Erschienen in: The International Journal of Biochemistry & Cell Biology ; 54 (2014). - S. 78-82
https://dx.doi.org/10.1016/j.biocel.2014.07.002

CCR7: Roles in cancer cell dissemination, migration and metastasis formation

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A B S T R A C T

The CC-chemokine receptor 7 (CCR7) coordinates the migration of cancer cells as well as immune cells towards lymphatic organs where its two ligands CCL19 and CCL21 are constitutively expressed. Here we provide a topological model of CCR7, which belongs to the class A of G-protein coupled, seven-transmembrane spanning receptors, and describe how CCR7 expression is regulated. We focus on its role in cancer cell migration and metastasis formation and discuss how cancer cells can utilize CCR7 or its ligands to escape from immune surveillance.

Keywords:
Chemokine receptor
Cancer
Metastasis formation
Cell migration
Lymph node homing

1. Introduction

Cell migration is an essential process in the development and maintenance of multicellular organisms and is defined by the orchestrated movement of cells in a particular direction to a specific location. Locally produced chemokines can form gradients (Weber et al., 2013) and represent major guidance cues that control directional cell migration in both health and disease, e.g. during cancer dissemination and metastasis formation. Migrating cells sense the chemokine gradient via specialized chemokine receptors, which belong to the family of G-protein coupled receptors (GPCRs) (Venkatakrishnan et al., 2013). The CC-chemokine receptor 7 (CCR7) was identified in 1993 as the first lymphocyte specific, but orphan GPCR and named Epstein–Barr virus-induced gene 1 (EBI1) (Birkenbach et al., 1993). The same gene was subsequently identified in a homology screen for chemokine receptors in Burkitt's lymphoma two years later and termed Burkitt's lymphoma receptor 2 (BLR2) (Burgstahler et al., 1995). EBI1/BLR2 was renamed to CCR7 after the identification of its chemokine ligand ELC (Yoshida et al., 1997). Additional synonyms are CC-CKR-7, CMKBR7, CD197 and CDw197. Two ligands for CCR7, termed CCL19 (ELC) and CCL21 (SLC), have been identified (Willimann et al., 1998). Both CCR7 ligands are predominantly produced constitutively by stromal cells within primary and secondary lymphoid organs and are therefore considered to be homeostatic chemokines. CCL21 is additionally expressed by lymphatic endothelial cells in peripheral tissues (Forster et al., 2008).

2. Structure

The gene encoding CCR7 is located on human chromosome 17q12-21.2 and is composed of three exons that encode a protein of 378 amino acids (Schweickart et al., 1994). The mouse homolog is on chromosome 11 and the protein shows 86% identity to human CCR7. Structurally, CCR7 belongs to the large class A subgroup of GPCRs which also includes rhodopsin, monoamine and β-adrenergic receptors (Venkatakrishnan et al., 2013). Based on the β1-adrenergic receptor crystal structure (Huang et al., 2013), we have modeled a putative structure of CCR7 (Fig. 1). Systematic analysis of recently solved crystal structures of class A GPCRs have revealed structural explanations for characteristic features of conserved sequences of GPCRs (Audet and Bouvier, 2012; Venkatakrishnan et al., 2013). Most prominently, a sequence element termed the DRY motif (DRYVAIV in CCR7, Fig. 1, light green box) at the end of transmembrane domain (TM)3 plays an essential role in controlling receptor activity and G-protein coupling. In addition, the presence of a polar interaction between the arginine of the DRY motif and a glutamate in TM6 stabilizes the inactive state of the receptor, forming the so called "ionic lock" (Fig. 1, dark green box). Disruption of the "ionic lock" of the β2-adrenergic receptor results

