

The role of STAT3 in the colorectal cancer therapy

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ABSTRACT

Colorectal cancer is a type of a malignant tumor in the digestive system and its incidence rate in the United States and the European Union increases by an average of 4.2% to 4.6% annually. Colorectal cancer is a common tumor affecting rather elderly than younger individuals. An increasing number of studies prove that deregulation of the signaling pathway and abnormal expression and activation of genes can be the main reason for the development of colorectal cancer. Signal transducer and activator of transcription (STAT3) is a transcription factor of signal transduction and transcriptional activation of target genes and plays important roles in proliferation, differentiation apoptosis and other physiological processes. Several data confirm that abnormal activation of STAT3 is involved in the development of tumors. Identifying compounds that inhibit STAT3 is a promising strategy for cancer chemoprevention and treatment of colorectal cancer. In this review, the roles of STAT3 in pathogenesis and treatment of colorectal cancer are discussed.

Introduction

Colorectal cancer (CRC) is the second most common cancer diagnosed in women and the third most common in men. The prevalence of CRC increases at an average rate of 2.5% annually. Moreover, the incidence of CRC worldwide is predicted to increase to 2.5 million new cases in 2035 [1]. Epidemiological studies have shown the strong dependence of the disease incidence on gender, males, and increasing age. Additionally, diet, lifestyle, medications, smoking, obesity and a sedentary lifestyle were associated with an increased risk of CRC. Moreover, genetic changes may play a crucial role in CRC pathogenesis [2].

CRC develops through a multistage process characterised by the accumulation of aberrant protein expression, which results in the formation of tumour cells [3]. Recently, increasing attention has been focused on transcription factors contributing to oncogenic signalling pathways such as signal transducer and activator of transcription (STAT3) [4, 5]. Persistent STAT3 activation is described in several neoplasias, including CRC. Blocking STAT3 in cultured CRC cells inhibits cell proliferation and induces apoptosis [6]. Although STAT3 is required for the survival of normal intestinal epithelial cells, long-term interference with STAT3 activation could promote gastrointestinal damage. Hence, STAT3 is a potential therapeutic target for CRC [7, 8].

Structure of STAT3

STAT3 belongs to the STAT family proteins and contains six domains: N-terminal domain (ND), coiled-coil domain (CCD), DNA binding domain (DBD), the linker region, Src homology domain (SH2), and a C-terminal transcriptional activation domain (TAD) (**Figure 1**). The ND domain stabilises the dimerised STAT3, promoting the formation of tetramers of two STAT3 dimers for more stable binding with DNA. The CCD domain mediates STAT3 direct binding to the receptor and promotes STAT3 phosphorylation on the 705-tyrosine site (Y705). The DBD domain initiates transcriptional activation of the target genes, while the SH2 domain plays a critical role in signal transduction. The TAD domain possesses conserved phosphorylation sites at Tyr705 and Ser727, and SH2 can recognise phosphotyrosine residues, thus are closely related to STAT3 activation [6, 9].

STAT3 possess four isoforms: STAT3 α , STAT3 β , STAT3 γ , and STAT3 δ , with STAT3 α being the most common and consists of ND, CCD, DBD, Linker, SH2 and TAD domains. STAT3 α is associated with the proliferation and transformation of cells [9].

Activation of STAT3

The classical STAT3 signalling pathway is activated through the binding of interleukins, cytokines or growth factors to their corresponding cell surface receptors (**Table 1**).

In normal conditions, STAT3 is situated in the cytosol, dimerising and translocating to the nucleus after being activated via phosphorylation of the tyrosine705 residue. In the nucleus, it controls the transcription of several apoptotic and cell cycle regulatory proteins [10]. STAT3 can be activated through Janus kinase (JAK), Ras/mitogen-activated protein kinase (MAPK) and non-receptor tyrosine kinase signalling pathways [11]. The JAK phosphorylates tyrosine residues on STAT3, especially at the Y705 site, leading to activation and dimerisation of STAT3, subsequent transport to the nucleus and binding to the GAS sequence for the initiation of the transcription of target genes [12]. Ras-MAPK phosphorylates the serine residue in STAT3 on S727, which leads to STAT3 dimerisation and its translocation to the nucleus, it also binds to DNA sequences in the promoters of genes [13]. The non-receptor tyrosine kinases such as activated Src kinase and MAPK family members (p36, ERK, JNK), PKC δ ,

