Chemokine Receptors (E.G., Ccr5, Cxcr4) As Therapeutic Targets in Cancer Metastasis and Hiv

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***Abstract*—Chemokine receptors, particularly C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4), have garnered significant attention due to their pivotal roles in both pathological and physiological processes. These receptors, which belong to the G-protein coupled receptor (GPCR) superfamily, are primarily known for their function in directing the migration and positioning of immune cells via chemokine gradients. However, their roles extend beyond immune surveillance and inflammation; they are also hijacked in various disease states, notably cancer and viral infections such as human immunodeficiency virus (HIV).**

In the context of HIV infection, CCR5 and CXCR4 serve as critical co-receptors facilitating viral entry into host CD4+ T cells. The virus initially uses CCR5 in early stages of infection (R5-tropic strains) and often shifts to CXCR4 usage (X4-tropic strains) as the disease progresses, contributing to immune system decline. This mechanism has led to the development of CCR5 antagonists like maraviroc, which blocks HIV entry and is approved for clinical use in HIV therapy. Similarly, in cancer biology, the aberrant expression of CCR5 and CXCR4 has been associated with tumor progression, angiogenesis, immune evasion, and particularly metastasis. CXCR4, in particular, interacts with its ligand CXCL12 (SDF-1) to promote cancer cell homing to distant metastatic niches such as bone marrow, liver, and lungs. This has positioned plerixafor (a CXCR4 antagonist initially used in stem cell mobilization) as a promising candidate in anticancer strategies. CCR5 overexpression has also been implicated in the aggressiveness of several cancers, including breast, prostate, and colorectal cancers. This review delves into the molecular and cellular mechanisms by which CCR5 and CXCR4 contribute to both HIV pathogenesis and cancer metastasis. We explore their downstream signaling cascades, cross-talk with other cellular pathways, and roles in the tumor microenvironment and immune modulation. Furthermore, we discuss current pharmacological modulators, including small molecule inhibitors, monoclonal antibodies, and gene-editing strategies targeting these receptors.Despite significant advances, challenges remain in the therapeutic exploitation of these targets. Issues such as drug resistance, receptor redundancy, and off-target effects complicate treatment efficacy. Moreover, the dualistic nature of these receptors—as both immune regulators and disease facilitators—requires nuanced approaches to ensure therapeutic success without impairing normal immune function.

1. INTRODUCTION

Chemokines are a family of small cytokines that play a central role in regulating immune cell trafficking, inflammation, and tissue homeostasis. Their actions are mediated through chemokine receptors, which are G-protein coupled receptors (GPCRs) expressed on the surface of various immune and non-immune cells. Among the numerous chemokine receptors identified, C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4) have emerged as particularly important due to their involvement in both physiological and pathological processes.

Originally, CCR5 and CXCR4 were recognized for their essential roles in immune surveillance—directing the migration of leukocytes to sites of infection, injury, or inflammation. However, accumulating evidence has highlighted their pathological significance, especially in the context of human immunodeficiency virus type

1 (HIV-1) infection and cancer metastasis. HIV-1 exploits these receptors as critical co-receptors for viral entry into CD4+ T lymphocytes. The viral envelope glycoprotein gp120 binds to the primary receptor CD4 and subsequently engages either CCR5 or CXCR4 to facilitate membrane fusion and viral entry. This receptor tropism plays a pivotal role in the viral life cycle, disease progression, and treatment outcomes.

Given the convergence of HIV and cancer biology on CCR5 and CXCR4, these receptors represent attractive therapeutic targets. Drugs such as maraviroc, a CCR5 antagonist, and plerixafor, a CXCR4 inhibitor, have demonstrated clinical utility in treating HIV and mobilizing hematopoietic stem cells, respectively. Moreover, ongoing research is investigating their potential in oncology for inhibiting tumor growth and dissemination.

This review aims to provide a comprehensive overview of the dual roles of CCR5 and CXCR4 in HIV infection and cancer. We will discuss their molecular mechanisms of action, downstream signaling pathways, clinical relevance, and the current landscape of pharmacological modulators targeting these receptors. Understanding the multifaceted roles of CCR5 and CXCR4 is essential for the development of innovative and effective therapeutic strategies in both virology and oncology.