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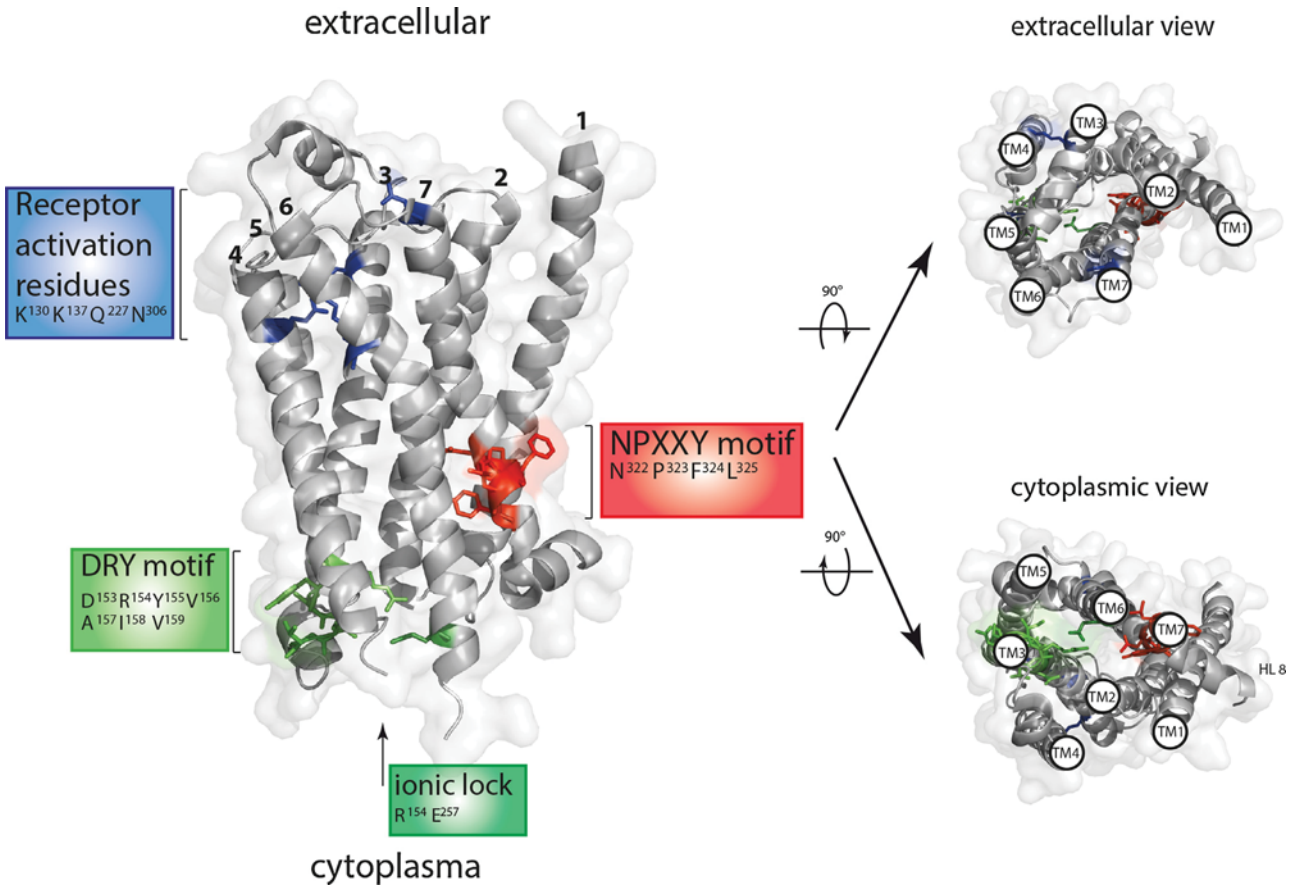