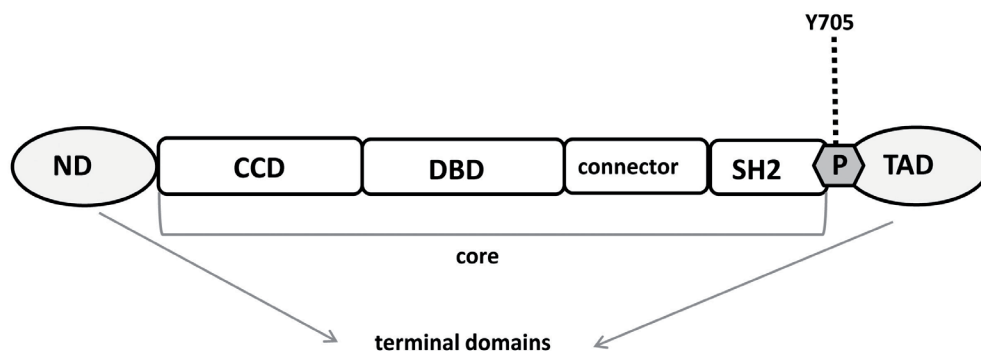


Figure 1. Structure of STAT3 protein. Functional domain: N-terminal domain (ND); coiled-coil domain (CCD); DNA binding domain (DBD); Src homology domain (SH2); C-terminal transcriptional activation domain (TAD). Post-translational modification occurs at the 705-tyrosine site (Y705)

Table 1. The inducers of STAT3

Interleukins	Cytokines	Growth factors
IL-6, IL-7, IL-10, IL-20	<ul style="list-style-type: none"> - leukaemia inhibitory factor (LIF), - ciliary neurotrophic factor (CNTF), - interferon γ (IFN- γ), - tumour necrosis factor (TNF-α), - monocyte-1 chemotactic protein (MCP-1), - macrophage inflammatory protein-1α (MIP-1α), - stem cell factor (SCF), - oncostatin M (OSM) 	<ul style="list-style-type: none"> - epidermal growth factor receptor (EGFR), - hepatocyte growth factor receptor (HGFR), - fibroblast growth factor receptor (FGFR), - platelet-derived growth factor receptor (PDGFR), - insulin-like growth factor receptor (IGFR), - vascular endothelial growth factor receptor (VEGFR)

mTOR phosphorylate STAT3 on S727 in the C-terminal domain [14].

Additionally, STAT3 is also acetylated on a single lysine residue located at position 685 by histone acetyltransferase p300. This acetylation regulates both transcriptional activity and homodimer stability. Other factors, such as UV radiation or sunlight, carcinogen, stress, smoke and infection are also known to play a significant role in STAT3 activation. STAT3 is negatively regulated by specific factors, including the suppressor of cytokine signalling (SOCS) and the protein inhibitor of activated STAT (PIAS) [15, 16].

Role of STAT3 in the pathogenesis of colorectal cancer

CRC cells and normal colon cells differ in their hallmarks. In normal cells, the activation of STAT3 is rapid and transient, whereas, in CRC cells, abnormal activation of STAT3 accelerates CRC cell proliferation, blocks their differentiation and inhibits apoptosis which leads to the occurrence and development of CRC. Several studies showed that STAT3 activation contributes to cellular proliferation and survival in the case of CRC. Persistent activation of STAT3 induces upregulated expression of CyclinD1, c-Myc and survivin and accelerates cell cycle progression in colon cancers [17–19]. The STAT3 signalling pathway suppresses apoptosis in CRC through upregulation of the expression of anti-apoptotic proteins such as Bcl-2 (B-cell lymphoma-2), Bcl-xl (B-cell lymphoma-2-like 1), and Mcl1 (myeloid cell leukaemia sequence 1) to prevent apoptosis of CRC cells [20, 21]. Inversely, inhibition of STAT3 decreases cell proliferation and promotes apoptosis in CRC [22]. Additionally, recent studies have demonstrated that increased phosphorylated STAT3 (phospho-STAT3) expression was detected in patients with colorectal carcinoma. However, the prognostic value and clinicopathological parameters of phospho-STAT3 expression in CRC remain undefined [2].

