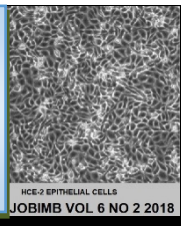
HIBISCUS PUBLISHER

JOURNAL OF BIOCHEMISTRY, MICROBIOLOGY AND BIOTECHNOLOGY

Website: http://journal.hibiscuspublisher.com/index.php/JOBIMB/index



Emerging Soluble Protein Markers in Colorectal Cancer

Nor Adzimah Johdi[1]* and Rahman Jamal[1]

[1]UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

*Corresponding author:
Dr. Nor Adzimah Johdi
UKM Medical Molecular Biology Institute,
Universiti Kebangsaan Malaysia,
Cheras, Kuala Lumpur, Malaysia.
Email: adzimah@ppukm.ukm.edu.my

HISTORY

Received: 5th Nov 2018
Received in revised form: 6th of Dec 2018
Accepted: 13th of Dec 2018

KEYWORDS

cytokines
chemokines
colorectal carcinoma
interleukins
expression

ABSTRACT

Small soluble proteins that are part of immune regulation such as cytokines, chemokines and growth factors are significantly involved in the pathogenesis of cancers. Their increase concentration in biological fluids and tissues suggest pathway activation that involves in inflammatory response or cancer progression. The knowledge of these soluble proteins has increasing clinical importance as a biomarker tool in screening, diagnosis classification, therapeutic surveillance and intervention. The review gives a short insight into the most commonly reported cytokines, chemokines and growth factors and their potential roles in the carcinogenesis. We discuss recent findings on their functions in colorectal carcinoma through analysis of their expression patterns, the use of selective inhibitors and signaling pathways involved.

INTRODUCTION

Colorectal carcinoma (CRC) is one of the commonest cancer worldwide with 746, 000 cases (10%) reported in men and 614, 000 cases (9.2%) in women worldwide [1]. Almost 55% of the cases occur in more developed regions but the number of incidents in the developing regions is increasing. Genetic (inherited or acquired) is known as the main risk factor in contributing factor to the CRC development and progression. However, other contributors such as evading immune response were also recognized as risk factors for cancer progression [2]. The immune system is believed to play a significant protective role in tumorigenesis [4–6]. One of the components of the immune system is the soluble proteins such as cytokines, chemokines and growth factors that support the network of immune function.

Cytokines, chemokines and growth factors are a group of small soluble proteins that have an important role in regulating the immune response. Under normal condition, their concentration in our biological fluids (serum or plasma) and tissues are usually below detectable range or very low. However, a significant increase in their concentration has been reported in many diseases including cancer [3, 4]. This suggests pathways activation which is related to inflammatory response or disease development. Although it has been previously underestimated, these proteins are suitable as a biomarker tool in the pathogenesis of diseases. In cancer, these proteins are produced as a result of interactions between cancer and immune cells that contribute to the carcinogenesis. In fact, these proteins can be produced by the cancer cells themselves to support their own survival. Indeed, these soluble proteins have the potential as a screening tool, diagnosis classification between stages of cancer or surveillance for therapy [5].

In this review, we will discuss the findings from recent studies investigating the role of these soluble proteins in CRC through analysis of their expression patterns, the use of selective inhibitors and signaling pathways involved. This review might be useful for the development of a biomarker panel that is specific to CRC. The panel will be useful to support the standard clinical Immunoscore technique. In addition, the soluble proteins could be used as targets for drug design and allow discrimination of sera derived from CRC and chronic inflammation in early diagnosis.

Interleukin-6 (IL-6)

IL-6 is one of the well-studied cytokines in diseases including cancer. IL-6 directly promotes tumor cell proliferation, differentiation and survival through STAT3 activation and these contribute significantly to the pathogenesis of CRC (6-8). It is also involved in controlling the balance between pro-inflammatory T cell subsets such as Th1 or Th17 cells and immunosuppressive regulatory T cells. IL-6 can activate targets cells via two signaling pathways which are “classic signaling” [9, 10] or “trans-signaling” pathways [**Fig. 1**] [11, 12]. This will then lead to further activation of several other intracellular signaling pathways such as JAK/STAT [13, 14], ERK/MAPK [15, 16] and PI3K/AKT [17] signaling pathways. CRC cells, unlike the normal intestinal epithelial cells, do not express the

