CCR5 and CXCR4 Antagonists in Carcinomas

Subjects: Oncology

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The interaction between malignant cells and the tumor microenvironment is critical for tumor progression, and the chemokine ligand/receptor axes play a crucial role in this process. The CXCR4/CXCL12 and CCR5/CCL5 axes, both related to HIV, have been associated with the early (epithelial–mesenchymal transition and invasion) and late events (migration and metastasis) of cancer progression. In addition, these axes can also modulate the immune response against tumors. Thus, antagonists against the receptors of these axes have been proposed in cancer therapy.

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1. Introduction

Cancer involves multiple events, such as uncontrolled proliferation and DNA repair failures, that trigger genetic instability, invasion, migration, angiogenesis, and metastasis. These later events depend on the interactions between malignant cells and many cells belonging to the tumor microenvironment, leading to tumor progression [1]. These processes require the activation or inhibition of different cell signaling pathways mediated by cell surface receptors and their ligands for which the chemokine ligand/receptor axes play key roles [2]. According to their chemical structure, chemokines comprise four subtypes of cytokines (C, CC, CXC, and CX3C) that act as the ligand on one or more receptors. On the other hand, chemokine receptors CR, CCR, CXCR, and CX3CR are G protein-coupled receptors activated for one or more subtypes of chemokines [3].

In cancer, and other diseases, a chemokine receptor may activate a proinflammatory or anti-inflammatory pathway, a duality exploited by neoplastic cells to improve the capacity to (i) evade the immune system, (ii) degrade the extracellular matrix, and (iii) invade the neural or vascular compartment producing metastasis [3][4]. In this sense, the bgreat interest is the role of CXCR4/CXCL12 and CCR5/CCL5 axes in the pathogenesis of epithelial malignancies, including lung [5], gastric [6], pancreatic [7], colorectal [8], breast [9], ovarian [10], prostatic [4], hepatocellular [11], and head and neck carcinomas [12][13], as well as adenocarcinomas [14] and non-epithelial cancers such as melanoma [15], multiple myeloma [16], and lymphomas [17].

Preclinical investigations (in vitro and in vivo) have proved the efficacy of HIV-related chemokine receptor (HIVrCR) antagonists for cancer treatment. Chemokine receptor antagonist (CRA) drugs such as maraviroc (CCR5 antagonist) or plerixafor (CXCR4 antagonist) have shown a role in the suppression of cancer cell proliferation, migration, and metastasis [18][19]. Thus, the CRA-promoted blockade of these axes arises as an alternative or

complementary therapy to improve outcomes in tumors resistant to radiotherapy and chemotherapy in carcinomas [11][20][21][22][23][24][25].

2. CXCR4/CXCL12 Axis

In normal tissues, this axis is important in developmental processes, hematopoiesis, and inflammation [26] and is expressed in leukocytes, stromal fibroblasts, and endothelial cells [27]. CXC chemokine receptor 4 (CXCR4) is a G-protein-coupled receptor highly expressed in different human carcinomas [4][6][7][8][11][13][28], at all stages of the epithelial–mesenchymal transition, invasion, or metastasis [29], and has been related to a poor prognosis. Leukocytes and CAFs are sources of CXCL12 [30], a chemokine that binds to CXCR4, forming the CXCL12/CXCR4 axis. This axis has a role in different tumor pathways involved in processes such as the epithelial–mesenchymal transition, cell migration, and metastasis, including drug resistance [31][32][33].

Small molecules, such as AMD3100 (plerixafor), WZ811, LFC131, AMD070, LY2510924, X4-136, BPRCX807, and others [19][34][35][36][37][38][39][40][41][42][43][44][45][46], have been reported to inhibit CXCR4, individually or in association with other drugs or therapies (doxorubicin, cisplatin, radiation, and others) [19][36][37][44][45][46][47][48], including different carriers for a better efficacy [10][29][48][49][50][51]. Preclinical studies have shown, both in vitro and in vivo, that the inhibition of CXCR4 is effective in treating cell proliferation, angiogenesis, tumor growth, and the metastasis of different carcinoma cells [19][25][34][35][36][37][38][39][40][47][48][49][50][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72], and it has been reported that CXCR4 blockade increases tumor-infiltrating lymphocytes (TILs) [73]. These drugs modify cell migration and invasion and reduce metastasis [34][36][37][50]. Additionally, they have also been demonstrated to enhance the sensitivity to chemotherapy or radiotherapy, increasing the reduction in cell viability, apoptosis, tumor growth, and metastasis, including the modulation of the crosstalk between tumor and stromal cells [19][36][37][47][48][51][74]. Finally, plerixafor can induce a better immune response against the tumor through the suppression of Treg cells and the regulation of T cell activity [33][55], and recent studies have reported that CXCR4 inhibition enhances the response to immunotherapy [46][75]. Clinical trials have provided interesting data to consider CXCR4 antagonists as an alternative in cancer therapy in multicenter, randomized, and even phase II studies. Using these drugs as coadjuvant therapy has been successful, showing acceptable safety and tolerability in patients with advanced refractory tumors and expanding the benefits of chemotherapy or immunotherapy [43][76][77][78].

3. CCR5/CCL5 Axis

The use of CCR5-inhibitor drugs in HIV patients is well tolerated, and diverse clinical outcomes have been observed as monotherapy or combined with other antiretroviral drugs (highly active antiretroviral therapy; HAART). The association of CCR5 with cancer progression is unveiling a new perspective on the use of these drugs.