Tang et al. [23] reported that the positive expression of JAK1 and STAT3 proteins in patients with colon cancer was not associated with sex, age, tumour differentiation degree and neurovascular invasion, but was dependent on the clinical stage of cancer, tumour infiltration depth and lymph node metastasis. The survival time

of CRC patients with positively-expressed JAK1 and STAT3 proteins was significantly shorter compared to patients with negatively-expressed JAK1 and STAT3. Thus, the JAK/STAT signal may be used as a novel tumour marker and prognostic factor for the diagnosis, assessment and prognosis of colon cancer [23].

STAT3 promotes cell invasion by activating the transcription of matrix metalloproteinases, mainly MMP-2 and MMP-9. In the case of CRC, a correlation between increased MMP-2 and MMP-9 expression and a poor outcome has been proven [24]. Several studies refer to the utility of serum MMPs as markers for CRC invasion. Dragutinović et al. [25] confirmed the higher levels of MMP-2 and MMP-9 proteins in the sera of patients with CRC compared to controls with no CRC. Additionally, Kryczka et al. [26] described the upregulation of MMP-2 expression in invasive CRC. The opposite effect was observed in the case of MMP-12, which is also called metalloelastase, which does not belong to any of the MMP sub-families. According to the studies in animal and human models, increased MMP-12 expression is associated with both reduced tumour growth and increased overall survival [27, 28].

STAT3 activation can also contribute to angiogenesis through its effects on vascular endothelial growth factor (VEGF) [29]. However, there is still controversy in terms of the relationship between serum VEGF and VEGF receptor (VEGF-R) tumour expression in CRC [30]. Evidence from preclinical and clinical studies indicates that VEGF is the predominant angiogenic factor in human CRC and is associated with the formation of metastases and poor prognosis [31].

The JAK/STAT/SOCS-signalling pathway plays a critical role in immune response and regulation of inflammation. Additionally, components of the pathway, such as STAT3, have been shown to promote cell growth and survival through impairment of the expression of genes involved in apoptosis, cell cycle regulation and angiogenesis [32]. SOCS3 is an important signal inhibition factor in the JAK2/STAT3 pathway. The reduction or deletion of SOCS3 expression causes sustained activation of STAT3 in many malignant tumours [33]. Other studies indicate that phospho-STAT3 in CRC is higher than in surrounding tissues, whereas the expression of SOCS3 is lower or absent in CRC tissues. The activation of this signalling

pathway promotes the transformation of colitis to CRC. SOCS3 protein inhibited the activation of the JAK/STAT3 pathway by negative feedback regulation of tyrosine phosphorylation of STAT3, which inhibits the growth of tumour cells. STAT3 activation also promoted hypermethylation of SOCS3 gene promoters in DLD1, HT-29 and SW480 cancer cells [34].

STAT3 as a target in CRC therapy

As STAT3 plays an important role in the development of CRC, it could be used as an essential target in the diagnosis and treatment of CRC. These inhibitors are not implemented in clinical practice but are suggested to be useful. However, clinical

studies are required to assess their usefulness, efficiency and potential anticancer activities.

Table 2 presents the chemical structure of potential inhibitors of STAT3. In this review, we focus on the representatives of different groups of compounds possessing the possible implications of targeting STAT3 in colon cancer. Moreover, the mechanism of STAT3 activation is multifaceted, thus **Figure 2** presents the suggested therapeutic intervention strategy in the STAT3 pathway during CRC therapy.

