The role of chemokine receptor 9/chemokine ligand 25 signaling: From immune cells to cancer cells (Review)

CONG WANG[1*], ZHENGHUAN LIU[2*], ZHIHUI XU[3], XIAN WU[4], DONGYANG ZHANG[5], ZIQI ZHANG[3] and JIANQIN WEI[6]

[1]Department of Hepatopancreatobiliary Surgery, Affiliated Hospital of Qinghai University, Xining, Qinghai 810001; [2]Department of Urology, West China School of Medicine, Sichuan University; [3]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center; Departments of [4]Ultrasound and [5]Gastrointestinal Surgery, West China School of Medicine, Sichuan University, Chengdu, Sichuan 610041, P.R. China; [6]The University of Miami Leonard M. Miller School of Medicine, University of Miami, Coral Gables, FL 33136, USA

Received December 4, 2017; Accepted May 15, 2018

DOI: 10.3892/ol.2018.8896

Abstract. Chemokine ligand 25 (CCL25) and chemokine receptor 9 (CCR9) are important regulators of migration, proliferation and apoptosis in leukocytes and cancer cells. Blocking of the CCR9/CCL25 signal has been demonstrated to be a potential novel cancer therapy. Research into CCR9 and CCL25 has revealed their associated upstream and downstream signaling pathways; CCR9 is regulated by several immunological factors, including NOTCH, interleukin 2, interleukin 4 and retinoic acid. NOTCH in particular, has been revealed to be a crucial upstream regulator of CCR9. Furthermore, proteins including matrix metalloproteinases, P-glycoprotein, Ezrin/Radixin/Moesin and Livin are regulated via phosphatidylinositol-3 kinase/ protein kinase B, which are in turn stimulated by CCR9/CCL25. This is a review of the current literature on the functions and signaling pathways of CCR9/CCL25.

Correspondence to: Dr Ziqi Zhang, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center, 17 People's South Road, Chengdu, Sichuan 610041, P.R. China
E-mail: zhangziqicd@126.com

Dr Jianqin Wei, The University of Miami Leonard M. Miller School of Medicine, University of Miami, Coral Gables, FL 33136, USA
E-mail: jwei@med.miami.edu

*Contributed equally

Abbreviations: CCR, chemokine receptor; CCL25, chemokine ligand 25; IL, interleukin; RA, retinoic acid; P-gp, P-glycoprotein; ERM, Ezrin/Radixin/Moesin; GPR-9-6, G-protein-coupled-receptor-9-6; TECK, thymus-expressed chemokine; Maf, muscular aponeurotic fibrosarcoma; T-ALL, T cell lineage acute lymphocytic leukemia; T-CLL, T cell chronic lymphocytic leukemia; CXCL12, CXC chemokine ligand 12; PE38, Pseudomonas exotoxin 38; HTLV-1, human T lymphotropic virus type 1; GSK-3β, glycogen synthase kinase 3β; FKHR, forkhead in human rhabdomyosarcoma; Wnt5a, wingless-type protein 5a; RhoA, Ras homologue; ROCK, Rho kinase; DLL4, delta-like 4, JAG1, Jagged 1; DLK1, delta-like proteins 1.

Key words: chemokine receptor 9, immune system, tumor suppressor genes

Contents

1. Introduction
2. Chemokine receptor 9 in leukocytes
3. Chemokine receptor 9 in cancer cells
4. Regulation of chemokine receptor 9
5. Downstream signaling of chemokine receptor 9/chemokine ligand 25
6. Hypothesis and conclusion

1. Introduction

The cDNA of CCR9 was submitted to Genbank (Genbank no. HSU45982) by Lautens in 1996 as G-protein-coupled-receptor-9-6 (GPR-9-6). The expression and function of GPR-9-6 was investigated by Zaballos *et al* (1) in 1999. GPR-9-6 was renamed as CCR9, due to its similarity in structure and sequence to chemokine receptor 6 (CCR6), chemokine receptor 7 (CCR7) and STRL33/Bonzo (1). Furthermore, *in vitro* stimulation of CCR9 with thymus-expressing chemokine (TECK) induced intra-cytoplasmic calcium mobilization and migration of 293 cells (1). TECK, also known as CCL25, was discovered in thymic dendritic cells in 1997 (2), and was subsequently confirmed to be the sole ligand of CCR9 (3). CCR9 expression was revealed to be low in human and murine spleen and lymph nodes but high in thymic tissues (1).

Further studies demonstrated that CCR9 is highly expressed in the colon, small intestine and several other tissues involved

in the development and maturation of T cells, macrophages and dendritic cells (DCs) (4-9). CCR9 signaling may therefore have an influence on processes, including inflammatory responses and transplantation rejection (10-12). Furthermore, CCR9 has been demonstrated to influence cancer cell migration, proliferation and drug resistance (13-15). This is a review of the current literature on the function of CCR9 in leukocytes and cancer cells.

2. Chemokine receptor 9 in leukocytes

The function of CCR9 in different leukocyte subtypes is relatively comparable (Fig. 1).

$CCR9^+$ DCs migrate to the small intestine and colon to interact with other leukocytes, particularly T cells, to induce local inflammation (4-6). Thymic epithelial cells are the principle source of CCL25 (7); however, thymic DCs also secrete CCL25, which may contribute toward DC-T cell interactions (2).

