

The IL-6/JAK/STAT3 pathway: Potential therapeutic strategies in treating colorectal cancer (Review)

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Abstract. Among the cytokines linked to inflammation-associated cancer, interleukin (IL)-6 drives many of the cancer 'hallmarks' through downstream activation of the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. Additionally, dysregulation of the interleukin (IL)-6-mediated JAK/STAT3 signaling pathway is closely related to the development of diverse human solid tumors including colorectal cancer (CRC). On this basis, modulation of the IL-6/JAK/STAT3 signaling pathway is currently being widely explored to develop novel therapies for CRC. The present review details the mechanisms and roles of the IL-6/JAK/STAT3 pathway in CRC, describes current therapeutic strategies, and the search for potential therapeutic approaches to treat CRC.

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1. Introduction

Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway is involved in various physiological processes, including immune function, cell growth, differentiation and hematopoiesis (1). Accumulating evidence indicates that abnormalities in the JAK/STAT3 pathway play a vital role in the oncogenesis of several cancers. It was reported (2) that constitutive activation of JAK2 was found in childhood T cell acute lymphoblastic leukemia. Constitutive activation of STAT3 is linked to cell proliferation in breast carcinoma (3) and non-small cell lung cancer (4), and also inhibits apoptosis (5). Studies have also revealed that oncogenesis can be altered by STAT3 activation (1). These published reports all demonstrate the crucial importance of the JAK/STAT3 pathway in tumorigenesis and progression.

Colorectal cancer (CRC) is the third most common cancer worldwide and it is reported that ~530,000 patients die of the disease each year (6). Although much progress has been made in treatment, outcomes remain poor as approximately half of patients receiving treatment still die of the disease (7,8). Some studies have indicated that elevated interleukin-6 (IL-6)/JAK/STAT3 signaling is one of the key pathways involving in colorectum tumorigenesis, this signaling has a critical role in various aspects including initiation, development and formation in CRC. The role of IL-6 in tumorigenesis has been well-established in CRC. Increased production of IL-6 has been reported in tumor tissue itself and in the serum of patients with CRC (9). Recent studies show that cytokine-driven JAK/STAT3 pathways play an important role in the processes of signal transduction, which are associated with the hyperproliferative and invasive phenotype of CRC cells (10). Although our knowledge of oncogenesis, proto-oncogene identification and tumor suppressor genes involved in the tumorigenesis of CRC are growing, the biologic and molecular mechanisms in CRC are still poorly understood. Moreover, the molecular mechanisms that control CRC progression are related to the alteration of different proto-

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Abbreviations: IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus-activated kinase; STAT3, signal transducer and activator of transcription 3; CRC, colorectal cancer; ADAM, A disintegrin and A metalloproteinase; VEGF, vascular endothelial growth factor; TGF- β , transforming growth factor- β ; Treg, regulatory T; Th, T helper; MDSCs, myeloid derived suppressor cells; DCs, dendritic cells; CAC, colitis-associated cancer; IBD, inflammatory bowel disease; CD, Crohn's disease; JH, JAK homology; FERM, four-point-one, ezrin, radixin and moesin; SH2, Src homology 2; MMP, matrix metalloproteinase; McAb, monoclonal antibody; SOCS, suppressor of cytokine signaling; CIS, cytokine-inducible SH2-containing; PIAS1, Gu/RNA helicase II-binding protein; GBE, *Ginkgo biloba* extract; ESHS1, enoyl-CoA hydratase short chain 1

Key words: interleukin-6, Janus kinase, signal transducer and activator of transcription 3, therapies, colorectal cancer

oncogenes, cytokines, tumor suppressor genes and their receptors (11). Notably, these abnormalities are involved in the JAK/STAT3 signal transduction pathway.

In this review, we summarize the mechanisms and roles of IL-6/JAK/STAT3 pathway in CRC and describe current therapeutic strategies to treat CRC by targeting the IL-6/JAK/STAT3 pathway. Importantly, we discuss how to use current knowledge to find potential therapeutic approaches.

