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Review article

CXCL13/CXCR5 signaling axis in cancer

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ABSTRACT

The tumor microenvironment comprises stromal and tumor cells which interact with each other through complex cross-talks that are mediated by a variety of growth factors, cytokines, and chemokines. The chemokine ligand 13 (CXCL13) and its chemokine receptor 5 (CXCR5) are among the key chemotactic factors which play crucial roles in deriving cancer cell biology. CXCL13/CXCR5 signaling axis makes pivotal contributions to the development and progression of several human cancers. In this review, we discuss how CXCL13/CXCR5 signaling modulates cancer cell ability to grow, proliferate, invade, and metastasize. Furthermore, we also discuss the preliminary evidence on context-dependent functioning of this axis within the tumor-immune microenvironment, thus, highlighting its potential dichotomy with respect to anticancer immunity and cancer immune-evasion mechanisms. At the end, we briefly shed light on the therapeutic potential or implications of targeting CXCL13/CXCR5 axis within the tumor microenvironment.

1. Introduction

The chemokines are a family of chemotactic cytokines or ligands which selectively attract and activate different cell types [1–3]. Chemokine ligands mediate their activity *via* interactions with seven-transmembrane-spanning G protein-coupled receptors (GPCRs), thus forming chemokine ligand/receptor pair axes [1]. The chemokine ligand/receptor interactions embrace enormous signaling plasticity and complexity, which is critical to fine-tune the chemoattraction of specific leukocyte subpopulations [1]. However, disruption of the chemokine signaling events may exert a large variety of functions that may dictate processes of tumor development and progression [4,5]. Elevated expressions of different chemokine ligands and receptors have been reported in many tumors [6–15], and in consequence, the abnormal activation of underlying signaling effectors has been shown to influence most-if not all-hallmark processes of cancer [1,16–18]. Chemokine (C-X-C motif) ligand 13 (CXCL13), and its cognate receptor, CXCR5 (*i.e.* CXCL13/CXCR5 axis), represent an emerging example of such functionally-disrupted chemokine ligand/receptor pair axes, for which, abnormal activation is mostly skewed towards cancer-promoting direction.

A plethora of functional studies conducted over the last two decades implicate the elevated levels of CXCL13 and/or CXCR5, and thereby the hyperactivation of underlying signaling effectors, in tumorigenesis, tumor cell growth, survival, and site-specific metastasis [19–24]. Emerging preliminary data also highlight the relevance of this pathway

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Abbreviations: AITL, Angioimmunoblastic T-cell lymphoma; BLR1, Burkitt's lymphoma receptor 1; BLC, B-lymphocyte chemoattractant; BCA-1, B cell-attracting chemokine 1; B-CLL, B-cell chronic lymphocytic leukemia; CCL, Chemokine (C-C motif) ligand; CTL, Cytotoxic T lymphocytes; CXCL13, Chemokine (C-X-C motif) ligand 13; CXCR5, Chemokine (C-X-C motif) receptor 5; DC, Dendritic cell; DLBCL, Diffuse large B cell lymphoma; ERK, Extracellular-signal regulated kinase; EMT, Endothelial-mesenchymal transition; FDCs, Follicular DCs; GPCRs, G protein-coupled receptors; IFN, Interferon; JNK, c-jun kinase; LT/TNF, Lymphotoxin/tumor necrosis factor; LTβR, LTβ receptor; MAPK, Mitogen-activated protein kinase; MMP, Matrix metalloproteinase; MDSCs, Myeloid-derived suppressor cells; NF-kB, Nuclear factor-kappa B; NFATc3, Nuclear factor of activated T cells c3; NK, Natural killer; OSCC, Oral squamous cell cancer; PEG10, Paternally expressed gene 10; PCNSL, Primary central nervous system lymphoma; PKCε, Protein kinase C epsilon; RANKL, Receptor activator of nuclear factor kappa-B ligand; RNAi, RNA-mediated genetic interference; SAPK, Stress-activated protein kinase; SPP1, Secreted phosphoprotein 1; T_{FH}, Follicular helper T cells; TLSs, Tertiary lymphoid structures; Treg, T regulatory cells

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in both the antitumor immune-surveillance, as well as tumor immune-evasion mechanisms. Indeed, a better understanding of CXCL13/CXCR5 signaling axis within the tumor microenvironment may lead to new insights into cancer treatment research. In this review, therefore, we discuss CXCL13/CXCR5 signaling axis to summarize its mechanism of activation, its roles in contexts of normal cellular physiology as well as cancer pathobiology and immunity, and its therapeutic potential as a target for cancer therapy.

2. The CXCL13/CXCR5 signaling axis

CXCL13, originally known as BLC (B-lymphocyte chemoattractant) or BCA-1 (B cell-attracting chemokine 1), is a homeostatic chemokine. It is constitutively secreted by stromal cells in B-cell areas of secondary lymphoid tissues (follicles), such as spleen, lymph nodes, tonsils, and Peyer's patches [25–29]. CXCL13 plays a key role in orchestrating cell migration within spatially distinct regions of the secondary lymphoid organs. It strongly attracts B lymphocytes while promoting migration of only small numbers of T cells and macrophages [25,30]. CXCL13 exerts its functions through its receptor CXCR5, which initially, was isolated from Burkitt Lymphoma and therefore designated as Burkitt's lymphoma receptor 1 (BLR1) [26,28,31]. CXCR5 is highly expressed on mature recirculating B-lymphocytes, a subpopulation of follicular helper T cells (T_{FH}) and skin-derived migratory dendritic cells (DCs), and controls their migration into secondary lymphoid organs towards the gradient of CXCL13 [32–34].

The signal transduction mechanisms following CXCL13:CXCR5 interactions largely remain unclear. Majority of the functional studies published in last few years suggest CXCL13/CXCR5 axis obeying the classical GPCR activation paradigms (Fig. 1). The mechanism of CXCR5 receptor activation is mediated by coupling to an intracellular heterotrimeric G-protein complex that is composed of Gα, Gβ and Gγ subunits (see Fig. 1 legend). Upon CXCL13 stimulation, the G-proteins dissociate from CXCR5 to initiate divergent signaling events downstream of ligand binding (Fig. 1), which ultimately can lead to variety of responses such as cell proliferation and/or survival, increase in intracellular calcium, invasion, migration, and gene transcription. Mostly, the Gα-subunit family members (particularly, $\alpha_{q/11}$, α_{i2} and α_{13}) relay the CXCR5 signaling *via* different routes [35,36]. This is also worth mentioning that the precise nature of the downstream molecular events of CXCL13/CXCR5-mediated signal transduction may be tissue-dependent and thus may differ between cell types [35]. Previously, it has been manifested that CXCR5 characterizes unique structural constraints that are of utmost importance not only for the activation of specific signal transduction pathways, but also for fine-tuning the cellular response towards the stimulus [35]. Especially, the presence of specific sequence motifs in the intracellular domains and probably the transmembrane spanning regions of the CXCR5 receptor are indispensable for coupling to the heterotrimeric G-proteins [35]. However, a more recent study by MacDonald et al. has demonstrated the lack of necessity for anticipated membrane partnering events for downstream CXCR5 signaling in HL-60 cells [37].

