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REVIEW

Progress in Understanding the IL-6/STAT3 Pathway in Colorectal Cancer

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Abstract: As a pleiotropic cytokine, interleukin-6 (IL-6) not only regulates the cellular immune response, but it also promotes tumor development by activating multiple carcinogenic pathways. IL-6 expression is significantly elevated in colorectal cancer (CRC) and is closely related to CRC development and patient prognosis. In CRC, IL-6 activates signal transducers and activators of transduction-3 (STAT3) to promote tumor initiation and tumor growth. IL-6/STAT3 signalling has a profound effect on tumor-infiltrating immune cells in the tumor immune microenvironment in CRC. Additionally, IL-6/STAT3 pathway activates downstream target genes to protect tumor cells from apoptosis; drive tumor cell proliferation, cell cycle progression, invasion and metastasis; promote tumor angiogenesis; and stimulate drug resistance. Therefore, a thorough understanding of the many effects of the IL-6/STAT3 pathway in CRC is needed, which the present review examines.

Keywords: IL-6/STAT3 pathway, colorectal cancer, tumor development

Introduction

Colorectal cancer (CRC) is one of the 10 most frequent malignancies in the world. In 2018, there were more than 1.8 million new colorectal cancers worldwide, accounting for about 10% of all cancer cases, and the number of related deaths was 881,000, making it the second-deadliest cancer in the world.[1] Incidence of CRC in China has been increasing due to changes in lifestyle and diet, with more than 521,000 new cases in 2018, when it was the second most common malignancy in the country.[2] The increasing burden of CRC and related mortality highlight the need for early detection and prevention.[3]

Many factors are involved in the pathogenesis of CRC, including intestinal flora disorder, abnormal immune response, as well as genetic, environmental and lifestyle risk factors such as obesity, alcohol consumption, smoking, poor diet, and lack of exercise. Intestinal inflammation is one of the most important factors leading to CRC and is associated with dysregulation of numerous signaling pathways.[4,5] Among them is the IL-6/STAT3 pathway, which promotes CRC cell proliferation and survival.[6,7] CRC patients show significantly higher IL-6 levels than healthy individuals, and those levels correlate with tumor size, stage, metastasis, and survival rate.[8–11] IL-6 appears to help drive CRC by activating the downstream signaling factor STAT3.[12]

The present review examines recent progress in understanding the many mechanisms through which the IL-6/STAT3 pathway contributes to CRC.

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The IL-6/STAT3 Pathway

First cloned in 1986, IL-6 was found to be a pleiotropic cytokine playing roles in immune regulation, hematopoiesis, inflammation and tumorigenesis.[13] IL-6 activates downstream signal pathways by forming complexes with its receptor, which consists of two subunits: a ligand-binding protein IL-6R (also called IL-6Ra or CD126), with a molecular weight of 80 kDa; and a signal-transducing glycoprotein-130 (gp130, IL-6Rb, CD130), with a molecular weight of 130 kDa.[14]

In the classical IL-6 signaling pathway, extracellular IL-6 and membrane-bound IL-6R (mIL-6R) combine to form a complex to which gp130 binds, yielding an isohexameric complex consisting of two IL-6, two IL-6R and two gp130 molecules. This complex activates the Janus kinase (JAK), which in turn causes STAT3 to dimerize and translocate to the nucleus to alter the expression of target genes.[15] The main function of the classical pathway is to induce anti-inflammatory effects during the acute-phase response.[16]

Alternatively, trans IL-6 signaling can occur, which is the same as the classical pathway except that IL-6 binds to soluble IL-6R (sIL-6R) rather than mIL-6R.[17] The soluble receptor sIL-6R is produced by limited proteolysis of mIL-6R or alternative splicing of the IL-6R mRNA.[18,19] The main function of trans signaling is to promote an inflammatory response,[16] so this pathway appears to contribute to cancers such as CRC (Figure 1).[20,21]

One or the other pathway may predominate in different cellular contexts. For example, mIL-6R is expressed mainly on neutrophils, monocytes, activated B cells, CD4 + cells, and hepatocytes, so these cell types participate primarily in the classical pathway.[22] At the same time, the IL-6/sIL-6R complex in serum can potentially affect a broad range of cell types because gp130 is ubiquitously expressed in all cells.[23,24]

