The CXCL5/CXCR2 Axis in Urothelial Bladder Carcinoma: Mechanistic Biology, Biomarker Evidence, and Therapeutic Prospects

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Abstract

Background: Urothelial bladder carcinoma is heterogeneous, and conventional clinicopathological variables incompletely explain recurrence, progression, and treatment resistance. C-X-C motif chemokine ligand 5 (CXCL5), which predominantly signals through CXCR2, may link malignant urothelial cells with vascular and myeloid compartments.

Objective: This narrative review evaluates the biological basis, clinicopathological evidence, biomarker potential, and therapeutic relevance of CXCL5/CXCR2 signaling in urothelial bladder carcinoma.

Experimental studies link CXCL5 to urothelial cancer-cell proliferation, migration, and invasion through PI3K/AKT, ERK1/2, Snail, and MMP2/MMP9 signaling. Tumor-endothelial crosstalk and recruitment of CXCR2-positive myeloid cells may influence angiogenesis and immunity. Tissue studies generally associate increased CXCL5 with adverse grade, stage, invasion, nodal disease, recurrence, or survival. Urinary CXCL5 is attractive as a noninvasive marker, but leukocyturia and infection reduce specificity. CXCL5-mediated epithelial-mesenchymal transition and NF-kappaB activation may contribute to mitomycin C resistance. Evidence remains dominated by cell lines, retrospective cohorts, immunohistochemistry, and database analyses. Moreover, a carcinogen-driven mouse model indicates that myeloid CXCR2 loss can accelerate early tumorigenesis, emphasizing context-dependent biology.

Conclusion: CXCL5/CXCR2 is a biologically credible but not yet validated clinical biomarker or therapeutic target in urothelial bladder carcinoma. Standardized assays, stage-specific validation, and biomarker-guided intervention studies are required before clinical adoption.

Keywords: bladder cancer; CXCL5; CXCR2; chemokines; tumor microenvironment

Introduction

Bladder cancer caused more than 600,000 new diagnoses and approximately 220,000 deaths worldwide in 2022. Urothelial carcinoma constitutes the dominant histologic type, but its clinical course ranges from repeatedly recurrent non-muscle-invasive disease to rapidly lethal muscle-invasive and metastatic cancer. This heterogeneity, together with reliance on invasive surveillance and the imperfect prognostic precision of grade and stage alone, sustains the search for biomarkers that reflect active tumor biology. [1,2]

Modern treatment includes transurethral resection and intravesical therapy for non-muscle-invasive bladder cancer, radical local treatment for muscle-invasive disease, and systemic chemotherapy, immune checkpoint inhibition, targeted therapy, or antibody-drug conjugates for selected advanced tumors. Despite this expanding therapeutic landscape, response and

resistance are strongly influenced by the tumor microenvironment. Chemokines are especially relevant because they can coordinate malignant-cell behavior, leukocyte trafficking, angiogenesis, and immune escape within the same signaling network. [3,4]

Muscle-invasive bladder cancer contains diverse molecular subtypes and immune states rather than a single biological entity. A marker such as CXCL5 therefore should not be interpreted as a stand-alone tumor-cell product. Its meaning depends on the expressing cell, the receptor-bearing compartment, tumor stage, inflammatory context, and concurrent signaling programs. The aim of this review is to integrate bladder-specific evidence on CXCL5 with mechanistic knowledge of its principal receptor, CXCR2, and to define what is established, what remains inferential, and what would be required for clinical translation. [5]

Biological Features of CXCL5 and CXCR2

Chemokines are small secreted proteins that direct cell movement through G-protein-coupled receptors. CXCL5, historically termed epithelial neutrophil-activating peptide 78, belongs to the ELR-positive CXC subgroup. The glutamic acid-leucine-arginine motif supports neutrophil chemotaxis and is commonly associated with proangiogenic activity. CXCL5 may be released by malignant epithelial cells, macrophages, neutrophils, endothelial cells, fibroblasts, and other stromal populations. Its abundance in a tumor therefore represents a composite of cancer-cell-intrinsic transcription and microenvironmental responses rather than a single source. [6–8]

