Review

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Chemokines—What Is Their Role in Colorectal Cancer?

Sara Pączek, MCM[1], Marta Łukaszewicz-Zając, MD[1], and Barbara Mroczko, MD[1,2]

Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related death. It is the second most frequently diagnosed malignancy in Europe and third worldwide. Colorectal malignancies diagnosed at an early stage offer a promising survival rate. However, advanced tumors often present distant metastases even after the complete resection of a primary tumor. Therefore, novel biomarkers of CRC are sorely needed in the diagnosis and prognosis of this common malignancy. A family of chemokines are composed of small, secreted proteins. They are best known for their ability to stimulate the migration of several cell types. Some investigations have indicated that chemokines are involved in cancer development, including CRC. This article presents current knowledge regarding chemokines and their specific receptors in CRC progression. Moreover, the prime aim of this review is to summarize the potential role of these proteins as biomarkers in the diagnosis and prognosis of CRC.

Keywords

colorectal cancer, chemokines, biomarkers, cancer, chemokine receptors

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Introduction

Colorectal cancer (CRC) is considered a serious global problem since it represents the second most commonly diagnosed malignancy in Europe and third worldwide.[1] Recently, a marginal increase in its incidence has been observed in Central and Eastern Europe.[2] The global incidence and mortality rates are, in principle, lower for females than for males.[3,4] Unless genetically determined, CRC very rarely occurs in patients younger than 40 years. Therefore, the majority of screening programs are targeted at individuals older than 50 years.[1,5] Structurally, CRC is a highly heterogeneous disease which may occur in the rectum as well as the colon.[6] A tumor may develop in the right- or left-side of the colon, causing different systemic symptoms. Patients diagnosed with right-sided CRC usually complain of abdominal pain and weight loss. They may also experience occult gastrointestinal bleeding, confirmed by a positive fecal occult blood test, which often results in iron-deficiency anemia.[7] By contrast, left-sided colon cancer frequently produces symptoms such as overt bleeding from the lower intestine and a change in defecation rhythm, for example, diarrhea or constipation.[7] Tumor stage at the time of diagnosis is considered to be one of the most significant prognostic factors for this malignancy. The 5-year survival rate depends, among other factors, on the presence or absence of distant metastases. It ranges from 90% for early-stage disease without distant or regional metastases to 10% for advanced-stage cancer with distant metastases.[8]

Risk Factors, Prevention, and Screening

Since there is no single, obvious cause of this malignancy, several risk factors in CRC development have been investigated. They have been divided into 2 groups: modifiable and

[1] Department of Biochemical Diagnostics, Medical University of Bialystok, Poland
[2] Department of Neurodegeneration Diagnostics, Medical University of Bialystok, Poland

Corresponding Author:
Marta Łukaszewicz-Zając, Department of Biochemical Diagnostics, Medical University in Bialystokul. Waszyngtona 15A, 15-269 Bialystok, Poland.
Email: marta.lukaszewicz-zajac@umb.edu.pl

nonmodifiable. Obesity, poor diet, tobacco or alcohol use, as well as a lack of physical activity are factors which can be modified.[9] The relationship between diet and CRC development has been investigated several times. It has been demonstrated that increased red meat consumption as well as a low fiber intake may raise the risk of developing CRC.[10] By contrast, a high intake of fish, green leafy vegetables, vitamin D, and calcium has been shown to have protective properties against CRC.[6,11] Other risk factors such as familial or personal history of CRC as well as colorectal polyps, Lynch syndrome, and the presence of type 2 diabetes are nonmodifiable factors.[11,12] However, the majority of cases with CRC are associated with an unhealthy lifestyle and therefore, in order to diminish the risk of CRC, it is recommended that the intake of red meat is reduced, excessive alcohol consumption avoided, and the duration and frequency of physical activity increased.[11,13] Factors contributing to an increase or decrease in CRC incidence are presented in Figure 1.

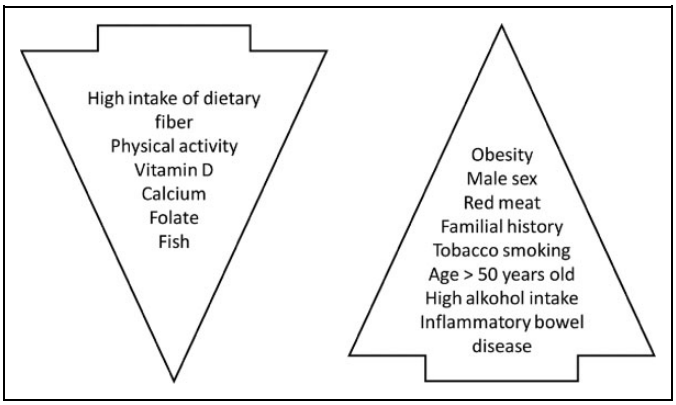

Figure 1. Factors which decrease or increase CRC risk.[6,10] CRC indicates colorectal cancer.