3. CXCL13/CXCR5 signaling axis, cellular physiology and physiopathology

Experimental data emerging both from mouse and human studies indicate that CXCL13/CXCR5 axis plays important roles in normal cellular physiology. It is involved in B-cell terminal differentiation, maintenance of lymphoid tissue microarchitecture, and the development of B- and T-cell-mediated immune responses [28,30,38–41]. Together with other cytokines, such as chemokine (C-C motif) ligand (CCL)19, CCL21 and members of the lymphotoxin/tumor necrosis factor (LT/TNF) family, CXCL13/CXCR5 axis contributes to the architectural organization of B-cells within lymphoid follicles [25,28,38]. As briefly depicted in Fig. 2, stromal cell-B cell signaling cascades, which derive the LTα1β2:CXCL13 positive feedback loop system for the induction of follicular DCs (FDCs), provide the underlying roads that circulating naïve B cells actively follow for localization within the follicles [27,42]. The B cell-derived LTα and LTβ cytokines interact with LTβ receptor (LTβR) on surrounding stromal cells, which in turn, leads to increased secretion of CXCL13 by stromal cells including FDCs [27,43,44]. The signaling by stromal-derived CXCL13, *via* CXCR5 (on B-cells), then reciprocally enhances the cell surface expression of LTα1β2 on B cells, which subsequently results in clustering of circulating naïve B cells in the proximity of FDCs, a prerequisite step for the formation of B-cell lymphoid follicles [39,45,46]. The activated B cells with high LTα1β2 can beget further expression of CXCL13 by stromal cells *via* LTβR signaling, thus keeping the biologic circuit “on” [28]. Mice lacking CXCL13 or CXCR5 failed to form structured lymphoid organs, which appears due to a lack of FDCs-derived CXCL13/CXCR5-mediated structural frameworks that are critical for the organization of recruited B cells into follicles [28,31].

Looking from the perspective of immunity, CXCL13:CXCR5 interactions also contribute to the development of B-cell-mediated, T-cell-dependent or -independent immune responses [47,48]. The axis particularly regulates the trafficking and homing of B-1 B cells into body cavities [41,48]. B-1 B cells are a subset of recirculating B cells that is predominately found in peritoneal and pleural cavities [49,50], where they produce nonspecific, natural IgM antibodies for early protection from infections [41,48]. CXCL13/CXCR5-derived B-1 B cells homing to body cavities is thus crucial to the development of an early B cell-mediated innate immune response [41]. CXCL13:CXCR5 interactions also facilitate B cell-regulated T cell-dependent immune responses against infections. In response to infection, antigen-bearing DCs and $CD4^+$ T cells are able to upregulate CXCR5 and can co-localize in a CXCL13-, B cell-, and LT-dependent fashion to sites of immune priming within the lymph nodes [47]. LT-expressing B cells abundantly enhance the CXCL13 expression and thereby regulate the CXCL13-dependent positioning of the $CXCR5^+$ DCs and $CD4^+$ T cells to sites of immune priming. This ultimately results in optimal development of interleukin (IL)-4-expressing T_{FH} and T_H2 effector cell responses against infection [47]. CXCL13 expression within lymphoid organs ensures effective participation of naïve B cells in ongoing immune reactions by facilitating antigen presentation [51].

Dysregulated CXCL13 and/or CXCR5 expression and signaling may correlate with disease evolution. For instance, abnormal overexpression of CXCL13 in nonlymphoid organs may promote the development of ectopic lymphoidlike structures (lymphoid neogenesis), which are also known as tertiary lymphoid structures (TLSs) [52–54]. TLSs are often associated with chronically inflamed, infected, or tumoral tissues, where they shape local adaptive immune responses [53,55]. TLSs are generally meant to limit the disease progression; however, in most of the pathological conditions, they would appear to be foes and not friends [53]. CXCL13/CXCR5-derived formation of TLSs has been implicated in the pathobiology of many disease processes, including myasthenia gravis [56,57], rheumatoid arthritis [58], Sjögren's disease [59,60], multiple sclerosis [61], Hashimoto's thyroiditis [62], other autoimmune [63] and chronic inflammatory disorders [52,64–66], and cancer [53,67,68]. Apart from TLSs formation, abnormal CXCL13/CXCR5 signaling may also derive different intracellular events that participate in pathobiology of various disease processes [69–72].

4. CXCL13-CXCR5 signaling axis, cancer development and progression

Aberrantly active CXCL13/CXCR5 signaling has been linked to the development and progression of several advanced human cancers (Table 1). A significant correlation between CXCL13 and/or CXCR5 expression occurs in human malignancies, and serum CXCL13 levels have been postulated as a biomarker of cancer progression and early diagnosis (Table 1). In brief, emerging data in last few years has