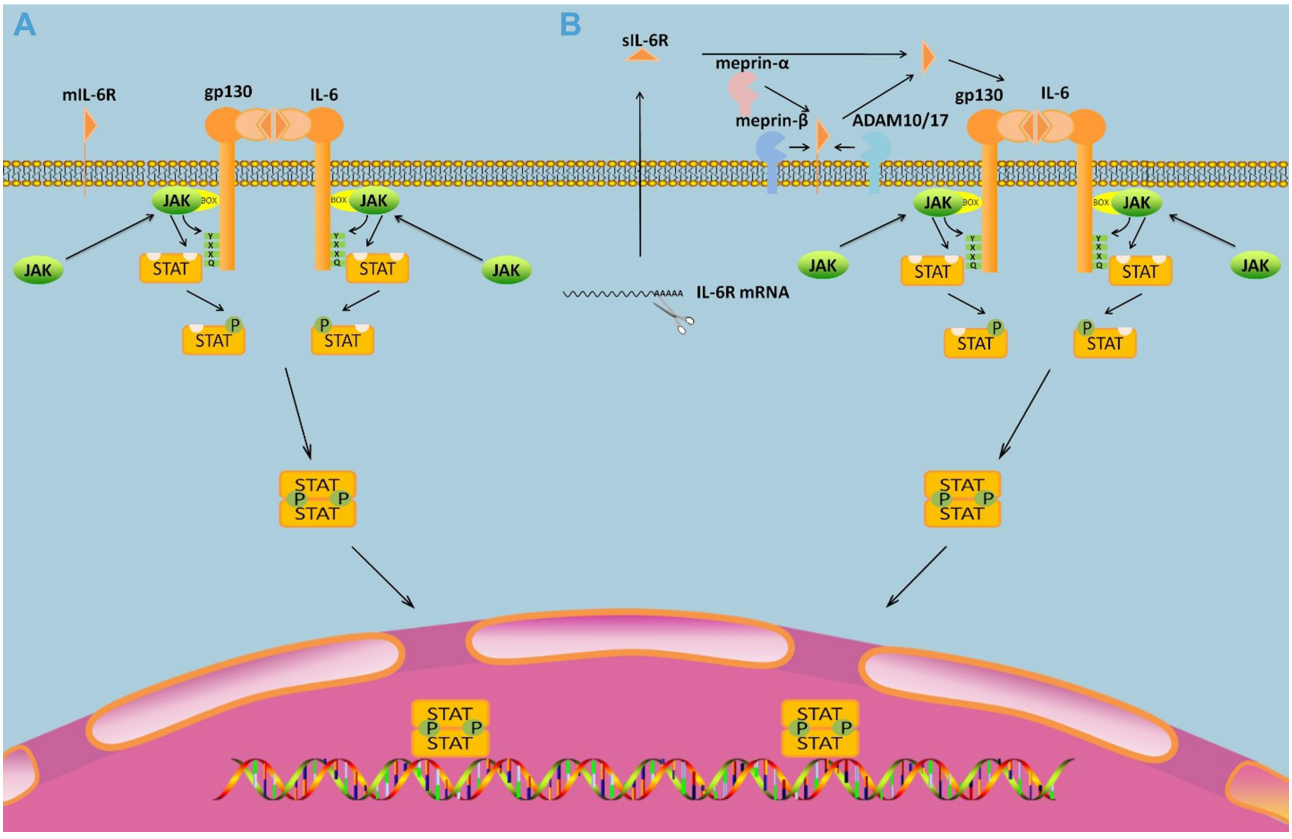

Figure 1 The IL-6/STAT3 signaling pathway. (**A**) In the classical IL-6 signaling pathway, IL-6 binds to mIL-6 on the cell membrane to form a complex, which induces gp130 to form a heterohexamer, which then initiates the JAK/STAT3 pathway. (**B**) In the trans IL-6 signaling pathway, IL-6 complexes with sIL-6R, previously generated by variable splicing of the IL-6 mRNA or as a result of IL-6R cleavage by metalloproteinase (ADAM) 10/17 or meprin metalloproteinase α/β.[18,19,25] The IL-6/sIL-6R complex then complexes with gp130 via intermolecular disulfide bonds[26]. The Box-1 and −2 domains in the cytoplasmic domain of gp130 bind and activate JAK,[15] which phosphorylates tyrosine residues in the cytoplasmic region of gp130. The phosphorylated pTyr-X-X-Gln motif on gp130 (X = any amino acid) recruits the Src homology 2 (SH2) domain in STAT3.[27,28] An adjacent JAK phosphorylates the conserved Tyr705 in STAT3, which then homodimerizes with another STAT3 via the SH2 domain. This dimer translocates to the nucleus, where it regulates expression of target genes.[29]

