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Overcoming Immunosuppression: The Role of Tumor-Infiltrating Tregs and Their Key Target CCR8 in Immunotherapy Resistance and Therapeutic Strategies

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Abstract

The immunosuppressive tumor microenvironment (TME), orchestrated largely by tumor-infiltrating regulatory T cells (TI-Tregs), represents a critical barrier to effective cancer immunotherapy. This review focuses on the chemokine receptor CCR8, which has recently emerged as a highly promising and specific target for therapeutic intervention due to its preferential and stable expression on highly suppressive TI-Treg subsets. We synthesize current evidence demonstrating that CCR8 is selectively upregulated on TI-Tregs across multiple solid tumor types, where its expression correlates with poor patient prognosis and resistance to immune checkpoint inhibitors (ICIs). This expression pattern—enriched within the tumor but minimal in peripheral blood and normal tissues—provides a compelling rationale for tumor-selective targeting. We critically examine the primary therapeutic strategies under development, including ADCC-enhanced monoclonal antibodies, which have shown the most clinical promise, alongside bispecific antibodies and small molecule antagonists. While early-phase clinical trials report encouraging safety and on-target pharmacodynamic activity, the field faces significant challenges. These include unresolved questions regarding CCR8's functional role versus its value as a targeting biomarker, a lack of validated predictive biomarkers for patient stratification, and the physical barriers to effective drug delivery in solid tumors. This review aims to provide a comprehensive and nuanced understanding of CCR8 biology and to outline the key steps necessary for the successful clinical translation of CCR8-targeted therapies.

Keywords

CCR8, tumor-infiltrating regulatory T cells, immunotherapy resistance, tumor microenvironment, immunotherapy

1. Introduction

Tumor resistance to immunotherapy is driven by a multifaceted immunosuppressive network orchestrated by tumor-infiltrating regulatory T cells (TI-Tregs) within the tumor microenvironment (TME). These cells not only directly suppress the activity of effector immune cells through diverse mechanisms but also actively remodel the surrounding TME, thereby establishing a barrier to immune evasion. This Treg-mediated

immune exclusion is recognized as a key determinant of resistance to immune checkpoint inhibitors (ICIs) [1].

Recent advances in single-cell transcriptome sequencing have uncovered pronounced functional heterogeneity among tumor-infiltrating regulatory T cells (TI-Tregs), identifying a distinct subset—termed Treg_S1—characterized by high expression of CCR8 and exhibiting the most potent immunosuppressive activity [1]. CCR8 has been consistently shown to be highly and specifically expressed on TI-Tregs across multiple solid tumor types, with positivity rates ranging from 40% to 80% across different tumor types [1, 2]. In stark contrast, its expression is minimal on peripheral Tregs and conventional effector T cells [1, 3], and its expression level strongly correlates with poor clinical outcomes in patients [4, 5]. Mechanistically, CCR8 expression is driven by the TCR-NF-κB signaling axis and represents a key component of a cross-species conserved "tissue-repair Treg" transcriptional program [6]. Functionally, CCR8+ Tregs contribute to multidimensional immune resistance through the secretion of immunosuppressive cytokines, elevated expression of immune checkpoint molecules, and active remodeling of the tumor microenvironment [4, 7]. Current therapeutic strategies targeting CCR8 broadly fall into three categories: ADCC-enhanced monoclonal antibodies, bispecific antibodies, and small molecule antagonists [1, 4, 7]. Several of these candidates have advanced into clinical trials, with emerging data supporting their safety profiles and capacity for selective TI-Treg depletion [2, 3, 5].

Despite promising advances, the field continues to grapple with several critical challenges, including ongoing debate regarding the precise functional role of CCR8, the absence of robust predictive biomarkers, and persistent obstacles related to efficient drug delivery into solid tumors [3, 5, 8, 9]. This paper synthesizes current mechanistic insights into CCR8+ TI-Treg-mediated immune resistance, highlights key developments in therapeutic targeting strategies—from preclinical validation to early translational progress—and critically examines existing hurdles and future directions. By integrating these perspectives, we aim to provide a framework that informs ongoing research and facilitates the clinical translation of CCR8-targeted therapies.