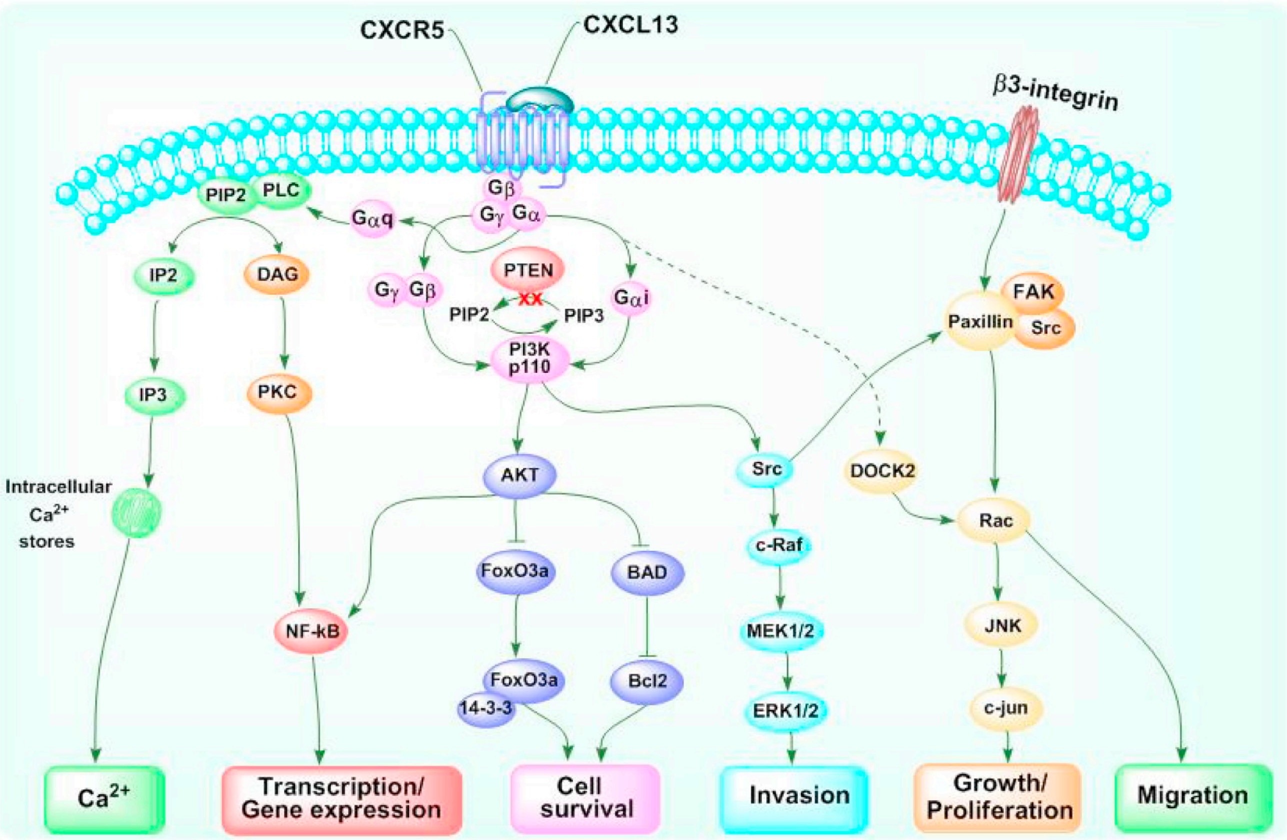

Fig. 1. A schematic representation of the mechanistic paradigms of CXCL13/CXCR5 signaling. Biological effects of CXCL13 are mediated by activation of CXCR5, coupled to G-protein heterotrimer. The heterotrimer is composed of Gα, Gβ and Gγ subunits, which in its basal state binds the guanine nucleotide (GDP). Upon CXCL13 binding, the Gα-subunit of the G-protein exchanges guanosine GDP for guanosine triphosphate (GTP) and then dissociates. Subsequently, the Gαq-subunit activates phospholipase C (PLC). This leads to conversion of phosphatidylinositol 4, 5-bisphosphate (PIP2) into diacylglicerol (DAG) and inositol triphosphate (IP3) and calcium release, followed by protein kinase C (PKC) activation and phosphorylation of target proteins. In parallel, Gαi and Gβγ-subunits activate phosphatidylinositol 3-kinase (PI3K), which leads to AKT pathway activation destined to tumor cell survival [36,118]. PI3K activation can also result in the activation of Raf/MEK/ERK, integrinβ3-focal adhesion kinase (FAK)/Src-paxillin, and DOCK2/Rac/JNK pathways involved in cell growth, invasion and migration [23,118]. DOCK2, dedicator of cytokinesis 2; ERK, extracellular signal-regulated kinase; JNK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase.

assigned crucial roles to CXCL13/CXCR5 signaling axis within the tumor microenvironment, which we summarize here in terms of hematological and solid tumor malignancies.

4.1. CXCL13/CXCR5 signaling axis in hematological malignancies

Hematological malignancies are malignant neoplasias, mainly encompassing tumors of the hematopoietic (leukemias) and lymphoid (lymphomas) tissues [73]. Tumor cell survival and progression in hematological malignancies are linked to cross-talks between lymphoid or leukemic cells and the nontumor stromal cells within the tumor tissue microenvironment [74–76]. CXCL13/CXCR5 axis contributes to the microenvironmental cellular cross-talks, and the downstream molecular pathways, which eventually confer pro-survival signals to, and thus foster the progression of, hematological malignancies.

A particularly important role of CXCL13/CXCR5 axis has been outlined in the microenvironmental regulation of B-cell chronic lymphocytic leukemia (B-CLL) cells [77]. B-CLL represents a monoclonal population of $CD5^+$ neoplastic B cells in peripheral blood, secondary lymphoid tissues and the bone marrow [78]. Secondary lymphoid organs and bone marrow are the sanctuary sites of B-CLL cell proliferation, also preserving them from spontaneous or drug-induced apoptosis [74,75,79]. CXCL13-CXCR5 signaling aids the recruitment of B-CLL cells into these sanctuary sites [75,80–83]. Enhanced expression of CXCR5 on B-CLL cells, and its stimulation by stromal-derived CXCL13, induces chemotaxis of B-CLL cells to a putative proliferation and survival niche within lymphoid organs [75,80–82]. It has been elucidated that CXCL13:CXCR5 interactions facilitate follicular tumor cell homing, shaping of a survival niche, and access to localized proliferation stimuli [83,84]. Particularly, CXCL13/CXCR5-derived stroma-leukemia cross-talks play a critical role to establish a paracrine feedback loop network, in which, CXCR5-dependent lodging of B-CLL cells reciprocally stimulates resident mesenchymal stromal cells through LTβR activation and, thus, results in CXCL13 secretion and stromal compartment remodeling [83]. Apart from recruiting B-CLL cells into specific anatomic sites, CXCL13/CXCR5 axis is an important component of homeostatic chemokine-induced specific signaling networks, which can aid leukemic cells to escape undergoing apoptosis [85–87]. To this regard, the phosphorylation and activation of two unique signaling networks: mitogen-activated protein kinase (MAPK)/extracellular-signal regulated kinase (ERK1/2)/p90RSK pathway, and phosphoinositide-3-kinase (PI3K)/Akt/FOXO3a pathway, are of critical importance [85]. CXCL13, along with other homeostatic chemokines (CXCL12, CCL21, and CCL19), provides strong survival signals to B-CLL cells mainly through the Akt-dependent inactivation of the proapoptotic transcription factor FOXO3a (Fig. 1) [85]. Moreover, CXCL13 and CCL19 have been demonstrated to cooperatively induce significant resistance to TNF-α-mediated apoptosis in B cell lineage acute and chronic lymphocytic leukemia (B-ALL and B-CLL) [86,87]. Both CXCL13 and CCL19, *via* frequent activation of their respective CXCR5 and CCR7 receptors, up-regulate the expression and function of paternally expressed gene 10 (PEG10). PEG10 subsequently stabilizes

