

повышать или стабилизировать экспрессию лиганда программированной клеточной смерти 1 (PD-L1) опухолевыми клетками, тем самым косвенно снижая эффективность противоопухолевых иммунных реакций (Morein et al., 2020). Установлено, что активация CXCR4 связана с усилением иммуносупрессии при тройном негативном РМЖ (Lu et al., 2021). Авторы показали, что комбинация анти-PD-L1 с антагонистом CXCR4 с липосомным составом (liposomal-AMD3100) продемонстрировала повышенный противоопухолевый эффект и пролонгированное время выживания по сравнению с монотерапией анти-PD-L1 на мышинной модели тройного негативного РМЖ (Lu et al., 2021). Аналогичные результаты получены и другими авторами как на моделях РМЖ, так и рака яичников и поджелудочной железы (Feig et al., 2013; Chen et al., 2019; D'Alterio et al., 2019; Zeng et al., 2019).

ЗАКЛЮЧЕНИЕ

Таким образом, данные литературы свидетельствуют о том, что хемокин CXCL12 и его рецепторы CXCR4/CXCR7 играют важную роль в процессах роста опухоли, инвазии, метастазирования, опухолевого ангиогенеза, индукции ЭМП, модуляции противоопухолевого иммунитета, а также развитии лекарственной устойчивости. Эта ось является многообещающей мишенью для терапевтического вмешательства. Однако следует учитывать тот факт, что CXCL12 и его рецепторы играют важную роль не только в опухолевой прогрессии, но и в гомеостазе и воспалении, что предполагает значительную токсичность фармакологических препаратов, нацеленных на эту ось. Помимо этого, недостаточно изучена роль и функции CXCR7 в прогрессировании рака. Выяснение этих функций и их механизмов, несомненно, внесет вклад в разработку более совершенных противоопухолевых средств, нацеленных на ось CXCL12. В перспективе необходимо исследовать возможность адресной доставки для антагонистов CXCR4, что повысит их эффективность и уменьшит их побочные эффекты (Shi et al., 2020). Другим перспективным направлением является разработка радиофармпрепаратов, нацеленных на CXCR4, которые можно использовать как с диагностической

целью (для визуализации опухоли и метастазов), так и с терапевтической (Yu et al., 2023).

ФИНАНСИРОВАНИЕ РАБОТЫ

Работа выполнена при поддержке Российского научного фонда (проект № 23-25-00183, <https://rscf.ru/project/23-25-00183/>).

СОБЛЮДЕНИЕ ЭТИЧЕСКИХ СТАНДАРТОВ

В работе не участвовали животные или люди в качестве объектов исследования.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют об отсутствии конфликта интересов.

СПИСОК ЛИТЕРАТУРЫ

- Ганцев Ш. Х., Пухов А.Г., Хуснутдинова Э.К., Галеев М.Г., Ганцев К.Ш., Ишмуратова Р.Ш., Исламгулов Д.В., Фролова В.Ю., Кзыргалин Ш.Р., Мусин Ш.И., Халикова Л.В. 2012. Неолимфогенез и профиль экспрессии хемокинов при раке молочной железы. Креативная хирургия и онкология. № 1. С. 4. (Gancev S.H., Puhov A.G., Husnutdinova E.K., Galeev M.G., Gancev K.S., Ishmuratova R.S., Islamgulov D.V., Frolova V.YU., Kzyrgalin S.H.R., Musin S.H.I., Halikova L.V. 2012. Neolimfogenez i profil' ekspressii hemokinov pri rake molochnoj zhelezy. Kreativnaya hirurgiya i onkologiya, № 1. P. 4.).
- Каприн А.Д., Старинский В.В., Шахзадова А.О. 2021. Злокачественные новообразования в России в 2020 году (заболеваемость и смертность). Москва: МНИОИ им. П.А. Герцена. (Kaprin A.D., Starinskij V.V., Shahzadova A.O. 2021. Zlokachestvennye novoobrazovaniya v Rossii v 2020 godu (zabolevaemost' i smertnost'). Moskva: MNIIOI im. P.A. Gercena.)
- Стукань А.И., Горяинова А.Ю., Шаров С.В., Андреев Д.В., Лымарь Е.В. 2021. Механизмы метастазирования и развития резистентности к терапии при раке молочной железы. Клинический случай эффективности иксабепилона при формировании множественной лекарственной устойчивости гормон-рецептор-позитивного рака молочной железы. Медицинский совет. № 20. С. 54. (Stukan' A.I., Goryainova A.Y., Sharov S.V., Andreev D.V., Lyumar' E.V. 2021. Mekhanizmy metastazirovaniya i razvitiya rezistentnosti k terapii pri rake molochnoj