CXCL5 signals mainly through CXCR2, a seven-transmembrane G-protein-coupled receptor that also recognizes several related ELR-positive chemokines. Ligand binding can activate PI3K/AKT, ERK, p38 MAPK, JAK/STAT, and NF-kappaB-associated programs. The resulting effect varies by cell type. In tumor cells, signaling may increase survival, motility, and epithelial-mesenchymal plasticity. In endothelial cells, it can promote migration and vessel formation. In myeloid cells, CXCR2 governs trafficking toward chemokine-rich tissues and may enrich neutrophils or myeloid-derived suppressor cells within tumors. [8,9]

The extracellular behavior of CXCL5 also matters. Glycosaminoglycan binding immobilizes chemokines on cell surfaces and extracellular matrix, creating gradients that guide receptor-bearing cells. The glycosaminoglycan-binding and CXCR2-interacting regions of CXCL5 overlap, so matrix association, proteolytic processing, local concentration, and oligomeric state may alter receptor availability. These features help explain why tissue staining intensity, circulating concentration, and biological activity are not interchangeable measurements. [8,9]

Tumor-Cell-Intrinsic Signaling in Urothelial Carcinoma

The most direct bladder-specific mechanistic evidence comes from cultured urothelial cancer cells. **Gao et al.** [10] found that CXCL5/CXCR2 signaling enhanced migration and invasion through PI3K/AKT-dependent upregulation of MMP2 and MMP9. These matrix metalloproteinases degrade basement membrane and extracellular matrix components, providing a plausible route from chemokine signaling to local invasion. The study also linked higher tumor CXCL5 expression with more advanced disease stage, although its experimental design does not establish that CXCL5 independently drives progression in patients. [10]

Complementary work by **Zheng et al.** [11] showed increased CXCL5 messenger RNA and protein in bladder tumor tissues and cell lines. Stable CXCL5 silencing in T24 cells reduced proliferation and migration, increased apoptosis, and altered Snail, PI3K/AKT, and ERK1/2 signaling. Together with the CXCR2-dependent invasion data, these findings support both autocrine and paracrine models: urothelial cancer cells may secrete CXCL5, respond to it through CXCR2, and reinforce signaling networks that favor survival and motility. [10,11]

CXCL5 also participates in reciprocal signaling between urothelial cancer cells and vascular endothelium. **Huang et al.** [12] reported that endothelial VEGFR2/NF-kappaB signaling increased mediators that activated EGFR pathways in bladder cancer cells, while tumor-endothelial interaction enhanced endothelial recruitment through the CXCL1/CXCL5/CXCL8-CXCR2 axis. This model connects angiogenesis to tumor growth rather than treating neovascularization as a passive consequence. It also shows why blocking one ligand may be insufficient when several ELR-positive chemokines converge on CXCR2. [12]

These studies collectively support a coherent pathway from CXCL5 secretion to receptor activation, epithelial-mesenchymal transition, matrix remodeling, endothelial recruitment, and invasion. However, the evidence is mainly based on selected cell lines and perturbation experiments. Cell lines lack the clonal diversity, stromal architecture, urinary exposure, and immune context of human tumors. The observed mechanisms are therefore biologically persuasive but require confirmation in organoids, spatially resolved human samples, and in vivo models that represent both non-muscle-invasive and muscle-invasive disease. [4,10–12]

CXCL5 in the Tumor Microenvironment

CXCL5 is a potent recruiter of CXCR2-positive neutrophils. Once present in tumors, neutrophils may release proteases, reactive oxygen species, vascular growth factors, and extracellular traps. Their effect is not uniform: neutrophil populations can support tumor growth and immune suppression, but under some conditions they retain inflammatory or antitumor functions. The biological meaning of a CXCL5-rich bladder tumor therefore depends on the phenotype and location of recruited cells, not simply their number. [4,6]

