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Rethinking Immune Resistance in HCC: Harnessing CXCR4/PD-1 Blockade's Potential to Enhance Dendritic Cell Function and Amplify Anti-Tumour Immunity

Abstract (50 words)

Immune checkpoint inhibitors greatly revolutionized hepatocellular carcinoma (HCC) treatment, yet efficacy is severely hindered by cDC1(conventional dendritic cells) scarcity. Dual CXCR4/PD-1 blockade shows promise in reviving cDC1 function, amplifying $CD8^+$ T-cell responses, and enhancing anti-tumour immunity to overcome current HCC treatment limitations (Darvin et al., 2018; Iranzo et al., 2022).

Background

Hepatocellular carcinoma (HCC) is one of the most aggressive and therapeutically resistant cancers worldwide, with limited treatment options and high relapse risk. Despite the advent of immune checkpoint inhibitors (ICIs), such as anti–PD-1 therapies, response rates in HCC remain dishearteningly low, underscoring the need for innovative combination strategies to improve treatment outcomes (Morita et al., 2025).

A hallmark of HCC is the depletion of conventional dendritic cells (cDC1s), which play a crucial role in orchestrating anti-tumour immunity by activating cytotoxic T lymphocytes (CTLs). The dysfunction and loss of cDC1s leads to impaired antigen presentation and weakened T-cell priming, facilitating immune evasion and tumour progression. Ineffective tumour antigen delivery and disrupted dendritic cell–T cell interactions further enable HCC to escape immune-mediated destruction (Sas et al., 2022).

A central question in this research is whether CXCR4 inhibition can amplify anti-tumour immunity when combined with anti–PD-1 therapy by restoring dendritic cell function and enhancing CTL responses. CXCR4 blockade has been shown to reverse tumour-supportive pathways by reducing the infiltration of myeloid-derived suppressor cells (MDSCs), limiting tumour-associated angiogenesis, and reinvigorating dendritic cell activity. These combined effects shift the tumour microenvironment (TME) from an immune-resistant "cold" state to an immune-permissive "hot" one, increasing tumour vulnerability to immune attack (Seo et al., 2021).

Emerging preclinical evidence suggests that targeting CXCR4 can restore dendritic cell functionality, leading to a more potent immune response when integrated with ICIs like anti–PD-1, a cornerstone treatment for HCC. Anti–PD-1 therapy functions by blocking the PD-1 receptor on T cells, preventing its engagement with PD-L1—an immune evasion tactic used by tumours to suppress T cell activation and avoid immune destruction. When PD-1 binds to PD-L1/PD-L2, it sends an inhibitory signal to the T cell, dampening its activation and effector functions, such as cytokine release and cytotoxic activity. By lifting this inhibitory mechanism, anti–PD-1 therapy reinvigorates exhausted T cells, enabling them to sustain a more effective and durable anti-tumour response (Song et al.,2021).

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Study Summary

This study addresses the limited success of anti-PD-1 monotherapy in HCC by investigating whether concurrent CXCR4 and PD-1 blockade can amplify anti-tumour immunity. Utilizing murine models of liver-damaged HCC, we assigned tumour-bearing mice to control, anti-PD-1, anti-CXCR4, or combination groups. We employed ultrasound imaging to track tumour burden, and immunofluorescence, flow cytometry, and RNA sequencing to assess how these treatments influenced immune activation and the tumour microenvironment (TME) (Wu et al., 2019). Notably, combination therapy led to increased tumour control, enhanced cDC1 and CD8+ T cell infiltration, and tighter spatial proximity between cDC1 and CD8+ T cells, facilitating efficient T-cell priming—an essential process for a robust immune response and effective tumour eradication (Morita et al., 2025).

RNA-seq data revealed that 90.3% of treatment effects were associated with immune antigen processing, underscoring the functional reactivation of the immune system. The 100 unique differentially expressed genes (DEGs) in the combination group reflected an immune shift, with GSEA confirming upregulated T-cell receptor signalling and dendritic cell maturation. These results position CXCR4 and PD-1 co-blockade as a promising candidate for clinical translation in HCC (Morita et al., 2025; Zeng et al., 2018).

Discussion

Murine models (Figure 1) provide a controlled setting to study tumour-immune interactions but fail to replicate the complexities of human HCC, which develops in a background of chronic liver disease, fibrosis, and metabolic dysregulation. Species-specific immune differences further limit clinical translatability.

This study highlights the CXCR4/cDC1/CD8+ T-cell axis, showing enhanced antigen presentation and T-cell activation. However, HCC's immunosuppressive microenvironment is multifaceted, with MDSCs, regulatory T cells, and alternative checkpoints also driving tumour evasion. Is this single-axis approach an oversimplification?

PD-1 blockade alone has shown limited success in HCC due to low response rates and resistance mechanisms (Morita et al.,2025). CXCR4 inhibition could, in theory, tilt the balance by promoting dendritic cell infiltration and T-cell priming. But at what cost? Chronic CXCR4 blockade raises concerns about immune homeostasis, off-target effects, and the sustainability of anti-tumour responses. Will this strategy hold up in long-term studies, or are we merely setting the stage for yet another transient immunotherapy response?