1.1 Mechanisms of Immunotherapy Resistance Mediated by Tumor-Infiltrating Tregs and Their Key Molecule CCR8

Building on the role of TI-Tregs in immunotherapy resistance highlighted in the Introduction, this section focuses on the mechanistic basis of this resistance and the key role of CCR8, a specific marker of highly suppressive TI-Treg subsets. Immunotherapy resistance in tumors is fundamentally driven by the intricate immunosuppressive network established by TI-Tregs within the TME. Far from being a functionally homogeneous population, TI-Tregs exhibit considerable transcriptional and functional heterogeneity. Single-cell transcriptome profiling has enabled the resolution of TI-Tregs into multiple distinct subsets, among which the Treg_S1 subset—characterized by high expression of CCR8, LAG-3, OX-40, and IL-10—consistently emerges as the most immunosuppressive. In contrast to other subsets such as the Th17-like Treg_S2 population, Treg_S1 exhibits markedly enhanced suppressive capacity and is increasingly recognized as a key mediator of resistance to immunotherapeutic interventions [1, 4]. These highly suppressive TI-Tregs orchestrate multifaceted antitumor immune impairment through distinct mechanistic pathways: they co-express CD39 and CD43, which synergistically hydrolyze pro-inflammatory ATP to generate immunosuppressive adenosine; concurrently, they upregulate CTLA-4 to competitively engage CD80/CD86 on antigen-presenting cells, effectively outcompeting effector T cells for co-stimulatory ligands and thereby blunting their activation [1, 7]. Collectively, these coordinated mechanisms reinforce the immunosuppressive barrier within the TME and underscore the rationale for targeting CCR8+ TI-Tregs as a therapeutic strategy.

Within this context, CCR8 has emerged as a particularly attractive target due to its specific enrichment on highly suppressive TI-Treg subsets. Integrated analyses using single-cell transcriptomics and flow cytometry across multiple tumor types have consistently demonstrated that CCR8 is highly and specifically expressed on tumor-infiltrating Tregs, with positivity rates ranging from 30% to 80%. In striking contrast, CCR8 is rarely detectable on peripheral Tregs, Tregs residing in normal tissues, or tumor-infiltrating effector lymphocytes—including conventional CD4+ T cells and CD8+ T cells [1, 5, 6]. This highly restricted expression pattern confers a distinct advantage in targeting specificity over broader Treg-associated markers such as CTLA-4 or CD25, which are also expressed on activated effector T cells and are therefore associated with on-target, off-tumor toxicities. Moreover, CCR8 expression levels closely correlate with the suppressive

potency of TI-Tregs and have demonstrated prognostic significance across multiple malignancies. In hepatocellular carcinoma, for instance, high CCR8 expression is associated with significantly shortened patient survival, and the intratumoral density of CCR8+ cells inversely correlates with the abundance of CD8+ T cells and NK cells [4]. These findings collectively validate CCR8 not only as a functionally relevant marker of pathogenic TI-Treg activity but also as a clinically informative prognostic biomarker.

Recent investigations into the regulatory mechanisms governing CCR8 expression have revealed the involvement of multiple intersecting signaling pathways. On one hand, TCR-mediated antigen recognition drives CCR8 upregulation through activation of the NF-κB pathway, wherein the p65 subunit directly binds to regulatory regions within the CCR8 gene locus to promote transcription [1]. On the other hand, CCR8-expressing Tregs represent a conserved component of the cross-species "tissue-repair Treg" transcriptional program. Single-cell ATAC-seq profiling has demonstrated that these cells harbor a distinct chromatin accessibility landscape, with CCR8 expression being directly modulated by the transcription factor BATF and potentially integrated with Tfh-like differentiation programs. Within the tumor microenvironment, this program appears to be co-opted: CCR8+ Tregs not only execute immunosuppressive functions but also secrete factors such as PDGFA and MMP25 that actively promote stromal remodeling. This dual functionality creates a pro-tumorigenic axis that couples immune evasion with tissue-repair-like activities, thereby reinforcing the immunosuppressive and protumoral architecture of the tumor microenvironment [10].

The mechanisms by which CCR8+ Tregs mediate immune resistance are multidimensional, extending beyond direct suppression of effector cells to encompass broader remodeling of the tumor microenvironment. In a hepatocellular carcinoma model, CCR8 signaling has been shown to further upregulate the expression of immunosuppressive molecules such as IL-10 and CTLA-4 within TI-Tregs, suggesting a positive feedback loop that amplifies their suppressive capacity [4]. Critically, the persistence of TI-Tregs within tumors represents a fundamental barrier to the efficacy of immune checkpoint inhibitors (ICIs). In "cold tumor" models characterized by resistance to anti-PD-1 therapy, TI-Treg infiltration is notably abundant, and targeted depletion of CCR8+ Tregs has been demonstrated to remodel the immune landscape, converting immunologically "cold" tumors into ICI-sensitive "hot" tumors [2, 11]. These findings collectively establish CCR8+ TI-Tregs as a central cellular hub for overcoming ICI resistance and highlight the therapeutic potential of strategies aimed at their selective elimination.