The Role of IL-6/STAT3 Signaling in the Immune Microenvironment of CRC

CRC formation is influenced by the intricate interactions between cancerous cells and the tumor microenvironment (TME). The immune components in the TME are called the tumor immune microenvironment (TIME), which can modulate tumour occurrence and development. The TIME is composed of various infiltrating immune cells [e.g. tumor-associated macrophages, T helper type 17 (Th17) cells, cancer-associated fibroblasts], tumor-associated endothelial cells as well as the extracellular matrix and complicated vasculature.[30] Various signaling pathways, such as IL-6/STAT3 pathways, are activated in the TIME and influences the growth and progression of CRC.

During CRC progression from occurrence to development, IL-6 expression is significantly elevated and is involved in multiple processes of tumor development.[8,9] Various cells have been identified as sources of IL-6 in the TIME. For instance, expression of IL-6 has been linked to macrophages, fibroblasts, dendritic cells, lymphocytes and CRC cells.[31,32]

Tumor-associated macrophages (TAMs) are major components of the TIME that are frequently associated with tumor metastasis in CRC. Studies have shown that TAMs promote migration and invasion by CRC cells.[33] Emerging studies have suggested that tumor-derived IL-6 can enhance the phagocytic capacity and migration of macrophages in the TIME via STAT3 phosphorylation, but the exact mechanism requires further study.[32] One study showed that TAM-derived IL-6 activates the JAK2/STAT3/miR-506-3p/FoxQ1 axis to modulate CRC cell migration and invasion.[34] The available evidence suggests that IL-6/STAT3 signaling promotes interaction between macrophages and factors secreted by CRC cells into the TIME.

As a specialized subset of CD4+ cells, Th17 cells and their cytokines are involved in regulation of the immune system and cancer development.[35] In the joint presence of IL-6 and TGF-β, Th17 cells differentiate from naive T cells are involved in intestinal inflammation.[36] Those two and related cytokines also regulate the expansion of Th17 cells in CRC[37]. Down-regulation of IL-6 can reverse the Th17-driven carcinogenic process in murine colon cancer.[38] IL-6 signaling drives Th17 cell differentiation in colitis-associated CRC by phosphorylating and activating STAT3, and Th17 cytokines overexpressed in CRC patients (IL-17A, IL-17F, IL-21, IL-22) can promote tumor angiogenesis and oncogenesis.[30,39]

Cancer-associated fibroblasts (CAFs) secrete factors that influence the TIME and CRC growth.[40] Recently, CAFs have been demonstrated to be an important source of IL-6.[31] IL-6-mediated STAT3 activation in CRC-CAFs promotes colorectal tumor development. STAT3-induced activation of vascular endothelial growth factor (VEGF) and proliferation-associated genes contribute to CRC initiation and growth.[41] CRC cells further augment IL-6 secretion from CAFs, but specific mechanisms still need to be revealed.[42] These studies indicate that CAFs produce abundant amounts of IL-6, and that CRC cells facilitate the process. IL-6/STAT3 signaling drives CAF activation in CRC, enhancing tumor progression.

So far, potential correlations between IL-6/STAT3 signaling and other immune cells in CRC, such as Treg cells, myeloid-derived stromal cells, and B lymphocytes, have not been reported. These are an important topic for future research.

The IL-6/STAT3 Signaling Pathway Promotes CRC Development

In CRC, the continuous activation of STAT3 by IL-6 signaling drives many malignant pathways in tumor cells, including cell cycle progression, proliferation, antiapoptosis, invasion and metastasis, the epithelial-mesenchymal transition (EMT), angiogenesis and drug resistance (Table 1).