IL-6 receptor (IL-6R). Thus, it is believed that the tumor-promoting effects of IL-6 in CRC depend on trans-signaling, a signal via soluble forms of its receptor (sIL-6R) [11, 12]. This is supported by a study in murine CRC model where the proliferation of tumor cells and activation of STAT3 were due to secretion of IL-6 by lamina propria T cells and macrophages [18]. In intestinal epithelial cells, IL-6 supports the expression of one of the receptors for the pro-angiogenic vascular endothelial growth factor, VEGFR2 [18]. This enables auto-/paracrine VEGF signaling in intestinal tumor cells and thus promotes tumor growth through STAT3 activation.

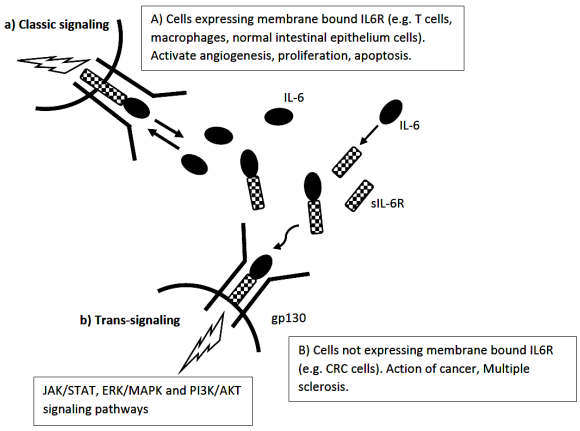


Fig. 1. The 2 types of IL-6 signaling pathways a) classic and b) trans-signaling. A) The classical signaling in cells expressing the membrane-bound receptor for IL-6 (IL-6R) such as T cells, macrophages, normal intestinal epithelium cells. In these cells circulating IL-6 binds directly to IL-6R that forms a signaling complex with the membrane-bound glycoprotein 130 (gp130). B) The trans-signaling involves cells (such as CRC cells) that do not express the membrane-bound IL-6R. In these cells, membrane-bound gp130 (ubiquitously expressed) is activated by the circulating IL-6/soluble IL-6R (sIL-6R) complex.

Increased expression of IL-6 has also been reported in serum and tumor tissue of CRC patients [6]. Factors such as tumor size, stage, metastasis and survival have been associated with IL-6 expression levels. In the human colorectal cancer-derived mesenchymal stem cells (CRC-MSCs), IL-6 was the most highly expressed cytokine and promoted the progression of CRC cells through IL-6/JAK2/STAT3 signaling, which then activated PI3K/AKT signaling [7]. Activation of IL-6/JAK2/STAT3 signaling was also shown in Ras-related protein 3C (RAB3C), which are important in the regulation of membrane trafficking and cell movement. The expression of RAB3C is significantly associated with the advanced pathological stage, distant metastasis and poor prognosis [8]. The IL-6 in combination with Tumor Necrosis Factor-Alpha (TNF-α), synergistically activate STAT3 which then increase telomerase activity by binding human telomerase reverse transcriptase (hTERT) promoter more tightly and thus constitute a central signaling pathway that promotes inflammation and tumor growth concurrently [19]. The interaction between IL-6 and IL-1β in the CRC microenvironment have been shown to have a significant role in the development and progression of human colorectal cancer [20]. In CRC tissues, both IL-1β and IL-6 mRNA and protein expressions were increased and have a statistically significant relationship with tumor invasion depth [20]. Overall, targeting this pathway show a promising strategy in CRC and several therapeutics targeting IL-6 dependent pathways have been developed [21-23].

SOCS-1

The suppressors of cytokine signaling (SOCS) are inhibitors of cytokine signaling. They function through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway [24-26]. The SOCS proteins have a similar central SH2 domain and a C-terminal domain and there are 8 have been identified so far in mammals (SOCS-1 to SOCS-7 and the alternatively named cytokine-inducible SH2-containing protein [CIS]) [27]. Their function in human cancer is not completely established. Thus, for the interest of this review, we focus the discussion on the role of SOCS-1 in CRC.