CC chemokine receptor 5 (CCR5) is a G-protein-coupled receptor reported in different kinds of carcinomas, with the primary role in the late events of cancer progression, such as metastasis [13][18]. CCL3 and CCL5 are the main

chemokines that bind to CCR5, forming the CCL3/CCR5 and CCL5/CCR5 activation axes. These chemokines are mainly involved in inflammation, promoting the recruitment of leukocytes to injury sites [79]. The CCR5/CCL5 axis has protumor effects, and the low expression of these proteins can lead to a better prognosis [80].

In carcinomas, some authors have described the relationship between high levels of CCL5 or CCR5 expression in tumors and advanced stages [12][13][81][82][83], including a proangiogenic role [84] and the stimulation of cancer stem cells [85]. Regarding immune modulation, CCL5 can differentiate leukocytes to a protumorigenic profile [86] and can inhibit the antitumorigenic role of CD8+ lymphocytes [87] but can also modulate the activation of Tregs [18] and myeloid-derived suppressor cells [88]. CCL5 was reported as an inducer of cell migration and invasion [89], leading to metastasis [90]. The aggressiveness of CCL5-releasing tumors relies on the fact that they are more aggressive because CCL5 promotes invasion, migration, and metastasis in CCR5-high-expressing tumors.

CCR5 inhibition has demonstrated promising results in controlling cancer development and progression in preclinical studies [18][20][22][90][91][92][93][94]. Maraviroc is a specific small-molecule antagonist of the CCR5 used in preclinical and clinical cancer studies. CCR5 inhibitors were tested to treat liver, pancreatic, and breast cancer cells, showing apoptosis induction, reduced cell invasion and metastasis, and increased survival [20][90][95]. In addition, some studies reported that CCR5 inhibition could modulate the immune response, diminishing Treg infiltration [96][97].

It was reported that the inhibition of CCR5 in colorectal cancer cells, as a single agent, can inhibit proliferation and migration but failed to inhibit metastasis in vivo [98]. However, a study reported that maraviroc could inhibit metastasis in an animal model of colorectal cancer. These contradictory results are probably related to the promiscuity of chemokine receptors and chemokines, suggesting that drugs with dual or multiple inhibitions, or combined therapies (immunotherapy or chemotherapy), could have a better effect against cancer progression and metastasis. Recent preclinical studies have reported that the combination of CCR5 antagonists with anti-PD-L1 can inhibit tumor growth and enhance the therapy outcome in several types of cancer [97][99]. A few reported clinical trials are using CCR5 antagonists [100]. They are in phase I and use maraviroc.

References

1. Hanahan, D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022, 12, 31–46.
2. Raza, S.; Rajak, S.; Tewari, A.; Gupta, P.; Chattopadhyay, N.; Sinha, R.A.; Chakravarti, B. Multifaceted role of chemokines in solid tumors: From biology to therapy. Semin. Cancer Biol. 2022, 86, 1105–1121.
3. Korbecki, J.; Grochans, S.; Gutowska, I.; Barczak, K.; Baranowska-Bosiacka, I. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of Receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 Ligands. Int. J. Mol. Sci. 2020, 21, 7619.

4. Parol-Kulczyk, M.; Gzil, A.; Ligmanowska, J.; Grzanka, D. Prognostic significance of SDF-1 chemokine and its receptors CXCR4 and CXCR7 involved in EMT of prostate cancer. Cytokine 2022, 150, 155778.
5. Wang, Y.; Lan, W.; Xu, M.; Song, J.; Mao, J.; Li, C.; Du, X.; Jiang, Y.; Li, E.; Zhang, R.; et al. Cancer-associated fibroblast-derived SDF-1 induces epithelial-mesenchymal transition of lung adenocarcinoma via CXCR4/beta-catenin/PPARdelta signalling. Cell Death Dis. 2021, 12, 214.
6. Perrot-Applanat, M.; Vacher, S.; Pimpie, C.; Chemlali, W.; Derieux, S.; Pocard, M.; Bieche, I. Differential gene expression in growth factors, epithelial mesenchymal transition and chemotaxis in the diffuse type compared with the intestinal type of gastric cancer. Oncol. Lett. 2019, 18, 674–686.
7. Singh, S.K.; Mishra, M.K.; Eltoum, I.A.; Bae, S.; Lillard, J.W., Jr.; Singh, R. CCR5/CCL5 axis interaction promotes migratory and invasiveness of pancreatic cancer cells. Sci. Rep. 2018, 8, 1323.
8. Ucuncu, M.; Serilmez, M.; Sari, M.; Bademler, S.; Karabulut, S. The Diagnostic Significance of PDGF, EphA7, CCR5, and CCL5 Levels in Colorectal Cancer. Biomolecules 2019, 9, 464.
9. Dayer, R.; Babashah, S.; Jamshidi, S.; Sadeghizadeh, M. Upregulation of CXC chemokine receptor 4-CXC chemokine ligand 12 axis ininvasive breast carcinoma: A potent biomarker predicting lymph node metastasis. J. Cancer Res. Ther. 2018, 14, 345–350.
10. Xue, J.; Li, R.; Gao, D.; Chen, F.; Xie, H. CXCL12/CXCR4 Axis-Targeted Dual-Functional Nano-Drug Delivery System Against Ovarian Cancer. Int. J. Nanomed. 2020, 15, 5701–5718.
11. Singh, S.K.; Mishra, M.K.; Rivers, B.M.; Gordetsky, J.B.; Bae, S.; Singh, R. Biological and Clinical Significance of the CCR5/CCL5 Axis in Hepatocellular Carcinoma. Cancers 2020, 12, 883.
12. Domingueti, C.B.; Janini, J.B.; Paranaiba, L.M.; Lozano-Burgos, C.; Olivero, P.; Gonzalez-Arriagada, W.A. Prognostic value of immunoexpression of CCR4, CCR5, CCR7 and CXCR4 in squamous cell carcinoma of tongue and floor of the mouth. Med. Oral Patol. Oral Cir. Bucal 2019, 24, e354–e363.
13. Gonzalez-Arriagada, W.A.; Lozano-Burgos, C.; Zuniga-Moreta, R.; Gonzalez-Diaz, P.; Coletta, R.D. Clinicopathological significance of chemokine receptor (CCR1, CCR3, CCR4, CCR5, CCR7 and CXCR4) expression in head and neck squamous cell carcinomas. J. Oral Pathol. Med. 2018, 47, 755–763.
14. Gao, T.; Shen, Z.; Ma, C.; Li, Y.; Kang, X.; Sun, M. The CCL5/CCR5 Chemotactic Pathway Promotes Perineural Invasion in Salivary Adenoid Cystic Carcinoma. J. Oral Maxillofac. Surg. 2018, 76, 1708–1718.
15. McConnell, A.T.; Ellis, R.; Pathy, B.; Plummer, R.; Lovat, P.E.; O'Boyle, G. The prognostic significance and impact of the CXCR4-CXCR7-CXCL12 axis in primary cutaneous melanoma. Br.

