

# CCR5 as a Cross-System Coordination Node: Implications for Tissue State, Therapeutic Timing, and Multi-System Integration

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## Abstract

CCR5 is a chemokine receptor historically studied in HIV infection, inflammation, immune cell trafficking, and oncology. Building on prior work that proposed CCR5 as a cross-disease signaling axis, this perspective expands the framework by examining CCR5 as a coordination node operating across vascular, lymphatic, stromal, metabolic, endocrine, neuroimmune, microbiome, and barrier systems. The central argument is that CCR5 should not be considered only as a disease-specific receptor or isolated therapeutic target, but as part of a broader signaling architecture that helps organize tissue state, immune access, inflammatory tone, feedback loops, and therapeutic responsiveness.

This paper introduces the concept of permissive and non-permissive tissue states and applies that framework to therapeutic timing and sequencing. In this model, therapies do not succeed or fail solely because of target validity; they succeed or fail in relation to the biological state in which they are applied. Cytotoxic therapy, radiation, CCR5 modulation, vascular normalization, myeloid reprogramming, metabolic intervention, and immune checkpoint inhibition may each have different effects depending on whether they are introduced before, during, or after a state transition. By situating CCR5 within this broader systems-level context, this work proposes a framework for understanding variability in therapeutic response and for designing strategies that better align interventions with the dynamic biology of disease.

## Keywords

CCR5; systems biology; chemokine signaling; immune trafficking; tumor microenvironment; fibrosis; therapeutic timing; sequencing; glioblastoma; inflammation; tissue state; neuroimmune signaling

## 1. Introduction

CCR5 is a chemokine receptor most widely recognized for its role in HIV infection, where it serves as a critical co-receptor for viral entry into CD4+ T cells. This function has made CCR5 a central focus of antiviral research, supported by both pharmacologic targeting and genetic evidence, including the well-characterized CCR5 $\Delta$ 32 mutation associated with resistance to HIV infection (Alkhatib, 2009; Liu et al., 1996). Beyond virology, CCR5 plays a central role in inflammation and immune cell trafficking, regulating the migration and positioning of leukocytes in response to chemokine gradients such as CCL5 (RANTES) and related ligands (Griffith et al., 2014).

More recently, CCR5 has been increasingly studied in oncology, particularly in the context of the tumor microenvironment (TME). In cancer, CCR5 signaling has been associated with immune cell recruitment, tumor-associated macrophage behavior, metastatic progression, and patterns of immune exclusion that influence therapeutic response (Aldinucci & Casagrande, 2018; Jiao et al., 2019). These observations have led to growing interest in CCR5 as a therapeutic target across multiple malignancies, particularly in metastatic solid tumors where the organization of the microenvironment plays a critical role in disease progression.

Despite these advances, most investigations of CCR5 have remained confined to individual disease domains or specific biological pathways. This has resulted in a fragmented view of its function, where CCR5 is interpreted as a disease-specific factor rather than as part of a broader system of biological coordination. In prior work (Fourqurean, 2026), CCR5 was proposed as a cross-disease signaling axis linking immunology, oncology, and neurobiology, with particular emphasis on its role in cellular communication and positioning within complex tissue environments.

The present analysis extends that framework by examining CCR5 not simply as a participant in isolated pathways, but as a coordination node operating across multiple interacting biological systems. These include vascular and endothelial networks that regulate tissue access, lymphatic systems that govern immune routing and antigen flow, extracellular matrix and stromal structures that define tissue architecture, and metabolic, endocrine, and neuroimmune systems that shape inflammatory tone and cellular behavior (Joyce & Fearon, 2015; Quail & Joyce, 2013).

This perspective reframes CCR5 from a molecular target to a systems-level regulator of tissue state. Disease processes such as cancer, chronic inflammation, and neurodegeneration can be understood not solely as consequences of intrinsic cellular abnormalities, but as emergent properties of disrupted communication across these systems. Structural features such as fibrosis reflect persistent alterations in tissue organization that influence immune access, signaling gradients, and long-term cellular behavior.

From a translational standpoint, this systems-level view introduces a critical consideration: interventions targeting CCR5 do not operate within static environments. Their effects depend on the biological state in which they are applied. As a result, therapeutic efficacy is not determined solely by target engagement, but by whether the surrounding system is in a state that allows that intervention to function.