CXCR2-mediated recruitment of polymorphonuclear myeloid-derived suppressor cells offers a second route to immune

escape. These cells can restrict T-cell activity through arginase, reactive oxygen and nitrogen species, and suppressive cytokines. In experimental cancers, interruption of CXCR2-dependent myeloid trafficking improved response to programmed cell death protein 1 blockade. This finding makes combination therapy attractive, but it arises mainly outside bladder cancer and cannot be transferred directly without disease-specific validation. [13]

CXCL5 may also modify adaptive immunity through tumor-cell signaling. In lung cancer, CXCL5 increased PD-L1 through paxillin/AKT signaling and promoted neutrophil chemotaxis, with suppression of CD8-positive T-cell immunity. This provides a plausible connection among tumor CXCL5, myeloid recruitment, and checkpoint resistance. In urothelial carcinoma, however, a dense lymphocytic infiltrate can coexist with myeloid inflammation, and transcript abundance cannot determine whether infiltrating lymphocytes are cytotoxic, exhausted, excluded, or regulatory. Spatial and functional immune profiling is therefore essential before CXCL5 is used as an immunotherapy biomarker. [14]

Clinicopathological and Biomarker Evidence

Human bladder-cancer studies generally point in the same direction but vary substantially in assay design. Tissue investigations have used immunohistochemistry, quantitative polymerase chain reaction, or protein analysis, with different antibodies, scoring systems, cutoffs, and case mixtures. Most report higher CXCL5 in tumor than adjacent or normal urothelium and associations with adverse pathological features. This consistency supports biological relevance, but methodological heterogeneity limits direct comparison and prevents a universal clinical threshold. [15–17]

The largest frequently cited clinical study included 255 urothelial bladder cancers. **Zhu et al.** [15] reported that high tissue CXCL5 correlated with TNM stage, grade, and lymph-node metastasis, and was associated with overall, progression-free, and recurrence-free survival in specified analyses. The same investigation found higher urinary CXCL5 in bladder cancer than in urinary tract infection or healthy groups. Creatinine-normalized urinary CXCL5 achieved 80.4% sensitivity and 61.3% specificity, but urine leukocyte count predicted CXCL5 concentration, identifying infection and inflammation as important confounders. [15]

Two Egyptian immunohistochemical studies added clinically relevant but relatively small retrospective datasets. **Abdalla et al.** [16] associated CXCL5 expression with adverse pathological features, including lymphovascular measures assessed alongside D2-40. **Ahmed et al.** [17] evaluated 60 primary invasive and noninvasive urothelial carcinomas and found high CXCL5 expression in 45% of cases; increased expression correlated with poor differentiation (P=0.025), advanced stage (P=0.039), and invasion (P=0.002). These studies support a pathological association but did not establish reproducible independent prognostic performance across external cohorts. [16,17]

Bioinformatic evidence is more complex. Analysis of public bladder-cancer datasets by **Sun et al.** [18] confirmed increased CXCL5 messenger RNA in tumor tissue and linked CXC chemokine expression to immune infiltration and multiple regulatory networks. Yet survival signals varied across members of the chemokine family and across databases. This illustrates a central limitation: bulk messenger RNA reflects mixed tumor and stromal compartments, while platform, cohort composition, stage distribution, and cut-point selection can change the apparent prognostic association. [18]

The broader cancer literature supports caution as well as interest. A meta-analysis of 15 studies comprising 19 cohorts and 5,070 patients associated elevated CXCL5 with worse overall survival (pooled hazard ratio 1.70; 95% confidence interval 1.36-2.12), progression-free survival (1.65; 1.09-2.49), and recurrence-free survival (1.49; 1.15-1.93). Associations differed by tumor type, and bladder-specific validation was not the principal basis of the pooled estimates. Pan-cancer results therefore strengthen biological plausibility but do not substitute for prospective urothelial carcinoma cohorts. [19]