- zhelezy. Klinicheskij sluchaj effektivnosti iksabepilona pri formirovanii mnozhestvennoj lekarstvennoj ustojchivosti gormon-receptor-pozitivnogo raka molochnoj zhelezy. *Medicinskij Sovet*. № 20. P. 54.)
<https://doi.org/10.21518/2079-701X-2021-20-54-61>
- Agarwal U., Ghalayini W., Dong F., Weber K., Zou Y.R., Rabbany S.Y., Rafii S., Penn M.S. 2010. Role of cardiac myocyte CXCR4 expression in development and left ventricular remodeling after acute myocardial infarction. *Circ Res*. V. 107. P. 667.
<https://doi.org/10.1161/CIRCRESAHA.110.223289>
- Aversa I., Zolea F., Ieranò C., Bulotta S., Trotta A.M., Faniello M.C., De Marco C., Malanga D., Biamonte F., Viglietto G., Cuda G., Scala S., Costanzo F. 2017. Epithelial-to-mesenchymal transition in FHC-silenced cells: the role of CXCR4/CXCL12 axis. *J. Exp. Clin. Cancer Res*. V. 36. P. 104.
<https://doi.org/10.1186/s13046-017-0571-8>
- Bianchi M.E., Mezzapelle R. 2020. The Chemokine Receptor CXCR4 in Cell Proliferation and Tiss. Regenerat. *Front Immunol*. V. 11. P. 2109.
<https://doi.org/10.3389/fimmu.2020.02109>
- Boesch M., Onder L., Cheng H.W., Novkovic M., Mörbbe U., Sopper S., Gastl G., Jochum W., Ruhstaller T., Knauer M., Ludewig B. 2018. Interleukin 7-expressing fibroblasts promote breast cancer growth through sustenance of tumor cell stemness. *Oncoimmunol*. V. 7. P. e1414129.
<https://doi.org/10.1080/2162402X.2017.1414129>
- Boimel P.J., Smirnova T., Zhou Z.N., Wyckoff J., Park H., Coniglio S.J., Qian B.Z., Stanley E.R., Cox D., Pollard J.W., Muller W.J., Condeelis J., Segall J.E. 2012. Contribution of CXCL12 secretion to invasion of breast cancer cells. *Breast Cancer Res*. V. 14. P. R23.
<https://doi.org/10.1186/bcr3108>
- Bolitho C., Hahn M.A., Baxter R.C., Marsh D.J. 2010. The chemokine CXCL1 induces proliferation in epithelial ovarian cancer cells by transactivation of the epidermal growth factor receptor. *Endocr. Relat. Cancer*. V. 17. P. 929.
<https://doi.org/10.1677/ERC-10-0107>
- Cambier S., Gouwy M., Proost P. 2023. The chemokines CXCL8 and CXCL12: molecular and functional properties, role in disease and efforts towards pharmacological intervention. *Cell. Mol. Immunol*. 2023. V. 20. P. 217.
<https://doi.org/10.1038/s41423-023-00974-6>
- Chang C.W., Seibel A.J., Avendano A., Cortes-Medina M.G., Song J.W. 2020. Distinguishing specific CXCL12 isoforms on their angiogenesis and vascular permeability promoting properties. *Adv. Healthcare Mater*. V. 9. Art. ID e1901399.
<https://doi.org/10.1002/adhm.201901399>
- Chatterjee S., Behnam Azad B., Nimmagadda S. 2014. The intricate role of CXCR4 in cancer. *Adv. Cancer Res*. V. 124. P. 31.
<https://doi.org/10.1016/B978-0-12-411638-2.00002-1>
- Chen H.J., Edwards R., Tucci S., Bu P., Milsom J., Lee S., Edelmann W., Gümüs Z.H., Shen X., Lipkin S. 2012. Chemokine 25-induced signaling suppresses colon cancer invasion and metastasis. *J. Clin. Invest*. V. 122. P. 3184.
<https://doi.org/10.1172/JCI62110>
- Chen I.X., Chauhan V.P., Posada J., Ng M.R., Wu M.W., Adstamongkonkul P., Huang P., Lindeman N., Langer R., Jain R.K. 2019. Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. *Proc. Natl. Acad. Sci. USA*. V. 116. P. 4558.
<https://doi.org/10.1073/pnas.1815515116>
- Cheng Y.H., Eby J.M., LaPorte H.M., Volkman B.F., Majetschak M. 2017. Effects of cognate, non-cognate and synthetic CXCR4 and ACKR3 ligands on human lung endothelial cell barrier function. *PLoS One*. V. 12. Art. ID e0187949.
<https://doi.org/10.1371/journal.pone.0187949>
- Chung B., Esmaeili A.A., Gopalakrishna-Pillai S., Murad J.P., Andersen E.S., Kumar Reddy N., Srinivasan G., Armstrong B., Chu C., Kim Y., Tong T., Waisman J., Yim J.H., Badie B., Lee P.P. 2017. Human brain metastatic stroma attracts breast cancer cells via chemokines CXCL16 and CXCL12. *NPJ Breast Cancer*. V. 3. P. 6.
<https://doi.org/10.1038/s41523-017-0008-8>
- Costa A., Kieffer Y., Scholer-Dahirel A., Pelon F., Bourachot B., Cardon M., Sirven P., Magagna I., Fuhrmann L., Bernard C., Bonneau C., Kondratova M., Kuperstein I., Zinovyev A., Givel A.M., Parrini M.C., Soumelis V., Vincent-Salomon A., Mechta-Grigoriou F. 2018. Fibroblast heterogeneity and immunosuppressive environment in human breast cancer. *Cancer Cell*. V. 33. P. 463.
<https://doi.org/10.1016/j.ccell.2018.01.011>
- Cui L., Qu H., Xiao T., Zhao M., Jolkkonen J., Zhao C. 2013. Stromal cell-derived factor-1 and its receptor CXCR4 in adult neurogenesis after cerebral ischemia. *Restor. Neurol. Neurosci*. V. 31. P. 239.
<https://doi.org/10.3233/RNN-120271>
- D'Alterio C., Buoncervello M., Ieranò C., Napolitano M., Portella L., Rea G., Barbieri A., Luciano A., Scognamiglio G., Tatangelo F., Anniciello A.M., Monaco M., Cavalcanti E., Maiolino P., Romagnoli G., Arra C., Botti G., Gabriele L., Scala S. 2019. Targeting CXCR4 potentiates anti-PD-1 efficacy modifying the tumor microenvironment and inhibiting neoplastic PD-1. *J. Exp. Clin. Cancer Res*. V. 38. P. 432.
<https://doi.org/10.1186/s13046-019-1420-8>

