Potential Role of CXCL13/CXCR5 Signaling

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Immunotherapy is currently the backbone of new drug treatments for many cancer patients. CXC chemokine ligand 13 (CXCL13) is an important factor involved in recruiting immune cells that express CXC chemokine receptor type 5 (CXCR5) in the tumor microenvironment and serves as a key molecular determinant of tertiary lymphoid structure (TLS) formation.

CXCL13/CXCR5 immune cells cancer

1. The Expression and Implications of CXCL13/CXCR5

CXCL13 is a chemoattractant that selectively interacts with its receptor, CXCR5, to promote the migration of $CXCR5^+$ cells toward high CXCL13 concentration areas. CXCL13 was originally identified as B cell attracting chemokine 1(BCA-1) and was shown to act on $CXCR5^+$ B cells to induce chemotaxis and Ca^{2+} mobilization [1]. In lymph nodes, the CXCL13/CXCR5 axis is essential for homing B lymphocytes to lymphoid tissue, and CXCL13/CXCR5 deficient mice show the disrupted localization of B cells [1].

CXCL13 recruits B cells to tumors, where they form tertiary lymphoid structures (TLSs) [2]. TLSs are similar to secondary lymphoid organs on the cellular, morphological, and molecular levels, and TLSs are considered with good prognostic markers, commonly associated with better survival rates. However, the mechanisms underlying TLS development remain unclear. Rodriguez et al. found that the organization of cancer-associated fibroblasts into reticular networks depends on tumor necrosis factor receptor signaling, which acts as a lymphoid tissue organizer [3]. Cancer-associated fibroblasts secrete CXCL13 to recruit $CXCR5^+$ B cells expressing lymphotoxin-α1β2, which expands TLSs in the tumor microenvironment. Moreover, $CD8^+$ T cells mediate cancer-associated fibroblast organization, serving as an inducer of lymphoid structures to drive the formation of TLSs.

$CXCR5^+$ T cells were originally defined as $CD4^+$ memory-like T cells, which function to assist B cells with antibody production. The colocalization of CXCL13, $CXCR5^+$ T cells, and B cells was detected in the follicular mantle zone. A unique subset of T cells that assist in B cell function was identified as T_{FH} cells [4]. High levels of BCL6 drive T_{FH} differentiation, and Blimp-1 is able to block T cells from differentiating into T_{FH} cells [5].

T_{FH} cells are the major CXCL13-producing cells in the lymphoid structure. In tumor microenvironments, tumor-infiltrating CXCL13-producing T_{FH} cells may be involved in promoting local B cell localization, differentiation, and maturation [6]. An activated germinal center of B cells then contributes to the formation of TLSs in tumors. Gu-Trantien et al. first observed CXCL13 producing T_{FH} cells in breast cancer and found that the T_{FH} signature

strongly predicted a positive clinical outcome in breast cancer [7]. Naïve $CD4^+$ T cells differentiate into T helper 1 (Th1)-oriented T_{FH} cells that produce CXCL13 in tumor microenvironments after being primed by antigen-presenting cells in the lymph node [8][9]. The balance of T_{FH}/Th1 differentiation from precursor cells is determined by the competitive expression of Bcl6 and T-bet [5][10][11][12]. Further investigation revealed that tumor-infiltrating T_{FH} cells produce CXCL13 to attract $CXCR5^+$ $CD8^+$ T cells and $CXCR5^+$ B cells toward the germinal centers within the TLS, where both T cells and B cells are primed, reinforcing their cytotoxic capacity against cancer cells [13]. These studies indicate that BCL6-dominant signaling promotes CXCL13 expression in T_{FH} cells [14]. Another subset of T_{FH} cells, which were PD-$1^{hi}CXCR5^{-}CD4^+$ T cells that expressed CXCL13, did not show elevated BCL6 expression.

In addition to T_{FH} cells, there are several CXCL13 producing cells in lymphoid tissue and would secrete CXCL13 to chemoattract cells that express CXCR5. Denton et al. identified pulmonary fibroblasts as CXCL13-producing cells induced by Type I interferon (Type I IFN) during Influenza A virus transfection, which facilitate the recruitment of $CXCR5^+$ B cells and T cells to the lungs to generate pulmonary germinal centers [15].

