STAT3 and the STAT3-regulated inhibitor of apoptosis protein survivin as potential therapeutic targets in colorectal cancer (Review)

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Received February 14, 2024; Accepted May 24, 2024

DOI: 10.3892/br.2024.1863

Abstract. Colorectal cancer (CRC) is one of the leading types of cancer worldwide. CRC development has been associated with the constitutive activation of signal transducer and activator of transcription 3 (STAT3). STAT3 is a master regulator of inflammation during cancer-associated colitis, and becomes upregulated in CRC. In CRC, STAT3 is activated by IL-6, among other pro-inflammatory cytokines, inducing the expression of target genes that stimulate proliferation, angiogenesis and the inhibition of apoptosis. One of the main STAT3-regulated inhibitors of apoptosis is survivin, which is a bifunctional protein that regulates apoptosis and participates in cell mitosis. Survivin expression is normally limited to foetal tissue; however, survivin is also upregulated in tumours. *In silico* and experimental analyses have shown that the STAT3 interactome is relevant during CRC progression, and the constitutive STAT3-survivin axis participates in development of the tumour microenvironment and response to therapy. The presence of a STAT3-survivin axis has been documented in CRC cohorts, and the expression of these molecules is associated with poor prognosis and a higher mortality rate in patients with CRC. Thus, STAT3, survivin, and the upstream activators IL-6 and IL-6 receptor, are considered therapeutic targets for CRC. Efforts to develop drugs targeting the STAT3-survivin axis include the evaluation of phytochemical compounds, small molecules and monoclonal antibodies. In the present review, the expression, function and participation of the STAT3-survivin axis in the progression of CRC were investigated. In addition, an update on the pre-clinical and clinical trials evaluating potential treatments targeting the STAT3-survivin axis is presented.

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Key words: colorectal cancer, signal transducer and activator of transcription 3, inhibitor of apoptosis protein, survivin, IL-6

Contents

1. Introduction

Colorectal cancer (CRC) accounts for ~10% of all new cases of cancer detected worldwide (1). CRC treatment is commonly based on a combination of chemotherapy, radiotherapy and, more recently, immunotherapy (2). However, the need for new drugs remains constant given the primary chemoresistance associated with CRC, which results in poor overall survival and prognosis, even in patients treated with combined therapy (3).

The aetiology of CRC is closely associated with chronic inflammation of the colonic epithelium, which can originate from genetic mutations or extrinsic factors, leading to the constant activation of different signalling pathways associated with the immune response. During the inflammatory process, the production of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-18 and tumour necrosis factor-α (TNF-α), induces the activation of signalling pathways associated with proliferation, vascularisation and inhibition of apoptosis through signal transducer and activator of transcription 3 (STAT3), which is a master regulator of pro-inflammatory pathways (4).

STAT3 has been reported to be upregulated in a high proportion of tumour types (5); thus, STAT3 is one of the most studied signal intermediaries in tumour development. STAT3 regulates the transcription of various genes implicated in the inhibition of apoptosis; among them, *BIRC5*, a member of the inhibitor of apoptosis protein (IAP) family that encodes

the protein survivin, is of particular interest because it has a dual role as a regulator of apoptosis and cell mitosis (6). Survivin is a subunit of the chromosomal passenger complex (CPC), along with the mitotic kinase Aurora-B, Borealin and inner centromere protein. The CPC serves an essential role for adequate segregation of chromosomes and cytokinesis during cell mitosis (6). In addition, survivin controls apoptosis mediated by caspase-3 and -7 (7). Although survivin expression is restricted to foetal tissues in healthy individuals, it has been found to be upregulated in various types of cancer, including CRC (6).

Because of the relevant participation of STAT3 and survivin in the control of molecular events promoting and maintaining the oncogenic phenotype in CRC, they have emerged as promising potential targets, given their selective expression in cancerous tissues. Additionally, since survivin is transcriptionally regulated by STAT3, and studies have demonstrated the relevance of their interaction for the acquisition of chemoresistance and the evasion of apoptosis, they may be considered targets for future therapeutic approaches (6,8).

