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CCR5 and CCL5 in metastatic colorectal cancer

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ABSTRACT

The CCR/L5 axis is known for its role in immune regulation in a variety of settings and has been shown to have dichotomous functions in cancer, influencing both tumor progression and immune responses. Battaglin et al investigated its role using genomic and transcriptomic data from several datasets of patients with advanced colorectal cancer (CRC), including patients treated on CALGB/SWOG 80405, a trial of chemotherapy plus cetuximab versus bevacizumab, as well as a larger population of patients whose CRCs underwent commercially available Caris NGS and CODEai assays. These authors showed that CCR/L5 expression was both prognostic and predictive. They reported that low expression of the CCR/L5 axis was correlated with improved survival broadly, with particular benefit in patients treated with chemotherapy plus cetuximab. They demonstrated that high expression of CCR/L5 was associated with infiltration by negatively prognostic Tregs, M1 and M2 macrophages, myeloid-derived suppressor cells, and cancer-associated fibroblasts. They also showed that increased expression was correlated a wide variety of immune suppressive proteins, including PD-1, PD-L1, PD-L2, CTLA4, CD80, CD86, TIM3, IDO1, LAG3, and IFN-γ. This suggests mechanisms by which CRC resists anti-cancer immune responses. This study enhances our understanding of the role of the CCR/L5 axis in advanced CRC.

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The C-C motif chemokine receptor and ligand type 5 (CCR5 and CCL5, respectively) axis is a well-described pathway in immune regulation famously associated with HIV-1 resistance due to mutations that inhibit viral infection and has emerged as a therapeutic target in the fight against AIDS.[1] CCR5 is a cell surface receptor that is expressed on various immune cells while CCL5 is a chemokine that interacts with CCR5 to mediate cellular migration and immune cell recruitment. In cancer, the function of the CCR/L5 axis is dichotomous, influencing both tumor progression and antitumor immune responses. CCR/L5 signaling has been shown to increase infiltration of regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment (TME), contributing to an immune effector cells desert that promotes cancer survival and progression,[2] and perhaps resistance to immunotherapy. This pathway has also been shown to be prognostic and predictive in metastatic colorectal cancer (CRC).[3 4] The accompanying article by Battaglin *et al*[5] evaluates the role of this pathway in metastatic CRC, a disease in which immunotherapy has historically been ineffective except in rare cases of mismatch repair deficient/microsatellite high (dMMR/MSI-H) disease. However, in the far more common MMR proficient/microsatellite stable (pMMR/MSS) CRC, there have been only hints of benefit from immune checkpoint blockade with tantalizing results in selected individuals.

Here, the investigators used next-generation sequencing (NGS) and transcriptomic data from patients with metastatic CRC tested using the Caris NGS and CODEai assays (Caris Life Sciences, Phoenix, Arizona, USA) and validated their findings on tissue prospectively collected as part of the Cancer and Leukemia Group B/South West Oncology Group (CALGB/SWOG, now Alliance) 80405 trial of first-line palliative 5-fluorouracil and leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus either bevacizumab or cetuximab for the first-line treatment of metastatic CRC. Both MSS and MSI-H cancers were included in this evaluation, but pooled analysis of these subtypes has little clinical relevance as these disease are biologically and therapeutically distinct. However, preplanned analysis of the MSS CRC cohorts made several striking findings. First, higher CCR/L5 expression was associated with increased levels of infiltration by Tregs, M1 and M2 macrophages, MDSCs, and cancer-associated fibroblasts (CAFs) among other cell types associated with poorer prognosis. They also report higher levels of expression of immune checkpoint genes and immune exhaustion signals in tumors with higher expression of CCR/L5. These authors note that CCL5 in particular has been reported to be elevated at the invasive margin of CRC liver metastases, suggesting a mechanism for particular resistance to immune checkpoint blockade in this setting.[6 7]

In their analysis of the CALGB/SWOG 80405 of first-line palliative FOLFOX or FOLFIRI plus bevacizumab versus cetuximab for metastatic CRC, these authors report that CCR/L5 expression is both prognostic and predictive, with low expression being associated with prolonged survival and particular benefit from FOLFOX plus cetuximab. However, this finding may be confounded by patient factors associated with the investigator choice of FOLFOX over FOLFIRI. While both regimens were allowed per protocol, the choice was not randomized. FOLFIRI is more likely to be chosen in patients with baseline neuropathy, most commonly diabetic neuropathy, as well as those who received prior adjuvant FOLFOX. Consequently, it is not possible to exclude the possibility that the population who received FOLFIRI over FOLFOX may have distinct patient factors that could impact the inflammatory milieu and oncological outcomes.