Antigen-specific $CD4^+$ T cells mediate and coordinate immune cell functions in antitumor activities. Although the effects of ICI have been thoroughly explored in $CD8^+$ T cells, the roles played by $CD4^+$ T cells in response to ICI remain poorly understood. Balança et al. studied exhausted $CD4^+$ T cells in head and neck, cervical, and ovarian cancers [16]. With exhausted $CD4^+$ T cells defined as those cells presenting high PD-1 and CD39 levels, which were found to secrete CXCL13 and express the transcription factor thymocyte selection-associated high mobility group box (TOX). The transcription factor SRY-box transcription factor 4 (SOX-4) mediates CXCL13 production on $CD4^+$ T cells, enriching transforming growth factor-β (TGF-β) and reducing IL-2 expression [17]. Similar to $CXCL13^+$ exhausted $CD8^+$ T cells, exhausted $CD4^+$ T cells recruit B cells and promote the formation of TLS, suggesting a good response to immunotherapy and indicating a crucial role for $CD4^+$ T cells in mediating the functions of various immune cells.

Cytotoxic $CD8^+$ T cells are the strongest effectors, playing important roles in the anticancer immune response. When examining the CXCL13/CXCR5 axis, Workel et al. found that TGF-β dependent $CD103^+CD8^+$ tumor-infiltrating T cells represent an important CXCL13 resource [18]. When TGF-β receptors are inhibited, CXCL13 signaling is abrogated. $CXCL13^+CD103^+CD8^+$ tumor-infiltrating T cells are associated with B cell recruitment, TLS formation, and neoantigen burden. Additionally, Thommen et al. also found that PD-$1^{high}CD8^+$ tumor-infiltrating T cells produce more CXCL13 than PD-$1^{-}CD8^+$ T cells in non-small-cell lung cancer (NSCLC) [19]. They also observed that CXCL13 recruited other CXCR5-expressing immune cells and induced the formation of TLSs in NSCLC. PD-$1^{high}CD8^+$ tumor-infiltrating T cells are enriched inside the TLS, and their presence successfully predicts the response to anti-PD-1 and is positively correlated with overall survival.

In chronic hepatitis B infection, Li et al. found that higher levels of CXCL13 facilitate the recruitment of $CXCR5^+CD8^+$ T cells to liver tissue in patients, which is associated with a favorable response to antiviral drug treatment [20]. $CXCR5^+CD8^+$ T cells secrete hepatitis B virus (HBV)-specific cytokines, such as IL-2, IFN-γ, IL-17, and IL-21. The subset of $CD8^+$ T cells is partially exhausted but not dysfunctional and is involved in controlling the viral infection load. Strikingly, the adoptive transfer of $CXCR5^+CD8^+$ T cells to an HBV mouse model resulted in a

significant decrease in HBV antigen expression. Finally, they found that B cell-deficient mice have a lower frequency of $CXCR5^+CD8^+$ T cells and decreased the HBV-specific IFN-γ^+ $CXCR5^+CD8^+$ T cells in the blood and liver. These data demonstrated that B cells are required for $CXCR5^+$ $CD8^+$ T cells, contributing to the functions and activities of $CXCR5^+CD8^+$ T cells.

In classical Hodgkin lymphoma, Le et al. identified a special $CD8^+$ T cell subset expressing CXCR5 and an inducible T cell costimulator (ICOS) [21]. This subset was functionally similar to T_{FH} cells, with low CCR7 expression and high levels of BCL6, PD-1, CD200, and OX40 expression. In addition, these cells displayed poor cytotoxic function and low interferon-secretion and produced IL-4, IL-21, and CXCL13, similar to $CD4^+$ T_{FH} cells. Gene profiling analyses demonstrated that $CXCR5^+ICOS^+CD8^+$ T cells are significantly similar to $CD4^+$ T_{FH} cells and are involved in the generation of lymphoma tumors with residual germinal centers. Overall, $CD8^+$ T cell differentiation pathways are functionally similar to those involved in $CD4^+$ T_{FH} cell differentiation in Hodgkin lymphoma.