Table 1. Principal bladder-specific evidence concerning CXCL5/CXCR2

Study	Material and design	Principal findings	Main limitation
Zheng et al.[11]	Human bladder tissues, cell lines, and CXCL5-silenced T24 cells	CXCL5 was increased in tumor tissue. Silencing reduced proliferation and migration, increased apoptosis, and altered Snail, PI3K/AKT, and ERK1/2 signaling.	Primarily in vitro; dependence on a single established cell model.
Gao et al.[10]	Bladder tumor sections with mechanistic cell experiments	Higher CXCL5 accompanied advanced stage. CXCL5/CXCR2 enhanced migration and invasion through PI3K/AKT-driven MMP2/MMP9 upregulation.	Preclinical mechanism; independent clinical prognostic value was not established.
Zhu et al.[15]	IHC in 255 urothelial cancers plus urinary CXCL5 ELISA cohorts	Tissue CXCL5 correlated with stage, grade, nodal disease, and survival outcomes. Urinary CXCL5/creatinine showed 80.4% sensitivity and 61.3% specificity.	Retrospective; urine leukocytes significantly confounded CXCL5 concentration.
Wang et al.[20]	Mitomycin-resistant M-RT4 and parental RT4 bladder cancer cells	CXCL5 promoted mitomycin C resistance; knockdown restored sensitivity and attenuated EMT and NF-kappaB activation.	No patient-level or in vivo validation.
Huang et al.[12]	Bladder cancer-endothelial cell interaction experiments	Tumor-endothelial crosstalk recruited endothelial cells through CXCL1/CXCL5/CXCL8-CXCR2 signaling and activated reciprocal VEGFR2/EGFR pathways.	Preclinical; several ligands converged on CXCR2, limiting ligand-specific inference.
Abdalla et al.[16]	Single-center immunohistochemical urothelial carcinoma series	CXCL5 expression was associated with adverse pathological features and was evaluated with D2-40-based lymphatic measures.	Small retrospective cohort; assay threshold lacked external validation.
Ismail et al.[21]	Myeloid Cxcr2 deletion in OH-BBN bladder carcinogenesis plus TCGA analysis	Cxcr2 loss increased early tumor development. Low human CXCR2 mRNA was associated with worse overall survival, suggesting context-dependent protection.	Mouse initiation model and retrospective database analysis; not equivalent to pharmacological blockade in advanced disease.
Ahmed et al.[17]	IHC in 60 primary invasive and noninvasive urothelial carcinomas	High CXCL5 occurred in 45% and correlated with poor differentiation (P=0.025), advanced stage (P=0.039), and invasion (P=0.002).	Single center; limited sample size and no independent outcome model.
Sun et al.[18]	Multi-database transcriptomic analysis of bladder cancer	CXCL5 mRNA was increased in tumors and related to immune-cell infiltration and chemokine regulatory networks.	Bulk transcriptomic data; platform, cohort, and cut-point heterogeneity.

Abbreviations: CXCL5, C-X-C motif chemokine ligand 5; CXCR2, C-X-C motif chemokine receptor 2; ELISA, enzyme-linked immunosorbent assay; EMT, epithelial-mesenchymal transition; IHC, immunohistochemistry; MMP, matrix metalloproteinase; OH-BBN, N-butyl-N-(4-hydroxybutyl) nitrosamine; TCGA, The Cancer Genome Atlas.