Nowadays, STAT3 inhibitors can be classified as indirect and direct (Table 2). The indirect strategy can block molecules and induce the STAT3 pathway, indirectly inhibiting the signal transduction functions of STAT3, mostly through inhibiting the function of JAKs, in turn, there are sev-

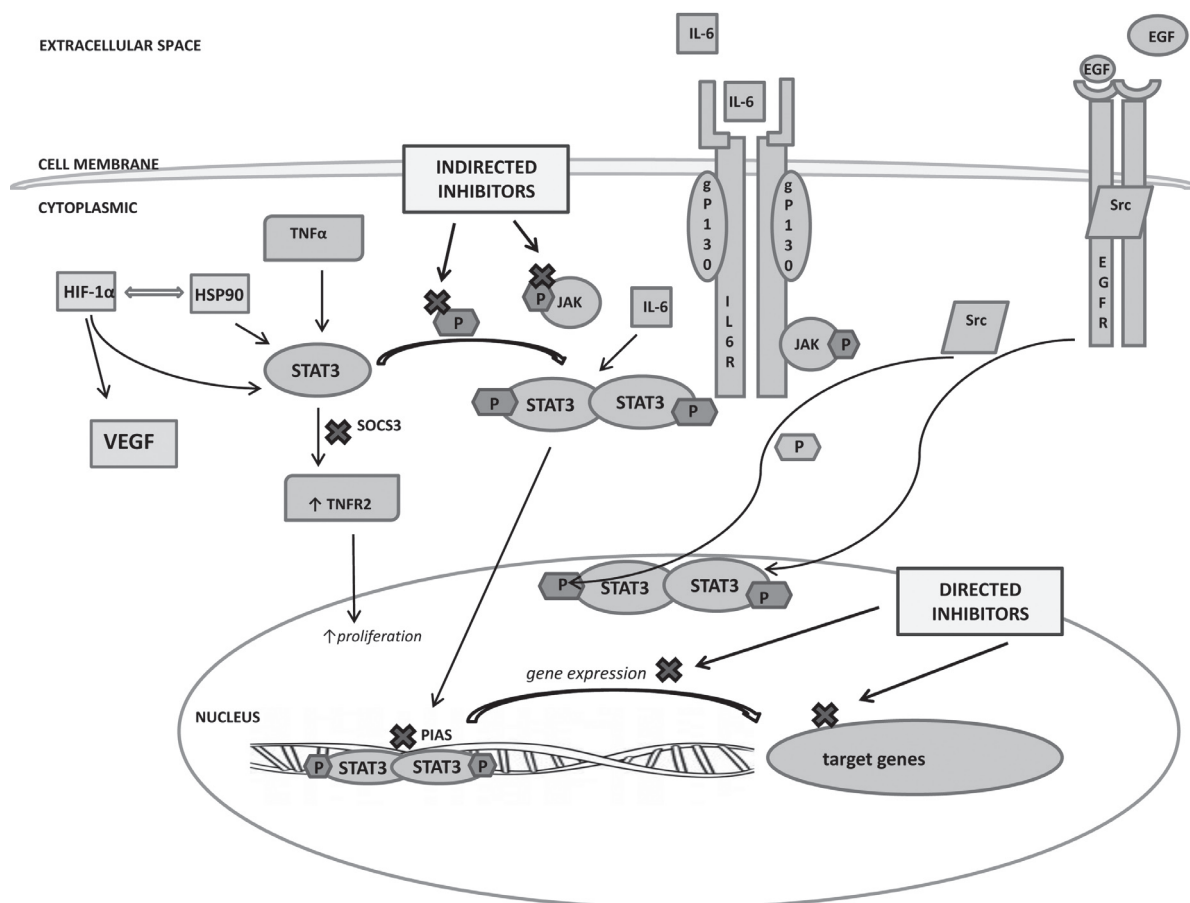


Figure 2. Therapeutic intervention strategy in the STAT3 signalling pathway for CRC therapy. Under physiological conditions, STAT3 is localised in the cytoplasm and nucleus and can be activated by IL-6 and other cytokines, including TNF- α . In response to stimulation of STAT3 by cytokines, JAK1 is usually involved in the dimerisation of STAT3, as well as nuclear transport and binding to DNA. Growth factors, like EGFR, VEGFR, and non-receptor tyrosine kinases (Src) can also stimulate STAT3. Activation of STAT3 is controlled by inhibitors of cytokine signalling (SOCS) and protein inhibitors of active STAT, protein inhibitors of activated STAT (PIAS). Signal transduction is initiated by dimerisation of glycoprotein 130 (gp130) due to the effect of growth factor or interleukin [36]. The activation of STAT3 can also be dependent on the functionality of the hypoxia-inducible factor 1- α (HIF-1 α). Both STAT3 and HIF-1 α are heat shock protein 90 (HSP90) client proteins, which transcribe VEGF [37], EGF, IL-6R and TNF2