2. Therapeutic Strategies Targeting CCR8 and Preclinical Validation

Based on the specific expression and functional significance of CCR8 in TI-Tregs, several therapeutic strategies have been developed to target this molecule, which can be categorized into three main classes. While all share the core objective of relieving CCR8+ Treg-mediated immunosuppression, they differ fundamentally in their mechanisms of action and structural design.

The first category encompasses cell depletion strategies, predominantly mediated by monoclonal antibodies, which currently represent the most advanced and extensively validated approach in clinical development. Representative agents in this class include BAY 3375968, GS-1811, RO7502175, CHS-114, and S-531011. A common design feature of these antibodies is the incorporation of afucosylated IgG1 Fc domains, which enhance binding affinity to FcγRIIIA on effector cells such as NK cells and macrophages, thereby enabling efficient and selective elimination of CCR8-high TI-Tregs through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) [2, 3, 11, 12]. Preclinical studies have demonstrated that these antibodies, as monotherapies, exert potent antitumor activity across multiple syngeneic models, including CT26 colorectal cancer, EMT6 breast cancer, and MC38 colon cancer, achieving tumor growth inhibition (TGI) rates ranging from 60% to 90% and, in some cases, complete tumor regression [2, 3, 6]. The mechanistic basis for this efficacy lies in active cellular depletion rather than receptor blockade alone; Fc-silent mutants lacking ADCC activity or antibodies designed purely for signaling blockade fail to suppress tumor growth, underscoring the indispensability of effector-mediated elimination [1, 5]. Importantly, owing to the minimal CCR8 expression on peripheral Tregs and conventional effector T cells, these antibodies achieve precise depletion of tumor-resident Tregs while sparing systemic Treg populations, thereby avoiding the autoimmune complications associated with broad-spectrum Treg depletion strategies and demonstrating a markedly improved safety profile [6].

The second category encompasses functional reversal strategies, primarily exemplified by small molecule antagonists. This strategy operates through a distinct, non-depleting mechanism: rather than eliminating CCR8+ cells, it aims to reverse their highly suppressive phenotype by blocking CCR8 binding to its cognate ligand CCL1 and disrupting downstream signaling cascades. A representative agent, IPG0521, has been shown to inhibit CCL1-induced calcium mobilization and chemotaxis in vitro, confirming effective receptor blockade. In a hepatocellular carcinoma model, treatment with IPG0521m did not reduce the absolute number of TI-Tregs but instead successfully remodeled their functional phenotype, shifting the population from the highly suppressive Treg-FoxP3int subset toward the less suppressive Treg-FoxP3hi subset, accompanied by significant downregulation of immunosuppressive molecules including IL-10 and CTLA-4 [4]. This mechanistic approach intersects directly with an ongoing debate regarding the fundamental functional role of CCR8. While some studies have posited that CCR8 primarily mediates Treg migration into tumors rather than directly modulating suppressive function—thereby questioning the therapeutic viability of signaling blockade alone [5, 9]—the encouraging preclinical data from IPG0521m suggest that CCR8 signaling may be critical for maintaining the highly suppressive state of Tregs within the tumor microenvironment. Adding further complexity, some studies propose that CCR8's primary function is to mediate chemotactic migration, while distinct molecular pathways govern the suppressive programs of these cells. The apparent discrepancies in these findings may reflect context-dependent effects that vary across tumor types or in response to different interventional strategies, underscoring the need for further mechanistic dissection [4].

