VIA MEDICA

ORIGINAL ARTICLE

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Assessment of the chemerin, IL-6, and IL-23 correlations and their impact on CRC progression: An observational study

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Medical Research Journal 2022; Volume 7, Number 2, 157–163
10.5603/MRJ.a2022.0026

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: The role of proinflammatory cytokines is said to be crucial in the development of colorectal cancer (CRC). IL-6, IL-23, and chemerin have all been proven to take part in tumor growth and progression.

Aim of the study: to determine the level of chemerin and the concentrations of interleukin-6 (IL-6) and interleukin-23 (IL-23) in the tumor and margin specimens of CRC in relation to histological grade and TNM staging.

Material and methods: The study involved 49 samples of tumor and margin tissues obtained from CRC patients. To assess the concentration of chemerin, IL-6, and IL-23, commercially available enzyme-linked immunosorbent assay (ELISA) kits were used.

Results: There was no difference in chemerin concentration between the tumor and margin. We found significantly increased levels of IL-6 in tumor tissue compared to margin tissue and higher concentrations of IL-23 in margin tissue than in tumor tissue. Tumor levels of chemerin were significantly correlated with those of IL-23, while its margin concentrations were associated with margin concentrations of IL-6. Additionally, tumor levels of IL-23 were positively correlated with margin levels of IL-6.

Conclusions: Chemerin might play an important role in CRC progression through its association with cytokine expression. More studies are needed to investigate the possible role of IL-6, IL-23, and chemerin as potential markers in the development of CRC.

Key words: Chemerin, Interleukin-6 (IL-6), Interleukin-23 (IL-23), Colorectal Cancer (CRC)

Med Res J 2022; 7 (2): 157–163

Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide in both sexes (following prostate cancer in men, breast cancer in women, and lung cancer) with almost 2 million new cases diagnosed in 2020, making it 10.7% of all cancers diagnosed [1]. Colorectal cancer caused approximately 0.9 million deaths worldwide in 2020 and was the second most common cause of cancer deaths (after lung and bronchus cancers) [2, 3]. The incidence of CRC is higher in highly developed countries than in middle- and low-income countries. Lately, there has been an increase in the number of early-onset CRC cases due to unclear reasons for the time being [4]. Thanks to effective screening measures, the mortality rate of CRC has decreased in the US. There has been a screening program for CRC implemented in Poland since 2020, and it has become more widespread over time.

Environmental and genetic factors play a major role in the pathogenesis and development of colorectal cancer. Lynch syndrome (hereditary nonpolyposis colorectal cancer), FAP (familial adenomatous polyposis), and MAP (MUTYH-associated polyposis) are hereditary colorectal cancer syndromes, which account for about 5% of colorectal cancer cases [5]. Well known associations with CRC include a history of colon cancer in first-degree relatives, male sex (with the lifetime risk being similar for both sexes, but shorter life expectancy for men), age, African American ethnicity, inflammatory bowel disease (ulcerative colitis more often that Leśniowski-Crohn disease), history of abdominal radiation, acromegaly, coronary artery disease, gut microbiota and many more. Modifiable risk factors include being

overweight and obese, a sedentary lifestyle, poor diet, and consuming red and processed meat, tobacco, and alcohol [6].

Chemerin (CHEM) is a protein encoded by the gene *Rarres2*, synthesized primarily by adipose tissue and liver, fulfilling a function of a paracrine and autocrine hormone simultaneously. Its function is to stimulate adipocytes' maturation and differentiation. It also plays a role in angiogenesis in adipose tissue. CHEM also acts as a chemoattractant for immune cells and regulates the innate and acquired inflammatory response [7]. Chemerin signaling enhances insulin secretion from pancreatic islets [8]. An important role for chemerin is indicated in the regulation of energy balance. It has been found that local and circulating chemerin levels are positively correlated with components of metabolic syndrome (obesity, type 2 diabetes, hypertension, and hyperlipidemia). Considering the functions of chemerin in inflammatory processes and adipogenesis, the levels of CHEM plasma concentration might be linked with the risk of colorectal cancer [8, 9].