In the present review, the function of the STAT3-survivin axis in CRC is discussed, with particular emphasis on the relationship between both molecules and CRC progression. This review also summarizes recent proposals for the clinical applications of STAT3 and survivin inhibitors.

2. STAT3-survivin axis

STAT3 is a member of the STAT family of transcription factors, which includes seven proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. These proteins transduce signals downstream of >50 ILs, hormones and growth factors (8,9). After being phosphorylated by Janus kinases, activated STAT3 [phosphorylated-STAT3 (pSTAT3)] molecules translocate into the cell nucleus to regulate the transcription of genes involved in the cell cycle, differentiation, proliferation, inflammation, immune response and apoptosis (10,11).

The structure of STAT3 includes a C-terminal transactivation domain, a coiled-coil domain, a DNA-binding domain, a linker, a Src homology 2 (SH2) domain and an N-terminal domain which mediates binding to gene promoters and enhancers (12,13). STAT3 induces the transcription of genes whose products are regulators of cell survival, such as the anti-apoptotic protein survivin. Survivin is a member of the IAP family; it contains a baculoviral IAP repeat domain, which mediates protein-protein interactions (PPIs) (14-16). Survivin is mainly expressed in foetal tissue, but it has also been found to be upregulated in multiple tumours (17).

Survivin is a small protein (142 amino acids; 16.5 kDa) encoded by the *BIRC5* gene. STAT3 is the main transcription factor activating *BIRC5* expression; however, hypoxia-inducible factor 1 and nuclear factor kB are also able to induce *BIRC5* transcription (18). Survivin is a bifunctional protein that participates in both the inhibition of apoptosis and the regulation of cell division, serving an important role during chromosome segregation and cytokinesis (19,20). Survivin prevents cells from apoptotic death by decreasing the activity of effector caspases (21); by interacting with other apoptosis regulators, such as XIAP, hepatitis B virus X-interacting protein (22), cIAP1 and cIAP2 (23); and by interfering with inhibitors of IAP activity (24). Notably, survivin has also been reported to participate in angiogenesis (25), autophagy (26) and stem cell maintenance (27).

3. STAT3-survivin axis in CRC

Given that STAT3 regulates the expression of an extensive number of genes associated with carcinogenic processes, the activity of this transcription factor has been studied in several tumour types. Immunohistochemical evaluation of tumour samples and the analysis of transcriptomic data from publicly available datasets demonstrated that STAT3 was upregulated in ~70% of cancer types, including CRC (28). The study of pSTAT3 expression in CRC and colorectal adenoma tissue samples by immunohistochemistry demonstrated that the level of pSTAT3 in CRC was significantly higher than that in adenoma, and it was associated with tumour progression (29). Furthermore, evaluation of pSTAT3 levels by immunohistochemistry in a prospective cohort of 724 patients with CRC demonstrated that pSTAT3 upregulation was negatively associated with a good prognosis in patients with CRC (30).

Using systems biology approaches, Erdogan *et al* (28) analysed the global STAT interactome. The authors collected data using the Integrated Interactions Database, which gathers PPI data from various databases, and allows segregation of these interactions into disease and tissue contexts. Specific STAT interactions in the context of CRC were confirmed when particular PPIs were reported in two or more independent publications, databases or experimental assays. The results suggested that STAT3 may be one of the most relevant molecules during CRC progression (28). Notably, STAT3 has been found to contribute to CRC malignancy by establishing cascades of interactions with other molecules. Atypical activation of STAT3 may be related to excessive concentrations of cytokines in the surrounding tumour microenvironment. Notably, CRC has been strongly associated with chronic inflammation, and IL-6 is produced by gut immune cells as a response to local inflammation, further inducing the activation of STAT3, creating a key circuit to stimulate colonic malignant transformation. Thus, among upstream STAT3 inductor factors, IL-6 has been widely recognised as a major activator in CRC, creating a pathway that stimulates proliferation, invasion and metastasis (31). Moreover, the detection of high levels of serum IL-6, measured using electrochemiluminescence assays, along with a positive immunohistochemical staining of IL-6 in tumour and stromal cells, have been shown to be correlated with poor prognosis and a local immunosuppressive state in patients with CRC (32). Although it is known that the number of cancer-associated STAT3 target genes is large, those encoding for inhibitors of apoptosis are of particular importance. Thus, survivin has long been considered a key participant in the STAT3-associated carcinogenic process (Fig. 1).