- Daniel S.K., Seo Y.D., Pillarisetty V.G. 2020. The CXCL12-CXCR4/CXCR7 axis as a mechanism of immune resistance in gastrointestinal malignancies. *Semin. Cancer Biol.* V. 65. P. 176.
<https://doi.org/10.1016/j.semcancer.2019.12.007>
- De Oliveira K.B., Guembarovski R.L., Guembarovski A.M., da Silva do Amaral Herrera A.C., Sobrinho W.J., Ariza C.B., Watanabe M.A. 2013. CXCL12, CXCR4 and IFN γ genes expression: implications for proinflammatory microenvironment of breast cancer. *Clin. Exper. Med.* V. 13. P. 211.
<https://doi.org/10.1007/s10238-012-0194-5>
- Döring Y., van der Vorst E.P.C., Duchene J., Jansen Y., Gencer S., Bidzhekov K., Atzler D., Santovito D., Rader D.J., Saleheen D., Weber C. 2019. CXCL12 derived from endothelial cells promotes atherosclerosis to drive coronary artery disease. *Circulation.* V. 139. P. 1338.
<https://doi.org/10.1161/CIRCULATIONAHA.118.037953>
- Dubrovskaya A., Hartung A., Bouchez L.C., Walker J.R., Reddy V.A., Cho C.Y., Schultz P.G. 2012. CXCR4 activation maintains a stem cell population in tamoxifen-resistant breast cancer cells through AhR signalling. *British J. Cancer.* V. 107. P. 43.
<https://doi.org/10.1038/bjc.2012.105>
- Elias S., Sharma R., Schizas M., Valdez I., Rampersaud S., Park S.M., Gonzalez-Figueroa P., Li Q.Z., Hoyos B., Rudensky A.Y. 2022. CXCR4⁺ Treg cells control serum IgM levels and natural IgM autoantibody production by B-1 cells in the bone marrow. *J. Exper. Med.* V. 219. Art. ID e20220047.
<https://doi.org/10.1084/jem.20220047>
- Esposito A., Klüppel M., Wilson B.M., Meka S.R.K., Spagnoli A. 2023. CXCR4 mediates the effects of IGF-1R signaling in rodent bone homeostasis and fracture repair. *Bone.* V. 166. Art. ID 116600.
<https://doi.org/10.1016/j.bone.2022.116600>
- Fang Y.Y., Lyu F., Abuwala N., Tal A., Chen A.Y., Taylor H.S., Tal R. 2022. Chemokine C-X-C receptor 4 mediates recruitment of bone marrow-derived nonhematopoietic and immune cells to the pregnant uterus†. *Biol. Reprod.* V. 106. P. 1083.
<https://doi.org/10.1093/biolre/ioac029>
- Feig C., Jones J.O., Kraman M., Wells R.J., Deonarine A., Chan D.S., Connell C.M., Roberts E.W., Zhao Q., Caballero O.L., Teichmann S.A., Janowitz T., Jodrell D.I., Tuveson D.A., Fearon D.T. 2013. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc. Natl. Acad. Sci. USA.* V. 110. P. 20212.
<https://doi.org/10.1073/pnas.1320318110>
- Gadalla R., Hassan H., Ibrahim S.A., Abdullah M.S., Gaballah A., Greve B., El-Deeb S., El-Shinawi M., Mohamed M.M. 2019. Tumor microenvironmental plasmacytoid dendritic cells contribute to breast cancer lymph node metastasis via CXCR4/SDF-1 axis. *Breast Cancer Res. Treat.* V. 174. P. 679.