2. STRUCTURE AND FUNCTION OF CHEMOKINE RECEPTORS

CCR5 and CXCR4 are members of the G-protein coupled receptor (GPCR) superfamily, characterized by their seven transmembrane α-helical domains, an extracellular N-terminus, and an intracellular C-terminal tail. These structural features enable them to recognize extracellular chemokines and transduce intracellular signals via interaction with heterotrimeric G-proteins, predominantly of the Gαi subtype**.**

2.1 CCR5: Ligands and Signaling

CCR5 primarily binds inflammatory chemokines**,** including:

- CCL3 (MIP-1α)
- CCL4 (MIP-1β)
- CCL5 (RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted)

These chemokines are typically produced during immune responses to infections or tissue injury, facilitating the recruitment of monocytes, T cells, dendritic cells, and other leukocytes to sites of inflammation. Upon ligand binding, CCR5 undergoes conformational changes that activate Gαi proteins, initiating several downstream pathways.

2.2 CXCR4: Ligand and Unique Features

CXCR4 is the sole receptor for CXCL12 (also known as stromal cell-derived factor-1 or SDF-**1)**, a chemokine with critical roles in development, hematopoiesis, and immune cell trafficking. Unlike CCR5, CXCR4 is widely expressed and also plays essential roles in embryogenesis, cardiovascular development, and neuronal patterning.

2.3 Downstream Signaling Events

Upon chemokine binding, both CCR5 and CXCR4 activate Gαi proteins**,** leading to:

- Inhibition of adenylyl cyclase**,** decreasing intracellular cAMP levels
- Activation of phospholipase C-β (PLC-β**)**, resulting in intracellular calcium mobilization
- Activation of PI3K/Akt and MAPK/ERK pathways, which regulate cell survival, proliferation, and migration
- Cytoskeletal rearrangement via Rho and Rac GTPases, enabling directed chemotaxis and cell migration
- Gene transcription associated with inflammation, survival, and immune modulation

2.4 Pathological Exploitation

These highly regulated signaling pathways are exploited in pathological states**:**

- HIV-1 uses CCR5 or CXCR4 as co-receptors for entry into CD4+ T cells. The virus's envelope glycoprotein gp120 initially binds CD4, then interacts with CCR5 or CXCR4, promoting membrane fusion and viral entry.
- In cancer, aberrant expression and signaling through CCR5 and CXCR4 contribute to tumor cell migration, invasion, metastasis, and interaction with the tumor microenvironment. CXCL12 gradients, for instance, guide CXCR4-expressing tumor cells to metastatic niches such as the bone marrow or lungs.

Thus, the structure-function dynamics of CCR5 and CXCR4 not only underlie critical physiological processes but also serve as points of vulnerability in

disease states, making them compelling therapeutic targets.

3. ROLE IN HIV INFECTION

3.1 CCR5 and CXCR4 as HIV Co-receptors

Human immunodeficiency virus type 1 (HIV-1) requires two key receptors to enter host cells: the CD4 receptor**,** which serves as the primary binding site, and a chemokine co-receptor, most commonly CCR5 or CXCR4**,** depending on the viral strain. These co-receptors are essential for viral entry, fusion, and subsequent infection of host immune cells, particularly CD4+ T lymphocytes**,** macrophages**,** and dendritic cells**.**

CCR5: R5-tropic Strains

During the early stages of infection**,** HIV predominantly utilizes CCR5 as a co-receptor, characterizing the virus as R5-tropic. These strains are most commonly transmitted through mucosal routes**,** such as sexual contact, and efficiently infect macrophages and memory T cells**,** which express high levels of CCR5. The preferential use of CCR5 during initial infection makes it a key determinant of viral transmission and establishment in the host.

CXCR4: X4-tropic Strains

As the disease progresses, particularly in the late stages of HIV infection, many viral strains evolve to use CXCR4 as their co-receptor, resulting in X4-tropic viruses. CXCR4 is more broadly expressed on naïve T cells, and its utilization is associated with faster depletion of CD4+ cells, increased viral load, and rapid progression to AIDS. The emergence of X4-tropic strains is considered a marker of poor prognosis and advanced disease.

3.2 Genetic Resistance: The CCR5-Δ32 Mutation

One of the most significant discoveries underscoring the importance of CCR5 in HIV infection is the identification of the CCR5-Δ32 mutation, a 32-base pair deletion in the CCR5 gene. This mutation results in a truncated, nonfunctional receptor that is not expressed on the cell surface. Individuals who are homozygous for CCR5-Δ32 (i.e., have two copies of the mutated gene) are highly resistant to R5-tropic HIV-1 infection, while heterozygous individuals exhibit delayed disease progression.