Immunohistochemical analyses of large numbers of CRC tumours demonstrated that expression of active pSTAT3 in the cytoplasmic and nuclear compartments was associated with higher mortality, increased reactive lymph nodes (30), clinical stage, tumour invasion depth and reduced overall survival (29). Simultaneously, studies of relative survivin mRNA expression levels, as determined by semi-quantitative PCR (33) and

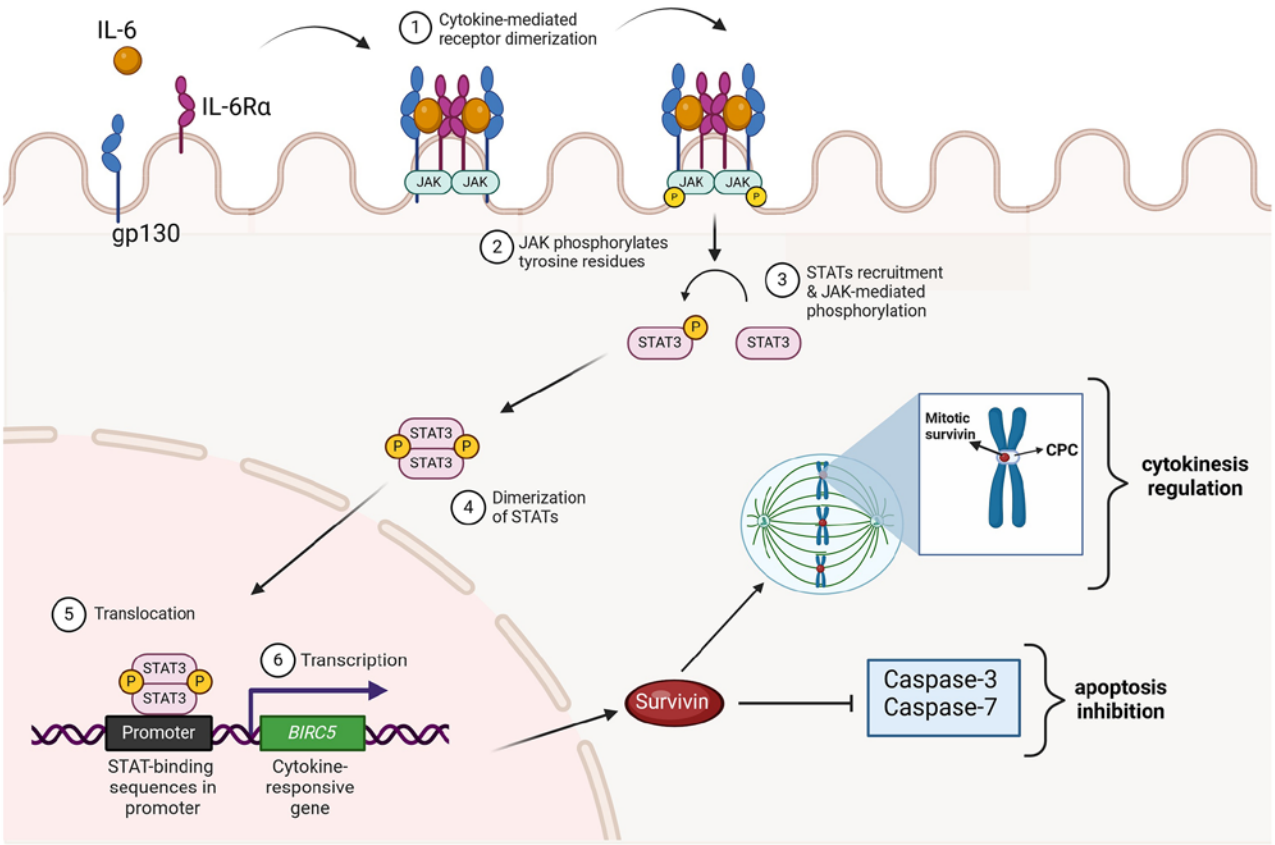

Figure 1. Cellular signalling associated with the STAT3-survivin axis in CRC. IL-6 is produced as a response to local inflammation in CRC. (1) Binding of IL-6 to IL-6R induces receptor dimerization. (2) Receptor-attached JAKs undergo transphosphorylation and consequent activation. (3) Active JAK phosphorylates STAT3. (4) Active STAT3 molecules form homodimers. (5) STAT3 homodimers translocate into the nucleus and bind to specific sequences in the promoter of target genes. (6) STAT3 induces the transcription of *BIRC5*, which encodes the inhibitor of apoptosis protein survivin. Survivin is a bifunctional protein that inhibits caspase-3 and -7-induced apoptosis, and also participates in the regulation of cell cytokinesis by forming the CPC. Figure created with BioRender.com. CRC, colorectal cancer; IL-6R, IL-6 receptor; gp130, glycoprotein 130; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; CPC, chromosomal passenger complex.

quantitative PCR (34,35), and evaluation of survivin expression by western blotting and immunostaining (33), have been performed in CRC cohorts showing a higher expression in tumour tissue as compared with that in paired adjacent tissue samples. As expected, survivin expression was revealed to be associated with lower apoptotic index in tumours (33). Survivin expression has also been associated with CRC progression. Kawasaki *et al* (36) evaluated survivin in colon hyperplastic polyp, low dysplastic adenoma, adenoma