Few studies suggest that SOCS-1 protein works as a tumor suppressor of metastasis in human. This is due to the overexpression of SOCS-1 protein in human SW620 CRC cells reduced the morphological transformation, invasion and metastasis of these cells without affecting its proliferation, anchorage-independent growth or tumorigenesis [28]. SOCS-1 protein controls the metastatic progression in CRC by preventing the mesenchymal-epithelial transition (MET), including E-cadherin expression, enhancement of p53 tumor suppressor activity and blocking inflammation [29-32]. The *SOCS1* gene is frequently silenced in cancers due to hypermethylation of its promoter resulting in significant suppression of SOCS-1 expression in tumors and correlation with lymph node metastasis and Tumor Node Metastasis (TNM) staging [33,34]. Reduced expression of SOCS-1, therefore, leads to development, progression, metastasis and poor overall survival rate among CRC patients.

On contrary, *SOCS1* mRNA expression was significantly up-regulated only in CRC tumor stage II relative to normal tissues with no correlation between *SOCS1* expression and overall survival [35]. The overexpression of SOCS-1 in CRC cells correlates with the cell growth enhancement, anchorage-independent growth and resistance to death stimuli. The knockdown experiment of SOCS-1 showed a reduction in these oncogenic features while overexpression of the gene promotes tumorigenesis [35]. This suggests that SOCS-1 may have a pro-oncogenic role in CRC cells rather than a tumor suppressor function. Overall, there are limited numbers of studies on the functional role of SOCS1 in CRC and whether it works as a tumor suppressor or as an oncogene, is still an area of debate.

Interleukin 8 (IL8) or chemokine ligand 8 (CXCL8)

One of the most significantly upregulated chemokines in CRC is interleukin 8 or CXCL8 and it has a significant value in CRC diagnostics [36] . IL-8 has multi-roles such as in tumor growth, invasion, proliferation, angiogenesis and migration through binding to the cell surface receptors, CXCR1/2 [37, 38] . Measurement of CRC patients-derived serum showed a significant increase in concentration (42.55 pg/ml) compared to CRC polyps and normal-derived serum (7.65 pg/ml and 13.84 pg/ml respectively) [39]. The expression of IL-8 has been associated with poor chemotherapeutic response [40, 41] , thus a potential use of IL-8 as a clinical marker for chemoresistance. In the *in vitro* studies on 5-Fluorouracil chemoresistant subline colorectal cells, HCT 116 (HCT116/5FU) showed upregulation of IL-8 at the mRNA and protein level compared to parental HCT 116 cells [38] . The mRNA expression levels of IL-8 after 5-Fluorouracil (5-FU) treatment in both HCT116/FU and HCT116 cells were 4-fold and 3.7 fold higher respectively compared to the untreated cells. This indicates that 5-FU stimulated the expression of IL-8 and plays an important role in tumor growth and invasion. In addition, the IL-8 level was also significantly increased in doxorubicin (Dox)-resistant HCT-116 and SW480 CRC cell lines as compared with their

corresponding parental cells [42]. Targeted inhibition of IL-8 via siRNAs or its inhibitor (tumoreparixin) leads to increase Dox sensitivity in these cells and decrease the mRNA and protein expression of multidrug resistance 1 (MDR1, encoded by ABCB1) [42]. In the tumor microenvironment, hypoxia is a known condition involving the direct binding and transcriptional up-regulation of HIF-1α. However, hypoxia-induced IL-8 expression in CRC is mediated through down-regulation of dual specificity phosphatase-2 (DUSP2) expression and involved intermediate transcription factor [C/EBPα] [43]. This alternative pathway for hypoxia-induced in a tumor instead of the standard and binding of HIF-1α shows the complexity within the tumor microenvironment.

Transforming growth factor beta (TGF-β)