The protective effect of this mutation has not only confirmed the critical role of CCR5 in HIV pathogenesis but has also inspired therapeutic strategies aimed at blocking or downregulating CCR5 expression. One such strategy led to the development of maraviroc, a small-molecule CCR5 antagonist, which prevents HIV from binding to and entering host cells. Other emerging approaches include gene-editing technologies such as CRISPR-Cas9 and zinc-finger nucleases, aimed at mimicking the Δ32 deletion in HIV-positive individuals.

3.3 Therapeutic Implications

- CCR5 antagonists like maraviroc are effective only against R5-tropic strains and are generally used in the early stages of infection or in patients confirmed to carry R5-tropic viruses.
- No clinically approved CXCR4 antagonists exist for HIV treatment, but agents like plerixafor—originally developed for stem cell mobilization—are under investigation for their potential anti-HIV activity.
- Viral tropism testing is now an essential component of personalized HIV therapy to determine which co-receptor the virus predominantly uses.

In conclusion, CCR5 and CXCR4 are not only central to the molecular pathogenesis of HIV but also represent key targets for antiretroviral therapy, immune-based interventions, and curative strategies. Their continued exploration holds promise for improving HIV treatment outcomes and potentially achieving functional cures.

4. THERAPEUTIC TARGETING IN HIV

The central role of CCR5 and CXCR4 in HIV entry has established them as critical therapeutic targets. While antiretroviral therapy (ART) traditionally targets viral enzymes such as reverse transcriptase, protease, and integrase, entry inhibitors—particularly co-receptor antagonists—offer an additional strategy by preventing viral access to host cells**.** This section discusses both pharmacological and gene-editing approaches aimed at inhibiting HIV entry through CCR5 and CXCR4.

4.1 CCR5 Antagonists

Maraviroc is the first and only FDA-approved CCR5 antagonist for the treatment of R5-tropic HIV-1 infections. It works by binding to CCR5 and inducing a conformational change that prevents HIV gp120 from interacting with the receptor, thereby blocking

viral entry. Maraviroc is generally well-tolerated and is prescribed for patients with documented R5-tropic strains based on viral tropism assays.

Other Investigational CCR5 Antagonists

- Vicriviroc: Showed initial promise but failed to demonstrate consistent efficacy in phase III trials and was discontinued.
- Aplaviroc: Demonstrated potent anti-HIV activity but was halted during development due to hepatotoxicity.

While these agents underscored the therapeutic potential of CCR5 antagonism, their development highlighted challenges related to toxicity, viral resistance, and the need for tropism testing prior to treatment.

4.2 CXCR4 Antagonists

Plerixafor (AMD3100)

Plerixafor, also known as AMD3100, was initially developed as a CXCR4 antagonist for HIV therapy. Though it demonstrated the ability to block X4-tropic HIV entry, its poor oral bioavailability and hematological toxicity limited its viability as an antiretroviral agent. However, it was successfully repurposed for stem cell mobilization in patients undergoing autologous hematopoietic stem cell transplantation, particularly in non-Hodgkin's lymphoma and multiple myeloma.

Emerging CXCR4 Antagonists

Newer CXCR4 inhibitors, such as:

- BKT140 (4F-benzoyl-TN14003): A peptide-based antagonist showing antitumor and antiviral properties.
- POL6326 (Balixafortide): Being investigated in cancer but also has potential as an antiviral.

These agents are currently in preclinical and early-phase clinical studies for HIV and oncology applications.

Despite their potential, CXCR4-targeting therapies face challenges such as toxicity, redundancy in chemokine networks, and lack of FDA approval for HIV use.

4.3 Gene Editing Approaches

Innovative gene-editing strategies are being explored to permanently disable CCR5 expression, offering a potential functional cure for HIV:

CRISPR/Cas9

CRISPR-Cas9 genome-editing technology has been used to target and disrupt the CCR5 gene in hematopoietic stem cells and T cells. Preclinical and early clinical studies have demonstrated the feasibility of ex vivo editing, followed by reinfusion into the patient. Challenges include off-target effects, immune responses to Cas9, and ensuring durable engraftment of edited cells.

Zinc Finger Nucleases (ZFNs)

ZFNs represent an earlier gene-editing platform used to knock out CCR5 in autologous CD4+ T cells. One of the most prominent trials by Sangamo Therapeutics demonstrated that modified T cells could persist in circulation and show partial resistance to HIV infection. Some patients also showed reduced viral load and increased CD4+ counts, though long-term efficacy remains under investigation.