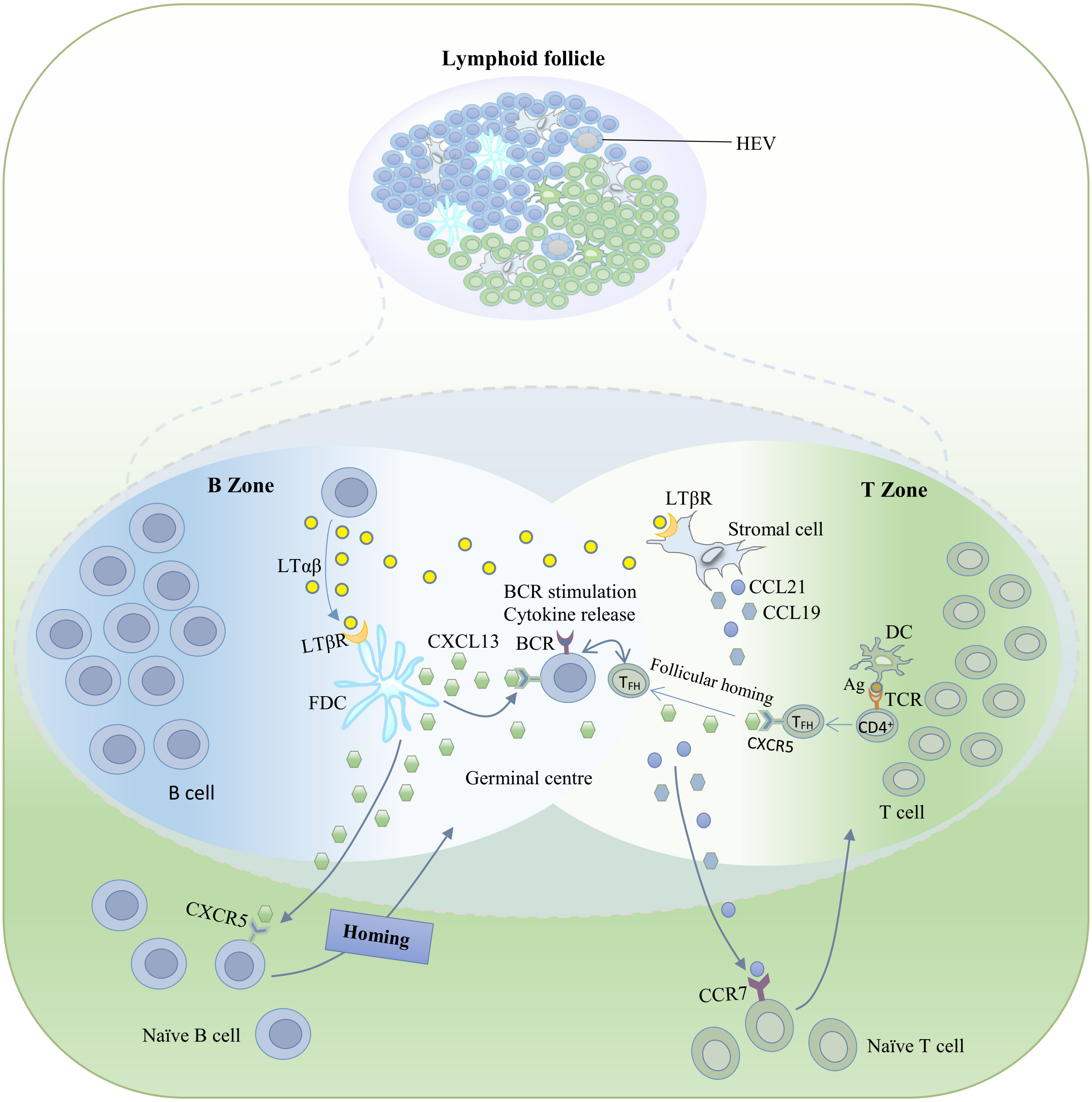

Fig. 2. A brief depiction of CXCL13/CXCR5 role in maintenance of lymphoid follicles. Resident stromal cells such as follicular dendritic cells (FDCs) contribute to lymphoid chemokines (CXCL13 and CCL19/CCL21) production and guide the cellular arrangement of the follicular structure. Different gradients of CXCL13 and CCL19/CCL21 support the segregation of B/T cells. The development of high endothelial venules (HEVs) is of fundamental importance for enhancing B and T cells recruitment. Antigen (Ag)-presenting dendritic cells (DCs) and the B/T-follicular helper (Tfh) cells shuttling into the germinal centre help maintaining the follicular structure.

caspase-3 and caspase-8 in B-ALL and B-CLL cells and further rescue them from TNF-α-mediated apoptosis [86,87]. Collectively, the data discussed above clearly infer that B-CLL cells can take advantage of CXCL13/CXCR5 signaling axis for infiltration to sanctuary sites, inappropriate proliferation, and resistance to apoptosis.

CXCL13 and CXCR5 also contribute to the pathobiology of lymphoproliferative disorders, both of B- and T-cell origin. Accumulating clinical data implicates the elevated molecular expression, as well as the pro-tumorigenic involvement, of CXCL13 and/or CXCR5 in the pathogenesis of different types of lymphomas. These include angioimmunoblastic T-cell lymphoma (AITL) [88–90], follicular lymphoma (FL) [91], diffuse large B cell lymphoma (DLBCL) [92], primary central nervous system lymphoma (PCNSL) [93,94], cutaneous B- and T-cell lymphomas [32,95], primary intraocular lymphoma [96], gastric lymphoma [66,97], and non-Hodgkin lymphoma (NHL) [98,99]. In DLBCL, CXCR5 expression by circulating $CD4^+$ T lymphocytes may assist the survival and proliferation of tumor cells through IL-10 pathway [92]. Similarly, cell-type specific expression and the microenvironmental interactions of CXCL13 and CXCR5 may facilitate the pathogenesis and intracerebral dissemination of PCNSL cells [93,94]. Emerging clinical evidence also validates elevated expression of CXCL13 (by neoplastic cells) as a new diagnostic tool for the early detection and treatment of AITL [100], PCNSL [101], human immuno-deficiency virus (HIV)-associated NHL (AIDS-NHL) [102,103], and extra-nodal natural killer (NK)/T-cell lymphoma [104].

Table 1
CXCL13-CXCR5 axis in human malignancies and its therapeutic implications.