Cell Cycle Progression

The IL-6/STAT3 signaling pathway can drive progression through the cell cycle and thereby promote proliferation of CRC cells. Most CRC patients overexpress c-Myc, which up-regulates oncogenic proteins and non-coding RNAs that drive the cell cycle, differentiation, growth and metabolism,[43,44] and higher c-Myc levels correlate with more severe disease and worse prognosis.[45,46] Continuous STAT3 activation by the IL-6/IL-6R complex in CRC activates c-Myc and triggers metabolic disorder and tumor progression.[47] STAT3 appears to up-regulate c-Myc by binding to the E2F site ($_{98}$TTGGCGGGAAA$_{106}$) in the c-Myc P2 promoter.[48]

The IL-6/STAT3 signaling pathway up-regulates cell cycle protein D1 (cyclinD1) in CRC. STAT3 binds to the so-called GAS site in the cyclinD1 promoter.[49] CyclinD1 drives progression from G1 to S phase of the cell cycle,

Table 1 Mechanisms Through Which the IL-6/STAT3 Signaling Pathway Promotes CRC Malignancy

Feature	Target Gene	Mechanism	Refs
Cell cycle	c-Myc	STAT3 binds to the E2F site in the c-Myc P2 promoter to induce c-Myc transcription	[48]
	cyclinD1	STAT3 binds to the GAS site in the cyclinD1 promoter to induce its transcription	[49]
	mtSSB	The IL-6/STAT3 pathway induces mtSSB expression, stimulates telomerase and promotes proliferation	[54]
Anti-apoptosis	Bcl-2, Bcl-xl	The IL-6/STAT3 pathway induces expression of Bcl-2 and Bcl-xl	[55]
	Mcl-1	STAT3 binds to the SIE element in the Mcl-1 gene to induce its expression	[57]
	Survivin	STAT3 binds to the survivin promoter to induce its transcription	[60,61]
Invasion metastasis and EMT	Fra-1	After K685 acetylation and Y705 phosphorylation, STAT3 binds to the Fra-1 promoter and up-regulates its expression	[63]
	miR-34a	The IL-6/STAT3/miR-34a feedback loop promotes EMT-mediated invasion and metastasis	[64,65]
	E-cadherin, vimentin	The IL-6/STAT3 pathway down-regulates E-cadherin and up-regulates vimentin	[66]
	FoxQ1	STAT3 indirectly up-regulates FoxQ1 by suppressing miR-506-3p	[34]
	Integrin β6	The IL-6/STAT3 pathway induces integrin β6 transcription	[42]
	CEA	STAT3 up-regulates HIF-1α, and HIF-1α binds to motif EP-1 of CEA promoter to promote its expression	[69]
Angiogenesis	VEGF	STAT3 binds the VEGF promoter to induce its transcription	[72,73]
Resistance	HIF-1α	Activation of HIF-1α under hypoxia relieves the inhibition of IL-6 by miR-338-5P, while the IL-6/STAT3 pathway maintains the continuous activation of HIF-1α	[78]
	p-STAT3	IL-6 activates p-STAT3, and p-STAT3-containing exosomes mediate 5-fluorouracil resistance through the caspase pathway	[79]

leading to cell proliferation.[50,51] Cyclin D1 expression negatively correlates with overall and disease-free survival.[52] A tea polysaccharide that inhibits IL-6/STAT3 signaling in CT26 mouse colon cancer cells concomitantly down-regulates cyclinD1.[53]

The IL-6/STAT3 signaling pathway promotes CRC cell growth also by up-regulating mitochondrial single-stranded DNA-binding protein (mtSBB). IL-6/STAT3 signaling induces the transcription factor FOXP1 to bind to the region between nt −800 and −700 in the mtSSB gene promoter, turning on the gene. The expressed mtSSB activates the ROS/Akt/mTOR pathway, which up-regulates telomerase reverse transcriptase (TERT), which stabilizes telomeres and thereby helps immortalize CRC cells.[54]

Inhibition of Apoptosis

STAT3 induces the expression of anti-apoptotic genes, which was demonstrated in studies of a mouse model of CRC treated with aspirin. The drug inhibited IL-6 as well as STAT3 phosphorylation, reversing STAT3-induced expression of the anti-apoptosis proteins Bcl-2 and Bcl-xl.[55]

The IL-6/STAT3 signaling pathway also up-regulates the anti-apoptotic protein Mcl-1, which protects CRC cells from apoptosis induced by tumor necrosis factor-associated apoptotic ligand (TRAIL).[56] STAT3 binds to the so-called SIE element in the Mcl-1 gene promoter.[57]