CCR9 serves an important role in the regulation of T cells. CCR9 (16) and CCR7 (17,18) have been demonstrated to contribute toward the recruitment of T cells to the thymus. T cell development is also regulated by CCR9 (19). CCR9-knockdown skewed T cell subgroup ratios; thymic αβ-T cell development was not affected in $CCR9^{-/-}$ mice, whereas the number of γδ-T cells located in the intestine was increased (19). In addition, CCR9 suppressed differentiation of forkhead box protein 3^+ regulatory T cells (20). Several T cell functions were revealed to be CCR9-dependent; $CD4^+$ $CCR9^+$ T helper cells expressed interleukin 21 (IL-21), inducible T cell co-stimulator, transcription factor B-cell CLL/lymphoma 6 and muscular aponeurotic fibrosarcoma (Maf), and supported B cell antibody production (21). In splenic T cells, blocking CCR9/CCL25 signaling reduced secretion of interferon-γ (IFN-γ) (12). This may serve a role in certain immunological processes, including transplant rejection and the inflammatory response. Anti-CCL25 antibodies decreased the infiltration of cells around skin allografts, which prolonged the survival of the graft (12). Recruitment of T cells to the intestine and colon was demonstrated to be CCR9-dependent (22,23). $CCR9^+$ T cells were recruited to inflammatory bowel disease lesions, and were revealed to be associated with disease activity (10). Similarly, during *Aggregatibacter actinomycetemcomitans* serotype b infection, CCR9 expression was increased in T cells (11).

Retinoic acid (RA) has been demonstrated to serve a role in DC-T cell interactions. Several studies revealed that CCR9 expression fluctuated at different stages of DC development (9,24). Furthermore, several other studies demonstrated that DCs produced RA, which mediated CCR9 expression in T cells (25) and induced interleukin 10 (IL-10) expression in $\alpha4\beta7^+$ $CCR9^+$ T cells (26). T cells were also mediated by RA directly via the RA receptor, which upregulated CCR9 expression (27,28). Therefore, decreased expression of the RA receptor was associated with a reduction in CCR9 expression and an attenuation of graft-versus-host disease (29).

Naïve B cell migration has been demonstrated to be regulated by CCR9 (30). A high CCR9 expression has also been revealed in memory B cells (31). Epstein-Barr virus-infected B cells demonstrated increased CCR9 expression (32). However, CCR9/CCL25 signaling does not appear to be vital for B development, as maturation of B cells was not impaired in $CCR9^{-/-}$ mice (19).

Macrophages migrate to infected peritoneal (33) and acute colitis lesions (6). Macrophages recruited by CCR9, which produced tumor necrosis factor-α (TNF-α), were crucial for liver fibrosis (34). CCR9 expression in these recruited macrophages was regulated by their interaction with hepatic stellate cells (35).

In summary, CCR9 serves a role in the migration, maturation and function of leukocytes.

3. Chemokine receptor 9 in cancer cells

Following the discovery of CCR9/CCL25 signaling pathways in leukocytes, oncology researchers revealed that CCR9 promotes invasion, migration, anti-apoptosis and drug-resistance in several types of tumors (Fig. 1).

CCR9/CCL25 signaling has been rigorously studied in hematological malignancies. In T cell lineage acute lymphocytic leukemia (T-ALL) $CD4^+$ cells, CCR9 was highly expressed, while T cell chronic lymphocytic leukemia (T-CLL) $CD4^+$ cells moderately expressed CCR9, and a low CCR9 expression was demonstrated in normal $CD4^+$ T cells (36). The $CCR9^+$ T-ALL Jurkat, MOLT-4, CEM, SupT1, TALL-1 and DND41 cell lines were revealed to be chemotactic to CCL25 (37). CCL25 stimulation resulted in pseudopodium formation (38), invasion and migration (39). It has been observed that T cells from adult patients with leukemia, that had infiltrated the gastrointestinal tract, were frequently positive for CCR9 (40), which was in line with conclusions from a study that reported that CCR9 expression was associated with gut relapse in pediatric T-ALL (41). Furthermore, CCR9/CCL25 signaling induced P-gp co-localization within the actin cytoskeleton (15). This mechanism led to drug resistance to doxorubicin in the MOLT-4 cell line (15). TNF-α mediated apoptosis was inhibited in $CD4^+$ T-ALL, T-CLL and MOLT-4 cells by CCR9/CCL25 signaling (42). Transformation of gastric mucosa-associated lymphoid tissue to gastric extra-nodal diffuse large B-cell lymphoma was mediated by several chemokines, including CCR9 (43). However, $CCR9^+$ multiple myeloma cells only migrated toward CXC chemokine ligand 12 (CXCL12), indicating a limited function of CCR9 in multiple myeloma (44).

The regulation of melanoma cell metastasis by CCR9/CCL25 signaling remains controversial. Certain studies have demonstrated that CCR9 expression is associated with organ-specific metastasis of melanoma cells (45,46). Melanoma cells that had metastasized to the intestine expressed CCR9, whereas cells that had metastasized to other organs did not (47). Besides the intestine, lymph nodes and skin were the sites where melanoma metastasis often occurred; however, $CCR9^+$ melanoma cells were not observed in these locations (47-49). $CCR9^+$ T cells in the melanoma microenvironment have been demonstrated to inhibit metastasis (50). However, certain studies have demonstrated that the function of CCR9 in melanoma was only moderate; the proportion of patients with intestine metastases was low (51), indicating limited organ-specific metastasis (49), which corresponds with the low proportion of $CCR9^+$ cells reported in circulating