Diagnosis of CRC is a complex process involving a number of investigations. It normally commences with laboratory tests, including carcinoembryonic antigen (CEA) concentration determination. However, this marker is not sufficiently sensitive and specific and therefore, it is useful primarily in monitoring the treatment. Other important examinations in CRC diagnosis include a colonoscopy/sigmoidoscopy and imaging tests. Nevertheless, the final diagnosis is confirmed by histopathological examination, which is an invasive procedure.[8,14]

Screening options for CRC used at present include several tests which have both advantages and limitations. However, the most important parameters of a test are diagnostic sensitivity and specificity, which define its accuracy.[15] Colonoscopy, which is currently the most sensitive method for CRC screening, is recommended every 10 years for individuals aged 50 years or older, who are considered an average-risk group for developing this type of cancer.[16] Importantly, the examination can detect both precancerous and cancerous lesions, which may be removed at the time of detection.[17] Another test is a semi-invasive sigmoidoscopy, which is similar to colonoscopy besides the fact that only the distal half of the colon is examined. However, it is performed less frequently. Computed tomography colonography, which does not require sedation, is another method used in CRC diagnosis. It can assist in detecting both proximal and distal lesions but does not offer the possibility of lesion removal.[9,17] Diet may also interfere with test results, for example, a high intake of vitamin C may provide false-negative results since it inhibits the activity of peroxidase used in FOBT, while hemoglobin found in red meat can lead to false-positive results.[17,18]

Biomarkers for Early Diagnosis of CRC

Inherited mutations are responsible of approximately 20% to 30% of CRC. Due to next generation sequencing with potential future therapeutic implications, genomics of CRC has been recently under extensive investigation. The predictive significance of various blood cell ratios in CRC has been studied by many authors, who indicate the potential role of the fractional albumin rate (FAR = 100 × fibrinogen/albumin), fibrinogen to prealbumin ratio (FPR = fibrinogen/prealbumin), and the neutrophil–lymphocyte ratio (NLR) in early CRC. It is suggested that increased FAR, FPR, and NLR have been reported in early CRC in comparison to healthy controls in the prognosis and survival of patients with CRC.[19] Moreover, low lymphocyte–monocyte ratio (LMR) is related to more advanced and poorly differentiated disease, whereas high LMR was associated with early stages and improved overall survival. Some clinical investigations have indicated that the diagnostic utility of FAR and FPR was higher than NLR, and the combination of FPR, CEA, and CA19-9 could optimize the discrimination ability of CRC from benign disease, what may suggest that these biomarkers can be implemented for early diagnostics of patients with CRC.[19] However, due to the variety of patients' population, analytical techniques, and timing of specimen collection, future studies are sorely needed.

Some clinical investigations have suggested the role of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA—cell-free DNA) as an noninvasive biomarkers for early diagnosis; ctDNA refers to small DNA fragments that are released by the tumor into the bloodstream and contribute complementary information for clinical decision. These potential biomarkers allowed for high-yield isolation directly from a small volume of unprocessed plasma. The assessment of CTCs and ctDNA-based liquid biopsies hold promise for early diagnosis of CRC, however their detection may not be widely adopted for routine practice until accuracy and reliability of these tests are validated on large, independent studies.[20]

The analyses of methylation of the promoter of Septin9 DNA have been also suggested as biomarker for early diagnosis of CRC. The authors indicate the significance of detection of methylated Septin9 DNA using a qualitative assay for the polymerase chain reaction in the early detection of CRC. This stool-based test is useful in the discrimination between patients with CRC and healthy controls.[21] Moreover, the biomarkers of microsatellite instability has been also suggested as useful tools in the early diagnosis of CRC and may serve as

screening markers for Lynch syndrome and detection of mutated DNA in stools.[22]

Chemokines—General Informations

Chemokines are a family of small, structurally related proteins involved in many processes including angiogenesis[23] and lymphoid tissue development.[24] Their functional activity is induced by binding to specific G protein-coupled receptors, which are found on the surface of targeted cells. Research studies have revealed that one chemokine can bind to many receptors and one receptor may be activated by a number of ligands.[25] Approximately 50 chemokines and 20 chemokine receptors have now been acknowledged to be responsible for several aspects of intercell interactions.[26] Thus, they are known for inducing chemotaxis in a variety of cells such as lymphocytes, neutrophils, eosinophils, and fibroblasts. However, chemokines also play an important role in many pathological processes, including artherosclerosis, HIV infection, autoimmune diseases, and even cancer.[27,28] It has been indicated that some of these proteins may support tumor development and metastatic spreads via different mechanisms.[29]

Structurally, chemokines have been divided into 4 subfamilies including CXC, CC, CX3C, and C. This classification is based on the position of *N*-terminal cysteine residues.[30] Moreover, the CXC group can be subdivided according to the presence or absence of the ELR motif, which is a sequence of 3 consecutive amino acids Glu-Leu-Arg. However, chemokines can also be classified as inflammatory, homeostatic, or dual function according to their function in the immune system and inflammatory response.[31] Homeostatic chemokines such as CC-chemokine ligand (CCL) 19 and CCL20 are produced constitutively. They participate in the migration and progression of various cells responsible for functioning of the immunological system.[32] By contrast, inflammatory chemokines such as CXC motif chemokine ligand (CXCL) 8 and CCL2 are produced by tissues and migrating leukocytes in response to bacterial toxins and proinflammatory cytokines, for example, interleukin (IL) 1 or tumor necrosis factor α (TNF-α).[33] Furthermore, they play an important role in cell activation, which promotes wound healing.[34] Chemokine receptors are structurally similar to chemokines. Their name is derived from the chemokine ligand with which they interact. They are divided into 4 groups: CXC chemokine receptor (CXCR), CC-chemokine receptor (CCR), CX3CR, and XCR.[35]

