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Regulatory role of the transforming growth factor-β signaling pathway in the drug resistance of gastrointestinal cancers

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Abstract

Gastrointestinal (GI) cancer, including esophageal, gastric, and colorectal cancer, is one of the most prevalent types of malignant carcinoma and the leading cause of cancer-related deaths. Despite significant advances in therapeutic strategies for GI cancers in recent decades, drug resistance with various mechanisms remains the prevailing cause of therapy failure in GI cancers. Accumulating evidence has demonstrated that the transforming growth factor (TGF)-β signaling pathway has crucial, complex roles in many cellular functions related to drug resistance. This review summarizes current knowledge regarding the role of the TGF-β signaling pathway in the resistance of GI cancers to conventional chemotherapy, targeted therapy, immunotherapy, and traditional medicine. Various processes, including epithelial-mesenchymal transition, cancer stem cell development, tumor microenvironment alteration, and microRNA biogenesis, are proposed as the main mechanisms of TGF-β-mediated drug resistance in GI cancers. Several studies have already indicated the benefit of combining antitumor drugs with agents that suppress the TGF-β signaling pathway, but this approach needs to be verified in additional clinical studies. Moreover, the identification of potential biological markers that can be used to predict the response to TGF-β signaling pathway inhibitors during anticancer treatments will have important clinical implications in the future.

Key Words: Drug resistance; Gastrointestinal cancer; Transforming growth factor-β; Epithelial-mesenchymal transition; Cancer stem cells; MicroRNAs

Core Tip: The transforming growth factor (TGF)-β signaling pathway is involved in the drug resistance of gastrointestinal (GI) cancers. This review summarizes the current understanding of the roles played by the TGF-β signaling pathway in resistance to conventional chemotherapy, targeted therapy, immunotherapy, and traditional medicine in GI cancers as well as the various processes by which this occurs, including epithelial-mesenchymal transition, cancer stem cell development, tumor microenvironment alteration, and microRNA biogenesis.

INTRODUCTION

Gastrointestinal (GI) cancer, including esophageal cancer (EC), gastric cancer (GC), and colorectal cancer (CRC), is one of the most prevalent types of malignant carcinoma, falling within the top six in mortality according to global cancer statistics in 2018. In both sexes, CRC is the second leading cause of cancer death (9.2% of total cancer deaths), closely followed by GC (8.2%), and EC as the sixth leading cause of mortality (5.3%)[1]. CRC is also the second most common cause of cancer death in the United States[2]. Despite improvements in current therapeutic strategies, including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, clinical prognoses and therapeutic responses of GI cancer patients are far from satisfactory because of delayed diagnosis, recurrence, poor clinical response, high cost, and medication side effects[3,4].

Chemotherapy is the most commonly used treatment for patients with advanced GI cancer. The most widely used chemotherapeutic regimens for GI cancer are fluorouracil and platinum[5-7]. Despite the continual development of new chemotherapeutic strategies, resistance to anticancer drugs remains a significant problem that is responsible for unfavorable clinical outcomes and treatment failures. Chemoresistance, including intrinsic and acquired drug resistance, is defined as the resistance of cancer cells to various structurally and functionally unrelated anti-cancer drugs[8]. The mechanisms of drug resistance are complex and closely related to various signaling pathways that are activated by many stimuli to promote chemoresistance[9].

The transforming growth factor (TGF)-β signaling pathway is deregulated in cancer and can have tumor-suppressive or tumor-promoting roles, depending on the molecular and cellular context[10,11]. In the GI tract, TGF-β has crucial and complex roles in many cellular functions related to drug resistance, such as maintaining stem cell homeostasis, regulating epithelial to mesenchymal transition, modulating immunity, and promoting fibrosis[12,13]. In this review, we discuss the role of the TGF-β signaling pathway in regulating chemoresistance in GI cancers.