<https://doi.org/10.1007/s10549-019-05129-8>
- Gao D., Tang T., Zhu J., Tang Y., Sun H., Li S. 2019. CXCL12 has therapeutic value in facial nerve injury and promotes Schwann cells autophagy and migration via PI3K-AKT-mTOR signal pathway. *Int. J. Biol. Macromol.* V. 124. P. 460.
<https://doi.org/10.1016/j.ijbiomac.2018.10.212>
- Ghosh M.C., Makena P.S., Gorantla V., Sinclair S.E., Walters C.M. 2012. CXCR4 regulates migration of lung alveolar epithelial cells through activation of Rac1 and matrix metalloproteinase-2. *Am. J. Physiol. Lung Cell Mol. Physiol.* V. 302. P. 846.
<https://doi.org/10.1152/ajplung.00321.2011>
- Gu Y., Liu Y., Fu L., Zhai L., Zhu J., Han Y., Jiang Y., Zhang Y., Zhang P., Jiang Z., Zhang X., Cao X. 2019. Tumor-educated B cells selectively promote breast cancer lymph node metastasis by HSPA4-targeting IgG. *Nat. Med.* V. 25. P. 312.
<https://doi.org/10.1038/s41591-018-0309-y>
- Harbeck N., Penault-Llorca F., Cortes J., Gnant M., Housami N., Poortmans P., Ruddy K., Tsang J., Cardoso F. 2019. Breast Cancer. *Nat. Rev. Dis. Primers.* V. 5. P. 66.
<https://doi.org/10.1038/s41572-019-0111-2>
- Heinrich E.L., Lee W., Lu J., Lowy A.M., Kim J. 2012. Chemokine CXCL12 activates dual CXCR4 and CXCR7-mediated signaling pathways in pancreatic cancer cells. *J. Translat. Med.* V. 10. P. 68.
<https://doi.org/10.1186/1479-5876-10-68>
- Janssens R., Struyf S., Proost P. 2018. Pathological roles of the homeostatic chemokine CXCL12. *Cytokine growth factor Rev.* V. 44. P. 51.
<https://doi.org/10.1016/j.cytofr.2018.10.004>
- Janssens R., Struyf S., Proost P. 2018. The unique structural and functional features of CXCL12. *Cell. Mol. Immunol.* V. 15. P. 299.
<https://doi.org/10.1038/cmi.2017.107>
- Khare T., Bissonnette M., Khare S. 2021. CXCL12-CXCR4/CXCR7 Axis in colorectal cancer: therapeutic target in preclinical and clinical studies. *Int. J. Mol. Sci.* V. 22. Art. ID 7371.
<https://doi.org/10.3390/ijms22147371>
- Kim H., Sung J., Kim H., Ryu H., Cho Park H., Oh Y.K., Lee H.S., Oh K.H., Ahn C. 2019. Expression and secretion of CXCL12 are enhanced in autosomal dominant polycystic kidney disease. *BMB Rep.* V. 52. P. 463.
<https://doi.org/10.5483/BMBRep.2019.52.7.112>
- Kobayashi K., Sato K., Kida T., Omori K., Hori M., Ozaki H., Murata T. 2014. Stromal cell-derived factor-1 α /C-X-C chemokine receptor type 4 axis promotes endothelial cell barrier integrity via phosphoinositide