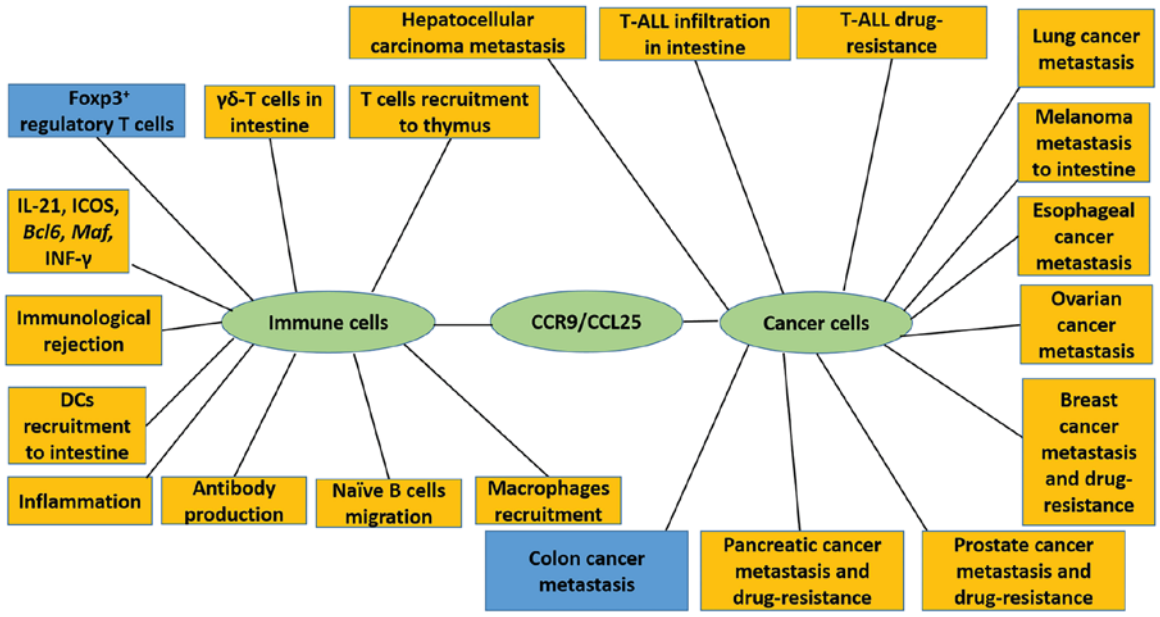

Figure 1. Function of CCR9/CCL25 signaling in immune cells and cancer cells. Blocks in orange indicate positive regulation, while blue indicates negative regulation by CCR9/CCL25 signaling. CCR9, chemokine receptor 9; CCL25, chemokine ligand 25; FoxP3+, Forkhead box P3; IL-21, interleukin 21; ICOS, inducible T cell co-stimulator; INF-γ, interferon-γ; DCs, dendritic cells; T-ALL, T-cell acute lymphoblastic leukaemia.

tumor cells (52). Clinical studies demonstrated that CCR7 and chemokine receptor 10 (CCR10), but not CCR9, were associated with a poorer prognosis (53).

Several types of ovarian carcinoma, including serous adenocarcinoma, serous papillary cystadenoma and endometrioid adenocarcinoma, revealed an increased CCR9 expression compared with normal ovarian tissues (54), and demonstrated migration and invasion potential toward chemotactic gradients of CCL25 (55). Intestinal cells, a source of CCL25, were also a frequent metastatic site for ovarian carcinoma (55).

CCR9 expression of two breast cancer cell lines, MDA-MB-231 and MCF7, and benign tissue, were high, medium and low, respectively, which corresponded with their respective aggressiveness (56). Lymph nodes, bone marrow, lung, liver and brain were frequent sites of breast cancer metastasis, and this process might be regulated by CCR9/CCL25 (56-58). CCR9/CCL25 signaling was also revealed to provide a survival advantage to breast cancer cells and inhibited cisplatin-induced apoptosis (59).

In prostate cancer, CCR9 was highly, moderately and lowly expressed in highly invasive LNCaP, moderately invasive PC3 and non-invasive prostatic epithelial cells, respectively (60). CCR9/CCL25 also regulated metastasis (60) and drug-resistance against etoposide (61) in prostate cancer.

In pancreatic cancer, pancreatic intraepithelial neoplasia and pancreatic cancer cells were demonstrated to be CCR9+ (62). The pancreatic cancer PANC-1 cell line was CCR9+, and enhanced invasion was observed following CCL25 treatment (63). Drug-resistance of gemcitabine was stimulated by CCL25 signaling in pancreatic cancer PANC-1, MIAPaCa-2 and AsPC-1 cell lines (14).

In colon cancer, injection of CCR9+ cancer-initiating cells led to formation of gastrointestinal xenograft tumors in mice, whereas blocking CCR9 signaling increased extra-intestinal tumors (13,64).

In the hepatocellular carcinoma cell lines HepG2 and HUH7, CCR9 promoted invasion and migration (65), and might be a marker to predict the prognosis of patients (66).

Similarly, CCR9 could be beneficial in predicting lymph node metastasis and prognosis in lung adenocarcinoma (67). Adenocarcinoma cells revealed a higher migratory and invasive potential in response to CCL25, compared with squamous cell carcinoma cells, which had lower expression of CCR9 and CCL25 (68). Esophageal cancer cells also highly expressed CCR9 and potentially achieved metastasis via CCR9 signaling (69).

Based on these findings, researchers attempted to design CCR9-specific therapies, including CCR9 antagonists, monoclonal antibodies against CCR9, and RNAi of CCR9. Computational modeling of CCR9 antagonists revealed several compounds, one of which inhibited proliferation and invasion of pancreatic cancer cell lines and interacted synergistically with gemcitabine (14). *In vivo* models revealed that a CCR9 monoclonal antibody increased apoptosis, necrosis of tumor tissue, complement-dependent cytotoxicity and antibody-dependent cytotoxicity by natural killer cells. The antibody was also demonstrated to decrease proliferation and tumor vascularization in MOLT-4 cell lines (70). CCR9 inhibition by RNAi facilitated T cell-associated immunotherapy of breast and pancreatic cancer cell lines (71). Another trial used CCL25 fused with Pseudomonas exotoxin 38 (PE38) toxin, a truncated derivative of Pseudomonas exotoxin A, which induced apoptosis in MOLT-4 cell lines (72).

In summary, CCR9/CCL25 signaling is an important mediator of malignant behaviors in a number of cancer cells. Blocking of CCR9/CCL25 signaling appears to be a potential novel strategy for cancer therapy.