J. Dermatol. 2016, 175, 1210–1220.

16. Beider, K.; Bitner, H.; Leiba, M.; Gutwein, O.; Koren-Michowitz, M.; Ostrovsky, O.; Abraham, M.; Wald, H.; Galun, E.; Peled, A.; et al. Multiple myeloma cells recruit tumor-supportive macrophages through the CXCR4/CXCL12 axis and promote their polarization toward the M2 phenotype. Oncotarget 2014, 5, 11283–11296.
17. Pansy, K.; Feichtinger, J.; Ehall, B.; Uhl, B.; Sedej, M.; Roula, D.; Pursche, B.; Wolf, A.; Zoidl, M.; Steinbauer, E.; et al. The CXCR4-CXCL12-Axis Is of Prognostic Relevance in DLBCL and Its Antagonists Exert Pro-Apoptotic Effects In Vitro. Int. J. Mol. Sci. 2019, 20, 4740.
18. Halvorsen, E.C.; Hamilton, M.J.; Young, A.; Wadsworth, B.J.; LePard, N.E.; Lee, H.N.; Firmino, N.; Collier, J.L.; Bennewith, K.L. Maraviroc decreases CCL8-mediated migration of CCR5+ regulatory T cells and reduces metastatic tumor growth in the lungs. OncoImmunology 2016, 5, e1150398.
19. Chaudary, N.; Pintilie, M.; Jelveh, S.; Lindsay, P.; Hill, R.P.; Milosevic, M. Plerixafor Improves Primary Tumor Response and Reduces Metastases in Cervical Cancer Treated with Radio-Chemotherapy. Clin. Cancer Res. 2017, 23, 1242–1249.
20. Pervaiz, A.; Zepp, M.; Georges, R.; Bergmann, F.; Mahmood, S.; Faiza, S.; Berger, M.R.; Adwan, H. Antineoplastic effects of targeting CCR5 and its therapeutic potential for colorectal cancer liver metastasis. J. Cancer Res. Clin. Oncol. 2021, 147, 73–91.
21. Huang, H.; Zepp, M.; Georges, R.B.; Jarahian, M.; Kazemi, M.; Eyol, E.; Berger, M.R. The CCR5 antagonist maraviroc causes remission of pancreatic cancer liver metastasis in nude rats based on cell cycle inhibition and apoptosis induction. Cancer Lett. 2020, 474, 82–93.
22. Pervaiz, A.; Zepp, M.; Mahmood, S.; Ali, D.M.; Berger, M.R.; Adwan, H. CCR5 blockage by maraviroc: A potential therapeutic option for metastatic breast cancer. Cell Oncol. 2019, 42, 93–106.
23. Toyoma, S.; Suzuki, S.; Kawasaki, Y.; Yamada, T. SDF-1/CXCR4 induces cell invasion through CD147 in squamous cell carcinoma of the hypopharynx. Oncol. Lett. 2020, 20, 1817–1823.
24. Yoshida, S.; Kawai, H.; Eguchi, T.; Sukegawa, S.; Oo, M.W.; Anqi, C.; Takabatake, K.; Nakano, K.; Okamoto, K.; Nagatsuka, H. Tumor Angiogenic Inhibition Triggered Necrosis (TAITN) in Oral Cancer. Cells 2019, 8, 761.
25. Taromi, S.; Kayser, G.; Catusse, J.; von Elverfeldt, D.; Reichardt, W.; Braun, F.; Weber, W.A.; Zeiser, R.; Burger, M. CXCR4 antagonists suppress small cell lung cancer progression. Oncotarget 2016, 7, 85185–85195.
26. Sharma, M.; Afrin, F.; Satija, N.; Tripathi, R.P.; Gangenahalli, G.U. Stromal-Derived Factor-1/CXCR4Signaling: Indispensable Role in Homing and Engraftment of Hematopoietic Stem Cells in Bone Marrow. Stem Cells Dev. 2011, 20, 933–946.