Follicular dendritic cells represent the primary cellular source of cytokines in lymphoid organs [22]. Previous research has identified that various dendritic cell subsets are able to secrete CXCL13, playing an important role in the establishment of interactions between lymphocytes and dendritic cells [23]. Additionally, CXCL13 serves as a plasma biomarker that reflects germinal center activity [24]. Follicular dendritic cells represent the primary source of CXCL13 expression in reactive tonsils and lymph nodes located in the B cell zone. Moreover, dysplastic and neoplastic follicular dendritic cells are able to secrete CXCL13 to recruit lymphocytes to areas of dense inflammatory infiltration [22]. Overall, dendritic cells secrete CXCL13 to recruit $CXCR5^+$ lymphocytes, orchestrating the immune response in lymphoid tissues.

Prior findings regarding CXCL13 and CXCR5 expression were summarized. $CD8^+$ and $CD4^+$ T cells, cancer-associated fibroblasts, cancer cells, and dendritic cells are able to secrete CXCL13, and $CD8^+$ and $CD4^+$ T cells, B cells, and cancer cells express CXCR5 (**Figure 1**). Increasing research has reported the detection of CXCL13 in the tumor microenvironment of many different types of cancer [25][26][27][28][29][30][31]. When the cancer microenvironment is enriched in CXCL13, the recruitment of CXCR5-expressing leukocytes to the tumor microenvironment increases. B cells are recruited by CXCL13 to promote TLS formation in the tumor microenvironment (**Figure 2**). Previous studies have correlated TLS formation with better prognosis among patients with cancer [32][33][34][35]; therefore, treatments that promote the development of TLSs represent potential therapeutic strategies.

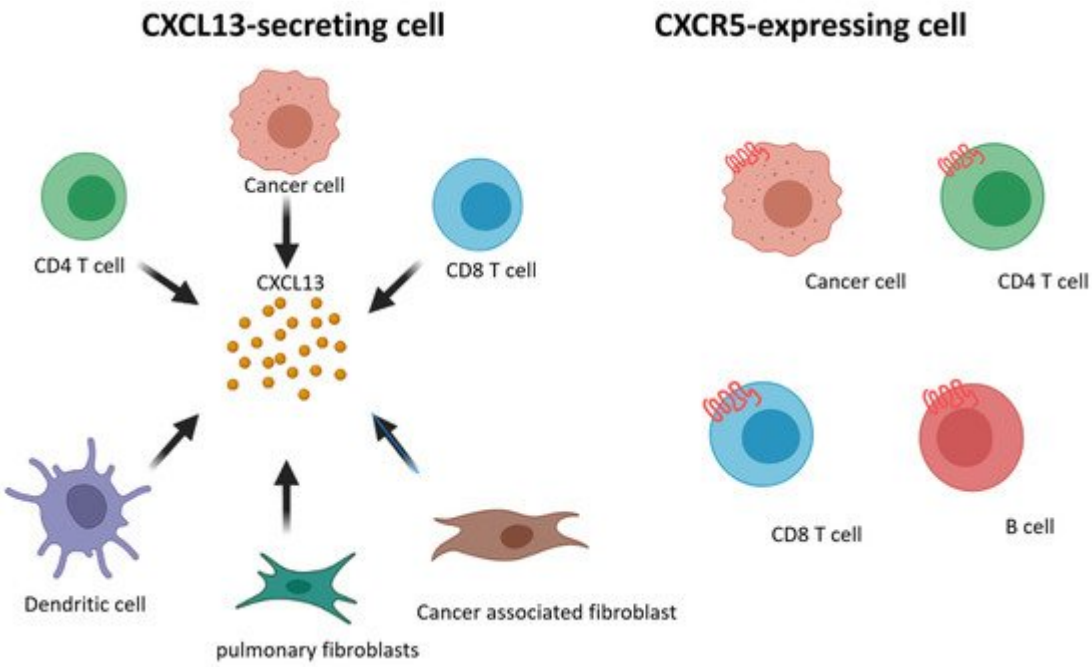

Figure 1. Schematic representation of CXCL13 and CXCR5 expressing on different cell subsets.