For clinical use, a CXCL5 assay would need to add value beyond established variables. A tissue marker should be tested in multivariable models incorporating stage, grade, lymphovascular invasion, nodal status, molecular subtype, and treatment. A urinary assay should be evaluated against hematuria, pyuria, bacterial culture, renal function, recent instrumentation, and intravesical therapy. Calibration, discrimination, preanalytic stability, assay reproducibility, and clinically meaningful decision thresholds are required; a significant group difference alone is insufficient. [2,15]

Treatment Resistance and Therapeutic Targeting

CXCL5 may contribute to resistance in non-muscle-invasive disease. **Wang et al.** [20] found CXCL5 overexpression in a mitomycin C-resistant bladder cancer cell line. Recombinant CXCL5 reduced mitomycin sensitivity in parental cells, whereas CXCL5 knockdown restored sensitivity and attenuated epithelial-mesenchymal transition and NF-kappaB activation. This work suggests that CXCL5 is not only a marker of aggressive phenotype but may participate in a reversible resistance circuit. Confirmation is needed in patient-derived models and tumors collected before and after intravesical chemotherapy. [20]

The strongest reason for caution comes from bladder-specific in vivo evidence. **Ismail et al.** [21] deleted Cxcr2 in myeloid cells in an OH-BBN model of invasive bladder carcinogenesis. Cxcr2 loss reduced early myeloid recruitment but increased tumor development; low CXCR2 messenger RNA in human TCGA muscle-invasive tumors was also associated with worse overall survival. The investigators concluded that CXCR2 could have a protective role during tumor initiation by supporting acute inflammatory responses. This does not invalidate later tumor-promoting CXCL5/CXCR2 activity, but it argues against

assuming that uniform CXCR2 inhibition will benefit every stage or immune context. [21]

Several therapeutic strategies are conceivable: neutralizing CXCL5, inhibiting CXCR2, interrupting downstream PI3K/AKT or NF-kappaB signaling, or combining myeloid modulation with chemotherapy or immune checkpoint blockade. CXCR2 inhibition has reduced progression and improved cisplatin activity in lung-cancer models, and the general oncology literature supports targeting CXCR2-dependent myeloid trafficking. In urothelial carcinoma, redundancy among CXCL1, CXCL2, CXCL5, CXCL6, and CXCL8 favors receptor-level or biomarker-guided approaches over single-ligand inhibition, although broader blockade may also increase toxicity and disrupt protective inflammation. [9,21,22]

A rational clinical-development strategy would therefore require paired biomarkers. Candidate measures include tumor-cell CXCL5, stromal CXCL5, CXCR2-positive myeloid density, neutrophil phenotype, PD-L1, T-cell localization and function, and a broader ELR-positive chemokine signature. Trials should distinguish prevention or early non-muscle-invasive disease from established muscle-invasive or metastatic cancer. Pharmacodynamic tissue and urine sampling could determine whether pathway inhibition reduces suppressive myeloid recruitment without eliminating beneficial inflammatory responses. [4,21,23,24]

Methodological Gaps and Research Priorities

The evidence base has five major weaknesses. First, several pivotal studies rely on one or two cell lines. Second, retrospective immunohistochemical series use nonuniform antibodies and cutoffs. Third, many cohorts combine non-muscle-invasive and muscle-invasive tumors despite different biology and treatment. Fourth, urinary CXCL5 is confounded by leukocytes and infection. Fifth, associations with grade or stage are sometimes described as prognostic even when recurrence, progression, cancer-specific survival, or overall survival was not independently modeled. [10,11,15–18]

Future work should use multicenter cohorts with prespecified endpoints and standardized tissue handling. Digital pathology should separate tumor-cell, invasive-front, endothelial, and stromal expression and quantify intratumoral heterogeneity. Single-cell and spatial transcriptomic methods can identify the cellular sources of CXCL5 and the phenotypes of CXCR2-positive cells. Longitudinal sampling before and after bacillus Calmette-Guerin, intravesical chemotherapy, systemic chemotherapy, or checkpoint inhibition would clarify whether the pathway is prognostic, predictive, pharmacodynamic, or merely correlated with inflammation. [4,23,24]