Table 2. Inhibitors of STAT3

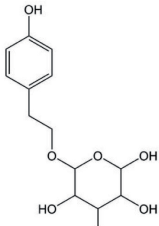
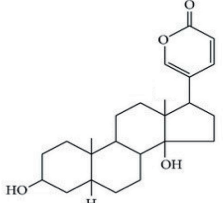
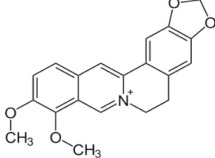
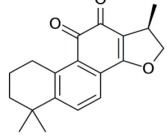
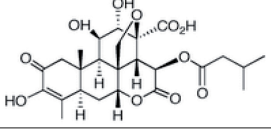
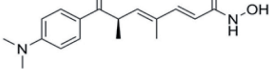
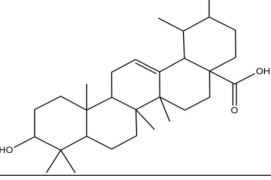
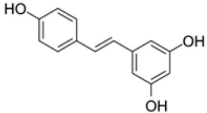
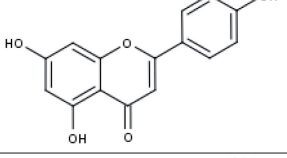
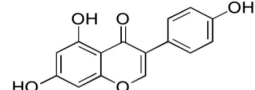
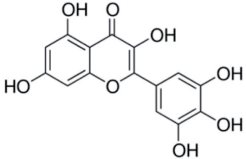
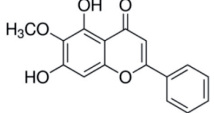
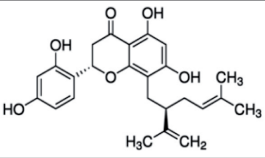
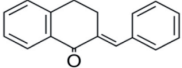
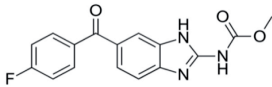
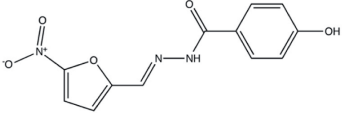
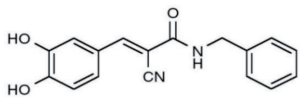
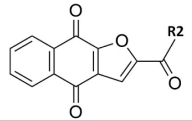
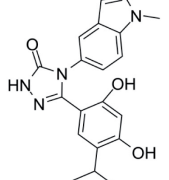
INDIRECT INHIBITORS OF STAT3			
Inhibitors	Synonyms	Chemical structure	
Natural inhibitors	Salidroside	(2R,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[2-(4-hydroxyphenyl)ethoxy]oxane-3,4,5-triol	
	Bufalin	(3β,3β)-3,14-dihydroxybufa-20,22-dienolide	
	Berberin	5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium chloride	
	Cryptotanshinone	(1R)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1H-naphtho[1,2-g][1]benzofuran-10,11-dione	
	Bruceantinol	(1R,2S,3R,6R,8R,13S,14R,15R,16S,17S)-3-[(E)-4-acetyloxy-3,4-dimethylpent-2-enoyl]oxy-10,15,16-trihydroxy-9,13-dimethyl-4,11-dioxo-5,18-dioxapentacyclo[12.5.0.01,6.02,17.08,13]nonadec-9-ene-17-carboxylic acid	
	Trichostatin A	2E,4E,6R)-7-(4-dimethylaminophenyl)-N-hydroxy-4,6-dimethyl-7-oxohepta-2,4-dienamide	
	Ursolic acid	3-beta-3-hydroxy-urs-12-ene-28-oic-acid	
	Resveratrol	3, 5, 4' -trihydroxy-trans-stilbene	
	Apigenin	4' ,5,7-trihydroxyflavone	
	Genistein	5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	