with high dysplasia and carcinoma samples by immunohistochemistry, finding that immunoreactivity of survivin was significantly augmented in the transition from adenoma with low dysplasia to high dysplasia and carcinoma. Further studies demonstrated that survivin encoding gene expression was elevated in more advanced CRC samples (37), and that positive cytoplasmic survivin immunostaining was strongly associated with lymph node metastasis (38). Notably, when CRC cases were stratified by age, survivin mRNA expression measured by quantitative PCR was revealed to be higher in elderly patients (>70 years) than that observed in younger patients (<70 years), suggesting that survivin might also be associated with age-related characteristics of colon cancer (39).

The concurrent expression of STAT3 and survivin in CRC has been detected in matching sections of normal colonic epithelium and invasive tumours by quantitative PCR and immunohistochemistry. Both pSTAT3 and survivin expression was shown to be significantly increased in CRC, and the presence of pSTAT3 at the nuclear compartment was directly associated with the expression of survivin (40). *In vitro* studies demonstrated the presence of an active STAT3-survivin axis in CRC-derived cells. Silencing the expression of STAT3 produced a reduction in cell proliferation, a significantly higher rate of apoptosis (41), and reduced colony formation and cell migration (42), which were associated with a significant suppression of survivin expression. Notably, inhibition of Smad7, a positive regulator of STAT3, significantly reduced the phosphorylation of STAT3 in CRC cells stimulated with IL-6, along with a decreased level of survivin (43), suggesting that an active STAT3-survivin axis, induced by CRC-associated cytokines, such as IL-6, serves a role in maintaining the malignant phenotype of CRC cells, and might also be important during CRC progression.

