Commentary

CCR5 antagonist, an ally to fight against metastatic colorectal cancer

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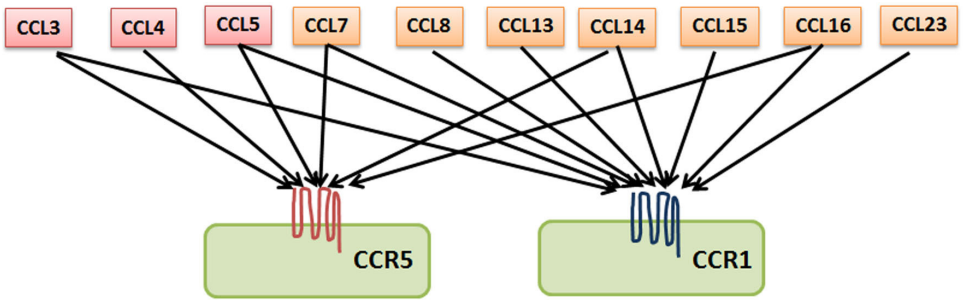
Colorectal cancer (CRC) is the third most commonly diagnosed cancer (1.36 million cases) in the world (1). Nearly three quarters of newly diagnosed CRC patients have localized disease and can be cured with surgical resection (2). However, the remaining patients present with metastatic diseases. Moreover, a considerable number of patients experience recurrence and/or metastatic disease even after curative surgery. These patients need systemic therapy consisting mainly of chemotherapy and/or molecular targeting therapy. The advancement in these therapeutic modalities has improved the prognosis of CRC patients with metastasis and/or recurrence, but their median overall survival still remains about 2 years (2). Thus, an additional type of therapy is required for the treatment of CRC patients with metastasis and/or recurrence.

Immune therapy has been proposed to be a candidate to supplement chemotherapy for a long time but with little success until recently. However, the recent advances in the understanding of molecular mechanisms of T cell activation and inhibition have allowed for the development of effective immune therapies for cancer, particularly those using monoclonal antibodies against inhibitory immune checkpoint pathways (3). The inhibition of two immune checkpoint pathways, CTLA-4 and PD-1-PD-L1, has been approved clinically in United States, European Union, and Japan. CTLA-4 blockade is effective for metastatic melanoma but is largely disappointing for other types of cancers, particularly solid ones (3). On the contrary, phase III clinical trials have proved that PD-1-PD-L1 blockade is effective for several solid tumors, particularly non-small cell lung cancer (NSCLC) besides melanomas (4,5). However, the objective response rate is about 20% to 30% among NSCLC patients. A low response rate promoted the research to identify biomarkers to predict the response to PD-1-PD-L1 blockade. As a consequence, mismatch repair-deficient CRCs have been identified to be a better responder to PD-1 blockade with 40% objective response rate, compared with mismatch repair-proficient ones, which did not show any apparent objective response (6). However, only less than 20% of CRC are mismatch repair-deficient (7) and therefore, additional immunological strategies may be required to combat CRC. Halama *et al.* identified a chemokine receptor, CCR5, as a potential target molecule to counteract CRC metastasis, particularly liver metastasis (8).

Chemokines are heparin-binding cytokines with four cysteine residues in the conserved position and are structurally divided into four subgroups, CXC, CC, CX3C, and C, depending on the alignment of the first and the second cysteins (9). Most chemokines are secretory proteins, but upon their secretion, they are immobilized on endothelium cells and/or extracellular matrix by interacting with proteoglycans and glycosaminoglycans. Chemokines exert their biological activities by binding their cognate receptors, which belong to trimeric G-protein coupled receptors (GPCR) with 7-span transmembrane portions (9). Thus, the target specificity of each chemokine receptor is determined by the expression pattern of its corresponding receptor. CCR5 is a specific receptor for several CC chemokines, such as CCL3, CCL4, and CCL5, and is expressed by myriad types of immune cells such



Neutrophils	–	+
Basophils	–	+
Monocytes/macrophages	+	+
Immature dendritic cells	+	+
Th1	+	+
Th17	+	–
Regulatory T cells (Treg)	+	–
Cytolytic T cells	+	–
Natural killer cells	+	–
Oteoclasts	+	+
Fibroblasts	+	–

Figure 1 Redundant usage of CCR5 and CCR1 by CC chemokines and cellular distribution of CCR1 and CCR5, the figure is made based on the reference (9), with some modifications.

as monocytes, macrophages, immature dendritic cells, myeloid-derived suppressor cells (MDSC), Th1 cells, activated T cells, natural killer cells, and regulatory T cells (Treg) (*Figure 1*) (9). Moreover, CCR5 is a major co-receptor for human immunodeficiency virus (HIV) entry (10) and homozygous CCR5 deletion mutant confers resistance to HIV infection but does not cause any apparent pathological changes (11). These observations implicate CCR5 as a druggable target for HIV infection and as a consequence, several small-molecule chemicals have been developed to antagonize CCR5 (10).