Preclinical models should represent distinct disease phases and retain an intact immune microenvironment. Human organoids co-cultured with fibroblasts, endothelial cells, neutrophils, and lymphocytes could test ligand redundancy and cell-specific blockade. In vivo studies should compare tumor-cell-specific and myeloid-cell-specific perturbation, because the same receptor may support invasion in one compartment and protective inflammation in another. Combination experiments should include efficacy, immune composition, infection risk, wound healing, and resistance escape pathways. [12,21]

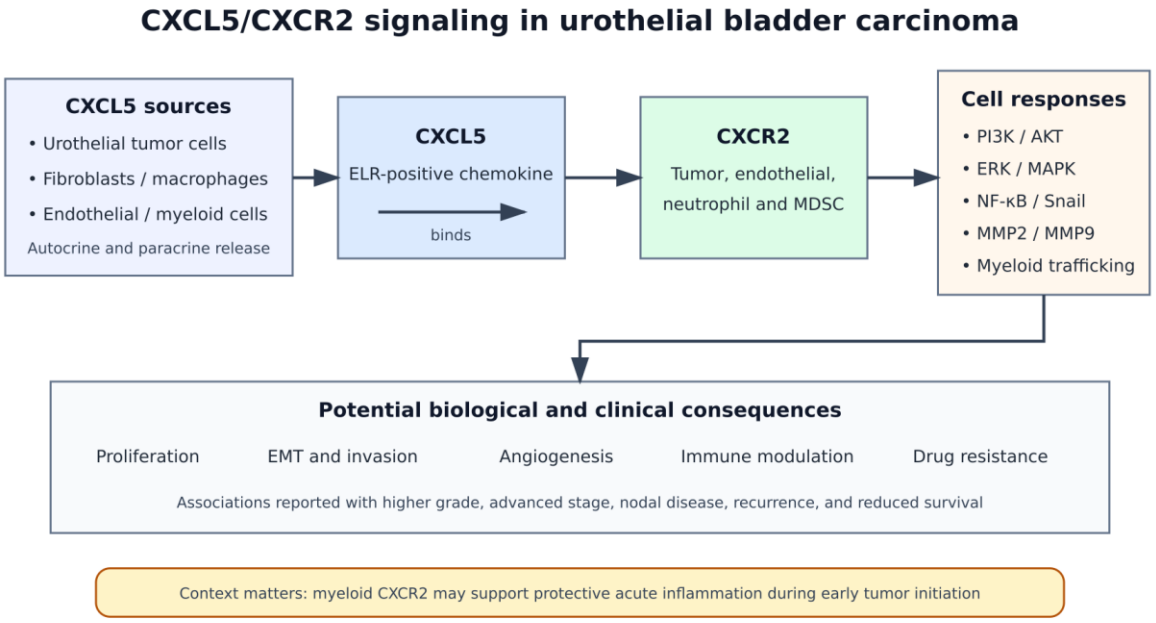

Figure 1. Integrated model of CXCL5/CXCR2 signaling in urothelial bladder carcinoma

The proposed model integrates tumor-derived and stromal CXCL5 with CXCR2-dependent signaling in urothelial cancer, endothelial, neutrophil, and suppressive myeloid compartments. Downstream PI3K/AKT, ERK, NF-kappaB, Snail, and MMP2/MMP9 programs can support proliferation, epithelial-mesenchymal transition, invasion, angiogenesis, immune modulation, and treatment resistance. The direction and magnitude of the effect remain stage- and cell-context dependent. [8–

14,20,21

Conclusion

CXCL5/CXCR2 signaling provides a credible biological bridge between urothelial cancer cells and the inflammatory, vascular, and immune microenvironment. Bladder-specific studies consistently support roles in migration, invasion, angiogenic crosstalk, adverse pathological features, and mitomycin resistance, while tissue and urinary measurements show potential biomarker value. Nevertheless, assay heterogeneity, retrospective design, limited independent validation, inflammatory confounding, and context-dependent CXCR2 effects prevent immediate clinical application. The next step is not another small single-marker series, but integrated, stage-specific validation that measures the ligand, receptor, cellular source, immune state, and treatment context together.

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