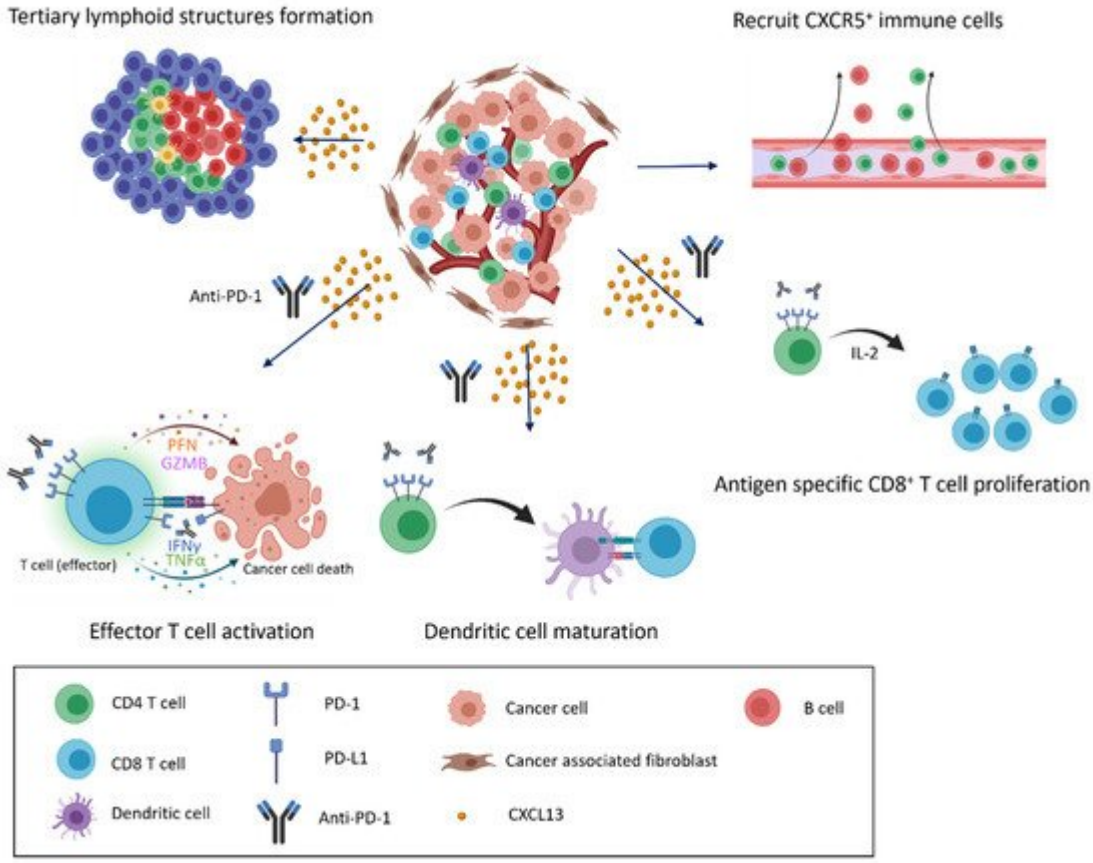

Figure 2. CXCL13/CXCR5 signaling and response to immune checkpoint blockade in the tumor microenvironment. CXCL13 secretion and enrichment in the tumor microenvironment alter the immune cell composition. CXCL13 recruits cells that express CXCR5 to infiltrate the cancer microenvironment, inducing the formation of tertiary lymphoid structures and the further infiltration of various immune cells (**top**). When anti-PD-1 antibodies are

present, recruited immune cells actively attack cancer cells, and exhausted cells transition into effector cells, leading to the proliferation of $CD8^+$ T cells and the maturation of dendritic cells in response to anti-PD-1 treatment (**bottom**).

2. CXCL13/CXCR5 Axis for ICI Response in Clinical Tumors

Immune checkpoint blockade can regulate tumor progression. Compared with chemotherapy, ICI therapy has a superior duration of response (20.4 months vs. 6.3 months) [36][37]. However, only 15–20% of patients benefit from immunotherapy [37] and the identification of biomarkers able to predict therapeutic response to ICI. Recently, some biomarkers were identified that were able to accurately predict the response of cancer patients to PD-1 blockade. Le et al. proposed that patients with mismatch repair deficiencies have a higher response rate to pembrolizumab treatment than patients with proficient mismatch repair processes [38]. In this section, clinical trials and research linking the CXCL13/CXCR5 axis with the ICI response in patients were summarized (**Table 1**).