Cancer type	Patho-physiological events	Underlying mechanisms	Therapeutic potential/implications	Reference
Colon or Colorectal cancer[a]	■ Growth, migration, invasion, and metastasis ■ Relapse of advanced colorectal cancer ■ Correlation with poor prognosis	■ Activation of PI3K/AKT pathway ■ *CXCR5* gene polymorphisms ■ Increased secretion of MMP-13	**RNA interference** ■ siRNA-mediated knockdown of CXCR5 *Impact*: inhibited the CXCL13-regulated functions of colon cancer cells **Pharmacological intervention** ■ Inhibitor of downstream signaling event (a) LY294002 (PI3K inhibitor) *Impact*: suppressed the CXCL13-mediated growth, migration, and invasion of colon cancer cells	[105–109]
Lung cancer[a]	■ Carcinogenesis ■ Invasive growth, progression and metastasis of advanced stage lung cancer ■ Correlation with poor prognosis	■ AhR-CXCL13-CXCR5-SPP1 signaling ■ SPP1-β-catenin positive feedback loop induces EMT	**RNA interference** ■ siRNA-AhR mediated decreased *CXCL13* expression ■ SPP1 silencing *Impact*: inhibited the CXCL13-mediated migration of lung tumor cells **Pharmacological intervention** ■ Anti-CXCR5 antibody *Impact*: significantly inhibited lung cancer cell migration ■ Dexamethasone *Impact*: inhibited the CXCL13 production, resulting in reduced tumor burden in mice	[110,111]
Breast cancer[b]	■ Tumor cells survival, growth, migration, and lymph node metastasis ■ Correlation with poor prognosis	■ CXCL13-CXCR5-ERK signaling ■ NF-kB-mediated expression of *CXCR5*; inverse correlation with p53-dependent tumor suppression ■ CXCL13-CXCR5-RANKL– PI3Kp110α-Src axis induces EMT and MMP-9 expression	**Pharmacological intervention** ■ Anti-CXCL13 and/or –CXCR5 antibodies *Impact*: successfully attenuated the tumor growth, EMT, and RANKL expression ■ Inhibitor of downstream signaling events: (a) PI-103 (PI3Kp110α inhibitor) (b) SU6656 (Src inhibitor) *Impact*: impaired the CXCL13-stimulated EMT and MMP-9 expression	[20,112–116]
Prostate cancer	■ Tumorigenesis, growth, proliferation, migration, metastasis, and survival	■ Autocrine CXCL13-CXCR5 loop: PKCε/PI3K-NF-kB pathway ■ Autocrine HIF-1/TGF-β/SMAD signaling promotes CXCL13 expression by tumor-associated myofibroblasts ■ CXCL13 modulates PI3K/Akt, SAPK/c-JNK, and Ras/ERK signaling events ■ Increased expression of MMPs	**RNA interference** ■ RNAi depletion of CXCL13/CXCR5 *Impact*: abrogated the growth, tumorigenic activity, and migratory ability **Pharmacological intervention** ■ anti-CXCL13 and –CXCR5 antibodies *Impact*: impaired the migratory and tumorigenic properties ■ Treatments that block CXCL13 expression: (a) immunodepletion of myofibroblasts (DNA vaccine) (b) inhibition of myofibroblasts activation (PDE5 inhibitors *e.g.* pentoxifylline and sildenafil) (c) blockade of TGF-β signaling (SB-431542) *Impact*: prevented the emergence of a more aggressive type of cancer ■ Inhibitors of downstream signaling events: (a) Pertussis toxin (Gαi/o-protein and PKC inhibitor) (b) U-73122 (G-protein β and γ inhibitor) (c) Wortmannin (PI3K inhibitor) (d) PI-103 (PI3Kp110α inhibitor) (e) TGX221 (PI3Kp110β inhibitor) (f) SU6656 (Src inhibitor) (g) PF-573228 (FAK inhibitor) *Impact*: significantly inhibited the cancer cell migration and invasion	[22–24,117–120]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Patho-physiological events	Underlying mechanisms	Therapeutic potential/implications	Reference
Oral squamous cell carcinoma[a]	■ Tumor development, invasion, and metastasis	■ CXCL13-CXCR5/c-JNK/NFATc3-RANKL in OSCC ■ CXCL13-CXCR5/c-MYC/NFATc3-RANKL in stromal/preosteoblast cells ■ Increased MMP-9 expression	**RNA interference** ■ shRNA knock-down of CXCL13 ■ siRNA suppression of c-Myc *Impact*: inhibited the CXCL13-induced RANKL and NFATc3 expression **Pharmacological intervention** ■ Anti-CXCR5 antibody *Impact*: abrogated the CXCL13-induced RANKL expression in OSCC and stromal cells	[21,121–123]
Gastric cancer[a,c]	■ Large tumor size	■ Not yet studied	■ Not yet studied	[124]
Hepatocellular carcinoma[a]	■ Correlated with large tumor size, metastasis, and tumor grade	■ Not yet studied	■ Not yet studied	[125]
Renal cell carcinoma[a,b]	■ Correlated with proliferation, migration and malignant stage ■ Correlation with poor prognosis	■ Activation of PI3K/Akt/mTOR pathway	**RNA interference** ■ siRNA-mediated knockdown of CXCR5 *Impact*: inhibited the CXCL13-regulated proliferation and pro-migration of renal cancer cells	[126]
Neuroblastoma	■ Pro-tumor effects	■ Not yet studied	■ Not yet studied	[19,127]
Leukemias[d]	■ Chemotaxis ■ Tumor cell homing ■ Shaping of a survival niche ■ Resistance to apoptosis	■ CXCL13-CXCR5/PI3K and p44/42 MAP kinase (ERK1/2) signaling events ■ CXCL13-CXCR5/PEG10 - stabilizes caspase-3 and caspase-8 (apoptotic resistance)	**Pharmacological intervention** ■ Anti-CXCL13 and -CXCR5 antibodies ■ Pertussis toxin ■ Wortmannin *Impact*: inhibited the CXCL13-induced chemotaxis/migration of B-CLL cells	[82,83,86,87]
Multiple myeloma	■ Tumor invasion and migration	■ p53/miRNA19a/CXCR5	■ miR19a knockdown abrogated the invasion and migration	[128]
Lymphomas[e,b]	■ Pathogenesis, survival, proliferation and dissemination	■ $CXCR5^+$ $CD4^+$ T cell-mediated pro-tumor effects/IL-10 secretion (DLBCL) ■ *CXCR5* polymorphisms (NHL)	■ Anti-IL-10 antibody compromised the $CXCR5^+$ $CD4^+$ T cell-mediated pro-tumor effects	[92,98]

AhR, aryl hydrocarbon receptor; B-ALL, B-cell acute lymphocytic leukemia; B-CLL, B-cell chronic lymphocytic leukemia; BaP, benzo(a)pyrene; CNS, central nervous system; EMT, epithelial mesenchymal transition; ERK, extracellular signal-regulated kinase; HIF-1, hypoxia-inducible factor 1;JNK, c-Jun N-terminal kinase-1; MMP, matrix metalloproteinase; NK, natural killer; NF-kB, nuclear factor-kappa beta; NFATc3, nuclear factor of activated T-cells cytoplasmic 3; OSCC, Oral squamous cell carcinoma; PDE5, phosphodiesterase 5; PEG10, paternally expressed gene 10; PI3K, phosphoinositide-3-kinase; PKCε, protein kinase C epsilon; PTEN, phosphatase and tensin Homologue; SAPK, stress-activated protein kinase; SMAD, small mothers against decapentaplegic; SPP1, secreted phosphoprotein 1; T-ALL, T-cell acute lymphocytic leukemia; TGF-β, transforming growth factor-beta; TNF, tumor necrosis factor.