The third category encompasses innovative strategies designed to enhance therapeutic synergy or overcome barriers to solid tumor delivery. A representative approach is the bispecific antibody 2MW4691, which simultaneously targets CCR8 and CTLA-4. This construct employs a high-affinity arm to achieve precise binding to CCR8+ Tregs, while a low-affinity arm enables selective blockade of CTLA-4 signaling specifically on these cells. This design achieves dual functionality: ADCC-mediated depletion of highly suppressive Tregs while sparing CD8+ effector T cells, which express only low levels of CTLA-4 and are thus protected from off-target depletion. Preclinical evaluation has demonstrated significantly superior efficacy compared to monotherapy or combination approaches [7]. Parallel efforts have focused on engineering cellular therapies to address the challenges of poor tumor infiltration and functional suppression that limit CAR-T cell efficacy in solid tumors. Dual-modified CAR-T cells have been developed to co-express the CCR8 chemokine receptor alongside a dominant-negative TGF-β receptor II (DNR). In this design, CCR8 directs tumor homing along CCL1 chemokine gradients, while DNR confers resistance to TGF-β-mediated immunosuppression within the tumor microenvironment. This synergistic modification has been shown to enhance both infiltration and cytotoxic activity in solid tumor models, including pancreatic cancer [13]. An additional metabolic intervention strategy has emerged from studies in glioblastoma, demonstrating that the LDHA inhibitor Oxamate can downregulate histone lactylation (H3K18la), thereby epigenetically suppressing the expression of multiple immunosuppressive molecules including CD39, CD73, and CCR8. This approach effectively relieves local immunosuppression and has been shown to significantly enhance CAR-T efficacy in preclinical models [14]. Collectively, these diverse strategies illustrate the expanding therapeutic arsenal targeting CCR8+ Tregs, each addressing distinct mechanistic limitations of current immunotherapeutic approaches.

3. Clinical Translation Progress and Current Challenges

With promising preclinical data supporting CCR8-targeted therapies, the translation of these strategies into clinical practice has advanced rapidly, though several critical challenges remain. The translation of CCR8-targeted therapies from bench to bedside has progressed with remarkable momentum. Several anti-CCR8 monoclonal antibodies have now advanced into early-phase clinical trials across multiple solid tumor indications. A Phase I trial of BAY 3375968 (NCT05537740) is currently evaluating its safety and tolerability both as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors [2]. Similarly, GS-1811 (NCT05007782) has entered clinical development, with ongoing dose-escalation studies [11]. Notably, RO7502175 exemplifies the application of model-informed drug development: its first-in-human dose was precisely determined through comprehensive preclinical pharmacokinetic/pharmacodynamic (PK/PD) modeling, and a Phase I trial (NCT05581004) has subsequently been initiated [8]. Preliminary clinical data have also emerged for CHS-114, with early Phase I results

demonstrating robust target engagement—an 86% reduction in CCR8+ Tregs at the 100 mg dose level—in the absence of dose-limiting toxicities [12]. S-531011 has likewise entered Phase Ib/II clinical evaluation [3]. Collectively, these clinical advancements underscore the therapeutic promise of CCR8-targeted depletion strategies, with emerging safety and pharmacodynamic data supporting continued development.

Despite the rapid progress in translating CCR8-targeted therapies, the field continues to grapple with several fundamental debates and critical challenges. Chief among these is the ongoing contention regarding the functional role of CCR8 itself. Studies utilizing CCR8 knockout mouse models have reported that CCR8 is not essential for either the accumulation of TI-Tregs within tumors or their suppressive function, suggesting that CCR8 may serve primarily as a phenotypic "bystander" marker rather than a functional driver of immunosuppression [5]. In contrast, gain- and loss-of-function experiments from other groups have provided evidence that CCR8 signaling actively contributes to enhancing and maintaining the suppressive activity of TI-Tregs within the tumor microenvironment [4, 6]. This discrepancy is not merely an academic debate; it has direct implications for therapeutic strategy, guiding the fundamental choice between "cell depletion" and "signaling blockade" approaches. The current consensus, informed by accumulating preclinical evidence, leans decidedly toward depletion-based strategies, as multiple independent studies have consistently demonstrated the efficacy of ADCC-dependent monoclonal antibodies, whereas signaling blockade alone has failed to show significant therapeutic effects across various model systems [1, 5, 6]. This convergence of evidence suggests that while the biological role of CCR8 may be context-dependent, its value as a targeting moiety for selective Treg depletion is unequivocally validated.

A second major challenge lies in the absence of reliable predictive biomarkers to guide patient selection and stratify responders. Although high intratumoral infiltration density of CCR8+ Tregs has been consistently associated with poor prognosis across multiple malignancies, well-defined, clinically validated cutoff values for identifying patient populations most likely to benefit from CCR8-targeted therapies have yet to be established. Compounding this issue is the marked heterogeneity of CCR8 expression across different tumor types—for instance, high expression in colorectal cancer versus relatively low expression in certain renal cancers—as well as intratumoral spatial heterogeneity, which may render a "one-size-fits-all" patient selection strategy ineffective [6, 12]. Furthermore, the relationship between CCR8 expression and established immunotherapy biomarkers, such as PD-L1 expression levels or tumor mutational burden (TMB), remains to be systematically characterized. Whether CCR8 status provides independent predictive value or can be integrated into composite biomarker signatures to enhance patient stratification is an open question that warrants prospective investigation in ongoing clinical trials.