Table 1. Cancer immunotherapy approaches relative to the CXCL13/CXCR5 axis based on clinical data.

Target in the Axis	Treatment	Disease	Method of Detection	Number of Patients Investigated	Value	Outcome
$CXCL13^+PD1^+CD8^+$ T cells	Anti-PD-1	Non-small cell lung cancer	Transcriptome analysis	Peripheral blood of healthy donors (n = 6) Fraction of PD-1^{bright} within $CD8^+$ TILs (n = 24)	Favorable	The presence of PD-1^+CD8^+ T cells can predict PD-1 blockade response and survival rate [19].
CXCL13	Anti-PD-1 Anti-PD-L1	Metastatic urothelial carcinoma and bladder cancer	Whole-exome sequencing data analysis TCGA analysis	CheckMate275 (n = 270) IMvigor210 (n = 310)	Favorable	CXCL13 expression plus ARID1A mutation work together to predict a favorable response to anti-PD-1 blockade [31].
CXCL13	Anti-PD-L1	Bladder cancer	Single-sample GSEA Gene ontology analysis	IMvigor210 (n = 310)	Favorable	CXCL13 expression plus TLS formation

Target in the Axis	Treatment	Disease	Method of Detection	Number of Patients Investigated	Value	Outcome
			KEGG analysis WGCNA			predict a favorable response to anti-PD-1 blockade [39].
$CXCL13^+/LAG3^+CD8^+$ T cells	Anti-PD-1 Anti-PD-L1	Hepatocellular carcinoma	Multiplex immunofluorescence staining TCGA-LIHC analysis Nanostring RNA analysis	Cohort 1 (*n* = 24) Cohort 2 (*n* = 18)	Favorable	CXCL13 expression plus exhausted T cells marker expression predict a favorable response to anti-PD-1 blockade [40].
$CXCL13^+CD8^+$ T cells $CXCL13^+CD4^+$ T cells	Anti-PD-1 Nab-Paclitaxel	Triple-negative breast cancer	ATAC-seq RNA-seq Single-cell RNA seq Whole-exome sequencing IHC	*n* = 22	Favorable	High levels of baseline $CXCL13^+$ T cells predict favorable response to anti-PD-L1 plus nab-paclitaxel combination therapy [41].
CXCL13 in $CD8^+$ T cells	Anti-PD-L1, Anti-PD-1, Anti-CTLA4	Seven cancer types	Single-cell RNA-seq ATAC-seq	*n* = 1008	Favorable	CXCL13 expression is a marker of clonal neoantigen-specific $CD8^+$ TILs that selectively expresses in CPI responders ("CR/PR"). [42].

2.1. Breast Cancer

Target in the Axis	Treatment	Disease	Method of Detection	Number of Patients Investigated	Value	Outcome
CXCL13 in tumor cells	Anti-PD-1	Pan-cancer	Nanostring RNA analysis IHC Gene expression profiles	NCT01295827 (n = 1260) NCT01848834 (n =297) NCT02054806 (n = 477)	Favorable	T cells expanded signature including CXCL13 and 17 other genes are necessary for clinical response to PD-1 checkpoint blockade [43].

[7] ... FH-related ... divided ... minimal ... ene. IHC ... nd CD4+ ... S) of 794 ... n breast ... cohort of ... pression ... omes for anti-PD-L1 blockade therapy in triple-negative breast cancer (TNBC) [41]. Twenty-two patients with late-stage TNBC were enrolled in this cohort, divided into two groups with equal numbers. Patients in one group were treated with paclitaxel, whereas the other group received paclitaxel plus atezolizumab. After 4 weeks, tumor biopsies and [illegible] in the Ti analysis, indicating a functional change in T cells during ICI therapy. The authors clustered T cells using a high-resolution T cell map, which identified expanded CXCL13^{+}CD8^{+} and CXCL13^{+}CD4^{+} populations in patients who responded to paclitaxel plus atezolizumab but not patients who did not respond to treatment. Furthermore, the analysis of CXCL13^{+}CD8^{+} T cells using a single-cell assay for transposase-accessible chromatin using sequencing (ATAC-seq) showed that CXCL13^{+}CD8^{+} cells had more accessible chromatin regions in the *IFNG*, *GZMK*, and *PDCD1* loci.