27. Guo, F.; Wang, Y.; Liu, J.; Mok, S.C.; Xue, F.; Zhang, W. CXCL12/CXCR4: A symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. Oncogene 2015, 35, 816–826.
28. Wang, H.; Pan, J.; Barsky, L.; Jacob, J.C.; Zheng, Y.; Gao, C.; Wang, S.; Zhu, W.; Sun, H.; Lu, L.; et al. Characteristics of pre-metastatic niche: The landscape of molecular and cellular pathways. Mol. Biomed. 2021, 2, 3.
29. Yang, X.; Gao, F.; Zhang, W.; Li, H.; Huang, X.; Wei, J.; Bian, J.; Yang, Y.; Qian, C.; Sun, M. “Star” miR-34a and CXCR4 antagonist based nanoplex for binary cooperative migration treatment against metastatic breast cancer. J. Control. Release 2020, 326, 615–627.
30. Orimo, A.; Gupta, P.B.; Sgroi, D.C.; Arenzana-Seisdedos, F.; Delaunay, T.; Naeem, R.; Carey, V.J.; Richardson, A.L.; Weinberg, R.A. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 2005, 121, 335–348.
31. Dillenburg-Pilla, P.; Patel, V.; Mikelis, C.M.; Zarate-Blades, C.R.; Doci, C.L.; Amornphimoltham, P.; Wang, Z.; Martin, D.; Leelahavanichkul, K.; Dorsam, R.T.; et al. SDF-1/CXCL12 induces directional cell migration and spontaneous metastasis via a CXCR4/Galphai/mTORC1 axis. FASEB J. 2015, 29, 1056–1068.
32. Zhang, F.; Cui, J.Y.; Gao, H.F.; Yu, H.; Gao, F.F.; Chen, J.L.; Chen, L. Cancer-associated fibroblasts induce epithelial-mesenchymal transition and cisplatin resistance in ovarian cancer via CXCL12/CXCR4 axis. Future Oncol. 2020, 16, 2619–2633.
33. Biasci, D.; Smoragiewicz, M.; Connell, C.M.; Wang, Z.; Gao, Y.; Thaventhiran, J.E.D.; Basu, B.; Magiera, L.; Johnson, T.I.; Bax, L.; et al. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. Proc. Natl. Acad. Sci. USA 2020, 117, 28960–28970.
34. Chittasupho, C.; Anuchapreeda, S.; Sarisuta, N. CXCR4 targeted dendrimer for anti-cancer drug delivery and breast cancer cell migration inhibition. Eur. J. Pharm. Biopharm. 2017, 119, 310–321.
35. Dragoj, M.; Bankovic, J.; Sereti, E.; Stojanov, S.J.; Dimas, K.; Pesic, M.; Stankovic, T. Anti-invasive effects of CXCR4 and FAK inhibitors in non-small cell lung carcinomas with mutually inactivated p53 and PTEN tumor suppressors. Investig. New Drugs 2017, 35, 718–732.
36. Zhou, K.X.; Xie, L.H.; Peng, X.; Guo, Q.M.; Wu, Q.Y.; Wang, W.H.; Zhang, G.L.; Wu, J.F.; Zhang, G.J.; Du, C.W. CXCR4 antagonist AMD3100 enhances the response of MDA-MB-231 triple-negative breast cancer cells to ionizing radiation. Cancer Lett. 2018, 418, 196–203.
37. Fang, X.; Xie, H.; Duan, H.; Li, P.; Yousaf, M.; Xu, H.; Yang, Y.; Wang, C. Anti-tumor activity of nanomicelles encapsulating CXCR4 peptide antagonist E5. PLoS ONE 2017, 12, e0182697.

38. He, W.; Yang, T.; Gong, X.H.; Qin, R.Z.; Zhang, X.D.; Liu, W.D. Targeting CXC motif chemokine receptor 4 inhibits the proliferation, migration and angiogenesis of lung cancer cells. Oncol. Lett. 2018, 16, 3976–3982.

39. Shen, D.; Zhu, L.; Liu, Y.; Peng, Y.; Lan, M.; Fang, K.; Guo, Y. Efficacy evaluation and mechanism study on inhibition of breast cancer cell growth by multimodal targeted nanobubbles carrying AMD070 and ICG. Nanotechnology 2020, 31, 245102.

40. Uchida, D.; Kuribayashi, N.; Kinouchi, M.; Sawatani, Y.; Shimura, M.; Mori, T.; Hasegawa, T.; Miyamoto, Y.; Kawamata, H. Effect of a novel orally bioavailable CXCR4 inhibitor, AMD070, on the metastasis of oral cancer cells. Oncol. Rep. 2018, 40, 303–308.

41. Galsky, M.D.; Vogelzang, N.J.; Conkling, P.; Raddad, E.; Polzer, J.; Roberson, S.; Stille, J.R.; Saleh, M.; Thornton, D. A Phase I Trial of LY2510924, a CXCR4 Peptide Antagonist, in Patients with Advanced Cancer. Clin. Cancer Res. 2014, 20, 3581–3588.