[a] CXCL13 and/or CXCR5 identified/proposed as independent prognostic biomarkers.

[b] CXCL13 proposed as a diagnostic tumor marker.

[c] CXCL13 proposed as a prognostic marker for adjuvant chemotherapy response.

[d] Such as B-ALL, B-CLL, T-ALL.

[e] Such as Angioimmunoblastic T-cell lymphoma, extranodal NK/T-cell lymphoma, diffuse large B cell lymphoma (DLBCL), HIV-associated non-Hodgkin B-cell lymphoma (AIDS-NHL), CNS lymphoma, cutaneous B-cell lymphoma, primary intraocular lymphoma, gastric lymphoma.

4.2. CXCL13-CXCR5 signaling axis in solid tumors

Enhanced expressions of CXCL13 and/or CXCR5 are tightly associated with the worse prognosis of many solid tumors (Table 1). Similar to that of hematological malignancies, solid tumor cells also utilize CXCL13/CXCR5 signaling as a central axis to integrate multiple intracellular signaling events and the cellular cross-talks which are involved in their acquired ability for invasive growth and metastases (Table 1).

4.2.1. Prostate cancer

Prostate cancer represents a particular example of solid tumor malignancies for which the underlying molecular events of CXCL13/CXCR5 signaling have been studied relatively in more detail [22,24,117,120,129]. CXCL13:CXCR5 interactions in the prostate tumor microenvironment may initiate divergent cell-signaling cascades, such as ERK, PI3K/Akt, stress-activated protein kinase (SAPK)/c-jun kinase (JNK), Rac, and protein kinase C epsilon (PKCε)/nuclear factor-kappa B (NF-kB), which ultimately lead to proliferative and migratory/invasive phenotypes of prostate tumor cells [23,117–119]. CXCL13 has been identified as a *bona fide* effector of PKCε in prostate cancer cells [117]. Upon stimulation by stromal-derived CXCL13, CXCR5 couples to Gα subunits and thus stimulates phospholipase C (PLC)/diacylglycerol (DAG)/PKCε signal transduction [36,117]. PKCε overexpression and Akt activation due to Pten (a tumor suppressor) loss may up-regulate the production of CXCL13 by prostate tumor cells, *via* a non-canonical NF-kB-mediated transcription of the *CXCL13* gene (Fig. 1) [117]. The increased CXCL13 secretion may then contribute to CXCR5 signal amplification, and eventually results in a cell-autonomous autocrine loop, which aids the growth, tumorigenic activity, migration and metastasis of prostate cancers [117]. Another study showed that CXCL13 produced by both cancer and stromal cells (specifically cancer-associated myofibroblasts) may create a pro-tumorigenic environment, leading to B-cell recruitment and castration-resistant prostate cancer [22]. CXCL13 has also been identified as a downstream target gene of androgen receptor (AR) [129]. The androgen/AR-induced overexpression of CXCL13 may increase the production of cyclin B1, Ets-1 and Snail in prostate cancer cells. This subsequently promotes cell cycle and cell phase (G2/M) transition, as well as enhances AR-mediated prostate tumor cell growth, proliferation, endothelial-mesenchymal transition (EMT), migration and invasion [129]. However, the underlying mechanism of CXCL13/CXCR5 signaling to regulate the expression of cyclin B1, Ets-1 and Snail has not yet been elucidated.

4.2.2. Breast cancer

CXCL13/CXCR5 signaling promotes progression and lymph node metastases of breast cancer [20,114–116,130]. Previously, two genetic knockdown studies [113,131] have linked the up-regulated expression of CXCR5 to the development and metastasis of breast tumor cells. A recent study [112] has demonstrated the connections between CXCL13/CXCR5 signaling and ERK-mediated release of inflammatory cytokines IL-1β and TNF in breast cancer. IL-1β and TNF may contribute to breast cancer progression through regulation of different transcriptional networks [132]. In addition, CXCL13/CXCR5 signaling may enhance the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in breast cancer cells. RANKL is a member of TNF-family, which can stimulate Src kinase/PI3K/Akt and Src kinase/ERK pathways *via* increased c-Src phosphorylation [133]. Following an autocrine mode of action, CXCL13/CXCR5-derived RANKL-Src kinase/PI3Kp110α signaling may up-regulate matrix metalloproteinase (MMP)-9 and different EMT regulators in breast tumor cells, which eventually promotes their migration and invasion [20]. Nevertheless, the downstream signaling events and transcriptional machinery which regulate CXCL13/CXCR5-induced RANKL expression in breast cancer cells still remains investigative.

4.2.3. Oral squamous cell cancer (OSCC)

OSCC are malignant tumors with local bone invasion/osteolysis. Elevated levels of CXCL13 and CXCR5 within the tumor-bone microenvironment of OSCC tumors are highly correlated with the osteolytic process and metastasis [21,121,122,134]. CXCL13/CXCR5-derived RANKL signaling is also crucial to the metastases of OSCC tumors [21,122]. RANKL acts as a critical osteoclastogenic factor and induces high levels of MMP-9 expression in OSCC, as well as in stromal/preosteoblast cells [21,122,123]. In OSCC tumor cells, CXCL13/CXCR5-mediated induction of RANKL involves up-regulation of JNK activity, which subsequently follows activation and nuclear translocation of nuclear factor of activated T cells c3 (NFATc3) transcription factor [122]. Nevertheless, in stromal/preosteoblast cells, the signaling occurs through c-Myc/NFATc3 pathway [21]. Whatsoever, NFATc3 serves as a downstream target for CXCL13/CXCR5 axis to enhance RANKL expression in the OSCC tumor-bone microenvironment [21,122].