Chemokines in Cancer

Inflammation is a multistep process associated with molecular and cellular alterations.[36] Previous investigations have demonstrated that controlled inflammation is a necessary process, which helps the body defend against various pathogens and repair damaged tissue, while uncontrolled inflammation is implicated in a number of pathological processes such as the development of neoplasms.[37] Inflammation has been acknowledged to be one of the features of many pathological processes including malignancies. Some studies suggest that chemokines may play a critical role in cancer.[38]

Despite the fact that chemokines were initially recognized as important immune cell migration mediators, new evidence indicates that they are also involved in the biology of nonimmune cells, which play a significant role in tumor development, growth, and progression.[39] They coordinate all intercell interactions and thus exert a considerable impact on tumor promotion.[40] These chemotactic cytokines are able to induce cancer cell proliferation and survival in a number of ways. Research studies have demonstrated that tumor cells can acquire the ability to express chemokine receptors and produce chemokines which promote tumor growth.[41] Angiogenesis is an important step in tumor progression. Cancer cells acquire the ability to form new vessels from pre-existing blood vessels to deliver oxygen and necessary nutrients as well as to eliminate waste. This process is regulated by several angiogenic factors, lipids, and enzymes.[42] Many members of the chemokine superfamily may act proangiogenically by supporting the formation of new vessels, while others are angiostatic—responsible for inhibiting these activities.[43] It has been established that melanoma expresses several chemokines such as CCL2, CCL5, CXCL1, CXCL2, CXCL3, and CXCL8, which are associated with both tumor growth and progression.[44] In addition, CXCR4, normally not expressed on breast epithelial cells, is frequently found on breast cancer cells.[45] Some investigators have demonstrated that the CXC-chemokine/CXCR2 axis may promote tumor-associated angiogenesis in pancreatic cancer. They have demonstrated that the ELR+ CXC-chemokines concentrations are significantly higher in patients with cancer compared to healthy individuals.[46] The potential role of CXCL8, which is san angiogenic CXC-chemokine, in ovarian cancer biology has been investigated since its enhanced expression was observed in ovarian cancer cell lines.[47]

Another important process in tumor progression is metastasis, which refers to the migration of malignant cells to areas distant from the site of a primary tumor.[48] Since the majority of cancer deaths are caused by distant metastasis rather than the excessive growth of a primary tumor, it is important to understand this multistep process in cancer biology as well as cancer treatment.[49,50] Metastasis comprises many independent processes and complex interactions including, inter alia, local invasion, tumor cell dissemination, colonization, and angiogenesis.[50,51] A number of studies have indicated that chemokines play a key role in metastasis. Tumor cells are able to express specific chemokine receptors which help to direct malignant cells to several anatomic sites to form metastases.[52] These metastatic sites start producing selected chemokines which attract CTCs to a supporting microenvironment.[53] The most thoroughly researched pair of proteins associated with metastasis is CXCR4 (CXC chemokine receptor 4) and its ligand CXCL12. It has been demonstrated that blocking this axis may suppress breast cancer lung metastasis.[24,54] However, its involvement in metastatic processes has also been observed in other cancers such as prostate cancer, lung cancer, and CRC.[55-57]

The Involvement of Chemokines and Their Receptors in CRC

A link between inflammation and cancer was suggested a number of years ago, based on the presence of inflammatory cells in tumor samples collected during biopsies. Furthermore, it was discovered that tumors frequently arise at sites of inflammation.[58] Since chronic inflammation is one of the key risk factors for CRC, it has been suggested that proinflammatory chemokines in particular may be involved in the development, progression, and metastasis of several types of cancer including CRC.[24] Evidence from a number of investigations demonstrates that selected chemokines and their specific receptors are involved in several stages of CRC development. However, the majority of the studies were based on the analysis of their expression levels in tissue samples.[59]

CXCL12, also known as stromal cell-derived factor 1, and its receptor CXCR4 (fusin) have been recognized as a representative pair involved in cancer metastasis.[54] In the liver, which is the most common CRC metastasis site, CXCL12 is normally secreted by Kupffer cells and endothelial cells.[60] CRC cells are also capable of expressing this chemokine ligand, although the process is fairly controversial since the expression is bidirectional—tumor suppressive[61] and tumor promotive.[62] Clinical studies have revealed that in CRC, the expression of CXCR4 correlated with poor survival rates and liver metastasis.[63,64] In addition, the enhanced expression of this receptor has been observed under hypoxia via the activity of hypoxia-inducible factor 1-α.[65] Another receptor that interacts with CXCL12 is CXCR7, which has also been found to be expressed by CRC cells. Wang et al[66] assessed the expression of CXCL12, CXCR4, and CXCR7 in CRC and lung metastasis tissue samples and found that the expression of both CXCL12 and CXCR7 was significantly higher in metastasis samples in comparison to those of primary lesions. Moreover, significantly higher expression of CXCL12 was observed in lung tissue with malignant changes when compared to tissue with benign lesions.[67]

