



# The Fractalkine-Receptor Axis Improves Human Colorectal Cancer Prognosis by Limiting Tumour Metastatic Dissemination

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## Introduction

Colorectal cancer represents one of the most frequent human neoplasia in Western Countries. Patient prognosis dramatically decreases in advanced tumour stage, when tumour cells acquire the capability to leave the primary tumour site and invade lymph nodes or distant organs. Chemokines and chemokine receptors have been largely demonstrated to play a crucial role in tumour metastatic progression, influencing the leukocyte composition of the tumour microenvironment through the recruitment of immune cells and driving tumour cells to distant metastatic sites [1,2].

In our recent paper, we unexpectedly found that the concomitant expression of the chemokine CX<sub>3</sub>CL1 (Fractalkine) and its specific receptor CX<sub>3</sub>CR1 by colorectal cancer cells strongly enforces homotypic tumour cell adhesion, retaining cells locally and avoiding tumour metastatic dissemination [3]. Clinically relevant, in colorectal cancer patients, the co-expression of ligand and receptor results in a significant reduced risk of tumour relapse and metastatic spreading and increased patients' survival.

Our study sheds light on the new idea that the relationship between chemokine expression and cancer cells is not always associated with tumour metastatization. Historically, chemokines are viewed as mobilizing factors, controlling cell trafficking in both healthy and pathological conditions, and chemokine receptor expression by tumour cells has been associated with metastatic dissemination [4-6]. Recently, this paradigm has been called into question by different studies, demonstrating that the same chemokine-receptor pair can act both as a mobilizing and retention factor, depending on the tissue context. For instance, the expression of the chemokine receptor CXCR4 by tumour cells has been widely associated with metastatic events [7,8]. On the contrary, CXCR4<sup>+</sup> hematopoietic stem cells are retained within the bone marrow niche by the chemokine CXCL12. Similarly, immature thymocytes are kept in the thymic cortex by the CXCL12-CXCR4 axis [9]. Another example is represented by the chemokine receptor pair CCL25-CCR9: the expression of the CCL25-CCR9 axis has been associated with metastatic dissemination in different tumours, such as lung cancer, melanomas and ovarian cancer [10-12]. Recently, Chen and colleagues demonstrated that the CCL25-CCR9 axis inhibits colorectal cancer invasion and metastasis: colon epithelial cells produce the chemokine CCL25 that retains chemokine-receptor CCR9<sup>+</sup> neoplastic cells at primary tumour site [13].

Our study is in line with this observation in the context of tumoural expression of the chemokine-receptor axis CX<sub>3</sub>CL1-CX<sub>3</sub>CR1. Of note, the chemokine CX<sub>3</sub>CL1 exists both as a secreted ligand and a trans-membrane protein; in this latter form, it functions as a perfect adhesion molecule. This effect was mechanistically demonstrated *in vitro* where the CX<sub>3</sub>CL1-CX<sub>3</sub>CR1 axis mediated homotypic tumour

cell adhesion, and in *in vivo* mouse experiments, where the axis prevented tumour cell metastatization to the liver, principally acting as a retention factor [3].

This new paradigm on the role of chemokines in local tumour retention needs to be integrated with the general dogma where chemokines are viewed as mobilizing factors favouring tumour dissemination. We and others have previously reported that CX<sub>3</sub>CR1 expression is involved in tumour metastatic spread in different neoplasia, including prostate, breast, pancreatic cancer, hepatocellular carcinoma and glioblastoma [14-18]. For instance, in prostate and breast cancer, CX<sub>3</sub>CR1<sup>+</sup> tumour cells, already circulating in the blood, are attracted to distant sites by CX<sub>3</sub>CL1-expressing cells, driving the metastatic progression of the disease [16,17]. In human pancreatic ductal adenocarcinoma, we previously demonstrated that CX<sub>3</sub>CR1<sup>+</sup> tumour cells adhere to nearby CX<sub>3</sub>CL1<sup>+</sup> neural cells and ganglia, leading to a local, rather than distant, tumour recurrence [15]. In our recent manuscript in colorectal cancer, we have shown that CX<sub>3</sub>CR1<sup>+</sup> tumour cells are retained within the primary tissue by tumour cells expressing the ligand and those patients with concomitant expression of both ligand and receptor have longer survival and lower risk of developing metastasis [3]. Although the final outcome can be dramatically different (metastatic progression versus longer survival and reduced metastatic risk), the underlying mechanism is always the attraction of chemokine receptor-positive tumour cells by its specific ligand. In evaluating the role of CX<sub>3</sub>CR1 (or any other chemokine receptor) in metastasis, the source of the ligand is of major importance: when it is highly expressed within primary tumour, receptor-positive cells refrain from dissemination, but if the ligand is locally absent and expressed at distant sites, receptor positive cells can spread out of the primary tumours, enter the circulation, and metastasize to distant organs. Among these two extremes (high local vs. no local expression), a wide range of conditions are possible, also considering the well-known genomic instability of cancer cells. However, it appears unlikely that tumours within the primary mass can sense chemokine ligands produced at distant sites.

In conclusion, we think that our and other recent studies challenge the concept that a chemokine-receptor axis always represents a metastatic driving force. Although chemokines remain key players of metastatic progression in a variety of tumours, some exceptions to this rule have been recently provided. Indeed, a new and more complex scenario is emerging; where the source of the ligand, as well as the cell types expressing the chemokine receptor play a crucial role in determining the metastatic outcome of the disease. This opposite effect of the same mechanism sheds new light on the role of chemokine-receptor axis in tumour progression, enforcing the need of deeper investigations of their function and their possibly anti-tumoural therapeutic targeting.

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