## **2. CCR5 as a Coordination Node**

CCR5 is most commonly described as a chemokine receptor involved in immune cell trafficking. While this characterization is accurate, it understates the broader functional role of CCR5 within biological systems. Rather than acting solely as a mediator of leukocyte migration, CCR5 operates within a dynamic signaling network that influences how cells are positioned, how they interact, and how tissues organize in response to internal and external stimuli.

At a fundamental level, CCR5 participates in the interpretation of chemokine gradients, particularly those involving ligands such as CCL5 (RANTES), CCL3, and CCL4. These gradients do not simply direct movement; they establish spatial patterns that determine which cell populations co-localize within specific tissue compartments. This positioning has downstream consequences for immune activation, suppression, and the persistence of inflammatory states. In this sense, CCR5 contributes to the formation of functional microenvironments rather than merely facilitating cellular transit.

Importantly, CCR5 signaling does not operate in isolation. It interacts with other chemokine receptors, cytokine networks, and adhesion systems to create a coordinated response that integrates signals from multiple sources (Ley et al., 2007). The result is not a linear pathway but a distributed network in which CCR5 functions as one of several nodes that influence system behavior.

This becomes particularly relevant in complex tissue environments such as tumors, sites of chronic inflammation, or areas of tissue injury. In these settings, CCR5-mediated signaling can contribute to the recruitment and retention of specific immune cell populations, including T cells, macrophages, and myeloid-derived suppressor cells. The balance of these populations, along with their spatial organization, plays a critical role in determining whether a tissue environment becomes immunologically active, suppressed, or resistant to intervention (Aldinucci & Casagrande,

2018).

Beyond immune cell positioning, CCR5 is also linked to processes that influence tissue structure and remodeling. Through interactions with inflammatory mediators and stromal signaling pathways, CCR5 activity has been associated with changes in extracellular matrix composition, fibroblast activation, and the development of fibrotic architecture (Seki et al., 2009; Berres et al., 2010). These structural changes further reinforce patterns of immune exclusion or access, creating feedback loops that stabilize specific tissue states over time.

An important feature of this coordination is the presence of feedback loops across systems. Signaling between compartments such as the gut and brain, or between immune and endocrine systems, is not unidirectional. These systems continuously influence each other, reinforcing specific biological states over time. CCR5-mediated trafficking and signaling may contribute to the maintenance of these loops by influencing which cell populations are present within key tissues and how they interact.

From a systems perspective, effective intervention may therefore require not only targeting individual pathways, but disrupting or resetting these feedback loops. This reframes CCR5 as a regulator of biological context rather than a single-pathway target.

### **3. Multi-System Integration**

Understanding CCR5 as a coordination node requires placing it within the context of multiple interacting biological systems rather than viewing it through a single pathway or disease lens. These systems do not operate independently. They function as an interconnected network in which changes in one domain influence behavior across others, often through reinforcing feedback loops that stabilize specific tissue states.

#### **Vascular and Endothelial System**

The vascular system serves as the primary gateway for cellular movement into and out of tissues. Endothelial cells regulate permeability, adhesion, and chemokine presentation through molecules such as ICAM-1, VCAM-1, and selectins, which govern leukocyte adhesion and extravasation. CCR5-mediated trafficking is inherently dependent on these vascular dynamics, as chemokine gradients must be interpreted within the context of endothelial activation and tissue perfusion (Ley et al., 2007).

Hypoxia within tissues further alters this environment through stabilization of HIF-1 $\alpha$ , which promotes angiogenic signaling, including VEGF expression. VEGF not only drives neovascularization but also increases vascular permeability, altering immune cell access and spatial distribution (Carmeliet & Jain, 2011). These changes directly influence how CCR5-expressing cells enter and position within tissues, linking vascular state to immune trafficking and tissue organization.

#### **Lymphatic System**

The lymphatic system complements vascular function by regulating immune cell routing, antigen transport, and communication between peripheral tissues and lymph nodes. Dendritic cells and lymphocytes utilize chemokine gradients, including those involving CCR5 ligands, to traffic through lymphatic vessels and initiate adaptive immune responses (Girard et al., 2012).

Disruptions in lymphatic flow or signaling can lead to impaired antigen presentation or chronic immune activation, reinforcing inflammatory states. In this context, CCR5 contributes to the coordination of local and systemic immune responses by influencing how signals propagate through lymphatic pathways.