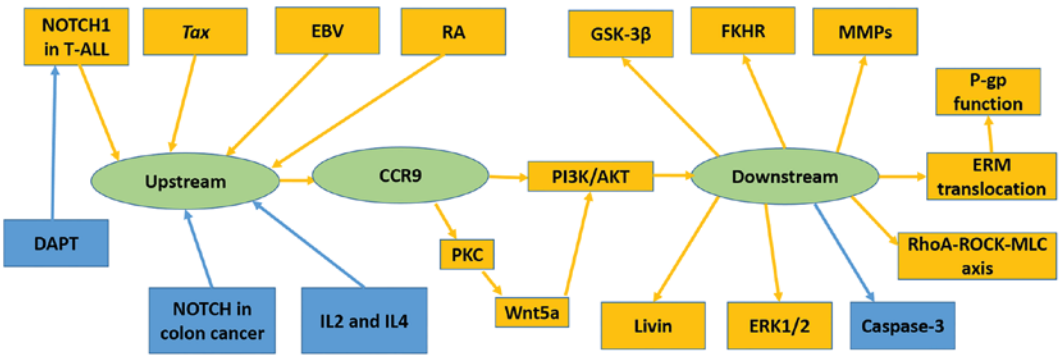

Figure 2. Associated immunological factors of CCR9/CCL25 signaling in immune cells and cancer cells. Blocks in orange indicate positive regulation, while blue indicates negative regulation. The arrow points indicate the direction of each regulation. CCR9, chemokine receptor 9; CCL25, chemokine ligand 25; DAPT, dual antiplatelet therapy; EBV, Epstein-Barr virus; RA, rheumatoid arthritis; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase; Akt, protein kinase B; GSK-3β, glycogen synthase kinase 3; FKHR, forkhead transcription factor; MMPs, matrix metalloproteinases; P-gp, P-glycoprotein; ERM, Ezrin-Radixin-Moesin protein; ERK1/2, extracellular signal-regulated protein kinases 1/2; RhoA, Ras homolog gene family member A; ROCK, Rho-associated protein kinase; MLC, myosin light chain; IL, interleukin.

4. Regulation of chemokine receptor 9

Several immunological factors have been demonstrated to upregulate CCR9, including human T-lymphotropic virus type 1 (HTLV-1)-encoded transcriptional activator Tax (40), RA (25) and Epstein-Barr virus (32). Others, including DAPT (37) and co-stimulation of IL-2 with IL-4 (36), have been revealed to downregulate CCR9. The NOTCH pathway has been revealed to mediate CCR9 expression; however, its function differs in T-ALL and colon cancer (Fig. 2).

NOTCH1 mutations were frequently identified in T-ALL; certain mutations resulted in δ1 ligand-independent NOTCH signaling or lengthened the half-life period of NOTCH1 signaling. Suppression of NOTCH1 by DAPT or RNAi, downregulated CCR9 in the T-ALL cell lines Jurkat, MOLT-4, CEM, SupT1, TALL-1 and DND41 (37).

However, in $CCR9^+$ colon cancer cells, NOTCH signaling was revealed to be reduced compared with that in $CCR9^-$ colon cancer cells. Since no significant difference in CCR9 mRNA levels was revealed between $CCR9^+$ and $CCR9^-$ cells, it was confirmed that NOTCH lowered CCR9 expression levels by increasing proteasomal degradation (13).

5. Downstream signaling of chemokine receptor 9/ chemokine ligand 25

CCL25 binding led to interactions between CCR9 $G_{\beta\gamma}$ and PI3K, which resulted in activation of Akt (73). In this study, glycogen synthase kinase 3 β (GSK-3β) and forkhead in human rhabdomyosarcoma (FKHR) were demonstrated to be downstream targets of Akt (73), which further influenced the migration, invasion and drug resistance of cancer cells. An alternative stimulation of PI3/Akt by wingless-type protein 5a (Wnt5a) following CCR9/CCL25 interaction was revealed in another study (74), indicating a complex cross-talk between these signaling pathways (Fig. 2).

Mediation of cell invasion and migration by CCR9/CCL25 signaling may involve matrix metalloproteinases (MMPs) (55,56,60), Ras homologue (RhoA)Rho kinase (ROCK)-myosin light chain (MLC) signal (39), Wnt5a (74) and ERM protein family (38). In the ovarian cancer OVCAR-3 and CAOV-3 cell lines, CCR9/CCL25 selectively regulated certain MMPs, which degraded the cell matrix to promote invasion (55). Different patterns of MMP regulation were observed in each cell line; for example, in the OVCAR-3 cell line, expression of MMP-2, 3, 8, 9, 10, 11 and 13 was increased, while MMP-1, 2, 3, 8 and 10 expression levels were elevated in the CAOV-3 cell line (55). A similar mechanism was observed in prostate cancer cell lines (60). CCL25 treatment increased MMP-1 and 2 expression in LNCaP, and MMP-2, 11 and 13 in PC3 cells (60). RhoA-ROCK-MLC signaling, which is associated with cell motility and morphology was stimulated by CCL25 in the MOLT-4 cell line (39). Another pathway has been demonstrated to promote the invasion and migration of MOLT-4 cells; CCL25 induced Wnt5a activation by promoting protein kinase C expression and activation in MOLT-4 cells (74). Activated Wnt5a further induced PI3K/Akt signaling and enhanced cell migration and invasion (74). Invasion-related ERM protein was revealed to be translocated from the cytoplasm to the cell membrane following CCL25 treatment, which contributed to metastasis (38).

Stimulation of drug-resistance by CCL25 might be achieved via P-gp (15), inhibition of GSK-3β and FKHR (59), Livin protein (42), anti-apoptosis protein (PI3K, AKT, extracellular-regulated kinase 1/2 (ERK1/2) and GSK-3β) and caspase-3 (61). P-gp was revealed to promote the extrusion of the antitumor agent, doxorubicin, from the cytoplasm to the extracellular space, resulting in multidrug resistance. This resistance was dependent on interactions between ERM and the actin cytoskeleton following CCL25 stimulation (15). In breast cancer, inhibition of CCR9/CCL25 downstream signaling via GSK-3β or FKHR, significantly improved the chemotherapeutic efficacy of cisplatin (59). Alongside upregulation of anti-apoptosis proteins, including PI3K, Akt, ERK1/2 and GSK-3β, CCL25 also induced drug resistance via downregulation of caspase-3 activity (61). CCL25 suppressed TNF-α-mediated apoptosis by increasing expression of Livin, a member of the inhibitor of apoptosis protein family, via c-jun-NH2-kinase 1 kinase activity (42).