The role of TGF-β role in cancer progression can be both as a promoter and suppressor of metastasis. Generally, the TGF-β pathway is the most commonly mutated pathway in cancer and associated with the processes of angiogenesis, metastasis and epithelial-mesenchymal transition (EMT). Molecular chaperone Hsp90 is believed to play a role in regulating the TGF-β pathway. When both TGF-β1 and Hsp90β are present, they are able to stimulate anchorage-independent growth, reduce adhesion and stimulate migration in the colorectal cell line [44]. This occurs via an alternate TGF-β1 pathway which is mediated by αvβ6 as opposed to the canonical TGF-β1 pathway [44, 45]. TGFβ can also affect inflammation through the extent and composition of inflammatory cells present in tumors [46, 47]. This, however, is poorly understood and contradicting, although the colon tumors display intratumoral inflammation. An increase in inflammatory burden is often associated with epithelial loss of TGFβ signaling; however, overexpression of TGFβ is associated with increased inflammation [47]. Furthermore, epithelial truncation of TGFβR2 can lead to lethal inflammatory disease and invasive colon cancer as seen in mutant APC models of murine tumorigenesis which was mediated by IL-8 and TGFβ1 [47]. Thus, treating colon cancer patients with TGFβ inhibitors may not be a wise approach as it may result in a worse outcome by enhancing inflammatory responses. On the other hand, overexpression TGFβ1 could be controlled with lithium by inhibiting Smad3 phosphorylation via GSK3β inactivation [48]. Lithium could also inhibit lymphatic endothelial cell migration, which is increased upon TGFB induce protein expression in tumor cells. Lithium was shown to prevent metastasis to the lungs, liver, and lymph nodes by inhibiting TGFBIp-induced tumor lymphangiogenesis [48].

IL-17

Interleukin-17 is a proinflammatory cytokine that contributes to the pathogenesis of inflammatory and auto-immune diseases [49]. It is also highly associated with cancer progression and resistance to anti-VEGF treatment [50]. IL-17 is mainly produced by CD4+ T helper 17 cells (Th17 cells) [51]. However, it is also secreted by other immune cell types including lymphocytes NKT-17, γδT-17, CD8+ Tc17, polymorphonuclear neutrophils and intestinal Paneth cells [52, 53]. The IL-17 family of cytokines is comprised of IL-17A-F (**Table 1**), which bind to IL-17 receptors (IL-17R) A–E [52, 54]. While most studies focused on IL-17A, new findings are reported with the other subtypes of IL-17. During spontaneous colorectal tumorigenesis, the expression of IL-17A is increased in CDX2- promoter regulated Cre (CPC)-APC mouse model [55]. IL-17A also promotes the invasion of CRC cells by activating the PI3K/AKT/NF-kB signaling pathway and subsequently upregulating the expression of MMP-2/9 [56]. Thus, IL-17A seems to have a pro-tumorigenic effect. By blocking IL-17A at tumor sites, tumor growth was suppressed through angiogenesis inhibition as well as cytotoxic T lymphocytes activation at tumor sites [57] .

Table 1. Interleukin-17 subtypes and their expression level in CRC.

Interleukin 17	Expression in CRC	References
A	increased	[44, 45]
B	increased	[47]
C	various expression depending differentiation grade	[47]
D	no report	-
E	unchanged	[47]
F	decreased	[47]

Looking at the other IL-17 subtypes in CRC samples, IL-17B showed strong expression in the epithelial and stromal compartments, IL-17C showed various expression depending on the grade of differentiation while IL-17E expression remained even [58]. In contrast, decreased in IL-17F expression was seen in CRC compared to healthy controls. As for the receptors for IL-17, the colon epithelial cells were stained positive for IL-17RA, IL-17RB, and IL-17RC in both CRC and healthy controls. The distinct expression patterns for IL-17 suggest a differential role exerted by each member of this cytokine in colon carcinogenesis. This could be the reason for the conflicting results reported in previous studies. Most of the studies focus on the detection of IL-17 in general without taking into account the subclassifications of the IL-17 groups.

CONCLUSION

Taken together, the significant expression level of IL-6, SOC-1, IL-8, TGF-β and IL-17 in CRC patients suggest their involvement in the pathogenesis of cancer. Collectively, these cytokines are the key soluble proteins in promoting tumorigenesis, including resistance to apoptosis, abnormal growth and proliferation, angiogenesis and metastasis. These soluble proteins are useful as a biomarker in broad-spectrum tool for screening, diagnosis classification between stages of disease or surveillance for therapy. Not only it can be used in primary tumors but also within the metastatic niche that is critical for patients' prognostication.

ACKNOWLEDGEMENT

This review is funded by the Ministry of Education, Malaysia FRGS/1/2017/SKK08/UKM/03/2.