Interleukin-6 is a pro-inflammatory, prototypical cytokine produced immediately after a disruption of homeostasis induced by infections or tissue injuries. It takes part in defense against emergent stress by activating acute-phase and immune responses. It also contributes to hematopoiesis. [10] The production of IL-6 is terminated after the restoration of tissue homeostasis [11]. A role for inflammatory cytokines has been proposed during tumor development, and IL-6 has been linked to the pathogenesis of sporadic and inflammation-associated colorectal cancer by several experimental and clinical studies [1, 12].

Interleukin-23 is a heterodimeric, inflammatory cytokine and is part of the IL-12 family of cytokines. It is involved in the induction and expansion of Th17 cells [13]. IL-23 is mainly secreted by activated dendritic cells, macrophages, and monocytes [14]. It is considered to play a crucial role in the development of intestinal inflammation, and it promotes tumor growth and metastases [15]. The role of circulating levels of IL-23 in patients with colorectal cancer is still under investigation.

Our study aimed to evaluate the concentrations of chemerin and two proinflammatory cytokines: IL-6 and IL-23 in tumor and margin tissue specimens obtained from CRC patients in relation to histological grade and TNM classification.

Material and methods

The samples from 49 patients obtained during surgery for CRC were used in the study. Patients were treated in the 1st Specialistic Hospital in Bytom, Poland (approval of the Research Ethics Committee PCN/0022/KB1/42/VI/14/16/18/19/20). The collected specimens included colorectal tumor tissues and surgical tissue margins. Inclusion criteria involved colorectal adenocarcinoma and surgical "tumor-free" margin tissue confirmed by histological examination, patients' age > 18 years, and signed consent. The exclusion criteria were as follows: no consent to participate in the study, tumors other than adenocarcinoma, tumors with involved margins, and age < 18 years. To classify the cancer stage, the TNM staging system and grading were used. Research sample characteristics are presented in Table 1.

Preparation of Samples for the Evaluation of Chemerin, IL-6, and IL-23

Fragments of the tumor tissue and surgical tissue margin were weighed and homogenized using a PRO 200 homogenizer (PRO Scientific Inc., Oxford, CT, USA) at 10 000 rpm in nine volumes of phosphate-buffered saline (BIOMED, Lublin, 06, Poland). The suspensions were sonicated with an ultrasonic cell disrupter (UP 100H, Hielscher Ultrasonics GmbH, Teltow, BB, Germany). Subsequently, the homogenates were centrifuged at 12 000 rpm for 5 min at 4°C. The total protein level was determined using a Universal Microplate Spectrophotometer (μQUANT, Biotek Inc., Winooski, VT, USA).

To assess the levels of the investigated proteins, an enzyme-linked immunosorbent assay (ELISA) was used, following the manufacturer's instructions. The chemerin levels were evaluated by a human Chemerin Elisa Kit [(Biovendor, Brno, Czech Republic) with a sensitivity of 0.1 ng/mL]. The levels of IL-6 and IL-23 were measured with ELISA Kits: Human IL-6 Elisa Kit (Diaclone, Besancon Cedex, France, sensitivity of 2 pg/mL) and Human IL-23 Elisa Kit (Diaclone, Besancon Cedex, France, sensitivity of 20 pg/mL). The absorbance of the samples was determined using a Universal Microplate Spectrophotometer (μQUANT, Biotek Inc., Winooski, VT, USA). The measurement was conducted at a wavelength of 450 nm. The obtained results were recalculated to the corresponding total protein level and presented as ng/mg of protein.