6. Hypothesis and conclusion

NOTCH and several other signaling proteins regulate CCR9, and CCR9/CCL25 signaling mediates certain downstream

proteins to promote metastasis and drug-resistance in cancer cells. Based on the findings that healthy intestine and colon cells physiologically produce CCL25 (2,6,7,75), we hypothesized that CCL25 induces chemotaxis and cell survival signaling in leukocytes and cancer cells. For extra-intestinal cancer, the CCL25 concentration in healthy intestinal micro-environment is higher than that in the primary tumor micro-environment; thus, $CCR9^+$ cancer cells tend to metastasize to the intestine. However, the micro-environment of colon cancer is rich in CCL25 and therefore, CCR9 may be downregulated by NOTCH to reduce chemotaxis and promote metastasis. Investigation of CCL25 levels in the micro-environment of primary and metastatic lesions would further test this hypothesis. Another possible mechanism is based on the seed-earth hypothesis, which states that CCL25 promotes the survival of circulating tumor cells that have metastasized to the intestine.

NOTCH signaling has an opposite function in T-ALL and colon cancer. This contradiction might be explained by the diversity in ligands and downstream signaling. In T-ALL, δ1 is a ligand of NOTCH1 (37), while delta-like 4 (DLL4), Jagged 1 (JAG1) and delta-like proteins 1 (DLK1) are the most probable ligands of NOTCH in colon cancer (13).

In summary, CCR9/CCL25 signaling mediated the migration, invasion and drug resistance of cancer cells. Further studies should focus on elucidating the mechanisms of associated upstream and downstream signaling of CCR9.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

CW and ZL were major contributors in writing the manuscript. ZX, XW, and DZ retrieved, selected the articles, and collected useful information from these articles. ZZ and JW proposed writing this review, made the outline, submitted and revised this manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zaballos A, Gutiérrez J, Varona R, Ardavín C and Márquez G: Cutting edge: Identification of the orphan chemokine receptor GPR-9-6 as CCR9, the receptor for the chemokine TECK. J Immunol 162: 5671-5675, 1999.
2. Vicari AP, Figueroa DJ, Hedrick JA, Foster JS, Singh KP, Menon S, Copeland NG, Gilbert DJ, Jenkins NA, Bacon KB and Zlotnik A: TECK: A novel CC chemokine specifically expressed by thymic dendritic cells and potentially involved in T cell development. Immunity 7: 291-301, 1997.
3. Yu CR, Peden KW, Zaitseva MB, Golding H and Farber JM: CCR9A and CCR9B: Two receptors for the chemokine CCL25/TECK/Ck beta-15 that differ in their sensitivities to ligand. J Immunol 164: 1293-1305, 2000.
4. Wendland M, Czeloth N, Mach N, Malissen B, Kremmer E, Pabst O and Förster R: CCR9 is a homing receptor for plasmacytoid dendritic cells to the small intestine. Proc Natl Acad Sci USA 104: 6347-6352, 2007.
5. Mizuno S, Kanai T, Mikami Y, Sujino T, Ono Y, Hayashi A, Handa T, Matsumoto A, Nakamoto N, Matsuoka K, *et al*: CCR9+ plasmacytoid dendritic cells in the small intestine suppress development of intestinal inflammation in mice. Immunol Lett 146: 64-69, 2012.
6. Wurbel MA, McIntire MG, Dwyer P and Fiebiger E: CCL25/CCR9 interactions regulate large intestinal inflammation in a murine model of acute colitis. PLoS One 6: e16442, 2011.
7. Wurbel MA, Philippe JM, Nguyen C, Victorero G, Freeman T, Wooding P, Miazek A, Mattei MG, Malissen M, Jordan BR, *et al*: The chemokine TECK is expressed by thymic and intestinal epithelial cells and attracts double- and single-positive thymocytes expressing the TECK receptor CCR9. Eur J Immunol 30: 262-271, 2000.
8. Schmutz C, Cartwright A, Williams H, Haworth O, Williams JH, Filer A, Salmon M, Buckley CD and Middleton J: Monocytes/macrophages express chemokine receptor CCR9 in rheumatoid arthritis and CCL25 stimulates their differentiation. Arthritis Res Ther 12: R161, 2010.
9. Dursun E, Endele M, Musumeci A, Failmezger H, Wang SH, Tresch A, Schroeder T and Krug AB: Continuous single cell imaging reveals sequential steps of plasmacytoid dendritic cell development from common dendritic cell progenitors. Sci Rep 6: 37462, 2016.
10. Eberhardson M, Marits P, Jones M, Jones P, Karlen P, Karlsson M, Cotton G, Woznica K, Maltman B, Glise H and Winqvist O: Treatment of inflammatory bowel disease by chemokine receptor-targeted leukapheresis. Clin Immunol 149: 73-82, 2013.
11. Alvarez C, Benítez A, Rojas L, Pujol M, Carvajal P, Díaz-Zúñiga J and Vernal R: Differential expression of CC chemokines (CCLs) and receptors (CCRs) by human T lymphocytes in response to different *Aggregatibacter actinomycetemcomitans* serotypes. J Appl Oral Sci 23: 536-546, 2015.
12. Li J, Xiong T, Xiao R, Xiong A, Chen J, Altaf E, Zheng Y, Zhu G, He Y and Tan J: Anti-CCL25 antibody prolongs skin allograft survival by blocking CCR9 expression and impairing splenic T-cell function. Arch Immunol Ther Exp (Warsz) 61: 237-244, 2013.
13. Chen HJ, Edwards R, Tucci S, Bu P, Milsom J, Lee S, Edelmann W, Gümüs ZH, Shen X and Lipkin S: Chemokine 25-induced signaling suppresses colon cancer invasion and metastasis. J Clin Invest 122: 3184-3196, 2012.
14. Lee S, Heinrich EL, Li L, Lu J, Choi AH, Levy RA, Wagner JE, Yip ML, Vaidehi N and Kim J: CCR9-mediated signaling through β-catenin and identification of a novel CCR9 antagonist. Mol Oncol 9: 1599-1611, 2015.
15. Zhang L, Xiao R, Xiong J, Leng J, Ehtisham A, Hu Y, Ding Q, Xu H, Liu S and Wang J, *et al*: Activated ERM protein plays a critical role in drug resistance of MOLT4 cells induced by CCL25. PLoS One 8: e52384, 2013.
16. Krueger A, Willenzon S, Lyszkiewicz M, Kremmer E and Forster R: CC chemokine receptor 7 and 9 double-deficient hematopoietic progenitors are severely impaired in seeding the adult thymus. Blood 115: 1906-1912, 2010.
17. Zlotoff DA, Sambandam A, Logan TD, Bell JJ, Schwarz BA and Bhandoola A: CCR7 and CCR9 together recruit hematopoietic progenitors to the adult thymus. Blood 115: 1897-1905, 2010.