Table 2. Continued

	Myricetin	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone	
	Oroxylin A	5,7-dihydroxy-6-methoxy-2-phenyl-4H-1-benzopyran-4-one	
	Sophoraflavanone G	(2S)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2R)-5-methyl-2-(prop-1-en-2-yl)hex-4-en-1-yl]-2,3-dihydro-4H-chromen-4-one	
Synthetic inhibitors	Benzylidenetetralones	(2E)-2-(phenylmethylidene)-1,2,3,4-tetrahydronaphthalen-1-one	
	Flubendazole	methyl(5-(4-fluorobenzoyl)-1H-benzimidazol-2-yl)carbamate	
	Nifuroxazide	4-hydroxy-N-[(E)-(5-nitro-2-furyl)methyleneamino]benzamide	
Small-molecule inhibitor	AG-490	2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide	
DIRECT INHIBITORS			
	Inhibitors	Synonyms	Chemical structure
Synthetic inhibitors	Napabucasin	2-Acetylnaphtho(2,3-b)furan-4,9-dione	
Small-molecule inhibitors	Ganetespiib	3-(2,4-Dihydroxy-5-isopropylphenyl)-4-(1-methylindol-5-yl)-5-hydroxy-4H-1,2,4-triazole	

eral direct strategies according to different target domains, including the SH2 domain [35–37].

Indirect inhibitors

Natural inhibitors

Salidroside is a glucoside extracted from *Rhodiola rosea* [38], which inhibits the proliferation and cell cycle and reduces migration and invasion of colon cancer SW1116 cells through blocking the phosphorylation of JAK/STAT3 [39]. Moreover, Li

and Chen [2017] suggest that salidroside down-regulates phosphoSTAT3 in HCT116 cells, which is correlated with the induction of autophagy.

Bufalin is a steroid isolated from Chinese toad venom, which inhibits JAK/STAT3 signalling through decreasing the level of phosphoSTAT3 and downregulates the Bcl-2 protein. Bufalin blocks the proliferation of colon adenocarcinoma SW620 cells and induces G2/M cell cycle arrest of these cells [40, 41]. Similar results were reported by Qiu et al. [42], that bufalin reduces the viability of HCT116 cells in a dose- and time-dependent manner.

Berberin is an alkaloid isolated from *Hydrastis canadensis* and can decrease phosphorylation of JAK and STAT3 proteins in CRC cells [43]. Other studies demonstrated that berberin affects the expression of *MMP-2* and *MMP-9*, but the mechanism has not been elucidated [44, 45]. Liu et al. [43] argue that berberin reduces COX-2/PGE2 levels, consequently decreasing JAK2/STAT3 activation, leading to dampened expression of downstream target genes *MMP-2* and *MMP-9*, reducing invasiveness and metastasis in CRC. A similar effect was presented by Hu et al. [46] and Hallajzadeh et al. [47], where the reduction in the JAK2/STAT3 signalling as a consequence of attenuating the COX-2/PGE2 expression by berberin was observed.

Cryptotanshinone is a quinoid diterpene isolated from *Salvia miltiorrhiza* Bunge. It inhibits the activation of STAT3 pathways through inactivating phosphorylation of STAT3 in SW480, HCT116 and LOVO CRC cell lines. Moreover, cryptotanshinone attenuates the expression of *Bcl-2*, *CyclinD1* and *survivin* in HCT116 and SW480 cells. The mechanism of action of cryptotanshinone by direct interaction with STAT3 can also rely on the inhibition of EGFR phosphorylation at higher doses of cryptotanshinone [48].

Bruceantinol is a triterpenoid isolated from *Brucinea javanica*, which reduces the level of phosphorylated STAT3 and downstream target expression of *Mcl-1*, *c-Myc*, and *survivin in vitro*. A reduction of phosphoSTAT3 was observed in mice with CRC xenografts treated with bruceantinol [49].