Another important pair in CRC is CCL20 and its specific receptor CCR6. CCL20, also known as liver and activation-regulated chemokine or macrophage inflammatory protein-3a, has been found to be expressed in several human tissues.[68] It has been indicated that this molecule might be involved in neoplastic processes. The expression of this chemokine ligand has been detected, inter alia, in liver, and lung tissues but not in bone marrow or spleen.[69-72] The CCL20 expression has been found to be elevated in both CRC and CR liver metastasis in comparison to non-malignant tissue.[73] Interestingly, CCR6 has been found to be overexpressed in CRC. Additionally, stimulation of its physiological ligand (CCL20) has been demonstrated to promote the proliferation and migration of this type of cancer in *in vitro* studies.[74] Some studies have revealed that CCR6 expression is significantly higher in both CRC and CR liver metastases.[75-77] Hu et al[78] demonstrated elevated CCR6 expression in CRC, but it was strongly linked with distant metastases to either lung or liver. However, it was also revealed that the observed overexpression was not organ-specific and thus there was no differentiation between lung and liver metastases. Significantly, research performed by Dellacasagrande et al[79] demonstrated that higher CCR6 expression was observed in small CRC metastatic tumors in comparison to the surrounding tissue, which suggests the impact of this receptor on the development of liver metastases. Conversely, lower CCR6 expression has been observed in large, existing metastatic tumors in comparison to primary tumors, which might imply that the expression of this receptor is not required by the CRC cells which have already formed distant metastases.[80]

Another extensively researched receptor is CXCR3 (CXC chemokine receptor 3), which has been found to be expressed on several cells including CRC cells.[57] The receptor was found to promote metastases to lymph nodes when both ligands for the receptor–CXCL9 (CXC motif chemokine 9) and CXCL10 (CXC motif chemokine 10)—were expressed at elevated levels.[81] In addition, some studies have revealed that at stage II or/and stage III of CRC, the expression of CXCL10 can be considered an independent prognostic factor for cancer recurrence,[82] while other researchers have demonstrated that the coexpression of both CXCR3 and CXCL10 in CRC is linked to poorer prognosis and metastatic recurrence.[83] In addition, elevated CXCL10 levels in the sera of patients with CRC have been found to be associated with advanced stages of the disease. Furthermore, the same study identified increased serum CXCL10 concentration as well as the presence of distant metastases as independent factors of poor prognosis.[84]

CXC motif chemokine 8, also known as IL8, is a factor responsible for granulocyte activation in immune responses during inflammation. Some authors suggest that the expression of CXCL8 is regulated by various stimuli such as steroid hormones (eg, oestrogens and androgens), environmental and chemical stress (eg, hypoxia), as well as inflammatory signals (eg, TNF-α).[85] It has been proven that this protein plays a key role in cancer invasion, progression, angiogenesis, and metastasis formation.[86] CXCL8 has been reported to be linked with metastatic potential.[87] Its specific receptor—CXCR2 (IL8 receptor β) may promote angiogenesis via interaction with ELR + CXC chemokines such as CXCL5 (CXC motif chemokine 5), CXCL2 (CXC motif chemokine 2), and CXCL1 (CXC motif chemokine 1).[88] In a knockout mouse model of tumor microenvironment, a lack of the CXCL8-CXCR2 axis has been observed to act against CRC growth and distant metastases.[89] In addition, CXCR1 and CXCR2 antagonists have inhibited CRC metastasis through the induction of tumor cell apoptosis.[90] The elevated serum concentration of chemokine CXCL8 has been found to be associated with advanced stages of CRC as well as the presence of distant metastases.[91]

Serum concentrations of CXCL5 (CXC motif chemokine 5) were assessed by Yildirim et al who demonstrated that in patients with CRC, the level of the chemokine was significantly higher in comparison to healthy volunteers.[92] The study also evaluated the diagnostic sensitivity and specificity of CXCL5. However, due to the statistically insignificant results obtained, CXCL5 cannot be recognized as a potential marker in CRC

Table 1. Chemokines and Their Receptors Involved in CRC.

Subfamily of Chemokines	Name of Chemokines	Changes in CRC	Reference
CXC (α) subfamily	CXCL5 (ENA-78)	Elevated serum concentrations in patients with CRC	92
	CXCL8 (IL-8)	Elevated serum concentrations in patients with CRC and distant metastases	91
	CXCL9 (Mig)	Elevated expression in CRC	81
	CXCL10 (IP-10)	Expression as an independent prognostic factor for CRC recurrence	82
	CXCL12 (SDF-1)	Elevated expression in patients with CRC and correlation with poor survival	62
	CXCL15	Elevated serum concentrations in patients with CRC	93
CC (β) subfamily	CCL20 (LARC, MIP-3a)	Elevated expression in CRC and CR liver metastasis	73
Specific receptors			
CXCR1, CXCR2		Elevated expression in patients with CRC and metastases	89,90
CXCR3		Expression promotes CRC metastasis to lymph nodes	81
CXCR4, CXCR7		Correlation with poor prognosis and liver metastasis	63,64
CCR6		Elevated expression in CRC and CR liver metastasis	75-77