18. Liu C, Saito F, Liu Z, Lei Y, Uehara S, Love P, Lipp M, Kondo S, Manley N and Takahama Y: Coordination between CCR7- and CCR9-mediated chemokine signals in prevascular fetal thymus colonization. Blood 108: 2531-2539, 2006.
19. Uehara S, Grinberg A, Farber JM and Love PE: A role for CCR9 in T lymphocyte development and migration. J Immunol 168: 2811-2819, 2002.
20. Evans-Marin HL, Cao AT, Yao S, Chen F, He C, Liu H, Wu W, Gonzalez MG, Dann SM and Cong Y: Unexpected regulatory role of CCR9 in regulatory T cell development. PLoS One 10: e0134100, 2015.
21. McGuire HM, Vogelzang A, Ma CS, Hughes WE, Silveira PA, Tangye SG, Christ D, Fulcher D, Falcone M and King C: A subset of interleukin-21+ chemokine receptor CCR9+ T helper cells target accessory organs of the digestive system in autoimmunity. Immunity 34: 602-615, 2011.
22. Tubo NJ, Wurbel MA, Charvat TT, Schall TJ, Walters MJ and Campbell JJ: A systemically-administered small molecule antagonist of CCR9 acts as a tissue-selective inhibitor of lymphocyte trafficking. PLoS One 7: e50498, 2012.
23. Greis C, Rasuly Z, Janosi RA, Kordelas L, Beelen DW and Liebregts T: Intestinal T lymphocyte homing is associated with gastric emptying and epithelial barrier function in critically ill: A prospective observational study. Crit Care 21: 70, 2017.
24. Drakes ML, Stiff PJ and Blanchard TG: Inverse relationship between dendritic cell CCR9 expression and maturation state. Immunology 127: 466-476, 2009.
25. Stock A, Booth S and Cerundolo V: Prostaglandin E2 suppresses the differentiation of retinoic acid-producing dendritic cells in mice and humans. J Exp Med 208: 761-773, 2011.
26. Bakdash G, Vogelpoel LT, van Capel TM, Kapsenberg ML and de Jong EC: Retinoic acid primes human dendritic cells to induce gut-homing, IL-10-producing regulatory T cells. Mucosal Immunol 8: 265-278, 2014.
27. Chen X, Dodge J, Komorowski R and Drobyski WR: A critical role for the retinoic acid signaling pathway in the pathophysiology of gastrointestinal graft-versus-host disease. Blood 121: 3970-3980, 2013.
28. Duurland CL, Brown CC, O'Shaughnessy RF and Wedderburn LR: CD161^{+} Tconv and CD161^{+} Treg share a transcriptional and functional phenotype despite limited overlap in TCRβ repertoire. Front Immunol 8: 103, 2017.
29. Aoyama K, Saha A, Tolar J, Riddle MJ, Veenstra RG, Taylor PA, Blomhoff R, Panoskaltsis-Mortari A, Klebanoff CA, Socié G, *et al*: Inhibiting retinoic acid signaling ameliorates graft-versus-host disease by modifying T-cell differentiation and intestinal migration. Blood 122: 2125-2134, 2013.
30. Wurbel MA, Malissen M, Guy-Grand D, Meffre E, Nussenzweig MC, Richelme M, Carrier A and Malissen B: Mice lacking the CCR9 CC-chemokine receptor show a mild impairment of early T- and B-cell development and a reduction in T-cell receptor gammadelta(+) gut intraepithelial lymphocytes. Blood 98: 2626-2632, 2001.
31. Demberg T, Mohanram V, Venzon D and Robert-Guroff M: Phenotypes and distribution of mucosal memory B-cell populations in the SIV/SHIV rhesus macaque model. Clin Immunol 153: 264-276, 2014.
32. Ehlin-Henriksson B, Liang W, Cagigi A, Mowafi F, Klein G and Nilsson A: Changes in chemokines and chemokine receptor expression on tonsillar B cells upon Epstein-Barr virus infection. Immunology 127: 549-557, 2009.
33. Mizukami T, Kanai T, Mikami Y, Hayashi A, Doi T, Handa T, Matsumoto A, Jun L, Matsuoka K, Sato T, *et al*: CCR9+ macrophages are required for eradication of peritoneal bacterial infections and prevention of polymicrobial sepsis. Immunol Lett 147: 75-79, 2012.
34. Chu PS, Nakamoto N, Ebinuma H, Usui S, Saeki K, Matsumoto A, Mikami Y, Sugiyama K, Tomita K, Kanai T, *et al*: C-C motif chemokine receptor 9 positive macrophages activate hepatic stellate cells and promote liver fibrosis in mice. Hepatology 58: 337-350, 2013.
35. Amiya T, Nakamoto N, Chu PS, Teratani T, Nakajima H, Fukuchi Y, Taniki N, Yamaguchi A, Shiba S, Miyake R, *et al*: Bone marrow-derived macrophages distinct from tissue-resident macrophages play a pivotal role in Concanavalin A-induced murine liver injury via CCR9 axis. Sci Rep 6: 35146, 2016.