2. IL-6/JAK/STAT3 pathway

Molecular cloning has identified two different forms of cellular receptors of IL-6: an 80-kDa ligand-binding chain, known as IL-6R (IL-6Ra, CD126) and a 130-kDa signal-transducing chain, gp130 (IL-6Rb, CD130). In contrast to the ubiquitous expression of gp130, IL-6R shows a highly limited expression pattern and is mainly confined to hepatocytes, leukocyte subsets and megakaryocytes (12). First, IL-6 binds to the IL-6R on target cells, then the complex of IL-6 and IL-6R contacts the gp130, thereby boosting its dimerization and the subsequent activation of intracellular signaling such as STAT3 phosphorylation by JAK. This so-called classical signaling pathway is activated during early immune responses and in turn activates the expression of various acute-phase proteins such as C-reactive protein (13). We believe that classical IL-6R signaling coordinates homeostatic properties of IL-6, which may act as a cytokine with hormone-like characteristics. In addition, a soluble type of the IL-6 receptor (sIL-6R), which is produced by limited proteolysis by A disintegrin and A metalloproteinase 10 (ADAM10) or ADAM17 of the membrane-bound IL-6R and translation from an alternatively spliced mRNA, can still bind to IL-6 and the complex of IL-6 and sIL-6R interplays with gp130. This so-called IL-6 trans-signaling represents an alternative to classical IL-6 signaling and allows IL-6 to regulate a broad spectrum of target cells including neutrophils, macrophages, epithelial cells and T cells (14). In our opinion, IL-6 trans-signaling acts as a danger signal to enhance IL-6 responsiveness and drive inflammatory events.

The signal transduction of IL-6 involves the activation of JAK, then leads to the activation of transcription factor STAT3 (15). Over 40 different cytokines or growth factors can activate STAT signaling pathway. Normally STAT3 resides in the cytoplasm. STAT3 will be phosphorylated and then forms dimers with other members of the STAT family when activated by upstream signaling pathways such as JAK, epidermal growth factor receptor and IL-6R activation. The activated STAT3 complex will then translocate from the cytoplasm to the nucleus initiating transcription of STAT3 target genes including cyclin D1, Bcl-xL, c-myc, Mcl1 and vascular endothelial growth factor (VEGF) by combining with consensus DNA elements (16). STAT3 is known to play an important role in promoting tumorigenesis of diverse human cancers (17), since it is regarded as an oncogenic transcriptional factor involving in cancer cell proliferation, differentiation, invasion, inflammation and immune function (Fig. 1).

JAK family proteins. The JAK family proteins of cytoplasmic tyrosine kinases include four mammalian members, which

are related to the cytoplasmic regions of signal transducing cytokine receptors. Three of them, JAK1, JAK2 and TYK2, are expressed in various tissues, yet JAK3 is expressed only in cells of the hematopoietic system (18). The unique structure of the JAKs easily differentiates them from other members of the protein tyrosine kinase family. The most attractive feature of these proteins is the presence of two JAK homology (JH) domains, JH1 and JH2, which have extensive homology to tyrosine kinase domains. JH1 domain at the C-terminus appears to be a functional tyrosine kinase domain, while the JH2 domain does not possess substantial tyrosine kinase activity (19). The JH3-JH7 regions, which form the N-terminal half of the JAKs, are related to binding to cytokine receptors. A portion of the N-terminal region of JAKs has similar sequence with the so-called four-point-one, ezrin, radixin and moesin (FERM) domains, and JAKs have been proved to shield a divergent type of FERM domain. The SH2 domain also contains JH3 and JH4 domains. The selectivity of STAT activation by various ligands mainly depends on the highly specific interactions between the SH2 domain and the phosphotyrosine residues on each receptor (20) (Fig. 2).

STAT family proteins. STAT family proteins have identified seven mammalian members: STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5 α and STAT5 β), and STAT6. Every STAT protein has several conserved domains including the N-terminal coiled-coil domain, DNA binding domain, a linker, Src homology 2 (SH2) domain, and a C-terminal transactivation domain, which are closely related to its functions (21). Several studies have indicated that the N-terminal domain promotes dimerized STAT molecules to polymerize and bind multiple DNA sites that are related to oncogenic growth signaling pathways (22). The DNA-binding domain is the central region of each STAT protein (except for STAT2) and regulates the DNA-binding specificity for each STAT protein (23). A linker domain, region of 500-575, is α -helical before the classical SH2 domain. The conserved SH2 domain exists in the region between 600 and 700 amino acid residues and it is crucial to form dimers between two activated STAT monomers via reciprocal phospho-tyrosine-SH2-domain interactions (20). The C-terminal transactivation domain is associated with transcriptional complexes, and builds structures when binding with interacting partners. The tyrosine residue of position 705 in this STAT domain plays an important role in STAT activation. Additionally, at position 727 (except STAT2 and STAT6), a conserved serine, is a phosphorylation site and regulates STAT transcriptional activity (24) (Fig. 2).