REFERENCES

1. Stewart BW, Wild CP. World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer. World Health Organization (2014): 630.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
3. Kantola T, Klintrup K, Väyrynen JP, Vornanen J, Bloigu R, Karhu T, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer. 2012;107(10):1729–36.
4. Krzystek-Korpacka M, Diakowska D, Kapturkiewicz B, Bębenek M, Gamian A. Profiles of circulating inflammatory cytokines in colorectal cancer (CRC), high cancer risk conditions, and health are distinct. Possible implications for CRC screening and surveillance. Cancer Lett. 2013;337(1):107–14.
5. Tang Y, Liao C, Xu X, Song H, Shi S, Yang S. Th1/Th2 cytokine profiles in G+/G- bacteremia in pediatric hematology/oncology patients. Pediatr Blood Cancer. 2012;58(1):50–4.

6. Lu CC, Kuo HC, Wang FS, Jou MH, Lee KC, Chuang JH. Upregulation of TLRs and IL-6 as a marker in human colorectal cancer. Int J Mol Sci. 2014;16(1):159–77.
7. Zhang X, Hu F, Li G, Yang X, Liu L, Zhang R, et al. Human colorectal cancer-derived mesenchymal stem cells promote colorectal cancer progression through IL-6/JAK2/STAT3 signaling. Cell Death Dis. 2018;9(2):25.
8. Chang YC, Su CY, Chen MH, Chen WS, Chen CL, Hsiao M. Secretory RAB GTPase 3C modulates IL6-STAT3 pathway to promote colon cancer metastasis and is associated with poor prognosis. Mol Cancer. 2017;16(1):135.
9. Pullamsetti SS, Seeger W, Savai R. Classical IL-6 signaling: a promising therapeutic target for pulmonary arterial hypertension. J Clin Invest. 2018;128(5):1720–3.
10. Ferreira RC, Freitag DF, Cutler AJ, Howson JM, Rainbow DB, Smyth DJ, et al. Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. PLoS Genet. 2013;9(4):e1003444.
11. Baran P, Hansen S, Waetzig GH, Akbarzadeh M, Lamertz L, Huber HJ, et al. The balance of interleukin (IL)-6, IL-6·soluble IL-6 receptor (sIL-6R), and IL-6·sIL-6R·sgp130 complexes allows simultaneous classic and trans-signaling. J Biol Chem. 2018;293(18):6762–75.
12. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci. 2012;8(9):1237–47.
13. Yadav A, Kumar B, Datta J, Teknos TN, Kumar P. IL-6 promotes head and neck tumor metastasis by inducing epithelial-mesenchymal transition via the JAK-STAT3-SNAIL signaling pathway. Mol Cancer Res. 2011;9(12):1658–67.
14. Chang Q, Bournazou E, Sansone P, Berishaj M, Gao SP, Daly L, et al. The IL-6/JAK/Stat3 feed-forward loop drives tumorigenesis and metastasis. Neoplasia. 2013;15(7):848–62.
15. Nishikai-Yan Shen T, Kanazawa S, Kado M, Okada K, Luo L, Hayashi A, et al. Interleukin-6 stimulates Akt and p38 MAPK phosphorylation and fibroblast migration in non-diabetic but not diabetic mice. PLoS One. 2017;12(5):e0178232.
16. Rodríguez-Berriguete G, Prieto A, Fraile B, Bouraoui Y, de Bethencourt FR, Martínez-Onsurbe P, et al. Relationship between IL-6/ERK and NF-κB: a study in normal and pathological human prostate gland. Eur Cytokine Netw. 2010;21(4):241–50.
17. Smith DA, Kiba A, Zong Y, Witte ON. Interleukin-6 and oncostatin-M synergize with the PI3K/AKT pathway to promote aggressive prostate malignancy in mouse and human tissues. Mol Cancer Res. 2013;11(10):1159–65.
18. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell. 2009;15(2):103–13.
19. Chung SS, Wu Y, Okobi Q, Adekoya D, Atefi M, Clarke O, et al. Proinflammatory Cytokines IL-6 and TNF-. Mediators Inflamm. 2017;2017:5958429.
20. Cui G, Yuan A, Sun Z, Zheng W, Pang Z. IL-1β/IL-6 network in the tumor microenvironment of human colorectal cancer. Pathol Res Pract. 2018.
21. Görtz D, Braun GS, Maruta Y, Djudjaj S, van Roeyen CR, Martin IV, et al. Anti-interleukin-6 therapy through application of a monogenic protein inhibitor via gene delivery. Sci Rep. 2015;5:14685.
22. Karkera J, Steiner H, Li W, Skradski V, Moser PL, Riethdorf S, et al. The anti-interleukin-6 antibody siltuximab down-regulates genes implicated in tumorigenesis in prostate cancer patients from a phase I study. Prostate. 2011;71(13):1455–65.
23. Xu Z, Bouman-Thio E, Comisar C, Frederick B, Van Hartingsveldt B, Marini JC, et al. Pharmacokinetics, pharmacodynamics and safety of a human anti-IL-6 monoclonal antibody (sirukumab) in healthy subjects in a first-in-human study. Br J Clin Pharmacol. 2011;72(2):270–81.