4. STAT3 and survivin as therapeutic targets

The relevance of the STAT3-survivin axis in CRC progression has prompted the development of drugs targeting molecular elements activating this pathway (Fig. 2). The

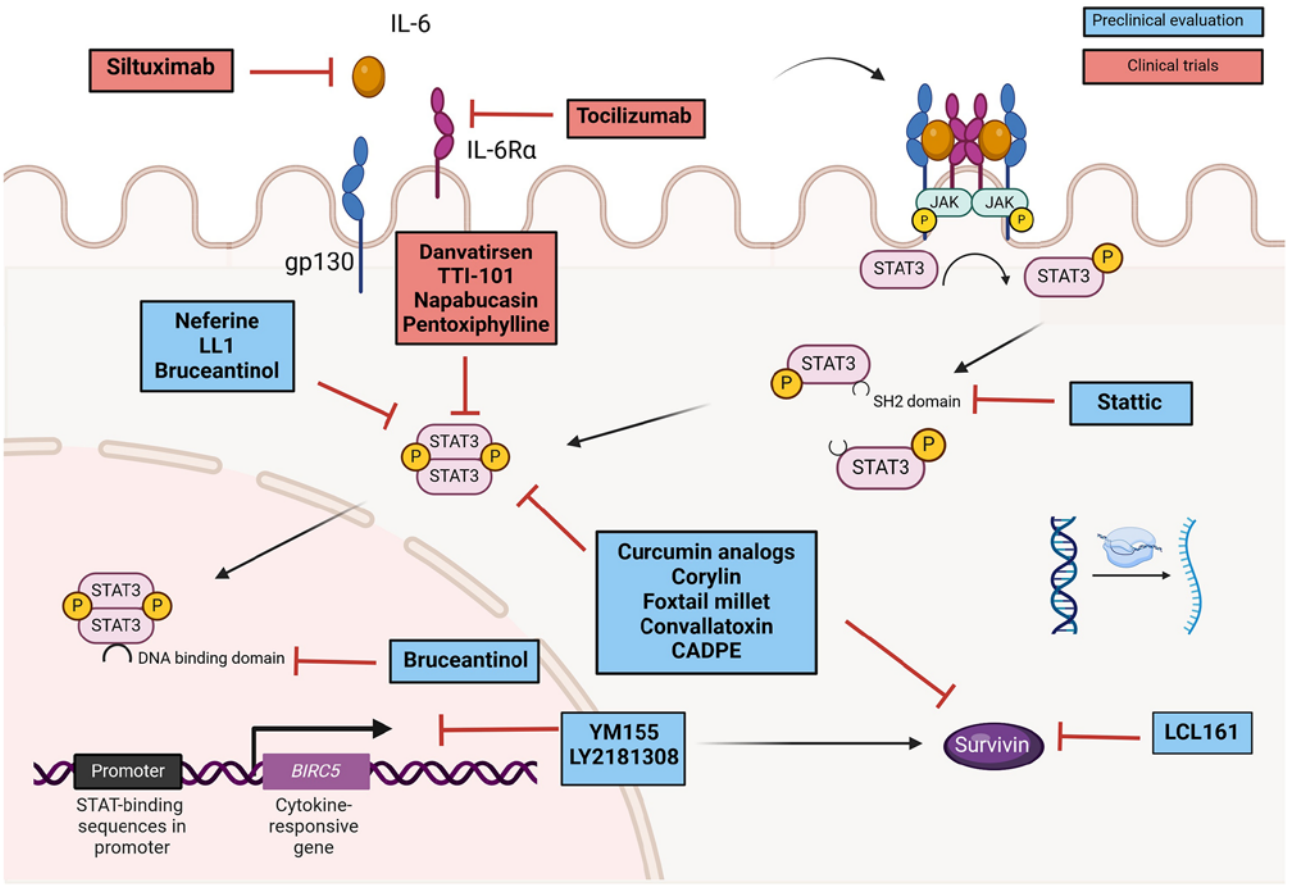

Figure 2. Pharmacological compounds targeting the STAT3-survivin axis and upstream activators IL-6 and IL-6R. Compounds that have been tested in cell lines and animal models are included in blue boxes (preclinical evaluation). Compounds included in clinical trials are depicted in red boxes. Figure created with BioRender.com. IL-6R, IL-6 receptor; gp130, glycoprotein 130; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; SH2, Src homology 2; CADPE, caffeic acid 3,4-dihydroxyphenethylester.