## **Extracellular Matrix, Stroma, and Fibrosis**

The extracellular matrix (ECM) and stromal environment define the structural and signaling framework within which cells operate. Beyond providing physical support, the ECM regulates cell migration, mechanical stiffness, and the distribution of signaling molecules. Persistent remodeling of this environment leads to fibrosis, characterized by collagen deposition, fibroblast activation, and altered tissue architecture.

CCR5 signaling has been implicated in fibrotic processes across multiple organ systems. Activation of CCR5 and its ligands contributes to fibroblast recruitment and activation, as well as macrophage polarization toward pro-fibrotic phenotypes (Seki et al., 2009; Berres et al., 2010). Conversely, blockade of CCR5 has been associated with reductions in fibrosis and remodeling of the ECM, suggesting that this axis plays a role not only in maintaining fibrotic states but potentially in reversing them.

This has direct implications for tissue accessibility and immune function. Fibrotic and dense stromal environments can limit immune cell infiltration and alter signaling gradients, creating non-permissive conditions for effective immune engagement. CCR5-mediated trafficking occurs within this structural context, meaning that stromal architecture directly influences the ability of immune cells to access and interact within tissues.

## **Metabolic System and Signaling Pathways**

Metabolic conditions within tissues play a critical role in shaping immune behavior and cellular function. Hypoxia, nutrient depletion, and metabolic byproducts such as lactate influence both immune cell activity and tumor biology. These conditions are tightly linked to signaling pathways including HIF-1 $\alpha$ , mTOR, and AMPK, which regulate cellular adaptation to stress and resource availability (O'Neill et al., 2016).

VEGF-driven angiogenesis, often induced under hypoxic conditions, further integrates metabolic and vascular responses, altering both tissue perfusion and immune accessibility. In parallel, inflammatory cytokines and chemokines, including CCR5 ligands, are modulated by these metabolic states, linking energy availability to immune trafficking and signaling.

## **Neuroimmune and Endocrine Systems**

The nervous and endocrine systems provide systemic regulatory input that influences immune tone, inflammation, and tissue behavior. Stress signaling through the hypothalamic-pituitary-adrenal axis and sympathetic nervous system alters cytokine production, vascular dynamics, and immune cell distribution (Dhabhar, 2014).

Communication between the gut and brain illustrates how signals originating in one system can propagate through others, influencing immune responses and tissue organization. These interactions form feedback loops that reinforce biological states over time.

## **Microbiome and Barrier Systems**

Barrier systems regulate interactions between the host and external environment. The microbiome influences immune signaling, inflammation, and metabolic function (Belkaid & Hand, 2014). Disruption of barrier integrity can lead to sustained inflammatory signaling, altering chemokine gradients and immune cell behavior.

## **Integrated System Behavior**

Across these systems, CCR5 functions as part of a coordinated network linking cellular movement to tissue state. Changes in vascular access, stromal architecture, metabolic conditions, or systemic signaling can alter the impact of CCR5-mediated processes, while CCR5-driven trafficking can reinforce or modify these system states.

## **4. Tissue State: Permissive vs Non-Permissive Environments**

The interaction of these systems gives rise to tissue state, which exists along a spectrum from permissive to non-permissive.

Permissive states allow immune access, signaling coordination, and effective response. Non-permissive states are defined by fibrosis, hypoxia, immune exclusion, and metabolic suppression (Carmeliet & Jain, 2011; O'Neill et al., 2016).

These states are stabilized by feedback loops spanning immune, metabolic, stromal, and neuroendocrine systems.

External interventions such as chemotherapy and radiation can disrupt these states. In glioblastoma, radiation and chemotherapy may transiently alter vascular permeability, stromal organization, and inflammatory signaling, creating a temporary shift toward a more permissive environment.

Within this window, CCR5-mediated trafficking may influence immune positioning and inflammatory tone. If the system transitions toward a more immune-active state, subsequent interventions such as immune checkpoint inhibition may become more effective when applied in sequence.

Additional factors may shape this window, including VEGF signaling, STING activation, myeloid reprogramming, and metabolic changes.

This introduces the concept of a state-dependent therapeutic window, in which interventions are most effective when aligned with system state rather than applied in isolation.

## **5. Therapeutic Timing and Sequencing**

If CCR5 functions as a coordination node, therapeutic effectiveness depends on timing relative to system state.

In non-permissive environments, therapies such as immune checkpoint inhibition often fail due to limited immune engagement.

Initial interventions such as chemotherapy and radiation may disrupt the environment by inducing antigen release, altering vascular permeability, and activating inflammatory pathways such as cGAS-STING signaling.