4.2.4. Other solid tumor malignancies

CXCL13/CXCR5 axis has been linked to benzo(a)pyrene (BaP)-a key carcinogen present in cigarette smoke and air pollution-induced lung carcinogenesis [110]. CXCL13 serves as a direct target of aryl hydrocarbon receptor (AhR), which is critical for the carcinogenic action of BaP [135]. In lung cancer, CXCL13:CXCR5 interactions may induce the production of secreted phosphoprotein 1 (SPP1) by tumor-associated macrophages (TAMs) [110]. The SPP1 may form a positive feedback loop network *via* activation and nuclear localization of β-catenin in epithelial and cancer cells, thereby promoting EMT and lung cancer progression [110]. In colon or colorectal cancer, CXCL13/CXCR5 signaling axis may promote the pathogenesis, migration and invasion of tumor cells through secretion of MMP-13, *via* PI3K/Akt pathway [105,106]. Similarly, a recent study by Zheng et al. [126] has also linked the CXCL13/CXCR5-mediated activation of PI3K/Akt pathway with enhanced progression of clear cell renal cell carcinoma (Table 1).

Overall, the data discussed above provides a strong evidence for pleiotropic central role of CXCL13/CXCR5 axis within the tumor microenvironment, by which, it integrates multiple signaling events that promote tumor cell proliferation, survival, and migration.

5. CXCL13-CXCR5 signaling axis, cancer immunity and immune evasion

Cancer cells are usually recognized by innate and adaptive components of host immune system and destroyed, a process called tumor immunosurveillance [136–138]. The effector mechanisms of tumor immune-surveillance are complex and driven by a dynamic network of intercellular mediators such as cytokines, chemokines and inflammatory enzymes [139]. To this context, chemokines are the key regulators of immune cell trafficking within the tumor microenvironment and significantly contribute to the initiation and execution of antitumor immune responses [5,140]. On the other hand, tumors can evade the host tumor immune-surveillance [138,141,142] by mechanisms involving a variety of immune-suppressive regulators (particularly the myeloid-derived suppressor cells (MDSCs) and T regulatory (Treg) cells) and immunoinhibitory mediators (such as enzymes, molecules, cytokines, *etc.*) [143]. To this end, the recruitment of immunosuppressive MDSCs and Treg cells to the tumor microenvironment is also mediated by different chemokine signaling networks [5]. This indicates the chemokine signaling within tumor microenvironments may be context-dependent *i.e.* neither entirely beneficial nor entirely harmful for the host tumor immune-surveillance. Looking from the perspective of CXCL13/CXCR5 axis, preliminary evidence emerged in recent years also highlight the “context-dependent” functioning of this pathway while characterizing its involvement in both the antitumor immune-surveillance, as well as tumor immune-evasion mechanisms (Fig. 3).

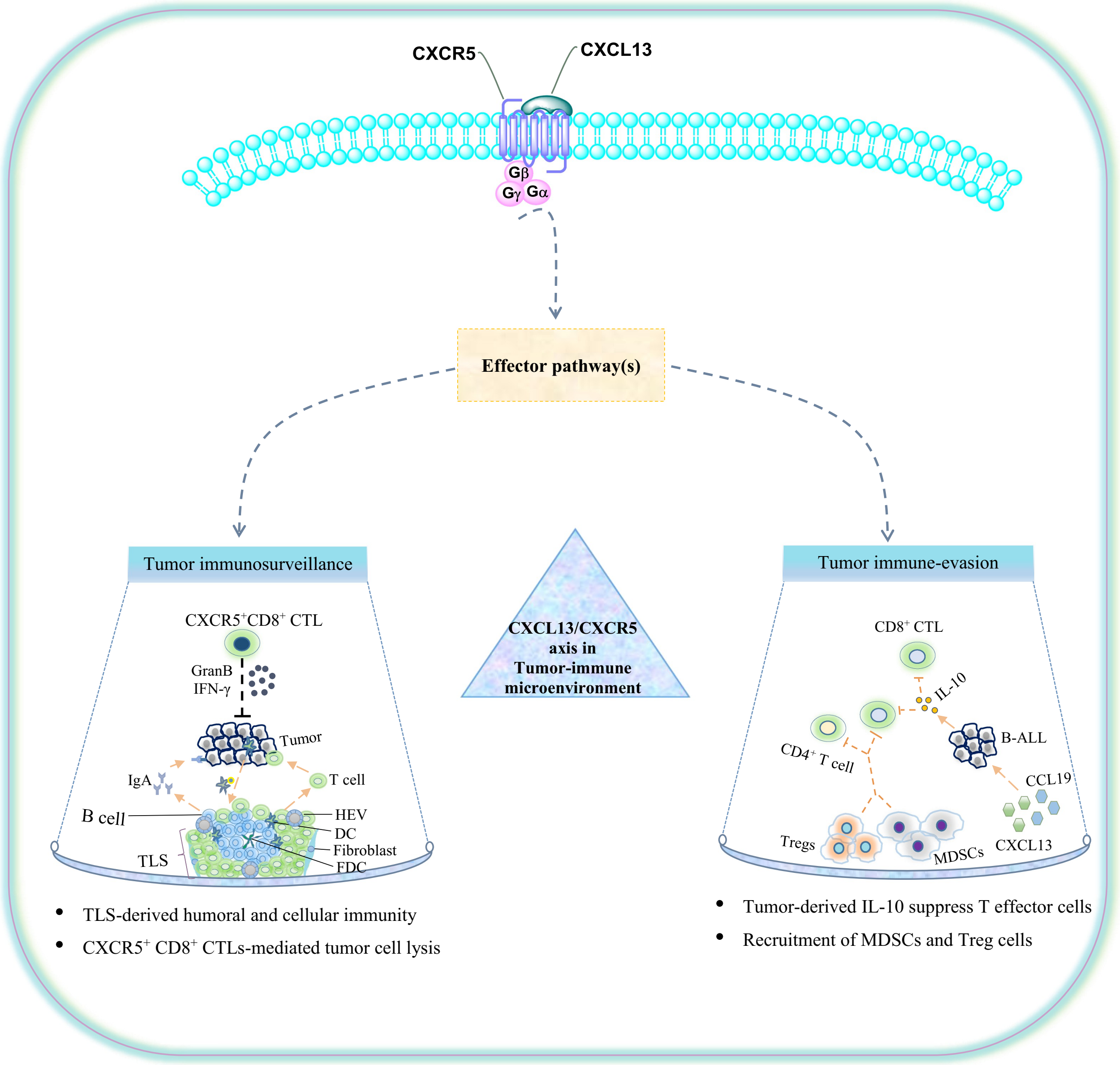

Fig. 3. A brief description of the potential dichotomy of CXCL13/CXCR5 axis within the tumor-immune microenvironment. B-ALL, B cell acute lymphocytic leukemia; CTL, cytotoxic lymphocyte; DC, dendritic cell; FDC, follicular dendritic cell; GranB, granzyme B; HEV, high endothelial venule, IFN, interferon; Ig, immunoglobulin; IL, interleukin; MDSCs, myeloid derived suppressor cells; Tregs, T regulatory cells; TLS, tertiary lymphoid structure.