IL-6/STAT3 signaling up-regulates the anti-apoptotic protein survivin,[53] which inhibits apoptosis and promotes proliferation and angiogenesis. Survivin is up-regulated in various tumors,[58] and its expression in CRC correlates positively with vascular infiltration and lymph node metastasis, and negatively with overall survival.[59] STAT3 has been shown to bind the survivin promoter.[60,61]

Invasion, Metastasis and EMT

The IL-6/STAT3 signaling pathway can enhance invasiveness and metastasis in CRC by inducing the expression of related oncogenes such as the gene encoding Fos-related antigen-1 (Fra-1).[62] After STAT3 is activated through acetylation of Lys685 and phosphorylation of Tyr705, it binds to the promoter of the Fra-1 gene approximately 600 bases upstream of the transcription initiation site and up-regulates its expression. The expressed Fra-1, in turn, up-regulates EMT-inducing transcription factors and matrix metalloproteinases (MMPs)-2 and −9.[63]

STAT3 in CRC down-regulates the microRNA-34a (miR-34a) by binding to its first intron. This miRNA normally inhibits the EMT and cancer development by down-regulating Snail 1. Thus, STAT3-mediated down-regulation of miR-34a up-regulates Snail 1. At the same time, it up-regulates IL-6R, because this mRNA is normally inhibited by miR-34a. The resulting up-regulation of IL-6R further enhances IL-6/STAT3 signaling.[64,65] Third, the IL-6/STAT3 signaling pathway down-regulates E-cadherin and up-regulates vimentin and the transcription factor Twist.[66] The net result of all these processes is promotion of the EMT and of CRC invasiveness and metastasis.

STAT3 can regulate FoxQ1 through miR-506-3p. As a transcription factor regulating the EMT, FoxQ1 promotes the EMT of CRC cells by inducing mesenchymal gene expression. Studies have shown that FoxQ1 is a direct target of miR-506-3p, and the latter can down-regulate FoxQ1 by directly binding its 3′UTR. STAT3, in contrast, inhibits miR-506-3p through its STAT3 binding site. In this way, IL-6 regulates the STAT3/miR-506-3p/FoxQ1 axis to induce the EMT and enhance CRC migration and invasion.[34]

Integrin β6 participates in IL-6-induced EMT and tumor cell invasion in CRC. IL-6-mediated activation of STAT3 can rapidly induce integrin β6 transcription, and the up-regulated integrin β6 inhibits E-cadherin and enhances vimentin expression to advance the EMT.[42] Further investigations are needed to uncover how STAT3 induces integrin β6 expression.

STAT3 can up-regulate hypoxia-inducing factor-1α (HIF-1α),[67,68] which binds to the positive regulatory element EP-1 (−153 to −148 bp) in the gene encoding carcinoembryonic antigen (CEA), inducing its expression.[69] CEA helps drive migration, invasion and metastasis of CRC cells and is an independent prognostic factor.[70,71]

Tumor Angiogenesis

STAT3 binds to the promoter of the gene encoding vascular endothelial growth factor (VEGF), inducing its expression.[72,73] VEGF stimulates the formation of tumor blood vessels, which provide nutrition and oxygen to sustain tumor growth and allow metastasis. Like levels of IL-6, levels of VEGF are elevated in CRC and correlate with disease progression.[74,75]

VEGF can bind to several receptors (VEGFRs), whose expression varies across tissue types. Which VEGFRs mediate the angiogenic effects of IL-6/STAT3 signaling in CRC remains to be established. A likely candidate is VEGFR2, which is up-regulated in intestinal epithelial cells by IL-6 and which mediates the angiogenic effects of VEGF in colitis-associated cancer.[76]

Tumor Resistance to Chemotherapy

Levels of STAT3 phosphorylated on Tyr705 positively correlate with resistance of CRC cells to chemoradiotherapy involving 5-fluorouracil, and inhibiting STAT3 renders CRC cells more sensitive to chemoradiotherapy.[77] By up-regulating HIF-1α (see section 2.3), STAT3 down-regulates the downstream HIF-1α target miR-338-5P. This miRNA normally down-regulates IL-6, so the activation of STAT3 up-regulates IL-6, leading to a positive feedback loop that confers resistance to the drugs oxaliplatin and 5-fluorouracil, but details of the drug resistance mechanism are unclear.[78] The caspase pathway may mediate the ability of exosomes to transfer STAT3 phosphorylated on Tyr705 and thereby promote resistance to 5-fluorouracil.[79]

High serum levels of IL-6 may reduce the therapeutic efficacy of the anti-VEGF antibody bevacizumab in metastatic CRC,[80] and whether and how this involves STAT3 activity remains to be elucidated.