MECHANISMS OF CHEMORESISTANCE IN CANCER

Molecular investigations have revealed several mechanisms underlying chemoresistance, including the epithelial-mesenchymal transition (EMT), the efflux of intracellular chemotherapeutic drugs, noncoding RNAs, stem cell development, and the tumor microenvironment[14-17]. EMT is a complex and important cellular program in which epithelial cells shed their differentiated characteristics and acquire mesenchymal phenotypes, including motility, invasiveness, and resistance to apoptosis. Cells undergoing EMT become more invasive and exhibit increased resistance to anticancer drugs[18,19]. In addition, EMT has been found to result in stem cell-like characteristics and is positively correlated with the expression of ATP-

binding cassette (ABC) transporters[18,20,21]. Different stimulus-induced EMT may contribute to chemoresistance *via* the upregulation of distinct transcription factors[19].

Failure of cancer chemotherapy can also be caused by changes in the expression or activity of membrane transporters, primarily those belonging to the ABC transporter family. ABC transporters can export chemotherapeutic agents out of the cell, thereby reducing intracellular drug levels and drug sensitivity and ultimately contributing to cancer chemoresistance[22,23]. In addition, ABC proteins transport signaling molecules that contribute to tumorigenesis[24].

Increasing evidence shows that non-coding RNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), can affect chemoresistance by forming a competing endogenous RNA regulatory network with mRNAs[25]. MiRNAs can play roles in drug resistance by targeting hundreds of tumor-related gene transcripts and affecting complex molecular pathways[14,26]. Specific miRNAs may be used as potential predictive biomarkers to guide individualized chemotherapy by reversing drug resistance[14].

Cancer stem cells (CSCs), which make up a distinct population within the tumor mass, possess unique self-renewal, multilineage differentiation, and potent tumorigenic abilities[27,28]. These cells acquire chemoresistance through various pathways involving apoptosis and DNA repair mechanisms[29]. In addition, upon exposure to cytotoxic therapies, CSCs can convert non-CSCs to CSC-like cells that may persist after treatment and serve as a mechanism for relapse. In GI malignancies, CSCs are abundant and contribute to chemotherapeutic resistance[15].

Interactions of tumor cells with alterations of the microenvironment, such as energy deprivation, hypoxia, and inflammation, give rise to heterogeneity and chemoresistance. Most tumor cells display deviations from the normal energy metabolism, allowing them to survive in hypoxic and low nutrient microenvironments[30,31]. Mitochondrial dysfunction and fatty acid (FA) metabolism are associated with chemotherapeutic resistance[31,32]. Hypoxia can also drive tumor resistance to chemotherapy by upregulating hypoxia-inducible factor-1 (HIF-1) and its downstream genes[33]. Inflammation and inflammatory mediators, including TGF-β, have been shown to contribute to the development, progression, metastasis, and chemoresistance of cancer[34,35]. In addition, the gut microbiota, which is linked to chronic inflammation and carcinogenesis[36], has an important role in the modulation of the host response to antitumor treatments, especially chemotherapy and immunotherapy[37]. Moreover, emerging evidence has demonstrated that cancer-associated fibroblasts (CAFs), one of the critical components of the tumor microenvironment, confer substantial resistance to chemotherapy and influence tumor cell responsiveness to immune checkpoint inhibitors[38].

ROLE AND ALTERATIONS OF THE TGF-β SIGNALING PATHWAY IN GI CANCER

The TGF-β signaling pathway can be subdivided into canonical Smad-dependent and noncanonical Smad-independent pathways. In the canonical pathway, TGF-β initially binds to the TGF-β type 2 receptor (TβRII), which recruits and phosphorylates the kinase domain of TGF-β type 1 receptor (TβRI), leading to the activation and phosphorylation of Smad2 and Smad3. Then, phosphorylated Smad2 and Smad3 bind to Smad4, allowing the entire complex to translocate into the nucleus. In the nucleus, the Smad complex regulates transcriptional activity by interacting with Smad binding elements within downstream target genes[39-41]. Smad7 negatively regulates the TGF-β signaling pathway by blocking the interaction between Smads and receptors and inhibiting the phosphorylation of Smad2 and Smad3[42,43]. In addition to the Smad-dependent pathway, the binding of the TGF-β ligand to its receptors also activates several Smad-independent signaling pathways, including the mitogen-activated protein kinase, phosphoinositide 3-kinase (PI3K)/AKT, and Rho-associated protein kinase pathways[44,45].