5.1. CXCL13/CXCR5 axis and antitumor immunity

CXCL13/CXCR5 signaling axis is vital for immune cell trafficking to the tumor microenvironment. Because of its ability to recruit circulating CXCR5$^+$ B-cell and CXCR5$^+$ CD4$^+$ T$_{FH}$ -cell populations to the site, CXCL13 is considered as the main orchestrator and organizer of TLSs formation in different tumor tissues [144,145]. With functional TLSs in place, efficient antigen presentation, cell activation and differentiation occurs for development of both a humoral and cell-mediated immune response against tumors (Fig. 3) [144,145]. Apart from this, the presence or absence of CXCR5 receptor has emerged as critical determinant of antitumor activity of CD8$^+$ CTLs. CD8$^+$ CTLs are key elements of the tumor immunosurveillance which kill tumor cells by lysosomes/proteases system (the perforin/granzyme B) and also secreting the tumoricidal lymphokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) [136]. Several studies have indicated that CXCR5$^+$ CD8$^+$ T cells demonstrate more potent proliferative capacity, granzyme B production, TNF-α and IFN-γ expression, and thereby specific lysis of tumor cells compared to CXCR5$^-$ CD8$^+$ T cells in different types of tumor tissues, including: colorectal cancer [146,147], FL [148], pancreatic cancer [149], DLBCL [150], thyroid cancer [151], and hepatocellular cancer [152]. Moreover, an upregulated expression of CXCR5 in NK cells has been postulated to be involved in their intratumoral recruitment to lung tumor tissues [153].

5.2. CXCL13/CXCR5 axis and tumor immune-evasion

CXCL13/CXCR5 axis may also help tumor cells to evade host immune-surveillance *via* down- or negative-regulation of T effector cell-mediated antitumor immunity (Fig. 3). CXCL13/CXCR5 axis may indirectly assist malignant cells to escape from T effector cell immunity through induction of IL-10 pathway. For instance, the CCL19/CXCL13-induced synergistic upregulation of IL-10 from B-ALL CD23$^+$ CD5$^+$ B cells could hamper tumor-specific CTLs response of syngeneic CD8$^+$ T cells *in vitro* [154]. Consistent with this, CXCR5$^+$ CD4$^+$ T cells have been shown to assist in the growth and survival of DLBCL malignant cells through IL-10 secretion [92]. Moreover, CXCL13/CXCR5 axis is actively involved in the recruitment of immunosuppressive MDSCs and

Treg cells within the tumor microenvironment, which act as negative regulators of tumor immunosurveillance. A preliminary evidence by Ding et al. [155] indicated that CXCL13/CXCR5-mediated recruitment of CD40$^+$ MDSCs may stimulate gastric tumor growth, by enabling immune evasion, *via* inhibition of T cell expansion within the tumor microenvironment. Chen et al. [156] demonstrated that histidine decarboxylase (HDC)-expressing myeloid cells-derived CXCL13/CXCR5 axis recruits Foxp3$^+$ Treg cells in colorectal carcinogenesis, which can suppress CD8$^+$ CTLs-mediated tumoricidal immunity. In FL, Treg cells have been shown to auto-regulate their own chemotaxis *via* a CXCL13/CXCR5 autocrine loop network, and thus contribute to expansion of malignant cells through suppression of effector T cell activity [157]. Similarly, CD4$^+$ CXCR5$^+$ Foxp3$^+$ follicular Treg cells have been demonstrated to suppress CD8$^+$ T cell proliferation in DLBCL [158].

6. Therapeutic potential of CXCL13/CXCR5 targeting in cancer

From a therapeutic perspective, recent and past reports highlight the potential benefits of targeting the CXCL13/CXCR5 pathway in various cancers (summarized briefly in Table 1). The genetic knockdown/suppression data emerged in last few years, encompassing the neutralization of overexpressed CXCL13 and/or CXCR5 activities *via* small interference RNAs (siRNA or shRNA) or RNA-mediated genetic interference (RNAi), have manifested the therapeutic potential/validation of this pathway in different types of human cancers [105,110,117,123] (Table 1). Pharmacologically, although small-molecule inhibitors that could directly target CXCL13 or CXCR5 have not yet been discovered, several attempts have been made to disrupt this signaling axis in various cancers with promising results. Many of the interventions were designed to directly target the ligand, CXCL13 or its receptor, CXCR5, through use of inhibitory antibodies, while a few other interventions were comprised of the pharmacological inhibition of up- or down-stream signaling events with a resultant effect on cancer chemotaxis, proliferation, invasion and metastasis (Table 1).

Some unconventional methods have also been used to block the CXCL13/CXCR5 signaling within the tumor microenvironment. Drug-loaded nanoparticles have recently been reported in the treatment of cancers with encouraging results [159]. Silica nanoparticles loaded with snake (*Walterinnesia aegyptia*) venom have demonstrated induced apoptosis and inhibited growth in human prostate cancer cells [160], and remarkably reduce the levels of several chemokines (including CXCL13) and their receptors (CXCR5 inclusive) with a concomitant reduction in chemokine-mediated migration in prostate and breast cancers [161]. Another approach was using the CXCL13-KDEL intrakine to trap CXCL13 in the endoplasmic reticulum in order to inhibit CXCR5 function [109]. Although this approach could not inhibit the initial colon tumor growth in the liver, it later arrested its prolonged growth [109].

7. Concluding remarks

To be more precise, the biologic effects of CXCL13/CXCR5 signaling axis within the tumor microenvironment are complex and potentially context-specific. This pathway may enhance tumor development and progression *via* different mechanisms in different tumor settings (Table 1). The context-specific functioning particularly refers to the potential dichotomy of this pathway with respect to antitumor immunosurveillance and tumor immune-evasion mechanisms. On one hand, this pathway seems contributing the endogenous antitumor immunity by enhancing the cytolytic capacity of CD8$^+$ CTLs, while on the other hand, it appears to potentially facilitate the down/negative regulation of T cell-dependent immunity *via* chemoattraction of immunoregulatory MDSCs and Treg cells within the tumor microenvironment. Therefore, in the context of generating novel therapeutics, it will be important to balance the positive and negative effects of enhancing or inhibiting the underlying signaling events that would result from the therapeutic targeting or manipulation of this pathway.

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Conflict of interest

The authors have no conflict of interest.

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