Additionally, the association between low CCR/L5 expression and benefit from cetuximab may be confounded by 'sidedness' of the CRC. In CALGB/SWOG 80405, right-sided cancers did not derive benefit from cetuximab over bevacizumab, and right-sided cancers did more poorly generally. Indeed, these authors note that the opposite effect was seen in prior analyses of the FIRE-3 trial. FIRE-3 enrolled patients with newly diagnosed metastatic CRC and treated them with first-line palliative FOLFIRI plus bevacizumab versus cetuximab.[8] Oxaliplatin was not offered so no conclusions can be made about the differential association between FOLFIRI and FOLFOX. Additionally, this trial only enrolled *KRAS* G12 wild-type cancers, which is in contrast to CALGB/SWOG 80405 in which there was no selection by mutation status. Given this, further validation is required to ascertain the use of CCR/L5 testing to guide therapeutic choices in metastatic CRC, and it seems premature to use this profile to choose FOLFOX over FOLFIRI or cetuximab over bevacizumab at this time.

These authors also report that CCR/L5 activity was positively associated with mutations in *BRAF* and *RNF43*. *BRAF* mutations are rare, occurring in around 3% of metastatic CRCs, but can be associated with both MSS and MSI-H cancers via *MLH1* promoter hypermethylation, and it is not clear from these data how to contextualize this association.[9] Mutations in *RNF43* have been shown to confer a poor prognosis and resistance to EGFR inhibitors, especially in right-sided colon cancers and in those treated with cetuximab in this exact same cohort of patients from CALGB/SWOG 80405.[10 11] In fact, *RNF43* is an emerging biomarker in CRC and has been shown to be 12 times more common in right-sided CRC than left-sided cancers and is associated with inferior survival (11.5 months vs 30.1 months). These findings may further confound the interpretation of CCR/L5's impact in isolation, and association versus causation is not clear here. Nevertheless, given the large effect size and large population assessed here, this association merits further study in other colon cancer datasets and should be investigated in future CRC trials.

Expression of immune regulatory genes including PD-1, PD-L1, PD-L2, CTLA4, CD80, CD86, TIM3, IDO1, LAG3, and IFN-γ was increased in pMMR/MSS cancers with higher expression of CCR/L5. This could suggest that these features of immunologically hotter tumors are 'chilled' to cold tumors by CCR/L5 activity, resulting in suppression of effector T cells, support of Tregs, and infiltration of the TME by MDSCs and CAFs. Several clinical trials are investigating the use of a CCR5 inhibitors in combination with checkpoint blockade (NCT04721301) or chemotherapy versus checkpoint blockade (NCT03184870). NCT04721301 investigates ipilimumab and nivolumab, CTLA-4 and PD-1 inhibitors, respectively, with maraviroc, a CCR5 receptor antagonist, while NCT03184870 investigates nivolumab versus chemotherapy with BMS-813160, a CCR5 and CCR2 receptor antagonist, but without CTLA-4 blockade. These authors speculate that CCR/L5 activity may be a predictive marker and offer mechanistic support for use of these agents. Results from these trials would provide strong evidence supporting the hypothesized role of this pathway and a therapeutic effect in patients would be the best possible data validation of these findings. Note, should these trials fail, it would make sense to look closely at the results of this current study to identify additional targets that may need to be addressed to overcome CRC's impressive resistance to conventional checkpoint blockade, especially in those with liver metastases. It remains to be seen which combinations will succeed.

Taken together, this and other work published by this group has contributed to our knowledge of the pathways contributing to the progression of CRC. These investigators are chipping away at the black box around the mechanisms of resistance to immunotherapy in MSS CRC. While it is too soon to make definitive conclusions about the exact role of CCR/L5 in CRC, these data suggest that this pathway is critical to understanding the immunosuppressive environment and treatment resistance to checkpoint blockade here. The data on chemotherapy backbones and EGFR inhibitors are somewhat less clear due to the limitations of the datasets used. The retrospective nature of the Caris participants and inability to stratify these patients more accurately is one challenge that cannot be addressed here. The data derived from patients treated on CALGB/SWOG 80504 must be approached with caution, as a selection of chemotherapy may be related to comorbid conditions that impact CCR/L5 activity. Hopefully, results of the open and enrolling trials of maraviroc and BMS-813160 will solidify the value of the CCR/L5 axis as a therapeutic target in advanced CRC. These results remain descriptive, and the ultimate test is therapeutic trials to validate these findings. These authors should be complimented for a detailed and focused analysis of the CCR/L5 axis in CRC.

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Competing interests From 2020 to present, JS has been Editor-in-Chief of Oncogene and has sat on SABs/advisory boards for Vaccitech, Heat Biologics, Lilly, Alveo Technologies, Pear Bio, Agenus, Equilibre Biopharmaceuticals, Graviton Bioscience Corporation, Celltrion, Volvox, Certis, Greenmantle, vTv Therapeutics, APIM Therapeutics, Onconox, IO Labs, Bryologyx, Clinical Ink, Zephyr AI, Benevolent AI, Sable Bio and Linkgevity. He has consulted with Lansdowne partners and Vitruvian. He chairs the Board of Directors for Xerion, is a board member for Graviton and Etira, and previously BB Biotech Healthcare Trust PLC. BS served on the advisory boards of Agenus, Janssen and Quercegen.

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