36. Qiuping Z, Qun L, Chunsong H, Xiaolian Z, Baojun H, Mingzhen Y, Chengming L, Jinshen H, Qingping G, Kejian Z, *et al*: Selectively increased expression and functions of chemokine receptor CCR9 on CD4+ T cells from patients with T-cell lineage acute lymphocytic leukemia. Cancer Res 63: 6469-6477, 2003.
37. Mirandola L, Chiriva-Internati M, Montagna D, Locatelli F, Zecca M, Ranzani M, Basile A, Locati M, Cobos E, Kast WM, *et al*: Notch1 regulates chemotaxis and proliferation by controlling the CC-chemokine receptors 5 and 9 in T cell acute lymphoblastic leukaemia. J Pathol 226: 713-722, 2012.
38. Zhou B, Leng J, Hu M, Zhang L, Wang Z, Liu D, Tong X, Yu B, Hu Y, Deng C, *et al*: Ezrin is a key molecule in the metastasis of MOLT4 cells induced by CCL25/CCR9. Leuk Res 34: 769-776, 2010.
39. Zhang L, Yu B, Hu M, Wang Z, Liu D, Tong X, Leng J, Zhou B, Hu Y, Wu R, *et al*: Role of Rho-ROCK signaling in MOLT4 cells metastasis induced by CCL25. Leuk Res 35: 103-109, 2011.
40. Nagakubo D, Jin Z, Hieshima K, Nakayama T, Shirakawa AK, Tanaka Y, Hasegawa H, Hayashi T, Tsukasaki K, Yamada Y and Yoshie O: Expression of CCR9 in HTLV-1+ T cells and ATL cells expressing Tax. Int J Cancer 120: 1591-1597, 2007.
41. Annels NE, Willemze AJ, van der Velden VH, Faaij CM, van Wering E, Sie-Go DM, Egeler RM, van Tol MJ and Révész T: Possible link between unique chemokine and homing receptor expression at diagnosis and relapse location in a patient with childhood T-ALL. Blood 103: 2806-2808, 2004.
42. Qiuping Z, Jei X, Youxin J, Wei J, Chun L, Jin W, Qun W, Yan L, Chunsong H, Mingzhen Y, *et al*: CC chemokine ligand 25 enhances resistance to apoptosis in CD4+ T cells from patients with T-cell lineage acute and chronic lymphocytic leukemia by means of livin activation. Cancer Res 64: 7579-7587, 2004.
43. Deutsch AJ, Steinbauer E, Hofmann NA, Strunk D, Gerlza T, Beham-Schmid C, Schaider H and Neumeister P: Chemokine receptors in gastric MALT lymphoma: Loss of CXCR4 and upregulation of CXCR7 is associated with progression to diffuse large B-cell lymphoma. Mod Pathol 26: 182-194, 2013.
44. Badr G, Lefevre EA and Mohany M: Thymoquinone inhibits the CXCL12-induced chemotaxis of multiple myeloma cells and increases their susceptibility to Fas-mediated apoptosis. PLoS One 6: e23741, 2011.
45. Letsch A, Keilholz U, Schadendorf D, Assfalg G, Asemissen AM, Thiel E and Scheibenbogen C: Functional CCR9 expression is associated with small intestinal metastasis. J Invest Dermatol 122: 685-690, 2004.
46. Seidl H, Richtig E, Tilz H, Stefan M, Schmidbauer U, Asslaber M, Zatloukal K, Herlyn M and Schaider H: Profiles of chemokine receptors in melanocytic lesions: de novo expression of CXCR6 in melanoma. Hum Pathol 38: 768-780, 2007.
47. Amersi FF, Terando AM, Goto Y, Scolyer RA, Thompson JF, Tran AN, Faries MB, Morton DL and Hoon DS: Activation of CCR9/CCL25 in cutaneous melanoma mediates preferential metastasis to the small intestine. Clin Cancer Res 14: 638-645, 2008.
48. Richmond A: CCR9 homes metastatic melanoma cells to the small bowel. Clin Cancer Res 14: 621-623, 2008.
49. Salerno EP, Olson WC, McSkimming C, Shea S and Slingluff CL Jr: T cells in the human metastatic melanoma microenvironment express site-specific homing receptors and retention integrins. Int J Cancer 134: 563-574, 2014.
50. Jacquelot N, Enot DP, Flament C, Vimond N, Blattner C, Pitt JM, Yamazaki T, Roberti MP, Daillère R, Vétizou M, *et al*: Chemokine receptor patterns in lymphocytes mirror metastatic spreading in melanoma. J Clin Invest 126: 921-937, 2016.
51. Park J, Ostrowitz MB, Cohen MS and Al-Kasspooles M: A patient with metastatic melanoma of the small bowel. Oncology (Williston Park) 23: 98-102, 2009.
52. Fusi A, Liu Z, Kümmerlen V, Nonnemacher A, Jeske J and Keilholz U: Expression of chemokine receptors on circulating tumor cells in patients with solid tumors. J Transl Med 10: 52, 2012.
53. Kühnelt-Leddihn L, Müller H, Eisendle K, Zelger B and Weinlich G: Overexpression of the chemokine receptors CXCR4, CCR7, CCR9, and CCR10 in human primary cutaneous melanoma: A potential prognostic value for CCR7 and CCR10? Arch Dermatol Res 304: 185-193, 2012.
54. Singh R, Stockard CR, Grizzle WE Lillard JW Jr and Singh S: Expression and histopathological correlation of CCR9 and CCL25 in ovarian cancer. Int J Oncol 39: 373-381, 2011.