- 3-kinase and Rac1 activation. *Arterioscler. Thromb. Vasc Biol.* V. 34. P. 1716.
<https://doi.org/10.1161/ATVBAHA.114.303890>
- Kong L., Guo S., Liu C., Zhao Y., Feng C., Liu Y., Wang T., Li C. 2016. Overexpression of SDF-1 activates the NF- κ B pathway to induce epithelial to mesenchymal transition and cancer stem cell-like phenotypes of breast cancer cells. *Int. J. Oncol.* V. 48. Art. ID 1085.
<https://doi.org/10.3892/ijo.2016.3343>
- Li S., Fan Y., Kumagai A., Kawakita E., Kitada M., Kanasaki K., Koya D. 2020. Deficiency in dipeptidyl peptidase-4 promotes chemoresistance through the CXCL12/CXCR4/mTOR/TGF β signaling pathway in breast cancer cells. *Int. J. Mol. Sci.* V. 21. Art. ID 805.
<https://doi.org/10.3390/ijms21030805>
- Lu G., Qiu Y., Su X. 2021. Targeting CXCL12-CXCR4 Signaling enhances immune checkpoint blockade therapy against triple negative breast cancer. *Eur. J. Pharm. Sci.* V. 157. Art. ID 105606.
<https://doi.org/10.1016/j.ejps.2020.105606>
- Marcuzzi E., Angioni R., Molon B., Cali B. 2018. Chemokines and chemokine receptors: orchestrating tumor metastasization. *Int. J. Mol. Sci.* V. 20. Art. ID 96.
<https://doi.org/10.3390/ijms20112651>
- McQuade A., Kang Y.J., Hasselmann J., Jairaman A., Sotelo A., Coburn M., Shabestari S.K., Chadarevian J.P., Fote G., Tu C.H., Danhash E., Silva J., Martinez E., Cotman C., Prieto G.A., Thompson L.M., Steffan J.S., Smith I., Davtyan H., Cahalan M., Cho H., Blurton-Jones M. 2020. Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. *Nat. Commun.* V. 11. P. 5370.
<https://doi.org/10.1038/s41467-023-36930-1>
- Miao R., Lim V.Y., Kothapalli N., Ma Y., Fossati J., Zehentmeier S., Sun R., Pereira J.P. 2020. Hematopoietic stem cell niches and signals controlling immune cell development and maintenance of immunological memory. *Front. Immunol.* V. 11. Art. ID 600127.
<https://doi.org/10.3389/fimmu.2020.600127>
- Morein D., Erlichman N., Ben-Baruch A. 2020. Beyond cell motility: the expanding roles of chemokines and their receptors in malignancy. *Front Immunol.* V. 11. P. 952.
<https://doi.org/10.3389/fimmu.2020.00952>
- Mukherjee D., Zhao J. 2013. The role of chemokine receptor CXCR4 in breast cancer metastasis. *Am. J. Cancer Res.* V. 3. P. 46.
- Murad H.A.S., Rafeeq M.M., Alqurashi T.M.A. 2021. Role and implications of the CXCL12/CXCR4/CXCR7 axis in atherosclerosis: still a debate. *Ann. Med.* V. 53. P. 1598.
<https://doi.org/10.1080/07853890.2021.1974084>
- Okuyama Kishima M., de Oliveira C.E., Banin-Hirata B.K., Losi-Guembarovski R., Brajão de Oliveira K., Amarante M.K., Watanabe M.A. 2015. Immunohistochemical expression of CXCR4 on breast cancer and its clinical significance. *Anal. Cell. Pathol. (Amst).* V. 2015. P. 891020.
<https://doi.org/10.1155/2015/891020>
- Price T.T., Burness M.L., Sivan A., Warner M.J., Cheng R., Lee C.H., Olivere L., Comatas K., Magnani J., Kim Lyerly H., Cheng Q., McCall C.M., Sipkins D.A. 2016. Dormant breast cancer micrometastases reside in specific bone marrow niches that regulate their transit to and from bone. *Sci. Transl. Med.* V. 8. Art. ID 340ra73.
<https://doi.org/10.1126/scitranslmed.aad4059>
- Rajagopal S., Kim J., Ahn S., Craig S., Lam C.M., Gerard N.P., Gerard C., Lefkowitz R.J. 2010. Beta-arrestin- but not G protein-mediated signaling by the “decoy” receptor CXCR7. *Proc. Natl. Acad. Sci. USA.* V. 107. P. 628.
<https://doi.org/10.1073/pnas.0912852107>
- Raman D., Sobolik-Delmaire T., Richmond A. 2011. Chemokines in health and disease. *Exp. Cell Res.* V. 317. P. 575.
<https://doi.org/10.1016/j.yexcr.2011.01.005>
- Ramos E.A., Grochoski M., Braun-Prado K., Seniski G.G., Cavalli I.J., Ribeiro E.M., Camargo A.A., Costa F.F., Klassen G. 2011. Epigenetic changes of CXCR4 and its ligand CXCL12 as prognostic factors for sporadic breast cancer. *PLoS One.* V. 6. Art. ID e29461.
<https://doi.org/10.1371/journal.pone.0029461>
- Righetti A., Giulietti M., Šabanović B., Occhipinti G., Principato G., Piva F. 2019. CXCL12 and Its isoforms: different roles in pancreatic cancer? *J. Oncol.* V. 2019. Art. ID 9681698.
<https://doi.org/10.1155/2019/9681698>
- Rot A., von Andrian U.H. 2004. Chemokines in innate and adaptive host defense: basic chemokines grammar for immune cells. *Annu. Rev. Immunol.* V. 22. P. 891.
<https://doi.org/10.1146/annurev.immunol.22.012703>
- Sainz J., Sata M. 2007. CXCR4, a key modulator of vascular progenitor cells. *Arterioscler. Thromb. Vasc. Biol.* V. 27. P. 263.
<https://doi.org/10.1161/01.ATV.0000256727.34148.e2>
- Sayyed S.G., Hägele H., Kulkarni O.P., Endlich K., Segerer S., Eulberg D., Klusmann S., Anders H.J. 2009. Podocytes produce homeostatic chemokine stromal cell-derived factor-1/CXCL12, which contributes to glomerulosclerosis, podocyte loss and albuminuria in a mouse model of type 2 diabetes. *Diabetologia.* V. 52. P. 2445.
<https://doi.org/10.1007/s00125-009-1493-6>
- Scala S. 2015. Molecular Pathways: Targeting the CXCR4-CXCL12 Axis—untapped potential in the tumor microenvironment. *Clin Cancer Res.* V. 21. P. 4278.
<https://doi.org/10.1158/1078-0432.CCR-14-0914>