42. Hainsworth, J.D.; Reeves, J.A.; Mace, J.R.; Crane, E.J.; Hamid, O.; Stille, J.R.; Flynt, A.; Roberson, S.; Polzer, J.; Arrowsmith, E.R. A Randomized, Open-Label Phase 2 Study of the CXCR4 Inhibitor LY2510924 in Combination with Sunitinib Versus Sunitinib Alone in Patients with Metastatic Renal Cell Carcinoma (RCC). Target. Oncol. 2016, 11, 643–653.

43. O'Hara, M.H.; Messersmith, W.; Kindler, H.; Zhang, W.; Pitou, C.; Szpurka, A.M.; Wang, D.; Peng, S.-B.; Vangerow, B.; Khan, A.A.; et al. Safety and Pharmacokinetics of CXCR4 Peptide Antagonist, LY2510924, in Combination with Durvalumab in Advanced Refractory Solid Tumors. J. Pancreat. Cancer 2020, 6, 21–31.

44. Zhou, J.; Le, K.; Xu, M.; Ming, J.; Yang, W.; Zhang, Q.; Lu, L.; Xi, Z.; Ruan, S.; Huang, T. CXCR4 Antagonist AMD3100 Reverses the Resistance to Tamoxifen in Breast Cancer via Inhibiting AKT Phosphorylation. Mol. Ther.-Oncolytics 2020, 18, 161–170.

45. Chaudary, N.; Hill, R.P.; Stulik, L.; Milosevic, M. The Oral CXCR4 Inhibitor X4-136 Improves Tumor Control and Reduces Toxicity in Cervical Cancer Treated with Radiation Therapy and Concurrent Chemotherapy. Int. J. Radiat. Oncol.*Biol.*Phys. 2021, 110, 1317–1324.

46. Song, J.S.; Chang, C.C.; Wu, C.H.; Dinh, T.K.; Jan, J.J.; Huang, K.W.; Chou, M.C.; Shiue, T.Y.; Yeh, K.C.; Ke, Y.Y.; et al. A highly selective and potent CXCR4 antagonist for hepatocellular carcinoma treatment. Proc. Natl. Acad. Sci. USA 2021, 118, e2015433118.

47. Dragoj, M.; Milosevic, Z.; Bankovic, J.; Tanic, N.; Pesic, M.; Stankovic, T. Targeting CXCR4 and FAK reverses doxorubicin resistance and suppresses invasion in non-small cell lung carcinoma. Cell Oncol. 2017, 40, 47–62.

48. Tang, S.; Hang, Y.; Ding, L.; Tang, W.; Yu, A.; Zhang, C.; Sil, D.; Xie, Y.; Oupicky, D. Intraperitoneal siRNA Nanoparticles for Augmentation of Gemcitabine Efficacy in the Treatment of Pancreatic Cancer. Mol. Pharm. 2021, 18, 4448–4458.

49. Liu, J.-Y.; Chiang, T.; Liu, C.-H.; Chern, G.-G.; Lin, T.-T.; Gao, D.-Y.; Chen, Y. Delivery of siRNA Using CXCR4-targeted Nanoparticles Modulates Tumor Microenvironment and Achieves a Potent Antitumor Response in Liver Cancer. Mol. Ther. 2015, 23, 1772–1782.
50. Zhang, F.; Gong, S.; Wu, J.; Li, H.; Oupicky, D.; Sun, M. CXCR4-Targeted and Redox Responsive Dextrin Nanogel for Metastatic Breast Cancer Therapy. Biomacromolecules 2017, 18, 1793–1802.
51. Fang, X.; Zhang, K.; Jiang, M.; Ma, L.; Liu, J.; Xu, H.; Yang, Y.; Wang, C. Enhanced lymphatic delivery of nanomicelles encapsulating CXCR4-recognizing peptide and doxorubicin for the treatment of breast cancer. Int. J. Pharm. 2021, 594, 120183.
52. Guo, H.; Ge, Y.; Li, X.; Yang, Y.; Meng, J.; Liu, J.; Wang, C.; Xu, H. Targeting the CXCR4/CXCL12 axis with the peptide antagonist E5 to inhibit breast tumor progression. Signal Transduct Target Ther. 2017, 2, 17033.
53. Li, H.; Chen, Y.; Xu, N.; Yu, M.; Tu, X.; Chen, Z.; Lin, M.; Xie, B.; Fu, J.; Han, L. AMD3100 inhibits brain-specific metastasis in lung cancer via suppressing the SDF-1/CXCR4 axis and protecting blood-brain barrier. Am. J. Transl. Res. 2017, 9, 5259–5274.
54. Reeves, P.M.; Abbaslou, M.A.; Kools, F.R.W.; Poznansky, M.C. CXCR4 blockade with AMD3100 enhances Taxol chemotherapy to limit ovarian cancer cell growth. Anticancer Drugs 2017, 28, 935–942.
55. Santagata, S.; Napolitano, M.; D'Alterio, C.; Desicato, S.; Maro, S.D.; Marinelli, L.; Fragale, A.; Buoncervello, M.; Persico, F.; Gabriele, L.; et al. Targeting CXCR4 reverts the suppressive activity of T-regulatory cells in renal cancer. Oncotarget 2017, 8, 77110–77120.
56. Izumi, D.; Ishimoto, T.; Miyake, K.; Sugihara, H.; Eto, K.; Sawayama, H.; Yasuda, T.; Kiyozumi, Y.; Kaida, T.; Kurashige, J.; et al. CXCL12/CXCR4 activation by cancer-associated fibroblasts promotes integrin beta1 clustering and invasiveness in gastric cancer. Int. J. Cancer 2016, 138, 1207–1219.
57. Zhu, W.B.; Zhao, Z.F.; Zhou, X. AMD3100 inhibits epithelial–mesenchymal transition, cell invasion, and metastasis in the liver and the lung through blocking the SDF-1α/CXCR4 signaling pathway in prostate cancer. J. Cell. Physiol. 2018, 234, 11746–11759.
58. Morimoto, M.; Matsuo, Y.; Koide, S.; Tsuboi, K.; Shamoto, T.; Sato, T.; Saito, K.; Takahashi, H.; Takeyama, H. Enhancement of the CXCL12/CXCR4 axis due to acquisition of gemcitabine resistance in pancreatic cancer: Effect of CXCR4 antagonists. BMC Cancer 2016, 16, 305.
59. Li, Z.; Chen, G.; Ding, L.; Wang, Y.; Zhu, C.; Wang, K.; Li, J.; Sun, M.; Oupicky, D. Increased Survival by Pulmonary Treatment of Established Lung Metastases with Dual STAT3/CXCR4 Inhibition by siRNA Nanoemulsions. Mol. Ther. 2019, 27, 2100–2110.
60. Wang, Y.; Kumar, S.; Rachagani, S.; Sajja, B.R.; Xie, Y.; Hang, Y.; Jain, M.; Li, J.; Boska, M.D.; Batra, S.K.; et al. Polyplex-mediated inhibition of chemokine receptor CXCR4 and chromatin-