Trichostatin A is a hydroxamic acid produced by *Streptomyces hygroscopicus* and an inhibitor of class I and II histone deacetylases. The hyperacetylation of histones is associated with SOCS1 and SOCS3 promoters in CRC cells [50]. According to Xiong et al. [50], trichostatin A can increase the level of SOCS1 and SOCS3 expression in SW1116 and HT-29 colon cancer cell lines. Consequently, it negatively modulates the JAK2/STAT3 pathway, subsequently downregulating *Bcl-2* and *survivin* and decreases growth and apoptosis of CRC cells.

Ursolic acid is a pentacyclic triterpenoid, abundant in apples, pears and prunes [51]. Studies conducted by Wang et al. [52] confirmed that ursolic acid selectively inhibits STAT3 phosphorylation at Y705 in CRC cell lines, HT-29, HCT116 and SW480. Moreover, some studies confirmed

the antiapoptotic properties of ursolic acid in HT-29 cells via inhibition of *Bcl-xl*, *Bcl-2* and *Cyclin D1* expression [53, 54].

Resveratrol is a plant polyphenol naturally occurring in grapes, red wine, and peanuts [55]. It can inhibit cell proliferation and promote cell apoptosis via the STAT3 signalling pathway in DLD1 and HCT15 colon cancer cells. Li et al. [56] demonstrated that resveratrol inhibits cell growth in CRC by inhibiting the serine/threonine-protein kinase AKT and its downstream signalling targets. AKT serves as an upstream regulator of STAT3. Additionally, the expression of phosphorylation of STAT3 at the Tyr705 site was suppressed by treatment with resveratrol in a dose-dependent manner [56].

Apigenin is a type of flavone identified in several types of berries and vegetables, which inhibits the nuclear localisation of STAT3 through the reduction of the expression of phosphoSTAT3 (Tyr705) in HCT116 colon cancer cells [57].

Genistein is a major isoflavone in soy and soy-based food products that are regularly consumed in Asian countries [58]. Genistein promotes apoptosis in HT-29 colon cancer cells by modulating caspase-3 and p38 MAPK signalling pathway [59]. Genistein also abolished the activation of STAT3, preventing translocation into the nucleus by downregulating the activity of JNK [60].

Myricetin is a common dietary flavonoid abundantly found in plants. It deregulates the JAK1/STAT3 signalling pathway that controls many processes such as cell growth, differentiation, senescence and apoptosis [61]. Myricetin directly binds with the catalytic domain of the JAK1 protein and inhibits the phosphorylation of STAT3 and JAK1. Moreover, myricetin has been found to increase EGF-induced autophosphorylation of EGFR at Tyr845, Tyr992, Tyr1045, Tyr1068, and Tyr1173, as well as inhibit the autophosphorylation of endogenous EGFR sites. The results indicated that myricetin exerts its chemopreventive effect by directly interacting with JAK1 and STAT3 proteins [62].

Oroxylin A is an O-methylated flavone found in the roots of *Scutellaria baicalensis*. It inhibits colitis-associated carcinogenesis through modulating the IL-6/STAT3 pathway in AOM/DSS mouse model and HCT116 cells. This study confirmed that oroxylin A induces *Bax* and *Bcl-2* binding in colon cancer Caco-2 cells [57].

Sophoraflavanone G is a plant material isolated from *Sophora leachiana*, *S. exigua* or *S. moorcroftiana*, *S. pachycarpa* or *S. flavescens*. Treatment of HCT116 cells with this small-molecule significantly inhibited tyrosine phosphorylation of STAT3, as confirmed by western blot analysis, where the level of phosphoSTAT3 protein was decreased in comparison to the control [63].

The ethanol extract of *Prunella vulgaris* L., termed **Spica Prunellae**, is a well-known traditional Chinese formulation, which can inhibit the STAT3 phosphorylation of Y705, increase the Bax/Bcl-2 ratio, reduce Cyclin D1 and subsequently inhibit CRC cell proliferation and promote apoptosis [64–66].