- Scherz-Shouval R., Santagata S., Mendillo M.L., Sholl L.M., Ben-Aharon I., Beck A.H., Dias-Santagata D., Koeva M., Stemmer S.M., Whitesell L., Lindquist S. 2014. The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. *Cell*. V. 158. P. 564. <https://doi.org/10.1016/j.cell.2014.05.045>
- Shi Y., Riese D.J., Shen J. 2020. The Role of the CXCL12/CXCR4/CXCR7 chemokine axis in cancer. *Front. Pharmacol.* V. 11. Art. ID 574667. <https://doi.org/10.3389/fphar.2020.574667>
- Song J.K., Park M.H., Choi D.Y., Yoo H.S., Han S.B., Yoon D.Y., Hong J.T. 2012. Deficiency of C-C chemokine receptor 5 suppresses tumor development via inactivation of NF- κ B and upregulation of IL-1Ra in melanoma model. *PLoS One*. V. 7. Art. ID e33747. <https://doi.org/10.1371/journal.pone.0033747>
- Stone M.J., Hayward J.A., Huang C., Huma Z., Sanchez J. 2017. Mechanisms of regulation of the chemokine-receptor network. *Int. J. Mol. Sci.* V. 18. P. 342. <https://doi.org/10.3390/ijms18020342>
- Strazza M., Azoulay-Alfaguter I., Peled M., Smrcka A.V., Skolnik E.Y., Srivastava S., Mor A. 2017. PLC ϵ 1 regulates SDF-1 α -induced lymphocyte adhesion and migration to sites of inflammation. *Proc. Natl. Acad. Sci. USA*. V. 114. P. 2693. <https://doi.org/10.1073/pnas.1612900114>
- Su H., Sobrino Najul E.J., Toth T.A., Ng C.M., Lelievre S.A., Fred M., Tang C.K. 2011. Chemokine receptor CXCR4-mediated transformation of mammary epithelial cells by enhancing multiple RTKs expression and deregulation of the p53/MDM2 axis. *Cancer Lett.* V. 307. P. 132. <https://doi.org/10.1016/j.canlet.2011.03.025>
- Tang X., Li X., Li Z., Liu Y., Yao L., Song S., Yang H., Li C. 2016. Downregulation of CXCR7 inhibits proliferative capacity and stem cell-like properties in breast cancer stem cells. *Tumour. Biol.* V. 37. P. 13425. <https://doi.org/10.1007/s13277-016-5180-1>
- Tang X., Tu G., Yang G., Wang X., Kang L., Yang L., Zeng H., Wan X., Qiao Y., Cui X., Liu M., Hou Y. 2019. Autocrine TGF- β 1/miR-200s/miR-221/DNMT3B regulatory loop maintains CAF status to fuel breast cancer cell proliferation. *Cancer Lett.* V. 452. P. 79. <https://doi.org/10.1016/j.canlet.2019.02.044>
- Thakar D., Dalonneau F., Migliorini E., Lortat-Jacob H., Boturyn D., Albiges-Rizo C., Coche-Guerente L., Picart C., Richter R.P. 2017. Binding of the chemokine CXCL12 α to its natural extracellular matrix ligand heparan sulfate enables myoblast adhesion and facilitates cell motility. *Biomaterials*. V. 123. P. 24. <https://doi.org/10.1016/j.biomaterials.2017.01.022>