CCR5 modulation may then influence immune cell trafficking and stromal dynamics, reshaping the tissue environment.

Additional interventions such as VEGF blockade, myeloid targeting, or metabolic modulation may further stabilize or enhance the permissive state.

Checkpoint inhibition becomes most effective when introduced after these transitions occur, rather than before.

This creates a sequence: disruption -> modulation -> stabilization -> exploitation.

Therapeutic failure is often not due to target irrelevance, but to misalignment between intervention timing and system state.

CCR5 represents a point of leverage within this sequence, influencing transitions between tissue states through its effects on trafficking, signaling, and tissue organization.

## 6. Cross-Disease Implications

While the framework outlined above is anchored in oncology, particularly in the context of solid tumors and glioblastoma, the underlying principles are not disease-specific. The concepts of tissue state, feedback loops, and state-dependent therapeutic windows reflect broader biological patterns that extend across multiple chronic disease states, including inflammatory, neurodegenerative, and fibrotic conditions.

In inflammatory diseases such as Crohn's disease, variability in response to established therapies highlights the importance of underlying system state. Agents targeting specific inflammatory pathways, such as TNF- $\alpha$  inhibitors, can produce significant benefit in some patients while demonstrating limited effectiveness in others. This variability is often attributed to patient heterogeneity or disease severity, but it may also reflect differences in tissue organization, immune cell composition, microbiome signaling, and the degree of structural remodeling within affected tissues. In advanced disease, where fibrosis and chronic feedback loops are established, modulation of a single inflammatory pathway may be insufficient to alter the overall system state. This suggests that therapeutic effectiveness may depend not only on pathway relevance but on whether the biological environment is permissive to change at the time of intervention.

A similar pattern can be observed in neuroinflammatory and neurodegenerative diseases, including multiple sclerosis and Alzheimer's disease. Early-stage disease is often characterized by active inflammatory processes and more dynamic signaling environments, while later stages involve structural changes, altered neural connectivity, and persistent neuroimmune dysregulation. Interventions targeting immune signaling or inflammation may be more effective during earlier phases, when the system retains a degree of flexibility, than in later stages where feedback loops and structural changes stabilize a non-permissive state. The role of barrier systems, particularly the blood-brain barrier, further reinforces the importance of timing, as access to central compartments and immune cell trafficking are highly dependent on local signaling and disease progression.

Fibrotic diseases provide another example of state-dependent behavior. Across organ systems, including liver, lung, and gastrointestinal tissues, fibrosis represents a structural endpoint of chronic inflammation and dysregulated repair. Once established, fibrotic architecture alters tissue mechanics, restricts cellular movement, and modifies signaling gradients in ways that can limit the effectiveness of therapeutic interventions. Treatments that may be effective in earlier stages of disease often fail to produce meaningful benefit once this structural state is stabilized. Conversely, interventions that modify or reverse fibrotic processes may alter the tissue environment sufficiently to restore responsiveness to other therapies, highlighting the importance of sequencing and system-level intervention.

Across these diverse conditions, a consistent pattern emerges: therapeutic variability may reflect differences in system state rather than differences in target validity alone. Treatments that are effective in one context may fail in another if the surrounding biological systems are not configured to support their mechanism of action. This perspective shifts the interpretation of therapeutic success and failure from a binary assessment of drug efficacy to a more nuanced understanding of context-dependent response.

Within this broader framework, CCR5 remains relevant not as a disease-specific target, but as a participant in the coordination of immune trafficking, inflammatory signaling, and tissue organization across systems. Its modulation may influence the conditions under which tissues transition between states, potentially affecting responsiveness to a range of interventions. However, as in oncology, its role should be understood within the context of system dynamics rather than as a standalone solution.

Taken together, these observations support a generalizable principle: the effectiveness of therapeutic interventions across diseases is shaped not only by the molecular targets they engage, but by the timing of their application relative to the evolving state of interconnected biological systems.

## 7. Translational Framework

The framework outlined in this analysis suggests a shift in how therapeutic strategies are conceptualized and applied. Rather than selecting interventions based solely on target presence or disease classification, a systems-level approach emphasizes the importance of tissue state, system interaction, and temporal context. This requires moving from a static model of treatment selection to a dynamic model in which interventions are aligned with the evolving biology of the system.