Synthetic inhibitors

Benzylidenetetralones are synthetic, cyclic chalcone analogues [67]. Natural and synthetic chalcones have also shown anticancer activity caused by their inhibitory potential against targets such as the JAK/STAT signalling pathway [68]. Benzylidenetetralones decrease the expression of Bcl-xl, consequently inducing cell cycle arrest and apoptosis in the HCT116 CRC cell line [67].

Flubendazole is a well-known anthelmintic drug, which blocks IL6-induced nuclear translocation of STAT3, leading to the inhibition of the transcription of STAT3 target genes, such as *MCL1* and *VEGF*. Flubendazole inhibition of STAT3 phosphorylation is partly dependent on the upstream kinases JAK2 and JAK3. Also, flubendazole reduces the expression of *P-mTOR*, *P62*, *Bcl-2*, and upregulates *Beclin1* and *LC3-I/II*, major autophagy-related genes, thereby inducing potent cell apoptosis in CRC cells. Furthermore, flubendazole displays a synergistic effect with the chemotherapeutic agent 5-fluorouracil in the treatment of CRC [69].

Nifuroxazide is a nifuran antibiotic, which downregulates the phosphorylation of tyrosine residues (Y705) on STAT3 as well as impairing the expression of MMP-2 and MMP-9 in HCT116 and HT-29 human CRC cell lines [70].

Small-molecule inhibitors

AG-490 is a pharmacological inhibitor of kinase JAK2, which decreases VEGF secretion in SW1116 and HT-29 cells, functioning like the JAK/STAT3 pathway in angiogenesis [71]. Additionally, the downregulation of phosphoJAK1, phosphoJAK2 and

phosphoSTAT3 was observed after treatment with AG490. This leads to a decline in Bcl-2 and survivin expression [71,72]. Furthermore, STAT3 inhibition by AG-490 treatment has been found to increase cell sensitivity to chemotherapeutic agents [73].

Direct inhibitors

Natural inhibitors

Curcumin is a natural polyphenol, the yellow pigment in *Curcuma longa* L. It reduces binding of STAT3 to DNA in CRC cells [74], thereby abrogating its phosphorylation and nuclear translocation, as well as the subsequent expression of target genes. This approach has mainly focused on targeting the SH2 domain, an important domain by which STAT3 maintains its biological functions [75].

Synthetic inhibitors

Napabucasin was the first compound to undergo a series of clinical trials (NCT03522649, NCT02753127, NCT01776307, NCT02851004, NCT01830621, NCT02641873) to determine its efficacy and safety in patients with metastatic CRC [76]. A napabucasin derivative with a 2-(piperidin-1-yl)ethylamino-group substituted at the R2 position significantly inhibited tumour growth in a mouse model. Molecular docking suggested that this compound bound to the SH2 domain of STAT3 in CT26 colon carcinoma mouse cell line [77].

Small-molecule inhibitors

Ganetespib is a small-molecule inhibitor of heat shock protein 90 (HSP90) activity. Ganji et al. [78] demonstrated that ganetespib inhibits STAT3 and disrupts angiogenesis of CRC cell lines HCT116 and HT-29, also downregulating the expression of VEGF transcription factors, hypoxia-inducible factor 1- α (HIF-1 α) and STAT3. Both STAT3 and HIF-1 α are dependent on HSP90 and transcribe VEGF, therefore, HSP90 inhibition by ganetespib also affects the expression of HIF1 α and STAT3, leading to decreased transcription of pro-angiogenic cytokines such as VEGF in CRC [79].

Conclusions

STAT3 is an important signal transducer and activator of transcription which is widely involved

in numerous cellular physiological processes, such as proliferation, differentiation and apoptosis. Available data indicate that STAT3 is involved in the pathogenesis of colorectal cancer, hence, it may be useful in colorectal cancer diagnosis, treatment and prognosis. However, further studies are needed to determine if STAT3 is of use in cancer diagnosis and prognosis of disease development, as well as the possible beneficial effects of STAT3 targeted therapy. There is an increasing evidence STAT3 inhibitors, such as phytochemicals or synthetic compounds, may be potential therapeutics for colorectal cancer, so further research regarding the inhibitory properties of natural or synthetic compounds is justified.

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Conflict of interest statement

The authors declare no conflict of interest.

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