The TGF-β signaling pathway has an important role in controlling tissue development, proliferation, apoptosis, differentiation, and homeostasis[46]. Disruption of this signaling pathway leads to various diseases, including some cancers. In cancer cells, TGF-β signaling causes EMT and CSC-like traits, resulting in an aggressive phenotype and a poor prognosis[47,48]. In addition to its direct effect on epithelial tumor cells, TGF-β controls tumor development by regulating the tumor microenvironment and growth factors from the surrounding stroma[13,49]. Furthermore, TGF-β signaling activation in the tumor microenvironment suppresses antitumor immune

responses and supports cancer cell survival[50]. TGF-β has been found to inhibit multiple components of the immune system, including natural killer cells, CD8+ cytotoxic T lymphocytes, B-cell proliferation, and immunoglobulin A secretion[51]. Therefore, the TGF-β signaling pathway is associated with drug resistance and immune system escape.

In CRC, TGF-β1 expression is markedly increased and is correlated with poor clinical outcomes and a high risk of relapse[52,53]. TGF-β1 expression is also increased in GC mucosa and precancerous gastric cells[54,55]. However, active TGF-β1 is expressed most highly in smooth muscle actin-positive fibroblasts rather than in the malignant epithelial cells of gastric tumors[56]. In GC patients, high serum and tissue TGF-β1 levels are associated with lymph node involvement and poor prognosis[57]. Moreover, increased expression of TGF-β is found in EC[58]. In sum, serum and tissue TGF-β levels are upregulated in GI cancers and are associated with metastases and poor prognoses. Alterations in the TGF-β signaling pathway, especially receptor and *Smad* gene mutations, are commonly observed in GI cancers where they lead to tumor formation and metastasis[13]. Mutations in the TGF-β signaling pathway are found in 80% of CRC cell lines and approximately one-third of CRC tumors[46]. A decreased or complete loss of TGF-β receptor expression is common in patients with esophageal adenocarcinoma, primary gastric tumors, and CRC[49]. TβRII mutations frequently occur in the advanced stages of the colon[59] and gastric tumors along with progressive microsatellite instability (MSI-H)[49,60]. The overall incidence of TβRII mutations is approximately 30% in CRC, while frameshift mutations can be found in approximately 80% of MSI-H CRC[60,61]. TβRII mutations in CRC cells can contribute to the malignant phenotype *via* multiple pathways, regulate the components secreted by cancer cells, and directly promote inflammation in the tumor microenvironment[50]. Compared with TβRII, mutations in its counterpart TβRI are less frequent in both CRC and GC[13,60].

A study of over 700 cases of sporadic CRCs reveals that the prevalence of Smad4, Smad2, and Smad3 mutations was 8.6%, 3.4%, and 4.3%, respectively, with a combined prevalence of 14.8%[62]. Both Smad2 and Smad4 are located on chromosome 18q, which is commonly deleted in CRC[63]. However, Smad2 and Smad4 mutations tend to occur in the early and advanced stages of CRC, respectively[13,61,64]. Loss of Smad4 contributes to colorectal carcinogenesis[46] and may be a predictive biomarker of the response to 5-fluorouracil (5-FU)-based chemotherapy[65]. In GC, the expression of Smad3 is low or even undetectable in 40% of tissues, so mutations in Smad2 and Smad3 have not been described[13].

TGF-β SIGNALING AND DRUG RESISTANCE IN GI CANCER

Accumulating evidence suggests that the expression levels of components of the TGF-β signaling pathway are closely associated with response to chemotherapy. Immuno-histochemical analysis of 78 patient biopsies reveals that p-Smad2/3 expression was elevated in C-type CRC tumors, which benefit the least from chemotherapy[66]. Mediator Complex Subunit 12 (MED12) negatively regulates TβRII through physical interactions; therefore, its suppression induces the activation of TGF-β signaling[67]. In CRC cells, both MED12 knockdown and recombinant TGF-β treatment result in resistance to cisplatin, oxaliplatin (OXA), and 5-FU[66,67]. However, another study shows that TGF-β2 suppression was associated with recurrence in patients with colorectal adenocarcinomas. In addition, disease-free survival (DFS) and overall survival (OS) are significantly longer in patients with tumors expressing TGF-β2[68]. Additionally, in esophageal squamous cell carcinoma (ESCC) patients, TGF-β 1–509C/T polymorphisms benefit from radiochemotherapy and therefore might be useful genetic markers for predicting radiochemotherapy response[69]. In GI cancers, the TGF-β pathway is correlated with resistance to antitumor agents, including conventional chemotherapy, targeted therapy, immunotherapy, and traditional medicine. In Table 1, we provide a summary of the relationships between the TGF-β signaling pathway and drug resistance in GI cancers.