A central implication of this approach is that clinical decision-making should incorporate an assessment of whether a tissue environment is permissive or non-permissive to a given intervention. This assessment extends beyond traditional biomarkers to include features such as vascular integrity, stromal architecture, metabolic conditions, immune cell composition, and the presence of reinforcing feedback loops. While not all of these variables are routinely measured in clinical practice, their collective influence shapes therapeutic response and may explain variability that is not accounted for by target expression alone.

Within this context, biomarkers should be interpreted as indicators of system state rather than as fixed determinants of treatment eligibility. For example, expression of molecules such as PD-L1 may reflect an evolving inflammatory environment rather than a stable characteristic of the tumor or tissue. Similarly, changes in circulating cytokines, imaging-based assessments of tissue structure, or functional measures of metabolism may provide insight into whether a system is transitioning toward or away from a permissive state.

This perspective also reframes the role of sequencing. Instead of viewing treatment regimens as predefined combinations, interventions can be conceptualized as components of a sequence designed to progressively reshape the system. Initial therapies may be selected for their ability to disrupt existing feedback loops or alter structural and metabolic constraints. Subsequent interventions can then be introduced when the system has shifted sufficiently to support their mechanism of action. In this model, the goal is not simply to apply multiple therapies, but to apply them in a manner that aligns with the underlying biology at each stage.

Importantly, this approach does not require abandoning established therapies. Many existing treatments may remain effective when applied in the appropriate context. What changes is the framework through which these therapies are used. Agents that appear ineffective in one setting may demonstrate benefit when introduced after prior interventions have altered tissue state. This may be particularly relevant for therapies that depend on immune engagement or tissue accessibility, where baseline conditions often limit their effectiveness.

From a research perspective, this framework suggests a need to design studies that account for system dynamics rather than evaluating interventions in isolation. Clinical trials may benefit from incorporating adaptive sequencing strategies, longitudinal biomarker assessment, and endpoints that capture changes in tissue state over time. This could enable a more accurate evaluation of how

and when specific interventions contribute to meaningful clinical outcomes.

Within this evolving model, CCR5 can be viewed as a point of integration that links multiple systems involved in these transitions. Its role in immune trafficking, inflammatory signaling, and tissue organization positions it as a potential lever for influencing system state. However, its modulation should be considered within the context of broader system dynamics rather than as an isolated therapeutic solution.

Ultimately, the translational implication of this framework is a shift from targeting disease to managing biological context. By aligning interventions with the state of interconnected systems, it may be possible to improve the consistency and effectiveness of therapies across a range of conditions.

## 8. Conclusion

CCR5 has traditionally been studied within the confines of individual disease processes, most notably in HIV, inflammation, and more recently in oncology. However, evidence across these domains points toward a broader role in coordinating cellular movement, signaling, and tissue organization. When viewed through a systems-level lens, CCR5 is better understood not as a disease-specific target, but as a participant in the regulation of biological context.

This perspective reframes how disease itself is interpreted. Conditions such as cancer, chronic inflammation, and neurodegeneration are not simply the result of isolated molecular dysfunction, but emerge from the interaction of multiple systems that collectively define tissue state. Features such as immune exclusion, fibrosis, metabolic constraint, and disrupted signaling networks represent stable configurations that can either resist or permit change.

Within this framework, therapeutic success is not determined solely by the selection of a target, but by the timing of intervention relative to system state. Treatments that fail in one context may succeed in another if applied at a point when the underlying biology has shifted. This emphasizes the importance of sequencing, where interventions are used to progressively reshape the system, creating conditions under which subsequent therapies can be effective.

CCR5, as a coordination node within this network, offers a point of leverage in this process. By influencing immune trafficking, inflammatory signaling, and tissue organization, modulation of this axis may contribute to transitions between non-permissive and permissive states. Its relevance lies not in isolation, but in how it interacts with vascular, stromal, metabolic, and systemic signaling processes that together define biological behavior.

The broader implication of this work is a shift in focus from targeting disease to understanding and managing system dynamics. This includes recognizing the role of feedback loops, the importance of tissue architecture, and the temporal nature of therapeutic opportunity. As biological systems are not static, neither are the conditions under which interventions operate.

Ultimately, a systems-level approach to CCR5 highlights a more general principle: effective therapy depends not only on what is targeted, but on when and within what context that target is engaged. Recognizing and integrating these dynamics provides a more consistent framework for interpreting variability in therapeutic response and for designing strategies that align more closely with the complexity of human biology.

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