55. Johnson EL, Singh R, Singh S, Johnson-Holiday CM, Grizzle WE, Partridge EE and Lillard JW Jr: CCL25-CCR9 interaction modulates ovarian cancer cell migration, metalloproteinase expression, and invasion. World J Surg Oncol 8: 62, 2010.
56. Johnson-Holiday C, Singh R, Johnson E, Singh S, Stockard CR, Grizzle WE and Lillard JW Jr: CCL25 mediates migration, invasion and matrix metalloproteinase expression by breast cancer cells in a CCR9-dependent fashion. Int J Oncol 38: 1279-1285, 2011.
57. Feng LY, Ou ZL, Wu FY, Shen ZZ and Shao ZM: Involvement of a novel chemokine decoy receptor CCX-CKR in breast cancer growth, metastasis and patient survival. Clin Cancer Res 15: 2962-2970, 2009.
58. Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN, *et al*: Involvement of chemokine receptors in breast cancer metastasis. Nature 410: 50-56, 2001.
59. Johnson-Holiday C, Singh R, Johnson EL, Grizzle WE, Lillard JW Jr. and Singh S: CCR9-CCL25 interactions promote cisplatin resistance in breast cancer cell through Akt activation in a PI3K-dependent and FAK-independent fashion. World J Surg Oncol 9: 46, 2011.
60. Singh S, Singh UP, Stiles JK, Grizzle WE and Lillard JW Jr: Expression and functional role of CCR9 in prostate cancer cell migration and invasion. Clin Cancer Res 10: 8743-8750, 2004.
61. Sharma PK, Singh R, Novakovic KR, Eaton JW, Grizzle WE and Singh S: CCR9 mediates PI3K/AKT-dependent antiapoptotic signals in prostate cancer cells and inhibition of CCR9-CCL25 interaction enhances the cytotoxic effects of etoposide. Int J Cancer 127: 2020-2030, 2010.
62. Shen X, Mailey B, Ellenhorn JD, Chu PG, Lowy AM and Kim J: CC chemokine receptor 9 enhances proliferation in pancreatic intraepithelial neoplasia and pancreatic cancer cells. J Gastrointest Surg 13: 1955-1962, 2009.
63. Heinrich EL, Arrington AK, Ko ME, Luu C, Lee W, Lu J and Kim J: paracrine activation of chemokine receptor CCR9 enhances the invasiveness of pancreatic cancer cells. Cancer Microenviron 6: 241-245, 2013.
64. Chen HJ, Sun J, Huang Z, Hou H Jr, Arcilla M, Rakhilin N, Joe DJ, Choi J, Gadamsetty P, Milsom J, *et al*: Comprehensive models of human primary and metastatic colorectal tumors in immunodeficient and immunocompetent mice by chemokine targeting. Nat Biotechnol 33: 656-660, 2015.
65. Zhang Z, Sun T, Chen Y, Gong S, Sun X, Zou F and Peng R: CCL25/CCR9 Signal promotes migration and invasion in hepatocellular and breast cancer cell lines. DNA Cell Biol 35: 348-357, 2016.
66. Zhang Z, Qin C, Wu Y, Su Z, Xian G and Hu B: CCR9 as a prognostic marker and therapeutic target in hepatocellular carcinoma. Oncol Rep 31: 1629-1636, 2014.
67. Zhong Y, Jiang L, Lin H, Li B, Lan J, Liang S, Shen B, Lei Z and Zheng W: Expression of CC chemokine receptor 9 predicts poor prognosis in patients with lung adenocarcinoma. Diagn Pathol 10: 101, 2015.
68. Gupta P, Sharma PK, Mir H, Singh R, Singh N, Kloecker GH, Lillard JW Jr and Singh S: CCR9/CCL25 expression in non-small cell lung cancer correlates with aggressive disease and mediates key steps of metastasis. Oncotarget 5: 10170-10179, 2014.
69. Mishan MA, Heirani-Tabasi A, Mokhberian N, Hassanzade M, Kalalian Moghaddam H, Bahrami AR and Ahmadiankia N: Analysis of chemokine receptor gene expression in esophageal cancer cells compared with breast cancer with insights into metastasis. Iran J Public Health 44: 1353-1358, 2015.
70. Chamorro S, Vela M, Franco-Villanueva A, Carramolino L, Gutiérrez J, Gómez L, Lozano M, Salvador B, García-Gallo M, Martínez-A C and Kremer L: Antitumor effects of a monoclonal antibody to human CCR9 in leukemia cell xenografts. MAbs 6: 1000-1012, 2014.
71. Khandelwal N, Breinig M, Speck T, Michels T, Kreutzer C, Sorrentino A, Sharma AK, Umansky L, Conrad H, Poschke I, *et al*: A high-throughput RNAi screen for detection of immune-checkpoint molecules that mediate tumor resistance to cytotoxic T lymphocytes. EMBO Mol Med 7: 450-463, 2015.
72. Hu Y, Zhang L, Wu R, Han R, Jia Y, Jiang Z, Cheng M, Gan J, Tao X and Zhang Q: Specific killing of CCR9 high-expressing acute T lymphocytic leukemia cells by CCL25 fused with PE38 toxin. Leuk Res 35: 1254-1260, 2011.
73. Youn BS, Kim YJ, Mantel C, Yu KY and Broxmeyer HE: Blocking of c-FLIP(L)-independent cycloheximide-induced apoptosis or Fas-mediated apoptosis by the CC chemokine receptor 9/TECK interaction. Blood 98: 925-933, 2001.
74. Deng X, Tu Z, Xiong M, Tembo K, Zhou L, Liu P, Pan S, Xiong J, Yang X, Leng J, *et al*: Wnt5a and CCL25 promote adult T-cell acute lymphoblastic leukemia cell migration, invasion and metastasis. Oncotarget 8: 39033-39047, 2017.
75. Shang L, Thirunarayanan N, Viejo-Borbolla A, Martin AP, Bogunovic M, Marchesi F, Unkeless JC, Ho Y, Furtado GC, Alcami A, *et al*: Expression of the chemokine binding protein M3 promotes marked changes in the accumulation of specific leukocytes subsets within the intestine. Gastroenterology 137: 1006-1018, 1018.e1-3, 2009.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.