Abbreviations: CRC, colorectal cancer; CXCL, CXC motif chemokine ligand; CXCR, CXC chemokine receptor; IL, interleukin; LARC, liver and activation-regulated chemokine; MIP-3a, macrophage inflammatory protein-3a.

screening. Matsushita et al[93] studied the concentrations of CXCL15 (CXC motif chemokine 15) in the sera of patients with CRC and discovered that serum CXCL15 levels were elevated in the cancer group in comparison to healthy controls. The concentrations increased with disease stage and correlated with poor survival. The chemokines as well as their specific receptors involved in CRC have been presented in Table 1.

The potential utilization of serum chemokines in targeted cancer therapy has been evaluated by a number of researchers,[94,95] but there is scant knowledge regarding serum concentrations of selected chemokines as biomarkers in the diagnosis of CRC.

Conclusions

Colorectal cancer has been the focus of worldwide research efforts. The thought-provoking, stable incidence rate of CRC as well as a great number of CRC-related deaths each year necessitate the enhancement of diagnostic and screening methods. Chemokines play a critical role in a number of both physiological and pathological processes, including tumor development and progression. Recently, a number of chemokines and their receptors have been suggested to be involved in CRC. As presented in this review, the expression of several chemokines is enhanced in CRC. Published research results indicate that the increased expression of selected chemokines and/or their specific receptors is linked to poorer prognosis and metastatic recurrence. Moreover, elevated levels of these proteins have been demonstrated to correlate with the advanced stage of the disease and poor survival rates of patients with CRC. Chemokines and their specific receptors have been suggested as potential tumor markers but more research investigating serum levels of these proteins is needed.

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ORCID iD

Marta Łukaszewicz-Zając https://orcid.org/0000-0002-0185-7327
Barbara Mroczko https://orcid.org/0000-0002-4075-8479

References

1. Hadhipetrou A, Anyfantakis D, Galanakis CG, Kastanakis M, Kastanakis S. Colorectal cancer, screening and primary care: a mini literature review. *World J Gastroenterol*. 2017;23(33):6049-6058. doi:10.3748/wjg.v23.i33.6049
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. 2012. *CA Cancer J Clin*. 2015;65(2):87-108. doi:10.3322/caac.21262
3. Bhat SK, East AJ. Colorectal cancer: prevention and early diagnosis. *Elsevier*. 2015;43(6):295-298.
4. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):359-386.
5. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90. doi:10.3322/caac.20107
6. Aran V, Victorino AP, Thuler LC, Ferreira CG. Colorectal cancer: epidemiology, disease mechanisms and interventions to reduce onset and mortality. *Clin Colorectal Cancer*. 2016;15(3):195-203. doi:10.1016/j.clcc.2016.02.008
7. Gajewski P, Szczeklik A. Interna Szczeklika—mały podręcznik 2018/2019. Kraków 2018. Wyd. 10. ISBN: 978-83-7430-549-5.
8. Garborg K. Colorectal cancer screening. *Surg Clin North Am*. 2015;95(5):979-989. doi:10.1016/j.suc.2015.05.007
9. Simon K. Colorectal cancer development and advances in screening. *Clin Interv Aging*. 2016;11:967-976. doi:10.2147/CIA.S109285
10. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut*. 2013;62(1055):933-947. doi:10.1136/gutjnl-2013-304701