3. Roles of IL-6/JAK/STAT3 pathway in CRC

IL-6 in CRC. IL-6, a pleiotropic inflammatory cytokine, not only has central roles in immune and inflammatory response, but also is regarded as a key growth factor for malignancy (25). Cancer cells utilize the autocrine production of growth and survival factors to upregulate growth and survival pathways. The increased expression of IL-6 in cancer cells manifests that IL-6 is an important autocrine growth factor promoting tumorigenesis (26). Tissue or infection will cause more secretion of IL-6. Thereby, IL-6 participates in the regulation of the acute phase response, the differentiation of monocytes

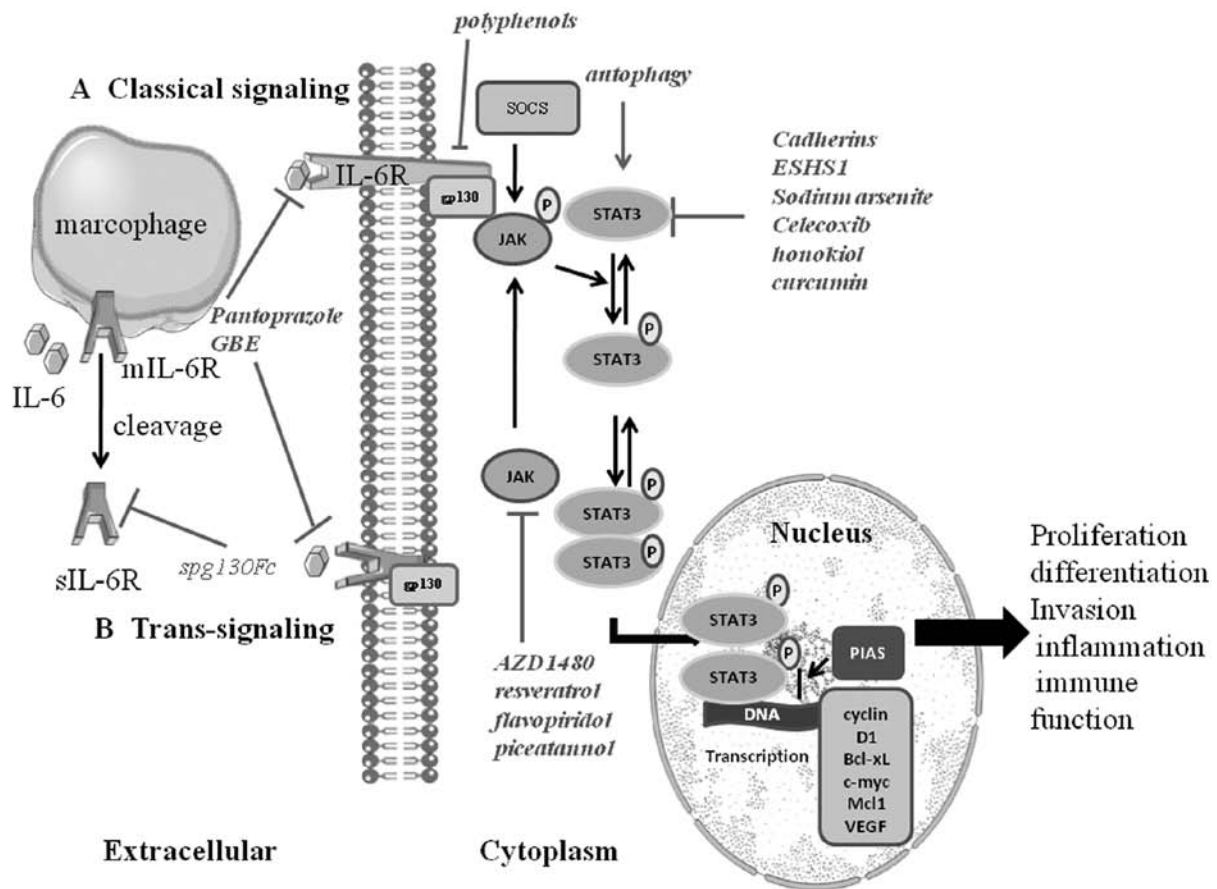


Figure 1. IL-6/JAK/STAT3 signaling pathway. IL-6 activation has two modes of: (A) classical signaling pathway: IL-6 binds to the IL-6R on target cells. Then the complex of IL-6 and IL-6R contacts the gp130; (B) trans-signaling pathway: a soluble type of the IL-6 receptor (sIL-6R) binds to IL-6 and interplays with gp130. Thereby both of them induce dimerization and initiates signaling. The signal transduction of IL-6 involves the activation of JAK, then leading to the activation of transcription factors of the signal transducers and activators of STAT3. Normally STAT3 resides in the cytoplasm. STAT3 is phosphorylated and then forms dimers with other members of the STAT family when activated by upstream signaling pathways such as JAK, EGFR, IL-6 receptor activation. The activated STAT3 complex will then translocate from the cytoplasm to the nucleus initiating transcription of STAT3 target genes (including cyclin D1, Bcl-xL, c-myc, Mcl1, survivin and VEGF) by combining with consensus DNA elements. STAT3 is regarded as an oncogenic transcriptional factor involved in cancer cell proliferation, differentiation, invasion, inflammation and immune function. Many factors can influence the range and duration of STAT activation. The protein inhibitors of activated STATs (PIAS) family of proteins are negative regulators of STAT-mediated gene transcription. In addition, the suppressors of cytokine signaling (SOCS) protein family affects the JAKs, and thus restrain the phosphorylation of gp130, STATs and the JAKs themselves.