These gene-editing approaches are inspired by the CCR5-Δ32 mutation, aiming to replicate its protective phenotype in treated individuals. Future directions include combining gene editing with ART or using dual targeting approaches for both CCR5 and CXCR4.

5. ROLE IN CANCER METASTASIS

Chemokine receptors, particularly CCR5 and CXCR4, are not only pivotal in immune regulation but are also extensively overexpressed in various malignancies, including both solid tumors and hematological cancers. Their aberrant activation contributes to several hallmarks of cancer, such as sustained proliferation, invasion, angiogenesis, and metastasis. By interacting with their respective ligands—CCL5 for CCR5 and CXCL12 (SDF-1) for CXCR4—these receptors facilitate tumor cell migration, enabling cancer cells to home to distant tissues that express high concentrations of these chemokines.

5.1 CXCR4–CXCL12 Axis

The CXCR4–CXCL12 signaling axis is among the most well-characterized chemokine pathways in cancer biology. CXCR4 is overexpressed in more than 23 types of human cancers, including breast, lung, prostate, colorectal, ovarian, and pancreatic cancers, as well as leukemias and lymphomas.

Key oncogenic roles of the CXCR4–CXCL12 axis include:

- Tumor Invasion and Migration: CXCL12 gradients drive the chemotactic migration of CXCR4-expressing tumor cells toward metastatic niches such as the bone marrow, liver, and lungs.

- Angiogenesis**:** CXCR4 activation promotes the secretion of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors, facilitating neovascularization that supports tumor growth.
- Cell Survival and Proliferation: Activation of downstream signaling pathways, such as PI3K/Akt, ERK/MAPK, and NF-κB, enhances tumor cell resistance to apoptosis and promotes proliferative signaling.
- Metastatic Organotropism: CXCL12 is highly expressed in organs commonly targeted by metastases. Thus, CXCR4 expression provides a "homing signal" for circulating tumor cells.

The strong correlation between CXCR4 expression and poor prognosis in many cancers has led to the investigation of CXCR4 antagonists (e.g., plerixafor, balixafortide) in clinical trials for metastasis suppression and chemosensitization.

5.2 CCR5–CCL5 Axis

Like CXCR4, CCR5 is aberrantly expressed in several tumor types and has been implicated in enhancing tumor progression via its interaction with CCL5 (RANTES). This axis plays critical roles in:

- Immune Evasion: CCR5 signaling recruits regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment, suppressing anti-tumor immune responses.
- Tumor Cell Motility and Invasion: CCR5 enhances cytoskeletal reorganization and matrix metalloproteinase (MMP) production, facilitating tissue invasion.
- Inflammatory Tumor Microenvironment: CCR5 activation contributes to the secretion of pro-inflammatory cytokines and chemokines that support tumor-promoting inflammation.

The CCR5–CCL5 axis is particularly relevant in:

- Breast cancer, where high CCR5 expression is associated with metastasis and chemoresistance
- Prostate cancer**,** in which CCR5 contributes to bone metastasis
- Melanoma, where it promotes immune escape and tumor growth

Inhibiting CCR5 with drugs like maraviroc has shown anti-metastatic and immune-modulatory effects in preclinical cancer models and is currently being explored in clinical trials for various cancers.

6. THERAPEUTIC TARGETING IN CANCER

Targeting chemokine receptors, particularly CXCR4 and CCR5, offers promising avenues for cancer therapy by disrupting the molecular mechanisms that drive tumor growth, immune evasion, and metastasis.

6.1 CXCR4 Inhibitors

- Plerixafor (AMD3100)

Initially developed as an HIV entry inhibitor, plerixafor has been repurposed in oncology to disrupt the CXCL12–CXCR4 axis. In acute myeloid leukemia (AML) and multiple myeloma, CXCR4 signaling helps leukemic and myeloma cells adhere to the protective bone marrow niche, contributing to chemotherapy resistance. Plerixafor mobilizes these cells into the peripheral circulation, thereby sensitizing them to cytotoxic agents. It is FDA-approved for hematopoietic stem cell mobilization and is being investigated for broader oncologic indications.

- Balixafortide (POL6326)

Balixafortide is a selective CXCR4 antagonist currently undergoing clinical trials in combination with eribulin for metastatic breast cancer. Early results suggest that CXCR4 blockade may enhance drug delivery, inhibit metastasis, and modulate the tumor microenvironment, thereby improving therapeutic efficacy.