remodeling enzyme NCOA3 impedes pancreatic cancer progression and metastasis. Biomaterials 2016, 101, 108–120.

61. Xie, Y.; Wehrkamp, C.J.; Li, J.; Wang, Y.; Wang, Y.; Mott, J.L.; Oupický, D. Delivery of miR-200c Mimic with Poly(amido amine) CXCR4 Antagonists for Combined Inhibition of Cholangiocarcinoma Cell Invasiveness. Mol. Pharm. 2016, 13, 1073–1080.
62. Mayr, C.; Neureiter, D.; Pichler, M.; Berr, F.; Wagner, A.; Kiesslich, T.; Namberger, K. Cytotoxic effects of chemokine receptor 4 inhibition by AMD3100 in biliary tract cancer cells: Potential drug synergism with gemcitabine. Mol. Med. Rep. 2015, 12, 2247–2252.
63. Muralidharan, R.; Panneerselvam, J.; Chen, A.; Zhao, Y.D.; Munshi, A.; Ramesh, R. HuR-targeted nanotherapy in combination with AMD3100 suppresses CXCR4 expression, cell growth, migration and invasion in lung cancer. Cancer Gene Ther. 2015, 22, 581–590.
64. Xiang, J.; Hurchla, M.A.; Fontana, F.; Su, X.; Amend, S.R.; Esser, A.K.; Douglas, G.J.; Mudalagiriyappa, C.; Luker, K.E.; Pluard, T.; et al. CXCR4 Protein Epitope Mimetic Antagonist POL5551 Disrupts Metastasis and Enhances Chemotherapy Effect in Triple-Negative Breast Cancer. Mol. Cancer Ther. 2015, 14, 2473–2485.
65. Huang, M.B.; Giesler, K.E.; Katzman, B.M.; Prosser, A.R.; Truax, V.; Liotta, D.C.; Wilson, L.J.; Bond, V.C. Small molecule CXCR4 antagonists block the HIV-1 Nef/CXCR4 axis and selectively initiate the apoptotic program in breast cancer cells. Oncotarget 2018, 9, 16996–17013.
66. Mei, L.; Liu, Y.; Zhang, Q.; Gao, H.; Zhang, Z.; He, Q. Enhanced antitumor and anti-metastasis efficiency via combined treatment with CXCR4 antagonist and liposomal doxorubicin. J. Control. Release 2014, 196, 324–331.
67. Wong, D.; Kandagatla, P.; Korz, W.; Chinni, S.R. Targeting CXCR4 with CTCE-9908 inhibits prostate tumor metastasis. BMC Urol. 2014, 14, 12.
68. Yang, Q.; Zhang, F.; Ding, Y.; Huang, J.; Chen, S.; Wu, Q.; Wang, Z.; Wang, Z.; Chen, C. Antitumour activity of the recombination polypeptide GST-NT21MP is mediated by inhibition of CXCR4 pathway in breast cancer. Br. J. Cancer 2014, 110, 1288–1297.
69. Jeong, W.-J.; Choi, I.J.; Park, M.-W.; An, S.-Y.; Jeon, E.-H.; Paik, J.H.; Sung, M.-W.; Ahn, S.-H. CXCR4 antagonist inhibits perineural invasion of adenoid cystic carcinoma. J. Clin. Pathol. 2014, 67, 992–998.
70. Heckmann, D.; Maier, P.; Laufs, S.; Wenz, F.; Zeller, W.J.; Fruehauf, S.; Allgayer, H. CXCR4 Expression and Treatment with SDF-1alpha or Plerixafor Modulate Proliferation and Chemosensitivity of Colon Cancer Cells. Transl. Oncol. 2013, 6, 124–132.
71. Greco, S.J.; Patel, S.A.; Bryan, M.; Pliner, L.F.; Banerjee, D.; Rameshwar, P. AMD3100-mediated production of interleukin-1 from mesenchymal stem cells is key to chemosensitivity of breast cancer cells. Am. J. Cancer Res. 2011, 1, 701–715.