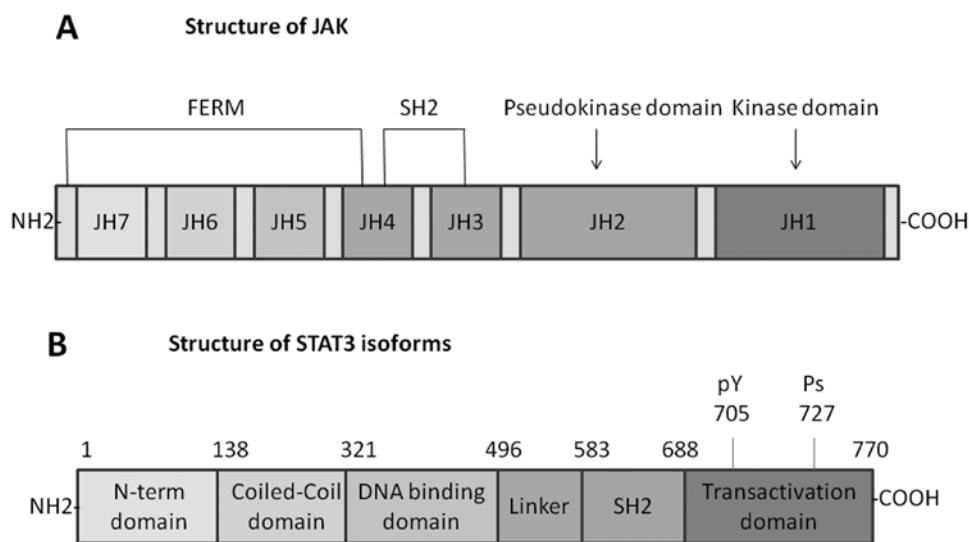


Figure 2. Structure of JAK and the STAT3 isoforms. (A) The structural domains of JAK are referred to as JAK homology regions (JH1-JH7). JAK also possesses four functional domains: the FERM domain, the SH2 domain, the pseudotyrosine kinase (TK) domain and a catalytically active TK domain. (B) Structure of the STAT3 isoforms including the N-terminal coiled-coil domain, DNA binding domain, a linker, Src homology 2 (SH2) domain, and a C-terminal transactivation domain are shown, as well as the tyr705 and ser727 phosphorylation sites.

to macrophages, the proliferation and apoptotic resistance of T cells and Th2 cytokine production (27). The IL-6 signaling pathway is considered as one of the most important ways linking inflammation to cancer (28).

The role of IL-6 in tumorigenesis has been well-established in a wide range of human cancers including lymphoma, glioma, melanoma, breast, ovarian, prostate, renal, pancreatic cancer, as well as CRC. An increasing number of studies have found that IL-6 levels elevate in tumor tissue itself and in the serum of patients with CRC (9). Additionally, a review survey by Knüpfner and Preiss shows that IL-6 expression is closely related to tumor stage, size, metastasis and survival of patients with CRC (29). IL-6/sIL-6R and inflammation function in the pathogenesis of CRC (30). IL-6 plays an important role in recruitment of immune cells that produce pro-inflammatory cytokines, and also in modulating Th17 and Treg cells in CRC (31). Moreover, IL-6 was reported to be localized at the sites of macrophage infiltration, suggesting an interaction between IL-6 and immune cells in the tumor microenvironment (32). Two recognized IL-6 polymorphisms have been reported to associate with a significantly reduced risk of CRC. In a study of 46 patients with CRC, multivariate analysis showed that the blood granulocyte/lymphocyte ratio and the serum IL-6 level were independent risk factors for poor prognosis, indicating that both factors may be significantly predictive for CRC cancer progression (33).