pro-inflammatory cytokine IL-6 is considered a major regulator of the STAT3-survivin axis in CRC (31,32); therefore, efforts to block this upstream element have been performed. Clinical trials using siltuximab (Sylvant®; Janssen Biotech), a chimeric monoclonal antibody that targets and neutralises IL-6, have shown that although siltuximab monotherapy was well tolerated in patients with CRC, no objective response occurred in a phase II study (44). In addition, human trials using tocilizumab, an antagonist monoclonal antibody to IL-6 receptor (IL-6R), have shown that clinical efficacy is still uncertain (45). Altogether, these observations suggest that targeting upstream elements may not be enough to control the STAT3-survivin axis in CRC.

STAT3 and survivin have been considered therapeutic targets for the development of diverse approaches to control and treat CRC, from plant derivatives to molecular therapies (Fig. 2). Phytochemicals have been widely explored as a potential source of STAT3-survivin axis regulators. One of the most studied natural dietary phytochemicals is curcumin, a polyphenol extracted from *Curcuma longa* (turmeric) rhizomes. Curcumin analogues have been demonstrated to inhibit STAT3 activation and survivin expression in CRC cells (46), and to increase caspase-3-mediated apoptosis in pre-clinical models (47). Moreover, different reports have indicated that the STAT3-survivin axis can be suppressed by other natural derivatives, such as corylin, foxtail millet (*Setaria italica*) and neferine. Corylin, an isoflavone isolated from *Cullen corylifolium* (L.) Medik, was found to inhibit STAT3 phosphorylation and survivin production, and significantly reduced tumour size in an animal model of CRC (48). Similarly, a previous evaluation of *S. italica*, a coarse cereal, in a murine model of azoxymethane/dextran sodium sulphate-induced CRC showed that *S. italica* diet supplementation reduced tumour burden by decreasing IL-6, pSTAT3 and survivin levels, alongside regulation of mice microbiota (49). Using the same murine model of colonic carcinogenesis, Zhou *et al* (50) showed that neferine, a natural bisbenzylisoquinoline alkaloid extracted from *Nelumbinis plumula*, was able to reduce the development of colorectal tumours by decreasing pSTAT3, among other molecules, and was shown to interact with STAT3 by molecular docking analysis (50). In addition, two more plant-derived molecules have been shown to be efficient inhibitors of the STAT3-survivin axis in CRC animal models. Convallatoxin, a cardiac glycoside derived from *Adonis amurensis* Regel & Radde (51), and caffeic acid 3,4-dihydroxyphenethylester extracted from *Sarcandra glabra* (Thunb) (52), have been reported to decrease CRC viability based on inhibition of the STAT3-survivin axis.

Alternatively, classical chemistry and innovative cellular approaches are being explored to develop new treatments for CRC, targeting the STAT3-survivin axis. In this regard, Xu *et al* (53) reported the design and synthesis of 27

cyanopyridines. Their anticancer activities were screened using CRC-derived cell lines, and the results indicated that at least one compound resulted in a significant reduction of CRC cell migration and colony formation. Notably, cyanopyridine-induced inhibition of cell migration and colony formation was mediated by a significant reduction of STAT3 activation and survivin expression (53). Finally, an innovative approach using macrophage-produced extracellular vesicles as nanocarriers of oxaliplatin, retinoic acid and *Libidibia ferrea*-derived polyphenols to modulate CRC progression was recently published (54). This previous study reported that extracellular vesicles loaded with antitumour reagents induced a significant reduction in tumour size and metastasis formation in an allographic mouse model, and that the cytotoxic effect was mediated by downregulation of STAT3 and survivin, among other cancer related factors (54). These observations reinforce the importance of the STAT3-survivin axis as a potential target for the development of new treatment strategies for patients with CRC.