6.2 CCR5 Antagonists

- Maraviroc

Best known for its use in HIV therapy, maraviroc has shown anti-tumor effects in preclinical models of breast, prostate, and colorectal cancers, primarily by inhibiting metastasis, reducing tumor-associated inflammation, and limiting immune suppression. Its repositioning for cancer treatment is supported by its safety profile and oral availability.

- Leronlimab (PRO 140)

Leronlimab is a humanized monoclonal antibody that blocks CCR5. Originally developed as an HIV therapeutic, it is now in clinical trials for triple-negative breast cancer (TNBC) and colorectal cancer. Leronlimab has shown the ability to reduce circulating tumor cells (CTCs) and modulate immune cell trafficking, offering hope for immune-based combination strategies in oncology.

7. CHALLENGES AND LIMITATIONS

- Redundancy in Chemokine Signaling

The chemokine network is highly redundant, with multiple chemokines capable of binding different receptors. This redundancy can compensate for blocked pathways, reducing the efficacy of single-agent therapies.

- Receptor Switching and Resistance

In HIV, the virus may shift from using CCR5 to CXCR4, rendering CCR5 antagonists ineffective over time. In cancer, tumor cells may upregulate alternative chemokine receptors or ligands to bypass blocked signaling, leading to therapeutic resistance.

- Tissue-Specific Expression

CCR5 and CXCR4 are expressed in both normal and malignant tissues, making selective targeting challenging. Systemic blockade may lead to off-target effects, including altered immune surveillance or hematopoietic imbalance.

- Immune Modulation Risks

Both receptors play roles in immune cell trafficking and homeostasis. Inhibiting them may lead to unintended immunosuppression, reduced antiviral immunity, or impaired inflammatory responses, especially with long-term use.

8. FUTURE PERSPECTIVES

- Dual Antagonists or Ligand Traps

Development of agents targeting both CCR5 and CXCR4, or decoy receptors/ligand traps, may overcome redundancy and receptor switching by broadly inhibiting chemokine-mediated signaling.

- Combination Therapies

Combining CCR5 or CXCR4 inhibitors with immunotherapies (e.g., immune checkpoint inhibitors) or antiretrovirals could yield synergistic effects, enhancing both anti-tumor and antiviral responses.

- Targeted Drug Delivery

Employing nanoparticles, liposomes, or antibody-drug conjugates (ADCs) to selectively deliver antagonists to the tumor microenvironment or infected tissues can improve efficacy while minimizing systemic toxicity.

- Precision Medicine Approaches

Profiling tumor receptor expression via biomarkers or imaging techniques can guide personalized therapy. Stratifying patients based on CCR5/CXCR4 status may maximize therapeutic benefit and minimize unnecessary exposure.

9. CONCLUSION

CCR5 and CXCR4 have emerged as pivotal players at the intersection of virology and oncology, with profound implications in HIV pathogenesis and cancer metastasis. As chemokine receptors central to immune cell trafficking, their physiological functions have been co-opted by pathogens and tumor cells to facilitate disease progression, immune evasion, and cellular invasion.

In HIV infection, CCR5 and CXCR4 serve as essential co-receptors for viral entry, making them strategic targets for antiretroviral therapy. The development and clinical success of maraviroc highlight the therapeutic value of CCR5 inhibition, while gene-editing approaches aim to replicate the naturally protective CCR5-Δ32 mutation. In cancer, these receptors contribute to tumor cell migration, metastasis, and immune suppression, with inhibitors like plerixafor, balixafortide, and leronlimab showing potential in clinical trials. Despite their promise, targeting CCR5 and CXCR4 is not without challenges. Redundant signaling networks, adaptive resistance mechanisms, and the risk of immune dysregulation require careful consideration in therapeutic design. Moreover, the tissue-specific expression of these receptors necessitates strategies that maximize efficacy while minimizing systemic toxicity.

Looking forward, the integration of precision medicine, combination therapies, and advanced drug delivery platforms will be key to overcoming current limitations. Continued translational research is essential to refine these approaches and extend their benefits to broader patient populations.Ultimately, targeting CCR5 and CXCR4 offers a unique opportunity to combat two of the most devastating global health threats— AIDS and metastatic cancer— through a unified molecular framework. As our understanding deepens, these chemokine receptors may serve not only as therapeutic targets but also as biomarkers of disease progression and treatment response, ushering in a new era of targeted, personalized interventions.

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