Statistical analyses

Data distribution was assessed using the Shapiro-Wilk test. The log transformation of the levels of the examined molecules provided a better fit to the Gaussian distribution. Data are presented as mean ± SD for variables with normal distribution and as median with interquartile range for variables with non-normal distribution. To compare the tumor and margin levels, paired Student's t-test was performed. Independent variables were also compared using Student's t-test. To assess the relationships between the examined variables,

Table 1. Characteristics of the patients

	Female	Male	
	21	28	49 (100%)
Age	63.06 ± 11.27	63.81 ± 8.61	63.47 ± 9.75
T parameter			
T1	0 (0%)	0 (0%)	0 (0%)
T2	7 (33.33%)	5 (17.86%)	12 (24.49%)
T3	11 (52.38%)	14 (50.00%)	25 (51.02%)
T4	3 (14.29%)	9 (32.14%)	12 (24.49%)
N parameter			
N0	9 (42.86%)	12 (42.86%)	21 (42.86%)
N1	9 (42.86%)	9 (32.14%)	18 (36.73%)
N2	3 (14.29%)	7 (25.00%)	10 (20.41%)
M parameter			
M0	18 (85.71%)	19 (67.86%)	37 (75.51%)
M1	3 (14.29%)	9 (32.14%)	12 (24.49%)
TNM stage			
I	6 (28.57%)	4 (14.29%)	10 (20.41%)
II	3 (14.29%)	7 (25.00%)	10 (20.41%)
III	9 (42.86%)	8 (28.57%)	17 (34.69%)
IV	3 (14.29%)	9 (32.14%)	12 (24.49%)
Grading			
G1	1 (4.76%)	0 (0%)	1 (2.04%)
G2	19 (90.48%)	28 (100%)	47 (95.92%)
G3	1 (4.76%)	0 (0%)	1 (2.04%)

Table 2. Levels of Chemerin, IL-6, and IL-23 proteins in the tumor and margin presented as log-transformed ng/mg of protein. Paired Student's t-test

	Tumor		Margin		P
	Mean	SD	Mean	SD	
log Chemerin	0.09	0.31	0.08	0.25	0.78
log IL-6	–2.47	0.52	–3.13	0.33	< 0.0001
log IL-23	–1.78	0.33	3.91	0.97	< 0.0001

including both variables with normal distributions, Pearson's coefficient was used. For those with nonnormal distributions, the Tau-Kendall's tau rank correlation coefficient was used. P values < 0.05 were considered significant. The statistical analysis was performed using STATISTICA 13software (Statsoft) and the ggplot2-R package dedicated to data visualization in RStudio software (Integrated Development for R. RStudio, PBC, Boston, MA, USA).

Results

No significant difference was observed in the chemerin levels between the tumor and margin tissues. The concentration of IL-6 was significantly higher in the tumor tissue compared to the margin tissue, while the concentration of IL-23 was significantly higher in the margin tissue compared to the tumor tissue (Tab. 2, Fig. 1). The tumor levels of chemerin positively correlated with