The risk of developing precancerous lesions and invasive carcinoma will increase exponentially when under the duration of inflammation in inflammatory bowel disease (IBD) patients such as Crohn's disease (CD) and ulcerative colitis (UC), and those who have not controlled inflammation will have higher risk of development of CAC (27). There is a 17.8% risk for CRC in patients with UC within 30 years (34). The cumulative risk for the development of CRC in patients with large bowel involvement of CD is ~8.3% over a period of 30 years (35). Similar to CRC, IL-6 expression is increased in patients with IBD (36). Many studies have manifested that IL-6 plays central roles in the pathogenesis of IBD, mainly due to its effect on immune cell function (27). IL-6 trans-signaling has been proved to activate T cells in the lamina propria of patients with IBD and leads to resistance of these cells against apoptosis via upregulation of anti-apoptotic factors such as Bcl-2 and Bcl-xL (37). According to the association of IL-6 expression with CRC prognosis and the increased expression of IL-6 in patients with IBD, IL-6 is known as a connection between chronic inflammation and tumor development. New data revealed a direct effect of a functional relevance for IL-6 acting on tumor cells in sporadic CRC, which is likely mediated by trans-signaling, as intestinal epithelial cells usually do not express mIL-6R (38).

JAK/STAT3 in CRC. Similarly to many malignant tumors, the hyperproliferative and invasive phenotype of CRC cells has showed to be related to abnormalities on the level of signal transduction. Cytokine-driven JAK/STAT3 pathways play crucial roles in these processes (10). Generally, the molecular mechanisms that regulate development of CRC are associated with the expression of different proto-oncogenes, tumor suppressor genes, cytokines, and their receptors, including Ras, Src, p27^{kip1}, p16^{ink4a}, interleukin and epidermal growth

factor receptor. These alterations markedly refer to the JAK/STAT3 signal transduction pathway (39). Though few studies of abnormal expression of JAK/STAT3 have been shown in CRC, STAT3 activity is constitutively upregulated in diverse human tumors including CRC (11).

So far several studies have indicated that elevated malignancy and invasive behaviour of CRC cells are closely associated with STAT3 activity (40). STAT3 is originally characterized as a mediator of IL-6 receptor signaling (41) with extremely widespread functions throughout the organism (reviewed in ref. 42) and it is the only embryonic lethal knockout within the STAT family (43). Not only cytokine and growth factor receptors, but several viral or cellular oncogenes such as src, fps, polyoma virus middle T-antigen, and sis are also known to activate STAT3 (reviewed in ref. 44). A constitutively active artificial variant of STAT3 generated by forced dimerization was shown to behave as an oncoprotein to induce tumorigenesis in nude mice (45). STAT3 activity is thought linked to elevated malignancy and invasive behaviour of CRC cells. STAT3 activation can increase the expression of matrix metalloproteinase (MMP), which also potentially promote CRC cells invasion and metastasis via proteolytic degradation of the extracellular matrix (46). The first evidence has been provided that Aloiin may inhibit tumor angiogenesis and growth by inhibiting STAT3 activation (47). Also recently it has been demonstrated that STAT3 signaling is important for the development of CRC and promotes angiogenesis by regulating VEGF-A and MMP2 expression (48). However, some research showed that STAT3 activity may also have negative effects on the development of colon cancer. From Apc^{Min} mouse models, STAT3 was demonstrated to inhibit tumor cell invasiveness and adenoma to carcinoma transition (49).

4. Modulation of IL-6/JAK/STAT3 pathway in CRC

Although in recent years significant progress was made in CRC treatment, CRC still remains the leading cause of cancer related to death in the worldwide. Therefore, new therapeutic methods, especially for patients with advanced disease, are greatly required. Therapeutics targeting the IL-6/JAK/STAT3 pathway are hopeful strategies because more and more evidence shows that IL-6/JAK/STAT3 pathway has a critical role in various aspects including initiation, development and formation in CRC.

Regulation of IL-6. IL-6 is an important tumor promoting cytokine that enforces proliferation and anti-apoptotic effects in tumor cells. Clinical and experimental data strongly propose a contribution of IL-6 signaling to the development of both sporadic and colitis-associated CRC development. In this regard, several components of the IL-6 signaling pathway such as IL-6R have been proposed as promising targets for CRC therapy.

Several studies have reported that IL-6 and STAT3 play an important role in the survival of intestinal epithelial cells and development of inflammation-associated cancer, anti-IL-6R antibody (anti-IL-6RAb) has been reported as an inhibitor to suppress CRC development (50). Subsequently, IL-6 ligand-blocking antibody was produced to express functions

Table I. Current therapies targeting the IL-6/JAK/STAT3 pathway in CRC.