72. Portella, L.; Vitale, R.; De Luca, S.; D'Alterio, C.; Ierano, C.; Napolitano, M.; Riccio, A.; Polimeno, M.N.; Monfregola, L.; Barbieri, A.; et al. Preclinical development of a novel class of CXCR4 antagonist impairing solid tumors growth and metastases. PLoS ONE 2013, 8, e74548.

73. Gong, R.; Ren, H. Targeting chemokines/chemokine receptors: A promising strategy for enhancing the immunotherapy of pancreatic ductal adenocarcinoma. Signal Transduct. Target. Ther. 2020, 5, 149.

74. Khan, M.A.; Srivastava, S.K.; Zubair, H.; Patel, G.K.; Arora, S.; Khushman, M.; Carter, J.E.; Gorman, G.S.; Singh, S.; Singh, A.P. Co-targeting of CXCR4 and hedgehog pathways disrupts tumor-stromal crosstalk and improves chemotherapeutic efficacy in pancreatic cancer. J. Biol. Chem. 2020, 295, 8413–8424.

75. Li, Z.; Wang, Y.; Shen, Y.; Qian, C.; Oupicky, D.; Sun, M. Targeting pulmonary tumor microenvironment with CXCR4-inhibiting nanocomplex to enhance anti-PD-L1 immunotherapy. Sci. Adv. 2020, 6, eaaz9240.

76. Bockorny, B.; Semenisty, V.; Macarulla, T.; Borazanci, E.; Wolpin, B.M.; Stemmer, S.M.; Golan, T.; Geva, R.; Borad, M.J.; Pedersen, K.S.; et al. BL-8040, a CXCR4 antagonist, in combination with pembrolizumab and chemotherapy for pancreatic cancer: The COMBAT trial. Nat. Med. 2020, 26, 878–885.

77. Bockorny, B.; Macarulla, T.; Semenisty, V.; Borazanci, E.; Feliu, J.; Ponz-Sarvise, M.; Abad, D.G.; Oberstein, P.; Alistar, A.; Muñoz, A.; et al. Motixafortide and Pembrolizumab Combined to Nanoliposomal Irinotecan, Fluorouracil, and Folinic Acid in Metastatic Pancreatic Cancer: The COMBAT/KEYNOTE-202 Trial. Clin. Cancer Res. 2021, 27, 5020–5027.

78. Choueiri, T.K.; Atkins, M.B.; Rose, T.L.; Alter, R.S.; Ju, Y.; Niland, K.; Wang, Y.; Arbeit, R.; Parasuraman, S.; Gan, L.; et al. A phase 1b trial of the CXCR4 inhibitor mavorixafor and nivolumab in advanced renal cell carcinoma patients with no prior response to nivolumab monotherapy. Investig. New Drugs 2021, 39, 1019–1027.

79. Weitzenfeld, P.; Ben-Baruch, A. The chemokine system, and its CCR5 and CXCR4 receptors, as potential targets for personalized therapy in cancer. Cancer Lett. 2014, 352, 36–53.

80. Aldinucci, D.; Casagrande, N. Inhibition of the CCL5/CCR5 Axis against the Progression of Gastric Cancer. Int. J. Mol. Sci. 2018, 19, 1477.

81. Ma, G.; Huang, H.; Li, M.; Li, L.; Kong, P.; Zhu, Y.; Xia, T.; Wang, S. Plasma CCL5 promotes EMT-medicated epirubicin-resistance in locally advanced breast cancer. Cancer Biomark 2018, 22, 405–415.

82. Wang, T.; Wei, Y.; Tian, L.; Song, H.; Ma, Y.; Yao, Q.; Feng, M.; Wang, Y.; Gao, M.; Xue, Y. C-C motif chemokine ligand 5 (CCL5) levels in gastric cancer patient sera predict occult peritoneal metastasis and a poorer prognosis. Int. J. Surg. 2016, 32, 136–142.