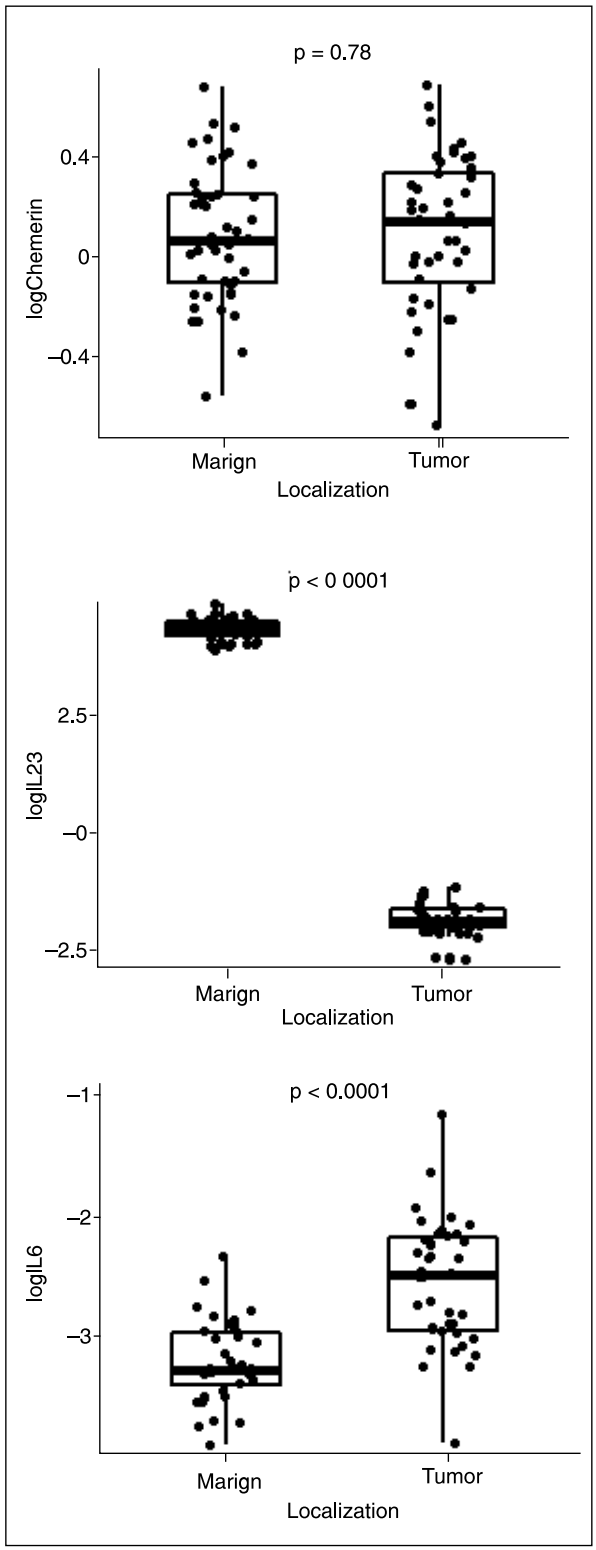

Figure 1. Box-plot- levels of Chemerin, IL-6 and IL-23 molecules in tumor and tissue margins; protein levels are presented as log-transformed values as ng/mg. Paired Student's t-test

the tumor levels of IL-23, while the margin levels of chemerin positively correlated with the margin levels of IL-6 (Fig. 3). Furthermore, a positive association between the tumor levels of IL-23 and the margin levels of IL-6 was observed (Fig. 3). No association between the concentrations of investigated proteins and clinicopathological features of patients was observed.

Discussion

Comparison of concentration of studied proteins between margin and tumor tissue

Chemerin is a preprotein largely secreted in adipose tissue and liver that undergoes enzymatic proteolysis and then acts as a chemoattractant for various cells that take part in innate and adaptive immunity. It might also be involved in the recruitment of immune cells to sites of injury. Higher concentrations of chemerin have been observed in patients with higher cardiovascular risk, obesity, and metabolic conditions. It has also been linked to tumor growth, angiogenesis, and metastasis [9]. In our study, the concentrations in chemerin levels in the tumor and margin tissue were comparable. One study has shown that chemerin concentrations were positively linearly associated with the risk of CRC. The same study showed that higher concentrations of chemerin were associated with a lower survival rate compared to lower concentrations of the substance [9]. In a different study, levels of serum chemerin have also corresponded with the TNM CRC tumor stage progression — the higher the levels, the further the progression of cancer. Also, higher concentrations of chemerin were found in CRC patients' serum compared to healthy patients' serum [16].

The protumorigenic effect of IL-6 as a proinflammatory cytokine has been widely reported as the protein works in association with a major oncogenic transcription factor STAT3 on up-regulation of genes responsible for tumor cell survival. [17] IL-6 also stimulates tumor development. In our study, the concentration of IL-6 was significantly higher in the tumor tissue compared to the margin tissue, which may have been caused by the fact that IL-6 is a cytokine produced by tumor cells [18]. Different studies have shown significantly increased expression of IL-6 in CRC tissue compared to normal mucosa samples [18]. One study showed stronger immunoreactivity of IL-6 in tumor cells as they invaded more deeply, meaning that higher expression of IL-6 was shown in the tumor region closer to the invasion front [1]. One study has also considered IL-6 an inhibitor of cancer growth rather than an enhancer [10].