Conventional chemotherapy
Fluorouracil: 5-FU belongs to the antimetabolite family[70] and is a commonly used chemotherapeutic regimen for CRC and GC. 5-FU, a pyrimidine analog and an inhibitor of thymidylate synthase, is incorporated into RNA or DNA in the place of uracil or thymine and leads to the prevention of DNA replication and cell death[71]. Unfortunately, the treatment effectiveness of 5-FU is reduced, and its clinical

Table 1 Studies of the transforming growth factor-β signaling pathway in drug resistance in gastrointestinal cancer

Cancer type	*In vivo/In vitro*	Upstream regulator	Alteration of TGF-β signaling	Effect	Downstream antitumor drug	Ref.
CRC	SK-CO-1 cells	MED12 knockdown	The activation of TGF-β signaling or TGF-β treatment	Resistance	DDP, OXA, and 5-FU	Brunen *et al* [66], 2013
CRC	HCT116/HCT116p53KO chemoresistant cell lines	-	TGF-β1 treatment/TβRI inhibition	Resistance/sensitivity	5-FU	Romano *et al* [82], 2016
CRC	HCT116 cells	-	Smad4 knockdown	Sensitivity	Dox	Li *et al*[103], 2015
CRC	*in vivo*, CRC animal model, stable OXA-resistant cell line HCT116/OXA	Curcumin	Inhibition of p-Smad2 and p-Smad3	Sensitivity	OXA	Yin *et al*[90], 2019
CRC	The resistant cell model HCT-8/5-FU cell line	*Hedyotis diffusa* Willd	Inhibition of TGF-β signaling	Antimetastasis in 5-FU-resistant cells	5-FU	Lai *et al*[116], 2017
CRC	HCT116 and DLD1 CRC cell lines	-	siRNA-mediated knockdown of SMAD2/3, TGF-β inhibitor SB431542	Sensitivity	OXA	Kim *et al*[89], 2019
CRC	RKO cells	-	Silencing of TβRII expression, TβRI inhibitor LY2157299	Sensitivity	BETi	Shi *et al*[112], 2016
CRC	HCT116 cells	-	TGF-β inhibitor LY2157299	Sensitivity	5-FU	Quan *et al* [81], 2019
CRC	CT26 cells	Chemokine C-C motif ligand-1 secreted by Snail-expression fibroblasts	Phosphorylated Smad2	Resistance	5-FU or paclitaxel	Li *et al*[143], 2018
CRC	5-FU resistant cell line(HCT-8/5-FU)	Pien Tze Huang (PZH)	Suppression of TGF-β and Smad4	Overcome MDR and inhibit EMT	-	Shen *et al* [117], 2014
CRC	Patients	-	P-Smad3 overexpression	Resistance	5-FU and leucovorin, capecitabine	Huang *et al* [78], 2015
CRC	HCT116 *Smad4*^{+/+} and *Smad4*^{-/-} cell lines	-	Smad4 defect	Resistance	5-FU	Papageorgis *et al*[76], 2011
CRC	*in vivo*, colorectal tumor biopsies	-	Normal SMAD4 diploidy	Sensitivity	5-FU and mitomycin	Boulay *et al* [73], 2002
CRC	Dukes CRC patients	-	Low SMAD4 mRNA and protein levels	Resistance	5-FU-based adjuvant chemotherapy	Alhopuro *et al*[75], 2005
CRC	Colorectal tumor biopsies	-	The amplification of *STRAP*, an inhibitor of TGF-β signaling	Resistance	5-FU /mitomycin C adjuvant chemotherapy	Buess *et al* [74], 2004
CRC	Colo205 and RKO cells	-	TGF-β1 treatment	Resistance	5-FU, etoposide	Moon *et al* [80], 2019
CRC	Mouse models	-	Blockade of TGF-β signaling	Sensitivity	Anti-PD-1-PD-L1 checkpoint therapy	Tauriello *et al* [115], 2018
CRC	Mice models of MC38-derived tumors	-	1D11 antibody anti-TGF-β mAb	Sensitivity	Anti-PD1 plus anti-CD137 mAb	Rodríguez-Ruiz *et al* [114], 2019
CRC	SNU-C5/5-FU -resistant cells.	(1S,2S,3E,7E,11E)-3,7,11,15-cembratetraen-17,2-olide (LS-1) from *Lobophytum* sp	The increase of Smad-3 phosphorylation and the nuclear localization of p-Smad3 and Smad4	Sensitivity	5-FU	Kim *et al* [118], 2015
CRC	The early stages of colorectal carcinogenesis in rats	5-FU/thymoquinone (TQ) combination therapy	Upregulation of the TGF-β1, TβRII, Smad4	Sensitivity	5-FU	Kensara *et al* [122], 2016
CRC	Azoxymethane (AOM) rat model	Vitamin D3/5-FU co-therapy	Upregulation of the TGF-β1, TβRII, smad4	Sensitivity	5-FU	Refaat *et al* [77], 2015