11. American Cancer Society. *Cancer Facts & Figure 2015*. Atlanta, GA: American Cancer Society; 2015.
12. ACS [webpage on the Internet]. What are the survival rates for colorectal cancer by stage? 2015. Available from: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-survival-rates; http://tinyurl.com/grroztx. Accessed March 3, 2016.
13. American Cancer Society. *Colorectal Cancer Facts & Figures 2011–2013*. Atlanta, GA: American Cancer Society; 2011.
14. Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. *Int J Cancer*. 2014;134(11):2513-2522. doi:10.1002/ijc.28384
15. Ling BS, Moskowitz MA, Wachs D, Pearson B, Schroy PC. Attitudes toward colorectal cancer screening tests. *J Gen Intern Med*. 2001;16(12):822-830.
16. Agency for Healthcare Research and Quality. *Clinical Summaries of Recommendations for Adults: Colorectal Cancer. Guide to Clinical Preventive Services*. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
17. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US multi-society task force on colorectal cancer, and the American college of radiology. *Gastroenterology*. 2008;134(5):1570-1595.
18. Stracci F, Zorzi M, Grazzini G. Colorectal cancer screening: tests, strategies, and perspectives. *Front Public Health*. 2014;2:210.
19. Boussios S, Ozturk MA, Moschetta M. The developing story of predictive biomarkers in colorectal cancer. *J Pers Med*. 2019;9(1):E12. doi:10.3390/jpm9010012
20. Tan CR, Zhou L, El-Deiry WS. Circulating tumor cells versus circulating tumor DNA in colorectal cancer: Pros and cons. *Curr Colorectal Cancer Rep*. 2016;12(3):151-161.
21. Lamb YN, Dhillon S. Epi proColon® 2.0 CE: a blood-based screening test for colorectal cancer. *Mol Diagn Ther*. 2017;21(2):225-232. doi:10.1007/s40291-017-0259-y
22. Zarkavelis G, Boussios S, Papadaki A, Katsanos KH, Christodoulou DK, Pentheroudakis G. Current and future biomarkers in colorectal cancer. *Ann Gastroenterol*. 2017;30(6):613-621. doi:10.20524/aog.2017.0191
23. Belperio JA, Keane MP, Arenberg DA, et al. CXC Chemokines in angiogenesis. *J Leukoc. Biol*. 2000;68(1):1-8.
24. Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol*. 2017;17(9):559-572. doi:10.1038/nri.2017.49
25. Griffith JW, Sokol CL, Luster AD. Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu Rev Immunol*. 2014;32:659-702.
26. Miller MC, Mayo KH. Chemokines from a Structural Perspective. *Int J Mol Sci*. 2017;18(10):2088.
27. Koenen RR, Weber C. Therapeutic targeting of chemokine interactions in atherosclerosis. *Nat. Rev Drug Discov*. 2010;9(2):141-153. doi:10.1038/nrd3048
28. Raman D, Sobolik-Delmaire T, Richmond A. Chemokines in health and disease. *Exp Cell Res*. 2011;317(5):575-589. doi:10.1016/j.yexcr.2011.01.005
29. Karin N. Chemokines and cancer: new immune checkpoints for cancer therapy. *Curr Opin Immunol*. 2018;51:140-145. doi:10.1016/j.coi.2018.03.004
30. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity*. 2000;12(2):121-127. doi:10.1016/S1074-7613(00)80165-X
31. Mortier A, Van Damme J, Proost P. Overview of the mechanisms regulating chemokine activity and availability. *Immunol Lett*. 2012;145(1-2):2-9.
32. Anders HJ, Romagnani P, Mantovani A. Pathomechanisms: homeostatic chemokines in health, tissue regeneration, and progressive diseases. *Trends Mol Med*. 2014;20(3):154-165. doi:10.1016/j.molmed.2013.12.002
33. Shachar I, Karin N. The dual roles of inflammatory cytokines and chemokines in the regulation of autoimmune diseases and their clinical implications *J Leukoc Biol*. 2013;93(1):51-61. doi:10.1189/jlb.0612293
34. Zaja-Milatovic S, Richmond A. CXC chemokines and their receptors: a case for a significant biological role in cutaneous wound healing. *Histol Histopathol*. 2008;23(11):1399-1407.
35. Murphy PM, Baggiolini M, Charo IF, et al. International union of pharmacology. XXII. nomenclature for chemokine receptors. *Pharmacol Rev*. 2000;52(1):145-176.
36. Kuprash DV, Nedospasov SA. Molecular and cellular mechanisms of inflammation. *Biochemistry (Mosc)*. 2016;81(11):1237-1239.
37. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454(7203):428-435. doi:10.1038/nature07201
38. Lazennec G, Richmond A. Chemokines and chemokine receptors: new insights into cancer-related inflammation. *Trends Mol Med*. 2010;16(3):133-144.
39. Charo I, Ransohoff R. The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med*. 2006;354(6):610-621.
40. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer*. 2004;4(7):540-550.
41. Chow MT, Luster AD. Chemokines in cancer. *Cancer Immunol Res*. 2014;2(12):1125-1131.
42. Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis*. 2017;20(4):409-426. doi:10.1007/s10456-017-9562-9
43. Caronni N, Savino B, Recordati C, Villa A, Locati M, Bonecchi R. Cancer and chemokines. *Methods Mol Biol*. 2016;1393:87-96. doi:10.1007/978-1-4939-3338-9_8
44. Payne AS, Cornelius LA. The role of chemokines in melanoma tumor growth and metastasis. *J Invest Dermatol*. 2002;118(6):915-922.
45. Luker KE, Luker GD. Functions of CXCL12 and CXCR4 in breast cancer. *Cancer Lett*. 2006;238(1):30-41.
46. Matsuo Y, Raimondo M, Woodward TA, et al. CXC-chemokine/CXCR2 biological axis promotes angiogenesis in vitro and in vivo in pancreatic cancer. *Int J Cancer*. 2009;125(5):1027-1037.