- Tung S.Y., Chang S.F., Chou M.H., Huang W.S., Hsieh Y.Y., Shen C.H., Kuo H.C., Chen C.N. 2012. CXC chemokine ligand 12/stromal cell-derived factor-1 regulates cell adhesion in human colon cancer cells by induction of intercellular adhesion molecule-1. *J. Biomed. Sci.* V. 19. Art. ID 91. <https://doi.org/10.1186/1423-0127-19-91>
- Wang Y., Gao F. 2023. Research progress of CXCR4-targeting radioligands for oncologic imaging. *Korean J. Radiol.* V. 24. P. 871. <https://doi.org/10.3348/kjr.2023.0091>
- Wani N., Nasser M.W., Ahirwar D.K., Zhao H., Miao Z., Shilo K., Ganju R.K. 2014. C-X-C motif chemokine 12/C-X-C chemokine receptor type 7 signaling regulates breast cancer growth and metastasis by modulating the tumor microenvironment. *Breast Cancer Res.* V. 16. Art. ID R54. <https://doi.org/10.1186/bcr3665>
- Wei C.Y., Zhu M.X., Lu N.H., Liu J.Q., Yang Y.W., Zhang Y., Shi Y.D., Feng Z.H., Li J.X., Qi F.Z., Gu J.Y. 2020. Circular RNA circ_0020710 drives tumor progression and immune evasion by regulating the miR-370-3p/CXCL12 axis in melanoma. *Mol. Cancer*. V. 19. P. 84. <https://doi.org/10.1186/s12943-020-01191-9>
- Wendel C., Hempling-Bovenkerk A., Krasnyanska J., Mees S.T., Kochetkova M., Stoeppler S., Haier J. 2012. CXCR4/CXCL12 participate in extravasation of metastasizing breast cancer cells within the liver in a rat model. *PLoS One*. V. 7. Art. ID e30046. <https://doi.org/10.1371/journal.pone.0030046>
- Wu B., Chien E.Y., Mol C.D., Fenalti G., Liu W., Katriitch V., Abagyan R., Brooun A., Wells P., Bi F.C., Hamel D.J., Kuhn P., Handel T.M., Cherezov V., Stevens R.C. 2010. Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science*. V. 330. P. 1066. <https://doi.org/10.1126/science.1194396>
- Yamada K., Maishi N., Akiyama K., Towfik Alam M., Ohga N., Kawamoto T., Shindoh M., Takahashi N., Kamiyama T., Hida Y., Taketomi A., Hida K. 2015. CXCL12-CXCR7 axis is important for tumor endothelial cell angiogenic property. *Int. J. Cancer*. V. 137. Art. ID 2825. <https://doi.org/10.1002/ijc.29655>
- Yang F., Takagaki Y., Yoshitomi Y., Ikeda T., Li J., Kitada M., Kumagai A., Kawakita E., Shi S., Kanasaki K., Koya D. 2019. Inhibition of dipeptidyl peptidase-4 accelerates epithelial-mesenchymal transition and breast cancer metastasis via the CXCL12/CXCR4/mTOR axis. *Cancer Res.* V. 79. P. 735. <https://doi.org/10.1158/0008-5472.CAN-18-0620>
- Yang Y., Li J., Lei W., Wang H., Ni Y., Liu Y., Yan H., Tian Y., Wang Z., Yang Z., Yang S., Yang Y., Wang Q. 2023. CXCL12-CXCR4/CXCR7 axis in cancer: from mechanisms to clinical applications. *Int. J. Biol. Sci.* V. 19. Art. ID 3341. <https://doi.org/10.7150/ijbs.82317>