83. Yaal-Hahoshen, N.; Shina, S.; Leider-Trejo, L.; Barnea, I.; Shabtai, E.L.; Azenshtein, E.; Greenberg, I.; Keydar, I.; Ben-Baruch, A. The chemokine CCL5 as a potential prognostic factor predicting disease progression in stage II breast cancer patients. Clin. Cancer Res. 2006, 12, 4474–4480.
84. Suffee, N.; Hlawaty, H.; Meddahi-Pelle, A.; Maillard, L.; Louedec, L.; Haddad, O.; Martin, L.; Laguillier, C.; Richard, B.; Oudar, O.; et al. RANTES/CCL5-induced pro-angiogenic effects depend on CCR1, CCR5 and glycosaminoglycans. Angiogenesis 2012, 15, 727–744.
85. Zhang, Y.; Yao, F.; Yao, X.; Yi, C.; Tan, C.; Wei, L.; Sun, S. Role of CCL5 in invasion, proliferation and proportion of CD44+/CD24- phenotype of MCF-7 cells and correlation of CCL5 and CCR5 expression with breast cancer progression. Oncol. Rep. 2009, 21, 1113–1121.
86. Laubli, H.; Spanaus, K.S.; Borsig, L. Selectin-mediated activation of endothelial cells induces expression of CCL5 and promotes metastasis through recruitment of monocytes. Blood 2009, 114, 4583–4591.
87. Chang, L.-Y.; Lin, Y.-C.; Mahalingam, J.; Huang, C.-T.; Chen, T.-W.; Kang, C.-W.; Peng, H.-M.; Chu, Y.-Y.; Chiang, J.-M.; Dutta, A.; et al. Tumor-Derived Chemokine CCL5 Enhances TGF-β–Mediated Killing of CD8+ T Cells in Colon Cancer by T-Regulatory Cells. Cancer Res. 2012, 72, 1092–1102.
88. Zhang, Y.; Lv, D.; Kim, H.J.; Kurt, R.A.; Bu, W.; Li, Y.; Ma, X. A novel role of hematopoietic CCL5 in promoting triple-negative mammary tumor progression by regulating generation of myeloid-derived suppressor cells. Cell Res. 2013, 23, 394–408.
89. Long, H.; Xie, R.; Xiang, T.; Zhao, Z.; Lin, S.; Liang, Z.; Chen, Z.; Zhu, B. Autocrine CCL5 signaling promotes invasion and migration of CD133+ ovarian cancer stem-like cells via NF-kappaB-mediated MMP-9 upregulation. Stem Cells 2012, 30, 2309–2319.
90. Velasco-Velazquez, M.; Jiao, X.; De La Fuente, M.; Pestell, T.G.; Ertel, A.; Lisanti, M.P.; Pestell, R.G. CCR5 antagonist blocks metastasis of basal breast cancer cells. Cancer Res. 2012, 72, 3839–3850.
91. Pervaiz, A.; Ansari, S.; Berger, M.R.; Adwan, H. CCR5 blockage by maraviroc induces cytotoxic and apoptotic effects in colorectal cancer cells. Med. Oncol. 2015, 32, 158.
92. Mencarelli, A.; Graziosi, L.; Renga, B.; Cipriani, S.; D'Amore, C.; Francisci, D.; Bruno, A.; Baldelli, F.; Donini, A.; Fiorucci, S. CCR5 Antagonism by Maraviroc Reduces the Potential for Gastric Cancer Cell Dissemination. Transl. Oncol. 2013, 6, 784–793.
93. Sicoli, D.; Jiao, X.; Ju, X.; Velasco-Velazquez, M.; Ertel, A.; Addya, S.; Li, Z.; Ando, S.; Fatatis, A.; Paudyal, B.; et al. CCR5 receptor antagonists block metastasis to bone of v-Src oncogene-transformed metastatic prostate cancer cell lines. Cancer Res. 2014, 74, 7103–7114.

94. Ward, S.T.; Li, K.K.; Hepburn, E.; Weston, C.J.; Curbishley, S.M.; Reynolds, G.M.; Hejmadi, R.K.; Bicknell, R.; Eksteen, B.; Ismail, T.; et al. The effects of CCR5 inhibition on regulatory T-cell recruitment to colorectal cancer. Br. J. Cancer 2014, 112, 319–328.
95. Ochoa-Callejero, L.; Perez-Martinez, L.; Rubio-Mediavilla, S.; Oteo, J.A.; Martinez, A.; Blanco, J.R. Maraviroc, a CCR5 antagonist, prevents development of hepatocellular carcinoma in a mouse model. PLoS ONE 2013, 8, e53992.
96. Tan, M.C.; Goedegebuure, P.S.; Belt, B.A.; Flaherty, B.; Sankpal, N.; Gillanders, W.E.; Eberlein, T.J.; Hsieh, C.S.; Linehan, D.C. Disruption of CCR5-dependent homing of regulatory T cells inhibits tumor growth in a murine model of pancreatic cancer. J. Immunol. 2009, 182, 1746–1755.
97. Wang, J.; Saung, M.T.; Li, K.; Fu, J.; Fujiwara, K.; Niu, N.; Muth, S.; Wang, J.; Xu, Y.; Rozich, N.; et al. CCR2/CCR5 inhibitor permits the radiation-induced effector T cell infiltration in pancreatic adenocarcinoma. J. Exp. Med. 2022, 219, e20211631.
98. Cambien, B.; Richard-Fiardo, P.; Karimdjee, B.F.; Martini, V.; Ferrua, B.; Pitard, B.; Schmid-Antomarchi, H.; Schmid-Alliana, A. CCL5 neutralization restricts cancer growth and potentiates the targeting of PDGFRbeta in colorectal carcinoma. PLoS ONE 2011, 6, e28842.
99. Liu, C.; Yao, Z.; Wang, J.; Zhang, W.; Yang, Y.; Zhang, Y.; Qu, X.; Zhu, Y.; Zou, J.; Peng, S.; et al. Macrophage-derived CCL5 facilitates immune escape of colorectal cancer cells via the p65/STAT3-CSN5-PD-L1 pathway. Cell Death Differ. 2019, 27, 1765–1781.
100. Haag, G.M.; Springfeld, C.; Grün, B.; Apostolidis, L.; Zschäbitz, S.; Dietrich, M.; Berger, A.-K.; Weber, T.F.; Zoernig, I.; Schaaf, M.; et al. Pembrolizumab and maraviroc in refractory mismatch repair proficient/microsatellite-stable metastatic colorectal cancer—The PICCASSO phase I trial. Eur. J. Cancer 2022, 167, 112–122.