A third critical challenge pertains to the physical and biological barriers limiting therapeutic efficacy within solid tumors. Antibody penetration into tumor tissue remains inherently inefficient, and studies have revealed that Treg depletion efficacy is markedly lower in tumor core regions compared to peripheral margins (achieving only 35-45% reduction in core areas), a limitation that may prove particularly consequential in bulky or stroma-rich tumors where antibody accessibility is further compromised [2]. Beyond these physical delivery constraints, the functional heterogeneity and adaptive plasticity of TI-Tregs introduce an additional layer of complexity. Notably, a subset of TI-Tregs co-expresses alternative chemokine receptors such as CCR4, raising the concern that CCR8-directed therapies could induce compensatory redistribution, with Tregs migrating along the CCR4-CCL22 axis to maintain intratumoral immunosuppressive populations [9]. This potential for pathway redundancy and adaptive resistance underscores a fundamental limitation of targeting a single chemokine-receptor axis and suggests that durable therapeutic responses may ultimately require combinatorial strategies that simultaneously address multiple recruitment and retention pathways.

Future research should advance along four interconnected dimensions. At the mechanistic level, integrating multi-omics profiling with functional assays will be essential to delineate the precise role of CCR8 across distinct differentiation stages of TI-Tregs and within diverse tumor contexts. Such investigations are critical to resolving the ongoing debate regarding whether CCR8 functions primarily as a phenotypic marker or as an active functional mediator—a distinction that carries profound implications for the rational design of next-generation therapeutics. At the translational level, there is an urgent need to embed correlative studies within ongoing clinical trials. Paired biopsy analyses examining dynamic changes in CCR8+ Treg depletion and their correlation with objective response and survival outcomes will facilitate the establishment of evidence-based predictive biomarkers. This will enable a strategic evolution from

treating all CCR8-expressing tumors toward precision selection of patients with high intratumoral CCR8+ Treg infiltration. At the technological level, exploration of innovative delivery platforms—including nanobodies, bispecific T-cell engagers, or localized administration strategies—may help overcome existing barriers to intratumoral drug exposure and enhance Treg depletion efficiency. Finally, at the combination therapy level, given evidence that CCR8 targeting can upregulate tumor PD-L1 expression [2], synergistic combinations with PD-1/PD-L1 inhibitors—already validated across multiple preclinical models—warrant prioritized clinical translation. Additional combinatorial approaches targeting orthogonal immunosuppressive pathways, such as metabolic modulation (e.g., Oxamate) or TGF-β signaling, have also demonstrated preclinical promise and merit further investigation [13, 14]. Collectively, these multidimensional efforts will be essential to fully realize the therapeutic potential of CCR8-targeted strategies and to establish them as durable components of the immuno-oncology armamentarium.

4. Conclusion

Targeting CCR8, a selectively expressed marker on tumor-infiltrating regulatory T cells (TI-Tregs), has garnered significant attention as a promising precision strategy to overcome immunotherapy resistance. Accumulating evidence has established that CCR8 specifically identifies a highly suppressive functional subset of TI-Tregs, and its expression is robustly correlated with poor patient prognosis and resistance to immune checkpoint inhibitors across multiple tumor types. At the forefront of therapeutic development are ADCC-enhanced, afucosylated monoclonal antibodies designed for selective depletion of CCR8+ Tregs; these agents have demonstrated in both preclinical and early clinical studies the capacity to precisely eliminate intratumoral CCR8+ populations, achieving potent antitumor activity with a favorable safety profile. Parallel efforts are actively exploring diversified approaches, including small molecule antagonists, bispecific antibodies, and engineered CAR-T cells, each offering distinct mechanistic advantages. The core therapeutic rationale underlying CCR8-targeted strategies lies in the precise dismantling of the Treg-dominated immunosuppressive network, thereby remodeling “cold” tumors into ICI-sensitive “hot” tumors—a paradigm shift that embodies the evolution toward precision immunotherapy. Nevertheless, the field confronts persistent challenges, including fundamental debates regarding the functional role of CCR8, the absence of validated predictive biomarkers for patient stratification, and physical barriers limiting antibody penetration within solid tumors. Future investigations should prioritize elucidation of CCR8's molecular function across diverse tumor contexts, establishment of evidence-based biomarker strategies to guide patient selection, and exploration of rationally designed combination regimens capable of achieving deep and durable therapeutic responses.

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