5. Clinical trials targeting the STAT3-survivin axis

Being at the centre of the oncogenic STAT3-survivin axis, the transcription factor is a major target for the development of new drugs for the treatment of CRC (Fig. 2). Several STAT3 inhibitor compounds have been developed. However, at least three highly selective inhibitors have shown enough evidence in pre-clinical studies to be considered promising drugs to be included in further clinical trials: Stattic, which binds to the SH2 domain thus resulting in the retention of STAT3 in the cytoplasmic compartment (55); LL1, which blocks STAT3 dimerization (56); and bruceantinol, which hampers STAT3 binding to target DNA (57).

A number of STAT3 inhibitors are currently being tested in human clinical trials. In the particular case of CRC there are four specific inhibitors: TTI-101, danvatirsen, pentoxiphylline and napabucasin, which have entered clinical trials (Fig. 2).

TTI-101 is a small molecule that competitively inhibits STAT3 by targeting the phospho-Y-peptide binding site within the SH2 domain, thus blocking STAT3 recruitment to activated receptors and further homodimerization (58). TTI-101 is being tested as an oral treatment for patients with histologically confirmed diagnosis of locally-advanced, inoperable, metastatic and/or treatment refractory CRC, among other types of tumours, in an active phase I trial (NCT03195699) to establish safety, tolerability, pharmacodynamic effects and efficacy. The study started in 2017; at present, the trial remains active and is no longer recruiting participants. The estimated completion date is December 2024.

Danvatirsen is a 16-nucleotide antisense oligonucleotide that specifically targets STAT3 RNA, downregulating the production of the protein (59). Danvatirsen is being evaluated as a co-treatment with durvalumab (IMFINZI™; AstraZeneca), a fully human antibody that blocks programmed cell death ligand 1. Data from the phase I trial have already been published (60). The authors assessed the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumour activity of danvatirsen and durvalumab in two cohorts of patients with advanced CRC, among other types of solid tumours. Patients in cohort one received danvatirsen as monotherapy, while patients in cohort two were treated with a combination of danvatirsen and durvalumab. The results demonstrated that danvatirsen was well tolerated as a monotherapy and when combined with durvalumab. It was also reported that STAT3 expression was decreased in patients of both cohorts (60). A phase II trial (NCT02983578) including patients with advanced and refractory pancreatic, non-small cell lung cancer and mismatch repair-deficient CRC was subsequently started. Researchers estimate that the study will be completed by April 2025.

In 2023, a clinical trial using pentoxiphylline (NCT06115174) was registered. Pentoxiphylline is a non-specific phosphodiesterase inhibitor that was initially approved by the FDA for the treatment of peripheral vascular disease (61). Subsequently, pentoxiphylline was demonstrated to inhibit melanoma growth by targeting STAT3 (62). Notably, pentoxiphylline was first evaluated as a protective agent against chemotherapy-induced toxicities in patients with CRC. Administration of pentoxiphylline induced significantly improved survival rates, weight gain and reduced the occurrence of stomatitis (63). The beneficial effects detected were further demonstrated to correlate with a significant reduction of systemic inflammatory cytokines, including IL-1β, IL-6, IL-8 and TNF-α (64). Given that STAT3 regulates the expression of most inflammatory cytokines, it may be hypothesized that the aforementioned effects were mediated by the capacity of pentoxiphylline to inhibit STAT3. However, the authors did not evaluate the level of pSTAT3 expression. A further clinical trial (NCT06115174) to evaluate the anticancer effect of pentoxiphylline in patients with metastatic colorectal cancer was recently registered. The authors estimate that the study will be completed by November 2024.