47. Yoneda J, Kuniyasu H, Crispens MA, Price JE, Bucana CD, Fidler IJ. Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. *J Natl Cancer Inst*. 1998;90(6):447-454.
48. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. *Nat Rev Cancer*. 2002;2(8):563-572.
49. Nguyen DX, Bos PD, Massagué J. Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer*. 2009;9(4): 274-284.
50. Steeg PS. Metastasis suppressors alter the signal transduction of cancer cells. *Nat. Rev. Cancer*. 2003;3(1):55-63.
51. Zeeshan R, Mutahir Z. Cancer metastasis—tricks of the trade. *Bosn J Basic Med Sci*. 2017;17(3):172-182. doi:10.17305/bjbms.2017.1908
52. Vicari AP, Caux C. Chemokines in cancer. *Cytokine Growth Factor Rev*. 2002;13(2):143-154.
53. Keeley EC, Mehrad B, Strieter RM. CXC chemokines in cancer angiogenesis and metastases. *Adv Cancer Res*. 2010;106:91-111. doi:10.1016/S0065-230X(10)06003-3
54. Müller A, Homey B, Soto H, et al. Involvement of chemokine receptors in breast cancer metastasis. *Nature*. 2001;410(6824): 50-56.
55. Zlotnik A, Burkhardt AM, Homey B. Homeostatic chemokine receptors and organ-specific metastasis. *Nat Rev Immunol*. 2011;11(9):597-606.
56. Darash-Yahana M, Pikarsky E, Abramovitch R, et al. Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. *FASEB J*. 2004;18(11):1240-1242.
57. Murakami T, Kawada K, Iwamoto M, et al. The role of CXCR3 and CXCR4 in colorectal cancer metastasis. *Int J Cancer*. 2013; 132(2):276-287. doi:10.1002/ijc.27670
58. Mantovani A, Muzio M, Garlanda C, Sozzani S, Allavena P. Macrophage control of inflammation: negative pathways of regulation of inflammatory cytokines. *Novartis Found Symp*. 2001; 234:120-131; discussion 131-135.
59. Itatani Y, Kawada K, Inamoto S, et al. The role of chemokines in promoting colorectal cancer invasion/metastasis. *Int J Mol Sci*. 2016;17(5):643. doi:10.3390/ijms17050643
60. Matsusue R, Kubo H, Hisamori S, et al. Hepatic stellate cells promote liver metastasis of colon cancer cells by the action of SDF-1/CXCR4 axis. *Ann Surg Oncol*. 2009;16(9):2645-2653. doi:10.1245/s10434-009-0599-x
61. Wendt MK, Johanesen PA, Kang-Decker N, Binion DG, Shah V, Dwinell MB. Silencing of epithelial CXCL12 expression by DNA hypermethylation promotes colonic carcinoma metastasis. *Oncogene*. 2006;25(36):4986-4997. doi:10.1038/sj.onc.1209505
62. Akishima-Fukasawa Y, Nakanishi Y, Ino Y, Moriya Y, Kanai Y, Hirohashi S. Prognostic significance of CXCL12 expression in patients with colorectal carcinoma. *Am J Clin Pathol*. 2009; 132(2):202-210. doi:10.1309/AJCPK35VZJEWCUTL
63. Kim J, Takeuchi H, Lam ST, et al. Chemokine receptor CXCR4 expression in colorectal cancer patients increases the risk for recurrence and for poor survival. *J Clin Oncol*. 2005;23(12): 2744-2753. doi:10.1200/JCO.2005.07.078
64. Ottaiano A, Franco R, Aiello Talamanca A, et al. Overexpression of both CXC chemokine receptor 4 and vascular endothelial growth factor proteins predicts early distant relapse in stage II-III colorectal cancer patients. *Clin Cancer Res*. 2006;12(9): 2795-2803. doi:10.1158/1078-0432.CCR-05-2142
65. Romain B, Hachet-Haas M, Rohr S, et al. Hypoxia differentially regulated CXCR4 and CXCR7 signaling in colon cancer. *Mol Cancer*. 2014;13:58. doi:10.1186/1476-4598-13-58
66. Wang M, Yang X, Wei M, Wang Z. The role of CXCL12 axis in lung metastasis of colorectal cancer. *J of Cancer*. 2018;9(21): 3898-3903.
67. Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature*. 2005;438(7069):820-827. doi:10.1038/nature04186
68. Chen W, Qin Y, Wang D, et al. CCL20 triggered by chemotherapy hinders the therapeutic efficacy of breast cancer. *PLoS Biol*. 2018;16(7): e2005869. doi:10.1371/journal.pbio.2005869
69. Schutyser E, Struyf S, Van Damme J. The CC chemokine CCL20 and its receptor CCR6. *Cytokine Growth Factor Rev*. 2003;14: 409-426.
70. Yoshie O, Imai T, Nomiyama H. Novel lymphocyte-specific CC chemokines and their receptors. *J Leukoc Biol*. 1997;62(5): 634-644.
71. Hromas R, Gray PW, Chantry D, et al. Cloning and characterization of exodus, a novel beta-chemokine. *Blood*. 1997;89(9): 3315-3322.
72. Hieshima K, Imai T, Opdenakker G, et al. Molecular cloning of a novel human CC chemokine liver and activation-regulated chemokine (LARC) expressed in liver. Chemotactic activity for lymphocytes and gene localization on chromosome 2. *J Biol Chem*. 1997;272(9):5846-5853.
73. Vicinus B, Rubie C, Stegmaier N, , et al. miR-21 and its target gene CCL20 are both highly overexpressed in the microenvironment of colorectal tumors: significance of their regulation. *Oncol Rep*. 2013;30(3):1285-1292.
74. Frick VO, Rubie C, Keilholz U, Ghadjar P. Chemokine/chemokine receptor pair CCL20/CCR6 in human colorectal malignancy: an overview. *World J Gastroenterol*. 2016;22(2):833-841.
75. Rubie C, Oliveira V, Kempf K, et al. Involvement of chemokine receptor CCR6 in colorectal cancer metastasis. *Tumour Biol*. 2006;27(3):166-174.
76. Ghadjar P, Rubie C, Aebersold DM, Keilholz U. The chemokine CCL20 and its receptor CCR6 in human malignancy with focus on colorectal cancer. *Int J Cancer*. 2009;125(4):741-745.
77. Frick VO, Rubie C, Kölsch K, et al. CCR6/CCL20 chemokine expression profile in distinct colorectal malignancies. *Scand J Immunol*. 2013;78(3):298-305.
78. Hu D, Du C, Xue W, Dou F, Yao Y, Gu J. The expression of chemokine receptors CCR6, CXCR2 and CXCR4 is not organ-specific for distant metastasis in colorectal cancer: a comparative study. *Histopathology*. 2013;63(2):167-173.
79. Dellacasagrande J, Schreurs OJ, Hofgaard PO, et al. Liver metastasis of cancer facilitated by chemokine receptor CCR6. *Scand J Immunol*. 2003;57(6):534-544.