Clinical Investigations of the IL-6/STAT3 Signaling Pathway in CRC Therapy

Relevant literature has established that downstream target genes mediated by aberrant activation of the IL-6/STAT3

pathway are involved in the development and progression of CRC, and thus targeting the IL-6/STAT3 pathway is highly likely to be a viable and effective approach for the treatment of CRC. Currently, clinical trials are underway for a number of drugs targeting the CRC IL-6/STAT3 pathway, such as IL-6 inhibitors (siltuximab), JAK inhibitors (itacitinib), and STAT3 inhibitors (OPB-31,121, AZD9150, and TTI-101) (Table 2).

Siltuximab, a monoclonal antibody against IL-6, is currently the only drug approved by the US Food and Drug Administration for multicentric Castleman disease (MCD).[81] Siltuximab monotherapy, however, does not show efficacy against advanced solid tumors, including CRC. In that CRC trial, the Phase II primary efficacy endpoint was complete response, partial response, or stable disease > 6 weeks, and only 5 of the 84 patients achieved stable disease > 6 weeks. Although adverse events occurred in 98% of treated patients, they were driven primarily by underlying metastatic disease. The majority of drug-related adverse events were low-grade: 29 patients (35%) had grade 1–2 adverse events (fatigue, nausea, constipation, etc.), and 10% (8) had grade > 3 adverse events (neutropenia, leukopenia, lymphocytopenia). These results suggest that IL-6 inhibition alone offers limited clinical benefit to advanced CRC patients. Other parallel pathways, including the IL-6/STAT3 pathway, may similarly regulate the development of CRC, and therefore the development of combination therapies may provide more benefit for advanced CRC.[82]

Regorafenib is a multi-targeted kinase inhibitor that improves OS in patients with metastatic CRC and has been approved for the treatment of metastatic CRC (mCRC).[83] Incyte Corporation performed a clinical trial to test the combination of ruxolitinib, a selective inhibitor of JAK1/JAK2, with regorafenib for the treatment of refractory mCRC.[84] Although the combination did not lead to more adverse effects, it did not improve efficacy over regorafenib alone. The 396 patients included in the trial were randomized into two subgroups. In subgroup 1, the ruxolitinib group (n=87) showed median overall survival of 4.6 (95% CI, 3.5–5.4) months and median progression-free survival of 2.2 (95% CI, 1.9–3.0) months, while the corresponding survival times in the placebo group (n=88) were 5.3 (95% CI, 4.3–6.0) and 2.1 (95% CI, 1.8–2.7) months. In subgroup 2, the ruxolitinib group (n=110) showed corresponding survival times of 11.4 (95% CI, 9.0–13.2) and 3.5 (95% CI, 3.0–3.8) months, while the placebo group (n=111) showed times of 10.9 (95% CI, 7.2- not estimated) and 2.0 (95% CI, 1.9–3.1) months. The differences between overall and progression-free survival were not significant in either subgroup. A clinical trial of ruxolitinib in combination with trametinib for RAS-mutant CRC is currently underway (NCT04303403) and was expected to conclude in June 2020, with no results yet published.

Table 2 Clinical Trials Targeting the CRC IL-6/STAT3 Pathway

Type	Inhibitor	Combined Drugs	Time	Study Phase	NCT Identifier	Trial Results	Refs
IL-6 inhibitors	Siltuximab	–	3/2009-4/2011	I/II	NCT00841191	No clinical activity observed but well tolerated as monotherapy	[82]
JAK inhibitors	Ruxolitinib	Regorafenib	3/2014-12/2016	II	NCT02119676	Trial discontinued, combination with regorafenib did not improve OS/PFS	[84]
	Ruxolitinib	Trametinib	7/2018-6/2020	I	NCT04303403	Ongoing	–
	Itacitinib	Pembrolizumab	1/2016-9/2020	I	NCT02646748	Ongoing	–
STAT3 inhibitors	OPB-31,121	–	4/2008-6/2009	I	NCT00657176	Safe and well tolerated; maximum tolerable amount: 800 mg/d	[87]
	AZD9150	Durvalumab	3/2017-3/2021	II	NCT02983578	Ongoing	–
	TTI-101	–	11/2017-7/2020	I	NCT03195699	Ongoing	–