CRC	RKO cells	Oxymatrine	Inhibition of the Smad2 phosphorylation and the formation of Smad2/3/4	Sensitivity	-	Wang *et al* [119], 2017
EC	Paclitaxel-resistant EC109 cells	-	BMP-4 and p-Smad1/5 overexpression	Resistance	Paclitaxel	Zhou *et al* [100], 2017
ESCC	KYSE-150 and KYSE-180 cells, xenograft tumors in nude mice	-	TβRI inhibitor LY2157299	Sensitivity	DDP and taxol	Zhang *et al* [142], 2017
ESCC	Xenotransplanted tumor mice model	-	Dual PD-1/PD-L1 and TGF-β blockades	Sensitivity	PD-1/PD-L1 blockade	Chen *et al* [139], 2018
EC and GC	EC cells T.T, GC cells MKN28 and MKN45	-	Pretreatment with TGF-β	Sensitivity	Adriamycin	Izutani *et al* [104], 2002
EAC	EAC cells, EAC patient-derived xenograft tumors	-	TβR inhibitor and trastuzumab, pertuzumab	Sensitivity	Trastuzumab and Pertuzumab	Ebbing *et al* [106], 2017
EC	KYSE150 andKYSE450 cells	Garcinol	Inhibition of the p300/CBP and p-Smad2/3 expression	Sensitivity	-	Wang *et al* [120], 2020
ESCC	Patients	-	High serum levels of VEGF-A and TGF-β1	Resistance	Taxane-based/5-FU -based chemotherapy	Cheng *et al* [79], 2014
ESCC	TE1	-	Anti-TGF-β2 neutralizing mAb and SB-431542	Sensitivity	Trastuzumab	Mimura *et al* [110], 2005
ESCC	TE1/TE5	-	Anti-TGF-β2 neutralizing mAb/exogenous addition of TGF-β2	Sensitivity/resistance	Cetuximab	Kawaguchi *et al*[109], 2007
ESCC	ECA109 and TE1 cells	Overexpression of LEF1	Upregulation of p-Smad2, p-Smad3, and TGF-β	Resistance	DDP	Zhao *et al* [130], 2019
GC	AGS cells	Glycoprotein from the *Capsosiphon fulvescens*	Inhibition of TGF-β1-activated FAK/PI3K/AKT pathways	Sensitivity	-	Kim *et al* [121], 2013
GC	SGC7901 and BGC823 cells	HMMR	Upregulation of p-Smad2 level and the nuclearaccumulation of Smad2	Resistance	5-FU	Zhang *et al* [84], 2019
GC	A peritoneal-metastatic cell line, 60As6	-	TGF-β treatment	Sensitivity	Docetaxel	Fujita *et al* [99], 2015
GC	MKN-45 cells	Eribulin	Inhibition of the TGF-β /Smad pathway	Sensitivity	-	Kurata *et al* [126], 2018
GC	Peritoneal mesothelial cells (HPMCs)	Paclitaxel	Inhibition of phosphorylation of Smad2	Reduce stromal fibrosis	-	Tsukada *et al* [98], 2013
GC	NCI-N87 cells	-	TGF-β treatment	Resistance	Trastuzumab	Zhou *et al* [107], 2018
	AGS and MKN45 cells	MSCs	Activated TGF-β signaling	Resistance	5-FU and OXA	He *et al*[146], 2019
CRC	Patients	-	TGF-β2 expression	Sensitivity	Fluoropyrimidine	Kim *et al*[68], 2009