Napabucasin is a STAT3 inhibitor that has been used in numerous clinical trials. Napabucasin is a natural naphthoquinone produced by various plants, including *Newbouldia laevis, Ekmanianthe longiflora* and *Handroanthus impetiginosus*. It is a small molecule targeting STAT3 that has been shown to possess an extensive range of inhibitory activities in diverse types of cancer (65). Napabucasin has been incorporated in various clinical trials, including those on patients with CRC; a phase III trial demonstrated that in pSTAT3-positive patients with CRC the overall survival was longer in the napabucasin group than that in the placebo group (66). In addition, two phase I trials testing napabucasin as a monotherapy (67), or in combination with fluorouracil, l-leucovorin, irinotecan and bevacizumab (68), in patients with advanced CRC demonstrated that the selected doses were well tolerated, with a manageable safety profile. Similarly, a multicentre phase I/II trial to assess the safety and efficacy of napabucasin in combination with pembrolizumab, an anti-PD1 blocking antibody (Keytruda®; Merck Sharp & Dohme) was performed in 55 patients with metastatic CRC. The combined therapy showed antitumour activity with tolerable toxicity levels; however, the therapy did not meet the primary endpoint of the study (immune-related objective response rate) (69). Finally, data from a multi-centre, open-label, phase III clinical trial (CanStem303C) has recently been published (70). The study included 1,253 patients with histologically confirmed metastatic CRC, who were randomized to napabucasin plus fluoropyrimidine, oxaliplatin and bevacizumab (FOLFIRI)

or FOLFIRI alone groups. The primary endpoint was overall survival. Notably, the addition of napabucasin to FOLFIRI did not improve overall survival in the evaluated population (70).

Strategies for the development of survivin inhibitors have provided molecules to block either survivin production or activity. YM155 (sepantronium bromide) was the first developed small molecule that specifically targets the survivin gene promoter, thus inhibiting its transcription. *In vitro* studies have demonstrated that YM155 is a promising treatment for CRC, since YM155 alone or in combination with 5-fluorouracil (5-FU) was more effective than 5-FU alone to treat CRC cells (71). Although other molecules, for example the antisense oligonucleotide LY2181308 (72), and the SMAC/Diablo mimetic LCL161 (73), which inhibit survivin transcription and activity, respectively, have shown promising results in pre-clinical assays, clinical trials have not reached objective responses.

6. Conclusions

The increasing numbers of cases and deaths due to CRC worldwide contributes to the urgent need for developing new, more efficient drugs. The STAT3-survivin axis is a regulator of CRC development, progression and response to treatment. Thus, molecular elements participating in this pathway have been considered potential therapeutic targets. Although pre-clinical studies have provided a number of potential drugs, only a limited number of them have reached clinical trials. In particular, blockade of upstream activators IL-6 and IL-6R using monoclonal antibodies has shown uncertain clinical efficacy. In line with the former observations, targeting survivin by means of small molecules and oligonucleotides to specifically hamper survivin expression has resulted in poor results in clinical trials. A rational explanation might be that the STAT3-survivin axis can be activated by a wide number of cytokines and growth factors present in the tumour microenvironment, as a consequence, inhibition of IL-6/IL-6R may not be enough to stop upregulation of the axis. Furthermore, STAT3 has several transcriptional targets that have important functions to maintain the tumour phenotype. Regarding apoptosis, STAT3 induces transcription of survivin, but also other proteins, such as Bcl-2 and Bcl-xL, which control apoptosis independently of survivin activity, suggesting that targeting survivin alone may have little impact in STAT3-associated inhibition of cell apoptosis. In general, pre-clinical and clinical trials targeting STAT3 have produced more promising results, particularly when the new drugs are used in combination with already tested treatments. However, to the best of our knowledge, no protocol has yet studied the joint effect of molecules targeting STAT3 and survivin; therefore, the potential clinical usefulness of inhibiting the complete STAT3-survivin axis has not been explored. Thus, we consider that combined therapeutic strategies that translate into a stronger inhibition of the STAT3-survivin axis deserve further investigation to potentially provide benefit to patients with CRC in the near future.

Acknowledgements

Liliana Cortés Ballinas is a student of Programa de Doctorado en Ciencias Bioquímicas, Universidad Nacional Autónoma de México (UNAM).

Funding

The present study was financed by a grant from PAPIIT, UNAM (grant no. IN206022). LCB received a fellowship from Consejo Nacional de Ciencia y Tecnología (CVU: 626746).

Availability of data and materials

Not applicable.

Authors' contributions

LCB, TVLP and LRZ participated in the design, conception, investigation, writing and editing of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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