80. Ghadjar P, Coupland SE, Na IK, et al. Chemokine receptor CCR6 expression level and liver metastases in colorectal cancer. *J Clin Oncol*. 2006;24(12):1910-1916.
81. Kawada K, Hosogi H, Sonoshita M, et al. Chemokine receptor CXCR3 promotes colon cancer metastasis to lymph nodes. *Oncogene*. 2007;26(32):4679-4688. doi:10.1038/sj.onc.1210267
82. Jiang Z, Xu Y, Cai S. CXCL10 expression and prognostic significance in stage II and III colorectal cancer. *Mol Biol Rep*. 2010; 37(6):3029-3036. doi:10.1007/s11033-009-9873-z
83. Wightman SC, Uppal A, Pitroda SP, et al. Oncogenic CXCL10 signaling drives metastasis development and poor clinical outcome. *Br J Cancer*. 2015;113(2):327-335. doi:10.1038/bjc.2015.193
84. Toiyama Y, Fujikawa H, Kawamura M, et al. Evaluation of CXCL10 as a novel serum marker for predicting liver metastasis and prognosis in colorectal cancer. *Int J Oncol*. 2012;40(2): 560-566. doi:10.3892/ijo.2011.1247
85. Alfaro C, Sanmamed MF, Rodriguez-Ruiz ME, et al. Interleukin-8 in cancer pathogenesis, treatment and follow-up. *Cancer Treat Rev*. 2017;60:24-31. doi:10.1016/j.ctrv.2017.08.004
86. Waugh DJ, Wilson C, The interleukin-8 pathway in cancer, *Clin Cancer Res*. 2008;14(21):6735-6741.
87. Ha H, Debnath B, Neamanti N. Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases. *Theranostics*. 2017; 7(6):1543-1588.
88. Sonoshita M, Takaku K, Sasaki N, et al. Acceleration of intestinal polyposis through prostaglandin receptor EP2 in *Apc*Δ*716* knockout mice. *Nat Med*. 2001;7(9):1048-1051. doi:10.1038/nm0901-1048
89. Lee YS, Choi I, Ning Y, et al. Interleukin-8 and its receptor CXCR2 in the tumour microenvironment promote colon cancer growth, progression and metastasis. *Br J Cancer*. 2012;106(11): 1833-1841. doi:10.1038/bjc.2012.177
90. Varney ML, Singh S, Li A, Mayer-Ezell R, Bond R, Singh RK. Small molecule antagonists for CXCR2 and CXCR1 inhibit human colon cancer liver metastases. *Cancer Lett*. 2011;300(2): 180-188. doi:10.1016/j.canlet.2010.10.004
91. Ning Y, Manegold PC, Hong YK, et al. Interkeukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity in vitro and *in vivo* in colon cancer cell line models. *Int J Cancer*. 2011;128(9):2038-2049. doi:10.1002/ijc.25562
92. Yildirim K, Colak E, Aktimur R, et al. Clinical Value of CXCL5 for determining of colorectal cancer. *Asian Pac J Cancer Prev*. 2018;19(9):2481-2484. doi:10.22034/APJCP. 2018.19.9.2481
93. Matsushita K, Toiyama Y, Tanaka K, et al. Soluble CXCL16 in preoperative serum is a novel prognostic marker and predicts recurrence of liver metastases in colorectal cancer patients. *Ann Surg Oncol*. 2012;19 (suppl 3):S518-S527.
94. Ruiz de Porras V, Bystrup S, Martínez-Cardús A, et al. Curcumin mediates oxaliplatin-acquired resistance reversion in colorectal cancer cell lines through modulation of CXC-Chemokine/NF-κB signalling pathway. *Sci Rep*. 2016;6:24675.
95. Abajo A, Boni V, Lopez I, et al. Identification of predictive circulating biomarkers of bevacizumab-containing regimen efficacy in pre-treated metastatic colorectal cancer patients. *Br J Cancer*. 2012;107(2):287-290.