Fig. 1. CCR7: Topological organization and signaling paradigm. Three dimensional illustration of the seven transmembrane topological conformation of CCR7. The model was created using PyMOL (www.pymol.org) and based on the β1-adrenergic receptor crystal structure (accession number 4GPO in the PBD database). Conserved structural features of class A GPCRs are highlighted: DRY motif in light green, NPXXY motif in red, ionic lock in dark green. In addition, the position of four known receptor activation residues are marked in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in an outward movement of TM6 creating a crevice for the interaction with the heterotrimeric G-protein. Furthermore, the tyrosine residue in the well conserved NPXXY motif at the end of TM7 (Fig. 1, red box) is repositioned as the entire motif moves inward in the active state of the receptor as demonstrated for opsin. This repositioning prevents the reverse movement of TM6 and hence stabilizes the open conformation of the receptor that forms the cradle for the G-protein. Although chemokine receptors generally do not signal in the absence of ligands, several single point mutations – primarily at the cytoplasmic ends of TM3 and TM6 – resulting in constitutive active receptors with involvement in cancer formation have been reported (Han, 2014). Apart from high conservation among certain sequence features and TM domains of GPCRs, substantial differences are found in the extracellular loop (EL) domains, especially in EL2, providing specificity for ligands entering the receptor binding pocket. Principally, chemokines are thought to bind to their receptors by a "two-step/two-site" mechanism (Crump et al., 1997). First, the N-terminus of the receptor binds to the extended loop of the chemokine (site 1) followed by the chemokine N-terminus binding to a second site (pocket) of the receptor causing receptor activation. For CCR7, four receptor activation residues were identified to be crucial for CCL19/CCL21-mediated receptor activation, but not for high affinity ligand-binding (Fig. 1, in blue) (Ott et al., 2004). Such structure–function-relations are key for the rational design of novel therapeutic drugs. Such an approach has successfully been persuited to develop CCR5 antagonists (like TAK-779, maraviroc and piperidine core containing lead compounds) to interfere with CCL5-mediated prostate cancer proliferation and/or invasion (Arnatt et al., 2013).

3. Expression, activation and turnover

CCR7 is naturally a homeostatic chemokine receptor and expressed on various subtypes of immune cells that migrate to and within lymphoid organs (Comerford et al., 2013; Forster et al., 2008). CCR7-expressing immune cells encompass naïve, central memory and regulatory T cells, B cells, NKs, subsets of thymocytes and (semi-)mature dendritic cells (DCs). Generally, T cell subsets constitutively express CCR7 enabling them to circulate between the bloodstream, lymphatics and secondary lymphoid organs. In contrast, DCs acquire CCR7 expression upon pathogen encountering, which enables homing to lymph nodes and antigen-presentation to cognate T cells. Of note, this CCR7-mediated homing of DCs is crucial for the initiation of an adaptive immune response. Under certain pathological conditions, CCR7-dependent naïve T cell migration to chronically inflamed non-lymphoid tissues contributes to the development of autoimmune diseases, including rheumatoid arthritis (Comerford et al., 2013).

An association of CCR7 with cancer was recognized in T cell leukemia patients where T cell leukemia cells from adult patients with lymphoid organ infiltration expressed significantly higher levels of CCR7 than normal T cells or leukemia cells from patients without lymphoid organ involvement (Hasegawa et al., 2000). Subsequently, a hallmark study identified a crucial role for chemokine receptors, including CCR7, in breast cancer metastasis formation (Muller et al., 2001). In fact, expression of a single chemokine receptor gene in cancer cells, as exemplified by CCR7 on melanoma, results in a significant increase in metastasis formation in draining lymph nodes, suggesting that cancer cells can

adopt normal mechanisms of lymph node homing (Wiley et al., 2001). Expression of CCR7 on tumor cells has mainly been reported for breast cancer, melanoma, non-small cell lung cancer, prostate cancer, head-and-neck cancer, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, T cell leukemia, stomach cancer, and colorectal cancer (Zlotnik et al., 2011).

The correlation between aberrant CCR7 expression and more aggressive, metastatic tumors associated with decreased survival has encouraged research on how CCR7 expression and function is regulated both under normal conditions and during disease. On the transcriptional level, a number of transcription factors and regulatory elements in the CCR7 promoter region have been described. Several binding sites for NF-κB have been identified in the promoter region and constitutive NF-κB activity was associated with the up-regulation of CCR7 expression on Hodgkin's disease-derived cells (Hopken et al., 2002; Mburu et al., 2012). Moreover, it has been shown that NF-κB and AP1 cooperatively regulate CCR7 expression in metastatic squamous cell carcinoma of the head and neck (Mburu et al., 2012).