Strategy	Compound	Disease	Phase
IL-6 inhibition	CNTO328	Solid cancer including CRC	Phase I + II
	Oroxylin A	Experimental model of cancer	Preclinical
IL-6R inhibition and sIL-6R inhibition	Anti-IL-6R antibody (tocilizumab)	Experimental model of cancer	Preclinical
Stat3 inhibition	<i>Pien Tze Huang</i> , ethanol extract of <i>Hedyotis diffusa</i> Willd, <i>Spica Prunellae</i>	CRC	Clinical
JAK/STAT signaling inhibition	Trichostatin A, bufalin	Experimental CRC	Preclinical

in antitumor and anti-inflammatory activities. CNTO-328, a human-mouse chimeric antibody, was generated from a murine anti IL-6 monoclonal antibody (McAb). CNTO-328 has a long half-life (~2 weeks) without remarkable immunogenicity and it also has a strong affinity with recombinant as well as native IL-6 (51). It is capable of blocking the signal transduction pathway of IL-6/IL-6R/gp130 by inhibiting the binding of IL-6 to the IL-6R, ultimately achieving antitumor and anti-inflammatory effects (52). In addition, the humanized anti-IL-6R McAb of IgG1 class, named anti-IL-6RAB (tocilizumab), was produced by grafting the complementarity-determining regions of a mouse antihuman IL-6R antibody onto human IgG1. The mechanism of anti-IL-6RAB is to control IL-6-mediated signal transduction by inhibiting the process of IL-6 binding to membrane-bound IL-6R and sIL-6R (53). Tocilizumab was reported to treat Castelman's disease and rheumatoid arthritis and may be used in cancers (54). Recently, it was shown that when expression of IL-6 and IL-1 β decreases, the IL-6/STAT3 signaling pathway also weakens in tumors in oroxylin A-treated mice. Through this mechanism it was demonstrated that oroxylin A inhibits colitis-associated carcinogenesis in an azoxymethane/dextran sodium sulfate mouse model and in the colon cancer cell line HCT-116 (55) (Table I).

The above treatments work in both classical and trans-signaling, and therefore also block physiological functions of IL-6. In contrast, modulation of sgp130Fc is a specific inhibition of trans-signaling. Sgp130Fc is a designer cytokine that specifically binds IL-6/sIL-6R complexes, and therefore it only blocks trans-signaling. It has been shown to be effective for the treatment of experimental CAC with sgp130Fc in the study by Becker *et al* (56). The substance will soon enter clinical development and it will be interesting to evaluate its effect on human cancer (57).

Regulation of JAK/STAT3. JAK/STAT3 has been shown in many aspects of CRC development, including cell growth, survival, invasion and migration (39,58). Therefore, inhibiting JAK/STAT3 is a valuable regulative strategy for cancers.

The suppressor of cytokine signaling (SOCS) proteins family comprise of eight members: SOCS 1-7, and cytokine-inducible SH2-containing (CIS)-1 (with similar structure to the other SOCS proteins). So far research has mainly focused on CIS and SOCS1-3, which have been found to serve as nega-

tive regulators of the JAK/STAT signaling pathway. However, the various family members seem to have different specific mechanism. CIS, first defined member, was proved to interact with STAT5 and then regulate the JAK2/STAT5 pathway. SOCS1 and SOCS3 are the most effective in inhibiting IL-6-mediated signaling pathways. Evidence has shown that both of above members affect the JAKs, thus restraining the phosphorylation of gp130, STATs and the JAKs themselves (59). Some studies reported that SOCS3 expression was decreased in a variety of inflammation-associated human cancers and cancer cell lines, which was correlated with strong STAT3 activity in these cells (60). New data demonstrate that sodium butyrate inhibits JAK2/STAT signaling through upregulation of SOCS1 and SOCS3, which are regulated by histone deacetylase 8 (61). Likewise, a study shows that honokiol increases the activity and protein expression of SH2-containing tyrosine phosphatase-1 further blocking the STAT3 pathway (62) (Fig. 2). It has been demonstrated that, like in various other tumors with high STAT3 activity, DNA methylation influences epigenetic regulation leading to the decline in SOCS3 expression in CRC (32). In addition, data exist suggesting that trichostatin A may increase SOCS1 and SOCS3 expression by inducing histone modifications and ultimately inhibit JAK2/STAT3 signaling in CRC cells (63) (Table I).