2.2. Bladder Cancer

Goswami et al. analyzed the combined data from two clinical trials, CheckMate275 and IMvigor210, to determine the correlations of the AT-rich interactive domain containing protein 1A (ARID1A) mutations and CXCL13 expression with the patient's response to immune checkpoint blockade therapy [31]. CheckMate 275 is a phase 2 trial of nivolumab for the treatment of metastatic urothelial carcinoma (n = 265). IMvigor210 is a phase 2 trial of atezolizumab for the treatment of advanced or metastatic urothelial bladder cancer. They identified that an ARID1A mutation alone or CXCL13-high expression is correlated with favorable responses to ICI, and ARID1A mutation in combination with high levels of CXCL13 expression could predict the better response of patients to immune checkpoint blockade therapy than ARID1A mutation in combination with low levels of CXCL13 or high levels of CXCL13 in combination with ARID1A wild-type.

2.3. Non-Small Cell Lung Cancer

Thommen et al. classified $CD8^+$ TILs derived from patients with NSCLC into three groups based on their PD-1 surface-level expression [19]. PD-1^- were $CD8^+$ TILs without detectable PD-1 expression; PD-1^N were $CD8^+$ TILs with PD-1 levels similar to those observed in healthy donors; PD-1^T were $CD8^+$ TILs PD-1 with considerably high expression levels. The reactive capacity of PD-1 TILs was confirmed by co-culturing PD-1^T, PD-1^N, and PD-1^-, respectively, with autologous tumors isolated from eight patients. Among the eight patient-derived tumors, PD-1^T TILs showed strong reactivity against the tumor cells in 6 of 8 cultures. Gene expression diversity among PD-1^T, PD-1^N, and PD-1^- populations was identified by transcriptome analysis, which revealed that CXCL13 was one of the most upregulated genes in the PD-1^T subset. The authors used bead-based immunoassays to quantify inflammatory cytokine and chemokine levels in sorted PD-1^T TILs after 24h of culture, identifying that the levels of CXCL13 were the highest in the array. These data indicated that PD-1^T TILs are likely to secrete CXCL13 into the tumor microenvironment. Of 21 stage IV NSCLC patients receiving anti-PD-1 therapy, 7 patients were identified as responders, whereas the other 14 patients were identified as non-responders. Responders were characterized by TIL subsets with a higher percentage of PD-1^T TILs and total PD-1^T TIL cell numbers. Those with PD-1^T subsets > 1% of total cells were associated with longer median survival than those with PD-1^T subsets < 1% of total cells following the administration of anti-PD-1 therapy. IHC and digital image analysis suggested that PD-1^T TILs were localized in TLSs that formed both intratumorally and peritumorally. Intensive B cell marker staining and $CD4^+$ T_{FH} markers colocalized with PD-1^T TILs, implying that $CD8^+$PD-1^T TILs might recruit $CXCR5^+$ B cells and T_{FH} cells into the tumor region and that B cells, as well as T_{FH} cells, could reinforce the antitumor capacity of $CD8^+$ T cells.

2.4. Hepatocellular Carcinoma

Liver cancer is one of the world's most common cancers and the second leading cause of cancer deaths [40][44][45]. Hsu et al. established a platform to assess various biomarkers associated with prognostic efficacy for the immunotherapy response of patients with hepatocellular carcinoma (HCC) using Nanostring RNA analysis and multiplex immunofluorescence staining methods [40]. In this cohort, RNA was isolated from tumor samples before patients received anti-PD-1 or combination anti-PD-1 and anti-PD-L1 blockade therapy (n = 42). RNA was then hybridized to nCounter® probes for the 770 predefined genes featured in the PanCancer Immune Profiling Panel. They found that exhausted $CD8^+$ T cells were enriched in responders and analyzed exhausted $CD8^+$ T cells using transcriptome analysis. In this Immune Profiling Panel, nine genes expressed on exhausted T cells were positively correlated with a better response to anti-PD-1 monotherapy or combination anti-PD-1 and anti-PD-L1 therapy, including CXCL13 gene expression. In another study, the exploratory analysis identified distinct gene signatures associated with tumor response and resistance to anti-PD-1 monotherapy in HCC patients also showed that CXCL13 was positively correlated with a better response to anti-PD-1 therapy [46].

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