Halama *et al.* determined the cytokine profiles in human CRC liver metastasis sites, after dissecting them into three parts, invasive margins, liver metastases, and adjacent liver tissues and demonstrated that CXCL9, CXCL10, and CCL5 were selectively expressed in the invasive margins (8). Both CXCL9 and CXCL10 were produced by myeloid cells and induced lymphocyte migration by acting their cognate receptor, CXCR3. On the contrary, CCL5 was expressed in the invasive margin, predominantly by CD3-positive T lymphocytes and was presumed to be associated with functional T cell exhaustion as evidenced by decreased interferon (IFN)-γ expression by T lymphocytes in the invasive margin. Moreover, CCR5 was expressed dominantly by metastatic tumor cells and to a lower extent by lymphocytes and myeloid cells.

By using organotypic explant models established from human CRC liver metastasis foci, Halama *et al.* demonstrated that CCR5 inhibition activated STAT3 in macrophages in the invasive margin (8). This induced macrophages to re-polarize into M1 state as evidenced by enhanced expression of IFN-α and IFN-γ and reciprocal decreased expression of CXCL8 and vascular endothelial growth factor and as a consequence, tumor cell viability was depressed (8). Taken into consideration that a CCR5 allosteric antagonist, maraviroc, is approved for HIV treatment in many countries and is well tolerated by HIV infected patients (10), Halama *et al.* further conducted phase I clinical trial of maraviroc for previously treated CRC patients with liver metastasis (8). Their clinical trials revealed that maraviroc treatment caused similar changes in cytokine expression patterns in the invasive margin of liver metastasis. Moreover, they demonstrated the absence of significant adverse effects for maraviroc treatment with partial responses in patients with previously refractory diseases (8). Collectively, they claimed that CCR5 inhibition can modulate tumor microenvironment and possibly tumor cells in the invasive margin, thereby mitigating tumor cell growth.

There are earlier literatures describing the therapeutic

efficacy of CCR5 inhibition in mouse models. CCR5 is expressed by immune suppressing cells including MDSC and Treg (9). Thus, CCR5 inhibition can augment tumor immunity by suppressing Treg infiltration (12,13) or MDSC generation (14), thereby delaying tumor growth. It is probable that similar mechanisms may also work in the invasive margin of liver metastasis sites. CCR5 is also expressed in cancer-associated fibroblasts (CAF) in mouse colon cancer tissues and CCR5 inhibition retarded colon tumor formation by reducing CAF (15). However, the paucity of CAF in the invasive margin may preclude the involvement of CAF in CRC liver metastasis.

Several groups reported that CCR5 is expressed by gastric cancer (16), breast cancer (17), and prostate cancer cells (18), consistent with Halama's observations (8). In these reports, the CCR5 axis has an important role in dissemination and distant metastasis by enhancing the motility of cancer cells. It is probable that CCL5 can enhance the motility of CRC cells in the invasive margin, thereby facilitating the invasion of CRC cells.

Considering Halama's observation together with these previous reports, CCR5 inhibition may provide us with a new strategy for the treatment of various cancers including CRC. However, CCR5 blockade possesses several snares. First of all, similar sets of CC chemokines exert their biological activities by acting on another chemokine receptor, CCR1 (*Figure 1*) (9). Thus, it is probable that CCR1-mediated signals may compensate the loss of CCR5-mediated ones. Of more importance is that CCR5 blockade enhanced proliferation of xenografts from breast cancer cells with wild-type p53, but it did not affect proliferation of breast cancer xenograft bearing p53 mutation (19). Consistently, disease-free survival was shorter in breast cancer patients with a CCR5 mutant allele, whose tumors expressed wild-type p53 (19). Thus, it is necessary to clarify the roles of p53 in CCR5-mediated promotion and progression of CRC, before employing CCR5 antagonists clinically for the treatment of CRCs, particularly those with metastasis.

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Footnote

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