Itacitinib, a novel oral JAK1 selective inhibitor, exerts anti-inflammatory effects by inhibiting IL-6-driven phosphorylation STAT3.[85] A Phase I clinical trial of itacitinib in combination with pembrolizumab in patients with CRC has been conducted (NCT02646748) and was expected to end on September 31, 2020, but no results have been released yet.

The development of STAT3 inhibitors has been one of the main focuses of medical researchers. OPB-31,121 is a novel STAT3 inhibitor with high affinity for the SH2 domain of STAT3, and it has demonstrated significant anticancer activity in preclinical studies.[86] The Otsuka Pharmaceutical-led Phase I study showed that OPB-31,121 is safe and well tolerated, with good antitumor activity in patients with advanced CRC. Most drug-related adverse events are grade 1–2 and a maximum tolerated dose of 800 mg/day has been established.[87]

AZD9150, a STAT3 antisense oligonucleotide, directly inhibits STAT3 by promoting the destruction of STAT3 mRNA or inhibiting its translation, and it is the only STAT3 antisense molecule to have entered clinical trials.[88] The MD Anderson Cancer Center launched a Phase II clinical trial of AZD9150 in combination with durvalumab, an anti-PDL-1 antibody, in patients with CRC (NCT02983578), and the trial is expected to end in March 2021. TTI-101, an oral inhibitor of STAT3 developed by Tvardi Therapeutics, has been shown in preclinical studies to inhibit the growth of a variety of solid tumors in mice, including liver, breast, lung, and head and neck cancers. A Phase I trial of TTI-101 for the treatment of advanced solid tumors, including CRC, has been carried out (NCT03195699). The novel STAT3 inhibitor, Bruceantinol (BOL), strongly inhibits STAT3 DNA-binding ability and thus blocks IL-6-induced STAT3 activation in CRC. BOL showed potent anticancer activity in human CRC models in vivo and in vitro, but it has yet to be tested in clinical trials.[89] To date, no inhibitors targeting the IL-6/STAT3 pathway have been approved for CRC treatment, and therefore drugs targeting the CRC IL-6/STAT3 pathway need to be further developed.

Conclusion

In recent years, the high incidence and mortality rates of CRC have led to an increasing tumor burden. Investigating the mechanisms and treatments of CRC has become a major concern for researchers. As one of the key pathways in the development of CRC, the IL-6/SAT3 pathway not only directly regulates tumor immune cells and thus suppresses tumor immunity, but it also up-regulates the expression of numerous oncogenic proteins to help drive CRC. Thus, targeting components of the IL-6/STAT3 pathway can inhibit tumor cell progression and relieve immunosuppression in the TIME. Novel inhibitors of the IL-6/STAT3 pathway are being developed, and early phase clinical trials are also ongoing. However, many of the complex processes affected by IL-6/STAT3 signaling remain to be clarified, and such research may reveal new insights into CRC and how to combat it.

Abbreviations

IL-6, interleukin-6; CRC, colorectal cancer; STAT3, signal transducers and activators of transduction-3; IL-6R, IL-6 receptor; gp130, glycoprotein −130; mIL-6R, membrane-bound IL-6R; JAK, Janus kinase; sIL-6R, soluble IL-6R; TIME, tumor immune microenvironment; EMT, epithelial-mesenchymal transition; cyclinD1, cell cycle protein D1; mtSBB, mitochondrial single-strand DNA-binding protein; TERT, telomerase reverse transcriptase; TRAIL, tumor necrosis factor-associated apoptotic ligand; Fra-1, Fos-related antigen-1; MMPs, matrix metalloproteinases; miR-34a, microRNA-34a; HIF-1α, hypoxia-inducing factor-1α; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

Author Contributions

All authors made a significant contribution to the work reported. YL, RL and ZQH drafted and revised the manuscript. YL, RL, ZQH, ZYL and XG guided the writing of the manuscript, edited it and prepared it for submission. YL, JZY, RL and XMS critically revised the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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