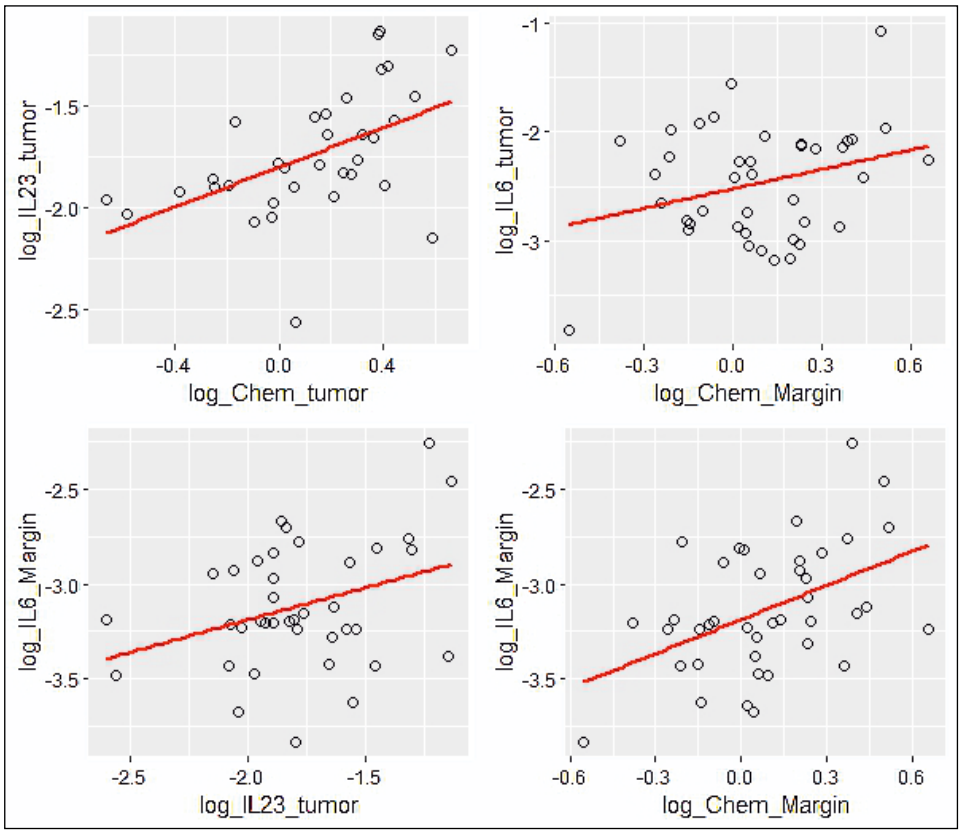

Figure 2. Correlations between tumor levels of IL-23 and margin levels of IL-6 (R = 0.37, p = 0.03), margin levels of Chemerin and IL-6 (R = 0.47, p = 0.002), tumor levels of Chemerin and IL-23 (R = 0.50, p = 0.002)

Table 3. Correlations between the Chemerin, IL-6, and IL-23 levels; R — Pearson's correlation coefficient

Pair of variables	R	P
Tumor log Chemerin and tumor log IL-23	0.50	0.002
Tumor log IL-6 and Margin log IL-6	0.53	0.001
Tumor log IL-23 and Margin log IL-6	0.37	0.03
Margin log Chemerin and Margin log IL-6	0.47	0.002

