms need to be further elucidated. CXCR4 is associated with poor survival and could be used as a prognostic marker for DLBCL. The CXCL12/CXCR4 axis may prove to be a novel therapeutic target for reducing metastasis in DLBCL.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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