In addition to transcriptional regulation, CCR7 expression was also shown to be modulated by lipid derivatives. For instance, overexpression of COX-2, an enzyme that converts arachidonic acid (derived from phospholipids) to prostaglandins, as well as treatment with prostaglandin (PG)E_2 was shown to up-regulate CCR7 expression in breast cancer cells, thereby increasing their lymphatic invasion (Pan et al., 2008). COX-2/PGE_2-dependent CCR7 expression in these cells was, at least in part, mediated by AKT-induced activation of the transcription factor Sp1 (Chuang et al., 2013). Notably, PGE_2 also significantly enhances DC migration towards CCR7 ligands (Legler et al., 2006) (see also Section 5).

Once expressed, CCR7 seems to be rather long-lived (Otero et al., 2006) and information on how CCR7 expression is down-regulated is sparse. However, Runx3 was found to be required for TGFβ-mediated transcriptional inhibition of CCR7 in DCs (Fainaru et al., 2005). Moreover, tumor-derived oxysterol was shown to interfere with CCR7 expression on DCs (Villablanca et al., 2010) (see also Section 5).

Meanwhile, other mechanisms have been identified that render cells non-responsive to CCR7 ligands. One of these mechanisms involves scavenging of chemokines by so-called decoy receptors. CCR7 ligands can be scavenged by ACKR4 (CCX-CKR) and ACKR5 (CRAM-B) (Comerford et al., 2013). Knock-out animals for either one of the two decoy receptors reveal a role in adaptive immunity and are prone to develop EAE more rapidly. A further mechanism is receptor desensitization. Interestingly, CCR7 stimulation by CCL19, but much less by CCL21, leads to robust receptor desensitization, which is mediated by CCR7 phosphorylation and β-arrestin binding resulting in a reduced chemotactic cell response (Kohout et al., 2004). Finally, an alternative mechanism of rendering cells non-responding to chemokines is through ligand-mediated receptor endocytosis. CCR7 was shown to be rapidly endocytosed via clathrin-coated pits predominantly upon binding of CCL19 (Otero et al., 2006). Of note, in endosomes, CCR7 dissociates from CCL19 and recycles via the TGN back to the plasma membrane to re-participate in chemotaxis, whereas CCL19 is sorted for lysosomal degradation (Otero et al., 2006; Schaeuble et al., 2012).

4. Biological functions

The CCR7-CCL19/CCL21 axis is well characterized for its crucial role in the formation of secondary lymphoid structures under physiological conditions mainly through orchestrating the recruitment of immune cells to these structures (Comerford et al., 2013; Forster et al., 2008). Mice lacking either CCR7 (by gene targeting) or its ligands (in the *plt/plt* mice, a spontaneous mutant strain lacking CCL19 and the lymphoid form of CCL21) show an altered architecture of lymphoid organs due to impaired homing of lymphocytes and DCs. Consequently, these mice have deficits in multiple aspects of development and execution of an adaptive immunity. Moreover, CCR7-deficient mice are prone to develop generalized multi-organ autoimmunity although they have a normal life span and do not suffer from clinically apparent autoimmune disease (Comerford et al., 2013; Forster et al., 2008).

