CXCR4 overexpression: an indicator of poor survival and predictor of response to Immunotherapy in patients with metastatic colorectal cancer.

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Background

CXC-chemokine receptor 4 (*CXCR4*) is a ubiquitous chemokine receptor activated by the CXCL12 ligand and is implicated in tumor invasion, metastasis, and immune cell (IC) trafficking. High *CXCR4* expression is associated with poor prognosis in colorectal cancer (CRC). < 10% of metastatic CRC cases harbor microsatellite instability (MSI-H) and demonstrate lower tumor mutation burden (TMB), decreased IC infiltration, and lack of response to current immunotherapy regimens. This study aims to interrogate the role of *CXCR4* mRNA expression on the the tumor microenvironment (TME) and its prognostic and predictive value to tailor immunotherapeutic treatment strategies in CRC.

Methods

A total of 15,026 CRC samples were analyzed using whole-exome sequencing, whole-transcriptome sequencing, and immunohistochemistry (Caris Life Sciences, Phoenix, AZ). Study cohort was stratified by *CXCR4* mRNA expression levels in quartiles (Q1 (low) vs Q4 (high)). TMB-H was classified based on a cut-off of ≥10 mutations per MB. IC fraction was calculated by QuantiSeq, and real-world overall survival information was obtained from insurance claims data and calculated from tissue collection time to last day of contact. Statistical significance was determined using chi-square/Fisher-Exact and adjusted for multiple comparisons ($q < 0.05$).

Results

Table 1- Patient demographics

	CXCR4 Q1	*CXCR4* Q4
Count (N)	3857	3856
Average Age (range)	61.9 (20 - >89)	61.6 (15 - >89)
Male	55.4% (2135/3857)	53.1% (2048/3856)
Female	44.6% (1722/3857)	46.9% (1808/3856)

Figure 1- *CXCR4* expression in consensus molecular subtypes.

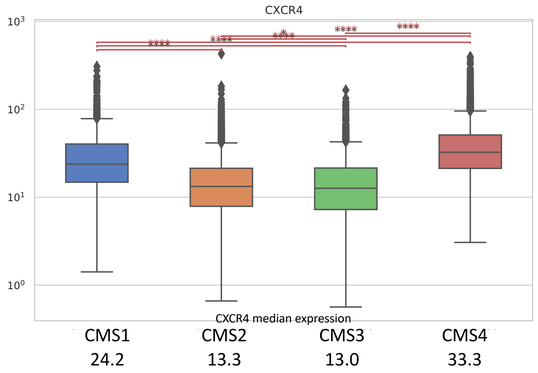


Figure 2- *CXCR4* expression for Primary/Local vs Metastatic

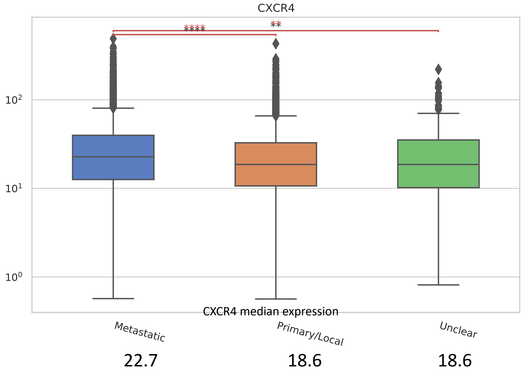


Table 2- *CXCR4* expression median for liver metastatic tumors vs non-liver (p value for comparison to non-liver metastasis).

	Median *CXCR4* expression (TPM)	N	*q* value
Primary/Local	18.6	8335	*q*<0.001
Liver Metastasis	21.5	2988	*q*<0.001
Non-Liver Metastasis	24.8	3392	*q*<0.001

Figure 3- IO markers in *CXCR4* expression quartiles Q1 (low) vs Q4 (High)