The protein inhibitors of activated STATs (PIAS) family of proteins are negative regulators of STAT-mediated gene transcription. The family of PIAS consists of five mammalian components: PIAS1, PIAS3, PIAS α , PIAS β and PIAS γ . Since Gu/RNA helicase II-binding protein (PIAS1) was recognized, it is widely accepted that PIASs are transcriptional co-regulator proteins important to the JAK/STAT pathway (64). Inhibitory molecules from PIAS can interact with activated STATs, but they inhibit different STAT proteins by distinct types. For instance, PIAS3 inhibits STAT3-mediated gene expression (after IL-6 stimulation), whereas PIAS1 blocks STAT1-dependent signaling and directly inhibits the STAT-DNA complex activity with other transcriptional suppressive co-operators (65). Recent studies have shown that curcumin controls activation of PIAS-3 to restrain JAK-STAT signaling, thus weakens STAT-3 phosphorylation and tumor cell growth (66) (Fig. 1). Inhibitor of activated STAT3 protein-PIAS3 expression was also reduced in various cancers including prostate, gastric, brain, and CRC (67).

Table II. Potential therapies targeting of the IL-6/JAK/STAT3 pathway in CRC.

Strategy	Compound	Indication
IL-6 inhibition	Pantoprazole	Gastric cancer
	GBE	Endothelial inflammation
IL-6R inhibition and SIL-6R inhibition	Polyphenols	Suppress angiogenesis
	REGN-88	Rheumatoid arthritis
JAK inhibition	AZD1480	Solid tumors
	Resveratrol flavopiridol piceatannol	Hematologic malignancies
	CEP-701	Reduce cytokine production
	XL019	Myelofibrosis
	INCB018424	Myeloproliferative disorders
		Hematologic malignancies
STAT3 inhibition	Cadherins	Control survival
	ESHS1	
	Sodium arsenite	Induce apoptosis
	Celecoxib	Induce cell apoptosis on nasopharyngeal carcinoma
	Honokiol	
	Curcumin STAT3 decoy	Head and neck cancer

Novel agents directly inhibiting STAT3 were designed mainly to target the SH2 domain, which block either STAT3 phosphorylation or dimerization. These contain designed small molecules and peptidomimetics. Studies from many preclinical cancer models, many of these agents with high specificity to disrupt STAT3 function have been found to inhibit cancer growth (68). However, these agents have not been applied in clinic (69). Continuous unregulated STAT3 could increase cell proliferation and reduce cell apoptosis, then leading to development of various cancers including CRC (39,70). Therefore, affecting the STAT3 pathway and its target gene expression could balance cell apoptosis with proliferation, which seems a promising strategy for the development of novel anticancer therapies. Recent studies have showed that treatment with some well-known traditional Chinese formulas such as *Pien Tze Huang* (71), ethanol extract of *Hedyotis diffusa* Willd (72), *Spica Prunellae* (73) would lead to the inhibition of cancer cell proliferation and the promotion of apoptosis in CRC mouse tumor tissues through suppression of STAT3 phosphorylation activation (Table I).

Since the IL-6/JAK/STAT3 pathway is important to CRC, research has been conducted to reveal its potential role in treating CRC. Abrogation of galectin-4 expression promotes cancer cell proliferation and the downregulation of galectin-4 elicits tumor promotion *in vitro* and *in vivo* through activation of IL-6/NF- κ B/STAT3 signaling, so regulation of galectin-4 may be a direction to treat CRC (74). Organo-Mg inhibits inflammation-related mouse colon carcinogenesis by modulating the proliferative activities and chromosomal instability of CRC and suppressing

colonic inflammation suggests potential use of organo-Mg for clinical chemoprevention trials of CRC in the inflamed colon (75). Leptin influences the growth and proliferation of cancer cells via activation of various growth and survival signaling pathways including JAK/STAT, PI3-kinase/AKT, and/or MAP kinases, showing promise as a molecule to treat CRC (76). Ganetespib, a potent heat shock protein 90 (HSP90) inhibitor disrupts angiogenesis in CRC through inhibition of HIF-1 α and STAT-3 CRC cell lines (HCT116 and HT29), and these results collectively suggest that inhibition of HSP90 is a promising anti-angiogenic strategy in CRC (77). Recently studies have showed that bufalin not only inhibits the growth of CRC SW620 cells, but also induces apoptosis of SW620 cells through inhibition of JAK/STAT3 signaling pathway (78), thus, more clinical studies are required to confirm the efficacy of bufalin to treat human CRC.