In cancer, chemokines in general can fulfill several functions. In particular, chemokines are part of the network of inflammatory mediators. They are also important for recruiting tumor-infiltrating immune cells and can act as angiogenic factors (Balkwill, 2012). The chemokine receptor CCR7, however, fulfills a distinct function. The CCR7-CCL19/CCL21 axis is primarily responsible for lymph node metastasis formation by recruiting tumor cells to the T cell zone of lymph nodes (Rehm et al., 2011; Zlotnik et al., 2011). The chemokine CCL21 is immobilized on lymphatic endothelial cells via its heparin-binding domain (Fig. 2) and thereby forms a gradient that gradually decreases in the direction of the interstitium (Weber et al., 2013). Cancer cells of several tumors up-regulate CCR7 and disseminate from the primary tumor presumably by sensing the immobilized CCL21 gradient and actively migrate towards the next lymphatic vessel (Fig. 2). Moreover, metastatic cancer cells were shown to produce CCR7 ligands that, under interstitial flow, create an autologous, transcellular chemokine gradient permitting cancer cells to migrate towards draining lymphatics (Shields et al., 2007). Remarkably, CCL21 released from lymphatic endothelial cells also promotes a directed growth of melanoma cells towards the lymphatics (Emmett et al., 2011). Interestingly, under inflammatory conditions, CCL19 and CCL21 were found to be up-regulated in endothelial cells of the blood–brain barrier (Alt et al., 2002) enabling acute T cell leukemia cells to infiltrate into the central nervous system in a CCR7-dependent manner (Buonamici et al., 2009). Furthermore, CCR7 also contributes to tumor cell survival by activating the PI3K/Akt signaling pathway (Wang et al., 2005).

5. CCR7 at the cross-road between cancer and immune cells

Since immune cells can recognize and kill tumor cells depending on their antigen profile, tumors have developed ways of escaping the immune surveillance, which involves the CCR7-CCL19/CCL21 axis. For instance, melanoma tumors have been proposed to create an immunotolerant microenvironment by releasing CCL21 and thereby inducing a lymphoid-like reticular stromal network (Shields et al., 2010). This tumor-associated microenvironment is rich in TGFβ and infiltrated by regulatory T cells and myeloid-derived suppressor cells. Other tumor cells have been shown to produce oxysterols that activate liver X receptor α (LXRα) on DCs (Villablanca et al., 2010). LXRα activation on DCs causes the down-regulation of CCR7 and consequently impairs DC homing, thereby preventing the induction of an anti-tumor immune response. However, tumor cells also produce PGE_2 (Fig. 2). In this scenario, PGE_2 is required for the formation of new blood vessels supplying solid tumors with nutrition, as well as for the secretion of matrix metalloproteinases MMP2 and MMP9 crucial for tumor cell invasion (Wang and Dubois, 2010). Notably, PGE_2 not only induces CCR7 expression on tumor cells (Pan et al., 2008), but also on DCs (Legler et al., 2006). Moreover, PGE_2 counteracts oxysterol-mediated down-regulation of CCR7 on DCs, restoring – at least in part – the ability of DCs to migrate and home to lymph nodes (Bruckner et al., 2012).

In summary, the CCR7-CCL19/CCL21 axis is simultaneously involved in cancer cell dissemination and metastasis formation as well as in adaptive immune cell homing to lymphoid organs. Its ambiguous role in cell homing to lymphoid organs seems to make it difficult to pharmaceutically target CCR7 in cancer therapies.