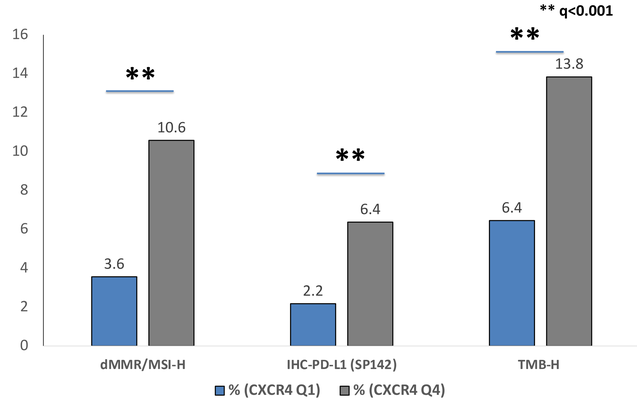


Figure 4- Tumor microenvironment for *CXCR4* expression quartiles Q1 (Low) vs Q4 (High). Values shown are median infiltration. Red bars indicate statistical significance.

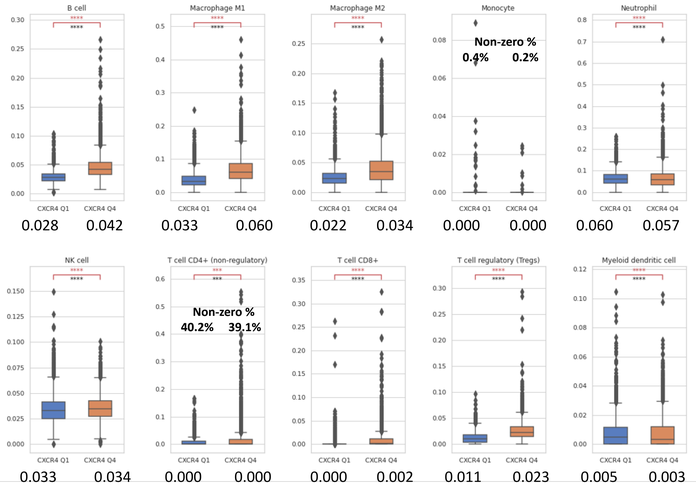


Figure 5a: High *CXCR4* expression in primary tumors was associated with poor prognosis

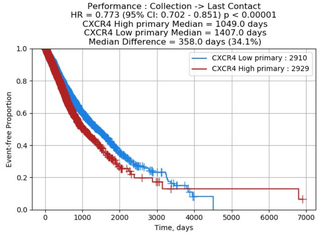
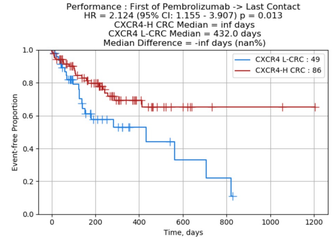


Figure 5b: High *CXCR4* expression was associated with improved survival in all patients with CRC who received pembrolizumab.



Conclusions

- *CXCR4* expression was significantly higher in metastatic tumors than in primary tumors (22.7 vs 18.6 median TPM). However, in liver metastasis, *CXCR4* expression was significantly lower than non-liver metastasis (21.2 vs 24.8 median TPM).
- *CXCR4* expression was highest in CMS4 (median 33.3) and lowest in CMS3 (13.0).
- When comparing high expressers vs low expressors, *CXCR4* expression was positively associated with TMB-H (3.6% vs 10.6%), MSI-H/dMMR (2.2% vs 6.4%) and PD-L1 positive (6.4% vs 13.8%).
- In the TME, high *CXCR4* expression was associated with high infiltration of B cells, M1/M2 macrophages, NK cells, CD8+ T cells and T-regs regardless of MSI status.
- For outcomes, high *CXCR4* expression in the primary tumor was associated with poor prognosis (HR 0.77, 95% CI 0.70-0.85; p < 0.001) regardless of MSI status.
- High *CXCR4* expression was associated with improved survival in all CRC patients who received pembrolizumab (HR 2.12, 95% CI 1.16-3.91; p = 0.013).
- This is the largest clinical dataset to date demonstrating high *CXCR4* expression as a predictor for poor survival in CRC. Furthermore, high *CXCR4* expression was associated with improved outcome after checkpoint inhibition immunotherapy, indicating its strong potential as a predictive biomarker that could inform immunotherapeutic strategies in CRC.

References