Several pressing questions remain:

- Is the sample size adequate to draw strong conclusions, given the ethical and financial constraints of animal studies?
- Could chronic CXCR4 inhibition lead to immune exhaustion or increased susceptibility to infections?

- Would targeting additional immune checkpoints alongside CXCR4 create more durable responses?

Future studies could:

- Investigate the impact of CXCR4/PD-1 co-blockade on metastatic spread, allowing us to get a larger sample sizes to obtain more robust and generalizable findings.
- Evaluate how CXCR4 inhibition influences immune cell trafficking, exploring the potential long-term consequences of chronic CXCR4 blockade on immune dynamics and tissue homeostasis.
- Assess the durability of immune memory responses following CXCR4/PD-1 co-blockade, to determine if the combination leads to lasting protection against tumour recurrence.
- Focus on developing next-generation CXCR4 antagonists with improved pharmacokinetic profiles, including enhanced selectivity, extended half-lives, and better tissue penetration, to increase the therapeutic potential and clinical applicability of CXCR4 inhibition.

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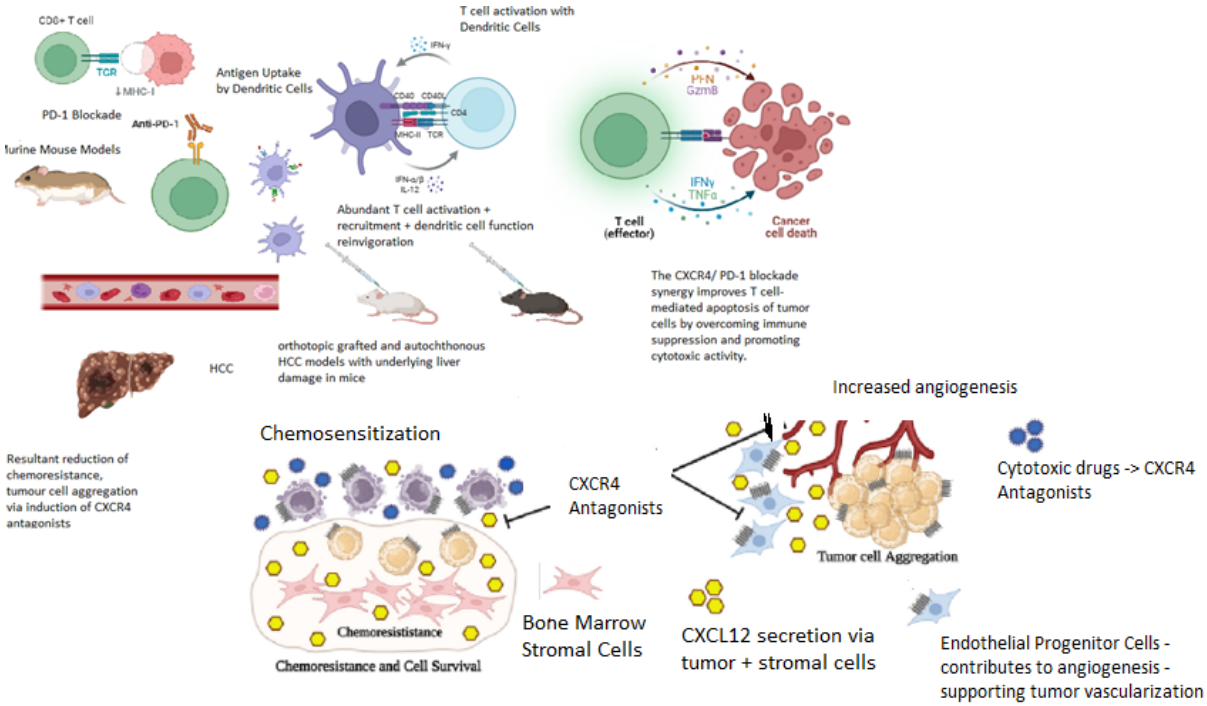

Summary Figure and Legend

Figure 1. Dual CXCR4/PD-1 Blockade Enhances Anti-Tumour Immunity in Orthotopic and Autochthonous HCC Mouse Models. *This figure demonstrates the synergistic effects of CXCR4 and PD-1 blockade in hepatocellular carcinoma (HCC) mouse models. In both orthotopic grafted and autochthonous HCC mouse models, dual blockade of CXCR4 and PD-1 significantly enhances immune cell infiltration, particularly dendritic cells and CD8+ T cells, within the tumour microenvironment. This combination therapy shifts the immune response from an immunosuppressive to an immune-activating state, promoting stronger anti-tumour immunity. Additionally, it improves immune cell recruitment and creates a pro-apoptotic environment, leading to better tumour control, highlighting its potential to become an effective therapeutic strategy for HCC treatment.*

Acknowledgement: *AI has been used to give feedback only and check that it fits the format of sounding like a commentary article. BioRender was used along with Paint and small images found online to create the summary figure.*