5-FU: 5-fluorouracil; BETi: Bromodomain and extraterminal domain protein inhibitors; BMP-4: Bone morphogenetic protein 4; CRC: Colorectal cancer; DDP: Cisplatin; Dox: Doxorubicin; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; GC: Gastric cancer; MDR: Multidrug resistance; MSCs: Mesenchymal stem cells; TGF-β: Transforming growth factor-β; TβRI: Type 1 TGF-β receptor; TβRII: Type 2 TGF-β receptor.

application is limited by the emergence of drug resistance. The response rate to 5-FU is limited to 10%–15% in CRC. Various strategies have been used to improve the efficacy of 5-FU, resulting in the extension of the median survival to 30 mo[72].

A study of colorectal tumor biopsies shows that CRC patients with normal Smad4 diploidy experienced a threefold higher benefit from postoperative 5-FU-based adjuvant chemotherapy than those with Smad4 deficiency[73]. Another study of the same collection of tumor specimens reveals that serine-threonine receptor-associated

protein, a TGF-β-signaling inhibitor that acts at the receptor level, was a predictor of unfavorable responses to 5-FU-based adjuvant chemotherapy[74]. Similarly, CRC patients treated with surgery and 5-FU-based adjuvant therapy and followed for over 6 years to evaluate the prognostic value of Smad4 expression, demonstrate that patients with a low level of Smad4 expression had shortened DFS and OS compared with those with a high level of Smad4 expression[75]. In HCT116 colon cancer cells, Smad4 deficiency is found to be responsible for 5-FU resistance[76]. Moreover, in an azoxymethane rat model of colon cancer, vitamin D3 supplementation promotes the efficacy of 5-FU through multiple mechanisms including increased expression of TGF-β1, TβRII, and Smad4[77]. In brief, the results indicate that the effectiveness of adjuvant 5-FU-based chemotherapy might depend on TGF-β signaling in CRC.

As the TGF-β signaling pathway appears to have both suppressive and promoting effects in cancer, other studies have suggested that activation of the TGF-β signaling pathway might induce resistance to 5-FU in GI cancers. Immunohistochemical staining in patients with stage II-III advanced rectal cancer showed that p-Smad3 overexpression was associated with poor preoperative responses to fluoropyrimidine-based chemoradiotherapy. Therefore, p-Smad3 could be a potential predictor of a poor response to radiochemotherapy[78]. Moreover, pre-CCRT serum TGF-β1 levels were found to be negatively correlated with DFS in patients with ESCC receiving concurrent neoadjuvant chemoradiotherapy with taxane-based/5-FU-based chemotherapy followed by esophagectomy[79]. In CRC cells, TGF-β1 treatment was found to increase apoptotic resistance in cells exposed to therapeutics including 5-FU and etoposide[80]. TGF-β inhibition was found to sensitize HCT116 cells to 5-FU treatment and suppress cell migration[81]. Likewise, TβRI inhibition reduced proliferation and increased cell death in chemoresistant cancer cells[82]. Furthermore, Moon *et al*[83] found that Smad3/4 acted as a drug sensitivity regulator in TGF-β-mediated chemoresistant CRC cells, and knockdown of Smad3/4 significantly decreased tumor propagation and migration in the presence of 5-FU[83]. In GC, hyaluronan-mediated motility receptor is a key regulator of chemoresistance, and its upregulation was found to promote EMT and CSC properties by activating the TGF-β/Smad2 signaling pathway, ultimately leading to 5-FU resistance[84].