The antitumor and antimetastatic role of IL-23 in CRC has been proven in various studies [19]. However, the cytokine is also associated with carcinogenesis. IL-23 positively affects the activity of STAT3 in tumor cells, and it also promotes tumor growth and progression of CRC via effects on a protumoral Th17 cytokine signature [20]. The role of IL-23 in CRC is still not entirely clear. However, various studies have indicated that serum levels of IL-23 were significantly elevated in CRC patients compared with healthy controls [21]. In our study, the concentration of IL-23 was significantly higher in the margin tissue compared to the tumor tissue. However, another study has compared levels of IL-23p19 mRNA between the tumor tissue and adjacent normal tissue and has shown a significantly higher concentration of IL-23p19 mRNA in CRC tumor tissue [22]. One study has also shown that IL-23 might be a potential mediator of intestinal tumor progression from adenomatous polyps to colorectal carcinoma [13]. The role of IL-23 in tumor growth and progression needs further examination. One study has compared concentrations of cytokines related to changes in Th17 cells, such as IL-6 and IL-23, in normal colorectal mucosa and CRC tissues. No significantly higher amounts of IL-6 and IL-23 were released by tumor tissues in comparison to normal mucosa; however, the release of IL-6 was significantly higher from the early CRCs than from the advanced ones. The release of IL-23 from the CRC tissues showed no significant change depending on the stage. A possible conclusion has been presented by the same study, stating that IL-6 among other substances may support accumulation of Th17 cells in tumor tissues in the early stages of CRC, and a possible high level of IL-23 following tumor progression with reduced levels of IL-6 might stimulate the expansion of Th17 cells in tumor tissues [23].

Correlations between investigated proteins

There was a positive correlation between tumor levels of chemerin and tumor levels of IL-23 in our study, probably because they both may take part in carcinogenesis, tumor growth, and progression. Our results confirm the results of many studies that have shown elevated levels of these proteins in CRC patients.

According to the results of our study, margin levels of chemerin positively correlated with the margin levels of IL-6. The results might be associated with the fact that both proteins are proinflammatory cytokines and take part in tumor growth and progression.

In our study, a positive correlation between tumor levels of IL-23 and margin levels of IL-6 was observed. It has been proven that the role of proinflammatory pathways, some of them being IL-6/STAT3 and IL-23/Th17, is crucial in the pathogenesis of CRC. It has been suggested that there is a crosstalk between these two pathways. The factors that participate in the production of IL-6 and the activation of STAT3 [1] are: NF- kB pathway that regulates IL-6 and COX-2 expression, proinflammatory effects of PGE2 through the IL-23/Th17 axis, and secretion of cytokines by Th17 cells.

Lack of correlation between our markers and clinicopathological features of patients

In our study, no correlation between the levels of IL-6, IL-23, chemerin, and clinicopathological features was observed. This may have been caused by the small number of our study's participants. However, different studies have previously shown a correlation between serum IL-6 levels and disease status in patients suffering from CRC. Higher levels of IL-6 might have correlated with larger tumor size, elevated serum CRP levels, venous invasion, and lymph node and liver metastases [24]. One study has shown that the levels of IL-6 expression were inversely associated with histological differentiation. At the other end of the spectrum, they are positively associated with the TNM stage [1]. Tissue expression of IL-6 was also reported as a possible predictor of prognosis in CRC; however, it should not be considered an independent prognostic factor [25]. IL-6 increases invasiveness of colon cancer cells, which suggests that IL-6 can accelerate tumor progression towards malignancy. One study found a significant correlation between increasing serum IL-6 levels and staging of the tumor. Another study demonstrated that preoperative serum IL-6 influences CRC recurrence [26]. That leads to the conclusion that overexpression of IL-6 in the tumor correlates with poor survival.

Whereas some studies, including ours, have shown no significant differences in IL-23 levels in different TNM stages of CRC [27], others have shown an increased expression of IL-23R in advanced TNM stages of CRC [20]. High levels of IL-23 in serum may correlate with a worse course of CRC illness as they might promote metastasis of colorectal carcinoma cells [28]. As IL-23 induces the expansion of IL-17, elevated expressions of Il-17 and IL-23 predict rapid progression to incurable metastatic disease [29].

Conclusions

Chemerin activity might be related to inflammation and affect expression of proinflammatory cytokines: IL-6 and IL-23 in CRC. IL-6 is upregulated in CRC tissue, whereas concentration of IL-23 is elevated in tumor-free margin tissue. Further studies are necessary to elucidate the possible role of chemerin, IL-6, and IL-23 as potential markers and therapeutic candidates in the development of CRC.