5. Further perspectives

To date, many studies have recorded potential therapies in IL-6/JAK/STAT3 pathway to treat many cancers. However, limited attention has been paid to CRC, even though IL-6/JAK/STAT3 pathway plays a vital role in CRC. The studies in other diseases have indicated the influence on relieving the pathology in IL-6/JAK/STAT3 pathway, and it indicates a promising future in CRC, while more studies need to be performed to verify the hypothesis.

Some studies have demonstrated that modulating the expression of IL-6 can prevent the development of other diseases. Pantoprazole decreased the secretion of IL-6 and

caused cell death specifically in gastric cancer. Therefore, it may be a potential substance to treat CRC, which shows similar mechanism of tumor progression to gastric cancer (79). Diet-derived polyphenols suppressed angiogenesis by regulating the expression of IL-6 signal transducing receptor (IL-6R α) and SOCS3 protein, which is also the signaling pathway inhibiting development of CRC (80). *Ginkgo biloba* extract (GBE) inhibited high-glucose-induced endothelial inflammation by restraining redox-dependent IL-6 pathways, so GBE may be a potential target to relieve intestinal inflammation, which relates to inflammation-associated CRC (81).

Another method is to specifically inhibit JAK activation, which involves the activation of transcription factor STAT3. Some preclinical trials have utilized a number of natural products such as resveratrol, flavopiridol and piceatannol to inhibit pathways involved in inflammation, whose mechanisms include inhibition of STAT3 phosphorylation, reduction of the cytokine production and direct inhibition of the JAK (69). The role of JAK inhibition in solid tumors was also tested preclinically. The JAK1/2 inhibitor AZD1480 suppressed tumor development in models of IL-6-driven breast, ovarian, and prostate cancers (82). Currently, there is little clinical data on the use of JAK inhibition in CRC. However, AZD1480 and these natural products may be potential substances to treat CRC in the future.

Regulating the activation of STAT3 can prevent the progress of diseases. Three classical cadherins, E-cadherin, N-cadherin and cadherin 11, can control survival via the gp130/STAT3 pathway, thus we may control cadherins to inhibit the progress of CRC through the STAT3 pathway (83). Enoyl-CoA hydratase short chain 1 (ESHS1) specifically inhibited STAT3 activity and decreased expression of several target genes of STAT3 (84). Additionally, sodium arsenite inhibited self-renewal and induced apoptosis in mouse embryonic stem cells, which was enhanced also by suppressing the STAT3 pathways simultaneously (85). Therefore, functions of ECHS1 and sodium arsenite may also come true in intestinal cells, which prevent the development of CRC via the STAT3 pathway. Celecoxib induced cell apoptosis and cell cycle arrest on nasopharyngeal carcinoma, which was partly mediated by the STAT3 pathway. So it may be used as the promising target to induce intestinal cell apoptosis and treat CRC, but more studies should be performed (86). Advanced glycation end product-specific receptor-mediated autophagy contributed to pancreatic tumorigenesis and bioenergetics via the IL6-pSTAT3 pathway, so inhibiting the receptor could be a potential therapeutic manner to control tumorigenesis of CRC and other solid tumors (87) (Fig. 1 and Table II).

Some studies show that combining with inhibition of the IL-6/STAT3 signaling can enhance the effect of chemoradiotherapy. Treatment together with IL-6 inhibition enhanced the radiation response of prostate cancer (88). Ganoderic acid A, inhibition of the JAK-STAT3 signaling pathway, increased chemosensitivity of HepG2 cells to cisplatin (89). Therefore, the inhibition may be applied to treat CRC and other solid tumors needing chemoradiotherapy.

Putoczki *et al* have revealed that the related cytokine IL-11 might have a stronger correlation with elevated STAT3 activation in human gastrointestinal cancers in genetic mouse models (90). Therefore, targeting the interference with IL-11

could be a potential therapeutic strategy for the treatment of gastrointestinal cancers.

6. Conclusions

The continuous evidence of recent years makes us convinced that IL-6/JAK/STAT3 pathway plays a crucial role in colorectum tumorigenesis. The use of inhibitors of this signal transduction pathway has provided critical information for a better understanding of molecular mechanisms of pathology and developing new therapeutic methods of CRC. Thus, strategies targeting the IL-6/JAK/STAT3 pathway have emerged as attractive options to treat CRC.

Many studies have showed the potential therapy of IL-6/STAT3 signaling pathway to various diseases. However, experimental research on the treatment of CRC in IL-6/JAK/STAT3 signaling pathway is limited, even if this signaling is one of the key pathways involved in colorectum tumorigenesis. The studies in other diseases have demonstrated the influence on relieving the pathology in IL-6/JAK/STAT3 pathway, and it indicates a promising future in CRC, while more research needs to be carried out to confirm the hypothesis.

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