Platinum compounds: Platinum compounds are used as single agents or in combinatorial regimens for the treatment of GI cancers. The molecular mechanism of platinum compound-induced apoptosis involves the inhibition of DNA synthesis and repair, resulting in cell cycle arrest. This effect is mediated by the activation of various signal transduction pathways[85]. OXA is an important platinum-based option for the treatment of CRC[86]. In two multicenter trials in which single-agent OXA was administered as first-line treatment of advanced CRC, response rates were 12% and 24%, progression-free survival was 4 mo, and median survival was 14.5 mo and 13 mo, respectively[87].

In CRC cells, TGF-β1 contributes to OXA resistance primarily through EMT, which leads to antiapoptotic effects and the attenuation of DNA damage[88]. Furthermore, both siRNA-mediated knockdown of Smad2/3 and treatment with the potent TGF-β inhibitor SB43154225 suppress migration and invasion and increase therapeutic sensitivity to OXA in HCT116 and DLD1 CRC cell lines[89]. Curcumin, a naturally occurring polyphenolic substance extracted from the Curcaceae plant *Curcuma longa,* sensitizes CRC to OXA treatment by inhibiting the TGF-β/Smad2/3 pathway in the OXA-resistant cell line HCT116/OXA and in an *in vivo* animal model of CRC[90]. In EC, TGF-β secreted from CAF-like fibroblasts induces chemoresistance to cisplatin, which is reversed after administration of TGF-β neutralizing antibodies[91].

Taxoid compounds: Paclitaxel (PTX) is an antineoplastic agent derived from the bark of the Pacific yew *Taxus brevifolia*[92]. Docetaxel is a semi-synthetic taxane that primarily acts to promote microtubule assembly and prevents the depolymerization of assembled microtubules[93]. Both PTX and docetaxel exert potent antitumor effects by stabilizing microtubules, resulting in cell cycle arrest and apoptosis[94]. The results of a multicenter trial in patients with advanced or recurrent GC showed that the response rate to PTX as a second-line monotherapy was 17.5%[95]. The median duration of response to PTX monotherapy was 2.8 mo in patients with advanced gastric or gastroesophageal junction adenocarcinoma, and the patients eventually developed resistance to PTX[96]. The results of a phase II study in previously-untreated GC patients reported overall response rates to single-agent docetaxel in the range of 17% to 24%[97].

Peritoneal dissemination is the most common mode of metastasis in GC. Low-dose PTX can significantly inhibit Smad2 phosphorylation in human peritoneal mesothelial

cells, leading to a decrease in stromal fibrosis[98]. The results of a microarray analysis showed that C-X-C chemokine receptor type 4 (CXCR4) was a novel marker for highly metastatic CSCs. Treatment with TGF-β enhanced the anticancer effect of docetaxel *via* the induction of cell differentiation/asymmetric cell division within the CXCR4-positive gastric CSC population, even when the cells were in a dormant state[99]. Bone morphogenetic protein 4 (BMP-4), which is involved in TGF-β signaling, is upregulated in PTX-resistant human esophageal carcinoma EC109 cells and docetaxel-resistant human GC MGC803 cells. p-Smad1/5, which is also involved in the TGF-β /Smad pathway, is also overexpressed in EC109/Taxol cells[100].

Doxorubicin: Doxorubicin (Dox), a chemotherapeutic agent extensively used to treat a wide range of cancers, exerts cytotoxic and DNA damaging effects through interference with nucleoside metabolism, but is less efficacious in GI cancers relative to other cancer types[101]. The antineoplastic activity of Dox is attributed to its intercalation into the DNA helix and its ability to generate free radicals[102]. In HCT116 colon cancer cells, long-term administration of low concentrations of Dox may promote resistance partly *via* the activation of TGF-β signaling. Moreover, knockdown of Smad4 significantly increases the sensitivity of HCT116 cells to Dox, in part *via* the inhibition of multidrug-resistant plasma membrane glycoprotein expression and reversal of the EMT process[103]. Therefore, the combination of Dox treatment and TGF-β downregulation might be a potential therapeutic strategy to overcome chemoresistance.