References

1. Zeng J, Tang ZH, Liu S, et al. Clinicopathological significance of overexpression of interleukin-6 in colorectal cancer. World J Gastroenterol. 2017; 23(10): 1780–1786, doi: 10.3748/wjg.v23.i10.1780, indexed in Pubmed: 28348483.
2. World Cancer Research Fund. Worldwide cancer data. https://www.wcrf.org/cancer-trends/worldwide-cancer-data/ (9.05.2022).
3. Centers for Disease Control and Prevention. An Update on Cancer Deaths in the United States.: Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Cancer Prevention and Control; 2022.
4. Akimoto N, Ugai T, Zhong R, et al. Rising incidence of early-onset colorectal cancer - a call to action. Nat Rev Clin Oncol. 2021; 18(4): 230–243, doi: 10.1038/s41571-020-00445-1, indexed in Pubmed: 33219329.
5. Jasperson K, Tuohy T, Neklason D, et al. Hereditary and Familial Colon Cancer. Gastroenterology. 2010; 138(6): 2044–2058, doi: 10.1053/j.gastro.2010.01.054.
6. Thanikachalam K, Khan G. Colorectal Cancer and Nutrition. Nutrients. 2019; 11(1), doi: 10.3390/nu11010164, indexed in Pubmed: 30646512.
7. Roguska J, Zubkiewicz-Kucharska A. Chemerin as an early marker of metabolic syndrome. Pediatric Endocrinology Diabetes and Metabolism. 2018; 24(1): 45–51, doi: 10.18544/pedm-24.01.0102.
8. Helfer G, Wu QF. Chemerin: a multifaceted adipokine involved in metabolic disorders. J Endocrinol. 2018; 238(2): R79–R94, doi: 10.1530/JOE-18-0174, indexed in Pubmed: 29848608.
9. Eichelmann F, Schulze MB, Wittenbecher C, et al. Association of chemerin plasma concentration with risk of colorectal cancer. JAMA Netw Open. 2019; 2(3): e190896, doi: 10.1001/jamanetworkopen.2019.0896, indexed in Pubmed: 30901045.
10. Komoda H, Tanaka Y, Honda M, et al. Interleukin-6 levels in colorectal cancer tissues. World J Surg. 1998; 22(8): 895–898, doi: 10.1007/s002689900489, indexed in Pubmed: 9673566.
11. Tanaka T, Kishimoto T. The biology and medical implications of interleukin-6. Cancer Immunol Res. 2014; 2(4): 288–294, doi: 10.1158/2326-6066.CIR-14-0022, indexed in Pubmed: 24764575.
12. Waldner MJ, Foersch S, Neurath MF. Interleukin-6 - a key regulator of colorectal cancer development. Int J Biol Sci. 2012; 8(9): 1248–1253, doi: 10.7150/ijbs.4614, indexed in Pubmed: 23136553.
13. Lan F, Zhang Le, Wu J, et al. IL-23/IL-23R: potential mediator of intestinal tumor progression from adenomatous polyps to colorectal carcinoma. Int J Colorectal Dis. 2011; 26(12): 1511–1518, doi: 10.1007/s00384-011-1232-6, indexed in Pubmed: 21547355.
14. Adamo V, Franchina T, Minciullo PL, et al. Role of interleukin-23 circulating levels increase in resected colorectal cancer before and after chemotherapy: preliminary data and future perspectives. J Cell Physiol. 2011; 226(11): 3032–3034, doi: 10.1002/jcp.22653, indexed in Pubmed: 21302302.