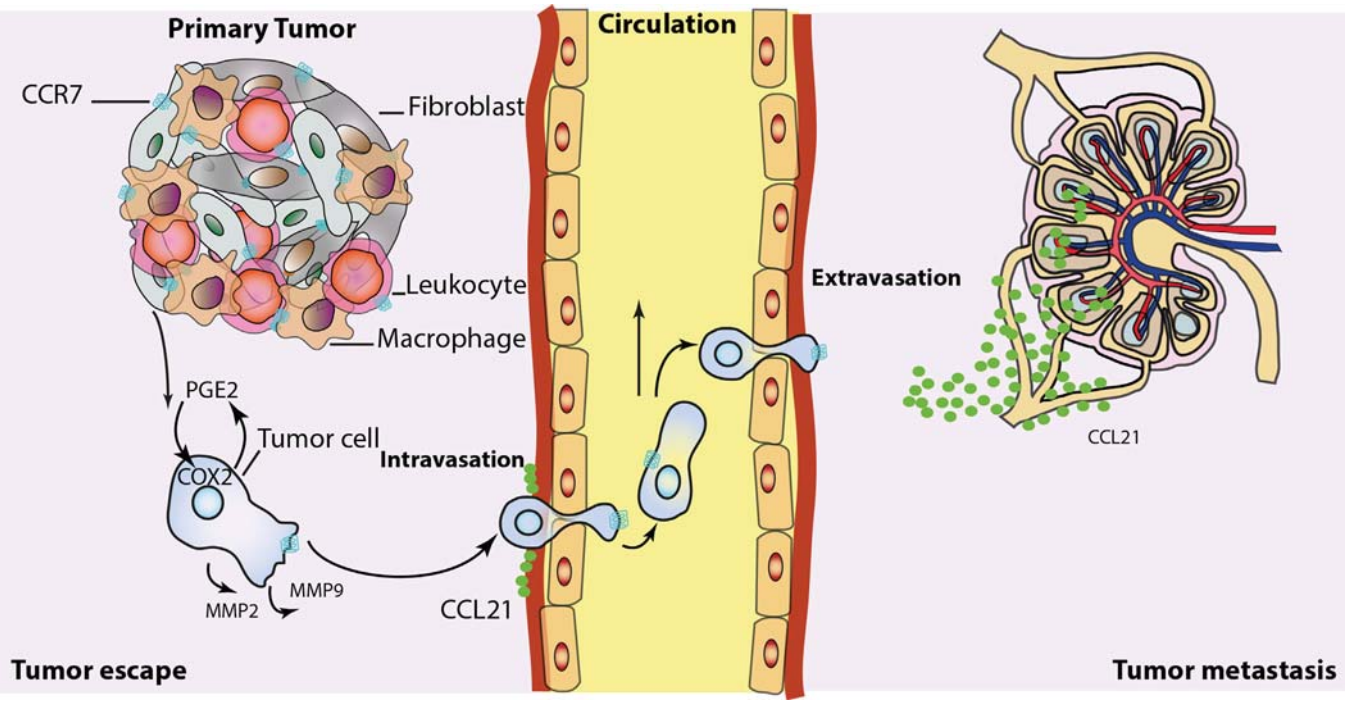

Fig. 2. CCR7: Central roles in tumor cell dissemination, migration and metastasis formation. Cancer metastasis is a process highly dependent on the interactions between tumor and host stromal cells. CCL21 promotes migration and invasion of cancer cells via CCR7. Cyclooxygenase2 (COX2) expressed in tumor cells generates prostaglandin E_2 (PGE_2) that amplifies tumor cell proliferation and extracellular matrix (ECM) degradation by metalloproteinase 2 (MMP2) and MMP9. In response to CCL21 tumor cells polarize, resulting in a leading edge that protrudes outward, coupled with contractile forces at the back and sides of the cell that leads to movement towards the CCL21 source. Cancer cells migrate along the CCL21 gradient until they reach the site for secondary colonization, e.g. the T cell zone of lymph nodes.

However, accumulating evidence is emerging that both the tumor and the immune system simultaneously evolve strategies to interfere each other by means of the CCR7-CCL19/CCL21 axis. Thus, co-evolution might be inherited to develop novel strategies to prevent tumor cell migration whilst leaving immune cell migration unaffected. Further studies on CCR7, particularly on its regulation of expression and on distinct signaling pathways, are thus required for a better understanding of this fundamental process of homing.

Acknowledgments

We thank Sarah Vanes for comments on the manuscript. This work was supported by research funding from the Swiss National Science Foundation (SNF 31003A-143841/1), the Thurguische Krebsliga, the Novartis Foundation for medial-biological research, the Thurgauische Stiftung für Wissenschaft und Forschung, and the Swiss State Secretariat for Education and Research to D.F.L. M.A.H. holds a scholarship from the Research Training Group 1331 founded by the German Research Foundation.

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