- Yu J., Zhou X., Shen L. 2023. CXCR4-targeted radiopharmaceuticals for the imaging and therapy of malignant tumors. *Molecules*. V. 28. Art. ID 4707. <https://doi.org/10.3390/molecules28124707>
- Yu P.F., Huang Y., Xu C.L., Lin L.Y., Han Y.Y., Sun W.H., Hu G.H., Rabson A.B., Wang Y., Shi Y.F. 2017. Down-regulation of CXCL12 in mesenchymal stromal cells by TGF β promotes breast cancer metastasis. *Oncogene*. V. 36. P. 840. <https://doi.org/10.1038/onc.2016.252>
- Zeng Y., Li B., Liang Y., Reeves P.M., Qu X., Ran C., Liu Q., Callahan M.V., Sluder A.E., Gelfand J.A., Chen H., Poznansky M.C. 2019. Dual blockade of CXCL12-CXCR4 and PD-1-PD-L1 pathways prolongs survival of ovarian tumor-bearing mice by prevention of immunosuppression in the tumor microenvironment. *FASEB J.* V. 33. P. 6596. <https://doi.org/10.1096/fj.201802067RR>
- Zhang J., Chen J., Wo D., Yan H., Liu P., Ma E., Li L., Zheng L., Chen D., Yu Z., Liang C., Peng J., Ren D.N., Zhu W. 2019. LRP6 Ectodomain prevents SDF-1/CXCR4-induced breast cancer metastasis to lung. *Clin. Cancer Res.* V. 25. P. 4832. <https://doi.org/10.1158/1078-0432.CCR-18-3557>
- Zhang M., Qiu L., Zhang Y., Xu D., Zheng J.C., Jiang L. 2017. CXCL12 enhances angiogenesis through CXCR7 activation in human umbilical vein endothelial cells. *Sci. Rep.* V. 7. P. 8289. <https://doi.org/10.1038/s41598-017-08840-y>
- Zhou W., Guo S., Liu M., Burow M.E., Wang G. 2019. Targeting CXCL12/CXCR4 axis in tumor immunotherapy. *Curr. Med. Chem.* V. 26. P. 3026. <https://doi.org/10.2174/0929867324666170830111531>
- Zielińska K.A., Katanaev V.L. 2020. The signaling duo CXCL12 and CXCR4: chemokine fuel for breast cancer tumorigenesis. *Cancers (Basel)*. V. 12. Art. ID 3071. <https://doi.org/10.3390/cancers12103071>
- Zou Y.R., Kottmann A.H., Kuroda M., Taniuchi I., Littman D.R. 1998. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature*. V. 393. P. 595. <https://doi.org/10.1038/31269>

CHEMOKININ CXCL12 AND ITS RECEPTORS CXCR4 AND CXCR7 IN THE PROGRESSION OF BREAST CANCER

E. Y. Zubareva^{a, b, *}, M. A. Senchukova^{a, b}, N. V. Saidler^a

^a Orenburg Regional Clinical Oncology Center, Orenburg, 460021, Russia

^b Orenburg State Medical University” of the Ministry of Health of the Russian Federation, Orenburg, 460000, Russia

* E-mail: tishkova_evgeniy@mail.ru

Breast cancer ranks first in terms of cancer incidence and mortality among the female population. The main cause of death from breast cancer, as with other malignant neoplasms, is tumor dissemination and the development of resistance to treatment. Chemokines have been found to play an important role in the progression of malignant neoplasms. In this short review, we describe the current understanding of the role of the most studied chemokine, CXCL12 and its receptors, CXCR4 and CXCR7 in the progression of breast cancer.

Keywords: breast cancer, progression, chemokines, CXCL12, CXCR4, CXCR7