15. Yan J, Smyth MJ, Teng MWL. Interleukin (IL)-12 and IL-23 and their conflicting roles in cancer. Cold Spring Harb Perspect Biol. 2018; 10(7), doi: 10.1101/cshperspect.a028530, indexed in Pubmed: 28716888.
16. Alkady MM, Abdel-Messeih PL, Nosseir NM. Assessment of serum levels of the adipocytokine chemerin in colorectal cancer patients. J Med Biochem. 2018; 37(3): 313–319, doi: 10.1515/jomb-2017-0062, indexed in Pubmed: 30598628.
17. Chonov DC, Ignatova MM, Ananiev JR, et al. IL-6 activities in the tumour microenvironment. Part 1. Open Access Maced J Med Sci. 2019; 7(14): 2391–2398, doi: 10.3889/oamjms.2019.589, indexed in Pubmed: 31592285.
18. Kinoshita T, Ito H, Miki C. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. Cancer. 1999; 85(12): 2526–2531, doi: 10.1002/(sici)1097-0142(19990615)85:12<2526::aid-cncr6>3.0.co;2-3.
19. Lo CH, Lee SC, Wu PY, et al. Antitumor and antimetastatic activity of IL-23. J Immunol. 2003; 171(2): 600–607, doi: 10.4049/jimmunol.171.2.600, indexed in Pubmed: 12847224.
20. Suzuki H, Ogawa H, Miura K, et al. IL-23 directly enhances the proliferative and invasive activities of colorectal carcinoma. Oncol Lett. 2012; 4(2): 199–204, doi: 10.3892/ol.2012.739, indexed in Pubmed: 22844353.
21. Ljujic B, Radosavljevic G, Jovanovic I, et al. Elevated serum level of IL-23 correlates with expression of VEGF in human colorectal carcinoma. Arch Med Res. 2010; 41(3): 182–189, doi: 10.1016/j.arcmed.2010.02.009, indexed in Pubmed: 20682175.
22. FM R, S H, MA Z, et al. Evaluation of expression pattern of vascular endothelial growth factor (VEGF) and interleukin-23 (IL-23) genes in human colorectal tumors. Journal of Molecular and Genetic Medicine. 2018; 12(1), doi: 10.4172/1747-0862.1000330.
23. Wang J, Xu K, Wu J, et al. The changes of Th17 cells and the related cytokines in the progression of human colorectal cancers. BMC Cancer. 2012; 12: 418, doi: 10.1186/1471-2407-12-418, indexed in Pubmed: 22994684.
24. Kim DK, Oh SY, Kwon HC, et al. Clinical significances of preoperative serum interleukin-6 and C-reactive protein level in operable gastric cancer. BMC Cancer. 2009; 9: 155, doi: 10.1186/1471-2407-9-155, indexed in Pubmed: 19457231.
25. Chung YC, Chaen YL, Hsu CP. Clinical significance of tissue expression of interleukin-6 in colorectal carcinoma. Anticancer Res. 2006; 26(5B): 3905–3911, indexed in Pubmed: 17094421.
26. Shiga K, Hara M, Nagasaki T, et al. Preoperative serum interleukin-6 is a potential prognostic factor for colorectal cancer, including stage II patients. Gastroenterol Res Pract. 2016; 2016: 9701574, doi: 10.1155/2016/9701574, indexed in Pubmed: 26858756.
27. Stanilov N, Miteva L, Deliysky T, et al. Advanced colorectal cancer is associated with enhanced IL-23 and IL-10 serum levels. Laboratory Medicine. 2010; 41(3): 159–163, doi: 10.1309/lm7t43aqziupiowz.
28. Zhang Le, Li J, Li Li, et al. IL-23 selectively promotes the metastasis of colorectal carcinoma cells with impaired Socs3 expression via the STAT5 pathway. Carcinogenesis. 2014; 35(6): 1330–1340, doi: 10.1093/carcin/bgu017, indexed in Pubmed: 24464786.
29. Wang K, Karin M. The IL-23 to IL-17 cascade inflammation-related cancers. Clin Exp Rheumatol. 2015; 33(Suppl 92): S87–90, indexed in Pubmed: 26457610.
30. Elessawi DF, Alkady MM, Ibrahim IM. Diagnostic and prognostic value of serum IL-23 in colorectal cancer. Arab J Gastroenterol. 2019; 20(2): 65–68, doi: 10.1016/j.ajg.2019.05.002, indexed in Pubmed: 31155425.