24. Kazi JU, Kabir NN, Flores-Morales A, Rönnstrand L. SOCS proteins in regulation of receptor tyrosine kinase signaling. Cell Mol Life Sci. 2014;71(17):3297–310.
25. Inagaki-Ohara K, Kondo T, Ito M, Yoshimura A. SOCS, inflammation, and cancer. JAK-STAT. 2013;2(3):e24053.
26. Sasi W, Sharma AK, Mokbel K. The role of suppressors of cytokine signaling in human neoplasms. Mol Biol Int. 2014;2014:630797.
27. Hilton DJ, Richardson RT, Alexander WS, Viney EM, Willson TA, Sprigg NS, et al. Twenty proteins containing a C-terminal SOCS box form five structural classes. Proc Natl Acad Sci U S A. 1998;95(1):114–9.
28. David M, Naudin C, Letourneur M, Polrot M, Renoir JM, Lazar V, et al. Suppressor of cytokine signaling 1 modulates invasion and metastatic potential of colorectal cancer cells. Mol Oncol. 2014;8(5):942–55.
29. Gui Y, Yeganeh M, Cepero-Donates Y, Ramanathan S, Saucier C, Ilangumaran S. Regulation of MET receptor signaling by SOCS1 and its implications for hepatocellular carcinoma. Curr Pharm Des. 2014;20(17):2922–33.
30. Gui Y, Yeganeh M, Donates YC, Tobelaim WS, Chababi W, Mayhue M, et al. Regulation of MET receptor tyrosine kinase signaling by suppressor of cytokine signaling 1 in hepatocellular carcinoma. Oncogene. 2015;34(46):5718–28.
31. Calabrese V, Mallette FA, Deschênes-Simard X, Ramanathan S, Gagnon J, Moores A, et al. SOCS1 links cytokine signaling to p53 and senescence. Mol Cell. 2009;36(5):754–67.
32. Jung SH, Kim SM, Lee CE. Mechanism of suppressors of cytokine signaling 1 inhibition of epithelial-mesenchymal transition signaling through ROS regulation in colon cancer cells: suppression of Src leading to thioredoxin up-regulation. Oncotarget. 2016;7(38):62559–71.
33. Kang XC, Chen ML, Yang F, Gao BQ, Yang QH, Zheng WW, et al. Promoter methylation and expression of SOCS-1 affect clinical outcome and epithelial-mesenchymal transition in colorectal cancer. Biomed Pharmacother. 2016;80:23–9.
34. Zhang J, Li H, Yu JP, Wang SE, Ren XB. Role of SOCS1 in tumor progression and therapeutic application. Int J Cancer. 2012;130(9):1971–80.
35. Tobelaim WS, Beaurivage C, Champagne A, Pomerleau V, Simoneau A, Chababi W, et al. Tumour-promoting role of SOCS1 in colorectal cancer cells. Sci Rep. 2015;5:14301.
36. Jin WJ, Xu JM, Xu WL, Gu DH, Li PW. Diagnostic value of interleukin-8 in colorectal cancer: a case-control study and meta-analysis. World J Gastroenterol. 2014;20(43):16334–42.
37. Shen T, Yang Z, Cheng X, Xiao Y, Yu K, Cai X, et al. CXCL8 induces epithelial-mesenchymal transition in colon cancer cells via the PI3K/Akt/NF-κB signaling pathway. Oncol Rep. 2017;37(4):2095–100.
38. Dabkeviciene D, Jonusiene V, Zitkute V, Zalyte E, Grigaitis P, Kirveliene V, et al. The role of interleukin-8 (CXCL8) and CXCR2 in acquired chemoresistance of human colorectal carcinoma cells HCT116. Med Oncol. 2015;32(12):258.
39. Johdi NA, Mazlan L, Sagap I, Jamal R. Profiling of cytokines, chemokines and other soluble proteins as a potential biomarker in colorectal cancer and polyps. Cytokine. 2017;99:35–42.
40. Park SY, Han J, Kim JB, Yang MG, Kim YJ, Lim HJ, et al. Interleukin-8 is related to poor chemotherapeutic response and tumourigenicity in hepatocellular carcinoma. Eur J Cancer. 2014;50(2):341–50.
41. Loosen SH, Schulze-Hagen M, Leyh C, Benz F, Vucur M, Kuhl C, et al. IL-6 and IL-8 Serum Levels Predict Tumor Response and Overall Survival after TACE for Primary and Secondary Hepatic Malignancies. Int J Mol Sci. 2018;19(6).
42. Du J, He Y, Li P, Wu W, Chen Y, Ruan H. IL-8 regulates the doxorubicin resistance of colorectal cancer cells via modulation of multidrug resistance 1 (MDR1). Cancer Chemother Pharmacol. 2018;81(6):1111–9.
43. Lin SC, Hsiao KY, Chang N, Hou PC, Tsai SJ. Loss of dual-specificity phosphatase-2 promotes angiogenesis and metastasis via up-regulation of interleukin-8 in colon cancer. J Pathol. 2017;241(5):638–48.
44. de la Mare JA, Jurgens T, Edkins AL. Extracellular Hsp90 and TGFβ regulate adhesion, migration and anchorage-independent growth in a paired colon cancer cell line model. BMC Cancer. 2017;17(1):202.
45. Biernacka A, Dobaczewski M, Frangogiannis NG. TGF-β signaling in fibrosis. Growth Factors. 2011;29(5):196–202.

46. Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity. 2006;24(2):179–89.
47. Principe DR, DeCant B, Staudacher J, Vitello D, Mangan RJ, Wayne EA, et al. Loss of TGFβ signaling promotes colon cancer progression and tumor-associated inflammation. Oncotarget. 2017;8(3):3826–39.
48. Maeng YS, Lee R, Lee B, Choi SI, Kim EK. Lithium inhibits tumor lymphangiogenesis and metastasis through the inhibition of TGFBIp expression in cancer cells. Sci Rep. 2016;6:20739.
49. Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. The role of interleukin 17 in tumor proliferation, angiogenesis, and metastasis. Mediators Inflamm. 2014;2014:623759.
50. Wang K, Kim MK, Di Caro G, Wong J, Shalapour S, Wan J, et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. Immunity. 2014;41(6):1052–63.
51. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11(10):763–76.
52. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011;34(2):149–62.
53. Hirota K, Ahlfors H, Duarte JH, Stockinger B. Regulation and function of innate and adaptive interleukin-17-producing cells. EMBO Rep. 2012;13(2):113–20.
54. Pappu R, Ramirez-Carrozzi V, Sambandam A. The interleukin-17 cytokine family: critical players in host defense and inflammatory diseases. Immunology. 2011;134(1):8–16.
55. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumor growth. Nature. 2012;491(7423):254–8.
56. Ren H, Wang Z, Zhang S, Ma H, Wang Y, Jia L, et al. IL-17A Promotes the Migration and Invasiveness of Colorectal Cancer Cells Through NF-κB-Mediated MMP Expression. Oncol Res. 2016;23(5):249–56.
57. Hayata K, Iwahashi M, Ojima T, Katsuda M, Iida T, Nakamori M, et al. Inhibition of IL-17A in tumor microenvironment augments cytotoxicity of tumor-infiltrating lymphocytes in tumor-bearing mice. PLoS One. 2013;8(1):e53131.
58. Al-Samadi A, Moossavi S, Salem A, Sotoudeh M, Tuovinen SM, Konttinen YT, et al. Distinctive expression pattern of interleukin-17 cytokine family members in colorectal cancer. Tumour Biol. 2016;37(2):1609–15.