Adriamycin: Adriamycin (ADM) generates superoxide radicals that kill tumor cells by damaging DNA, directly intercalating into DNA, and preventing DNA replication. In human EC cells (T.T) and GC cells (MKN28 and MKN45), pretreatment with TGF-β1 results in increased sensitivity to ADM. *In vivo*, the combined administration of TGF-β 1 and ADM delayed tumor growth better than either treatment alone and further exhibited synergistic antitumor effects[104].

Targeted therapy
Knockdown of MED12 in the CRC cell lines SK-CO-1 (KRASV12) and SW1417 (BRAFV600E) resulted in the activation of MEK/ERK and induced resistance to the MEK inhibitor AZD6244 (selumetinib). Moreover, TGF-β-induced resistance to AZD6244 and the BRAF inhibitor PLX4032 (vemurafenib) have also been observed in CRC cells[67]. However, another study demonstrated that vemurafenib downregulated the expression of TGF-β and p-Smad3 in HT29 CRC cells[105]. Trastuzumab, a human epidermal growth factor receptor (HER)2-targeting antibody, is the only available targeted agent for first-line palliative systemic treatment of HER2-positive esophagogastric adenocarcinoma (EAC). EAC cells become resistant to trastuzumab and the HER2-HER3 signaling inhibitor pertuzumab by activating TGF-β signaling, which subsequently induces EMT. TGF-β receptor inhibitors were shown to increase the antitumor efficacy of trastuzumab and pertuzumab in EAC cells and EAC patient-derived xenograft tumors[106]. Sensitivity of the GC cell line NCI-N87 to trastuzumab was significantly decreased after treatment with TGF-β. Moreover, TGF-β was upregulated in trastuzumab-resistant NCI-N87/TR cells[107]. Cetuximab and trastuzumab, humanized antibodies against the HER family, exert antitumor effects by directly inhibiting epidermal growth factor receptor (EGFR) tyrosine kinase activity, inhibiting cell cycle progression, and activating proapoptotic molecules[108]. In addition, an anti-TGF-β2 neutralizing mAb enhances cetuximab-mediated and trastuzumab-mediated antibody-dependent cellular cytotoxicity (ADCC) in TE1 TGF-β -producing ESCC cells. The TGF-β signaling inhibitor SB-431542 was found to enhance trastuzumab-mediated ADCC of TE1 cells. Furthermore, the exogenous addition of TGF-β2 significantly decreased cetuximab-mediated ADCC in non-TGF-β2-producing TE5 cells, and TGF-β2 inhibited the activity of trastuzumab-mediated ADCC in TE1 cells[109,110]. TGF-β expression is upregulated in three FGFR2-amplified SNU-16 GC cell lines that are resistant to AZD4547, BGJ398, and PD173074. However, parental SNU-16 cells treated with TGF-β1 did not undergo EMT, and inhibition of TβRI was not sufficient to reverse EMT in the resistant cells[111]. Bromodomain and extraterminal domain protein inhibitors (BETis) are in clinical trials as a novel class of cancer therapeutics. Both TβRII knockdown and treatment with the small-molecule Tβ RI inhibitor LY2157299 (galunisertib) were reported to increase the sensitivity of RKO colon carcinoma cells to BETis[112].

Immunotherapy
Treatment with the TGF-β inhibitors P144 and P17 may be able to enhance the efficacy

of immunotherapies by increasing antitumor immune responses[113]. Moreover, treatment with the TGF-β-neutralizing mAb 1D11 enhanced the abscopal effect of radiotherapy as well as overall treatment efficacy in subcutaneous large MC38 colorectal tumors in conjunction with anti-programmed cell death protein 1 (PD-1) plus anti-CD137 mAb[114]. In mice with progressive metastatic liver disease, enabling immune infiltration using TGF-β inhibitors render tumors susceptible to anti-PD-1/Programmed cell death ligand 1 (PD-L1) checkpoint-based therapies[115]. Immuno-therapies directed against TGF-β signaling may have broad applications in treating patients with advanced CRC.

Traditional medicine

Traditional herbal medicine has an important role in reversing the resistance of CRC cells to 5-FU. *Hedyotis diffusa* Willd, a traditional Chinese herbal medicine in the family of Rubiaceae, may exert its antimetastatic activity by suppressing TGF-β/Smad4 signaling pathway-mediated EMT in 5-FU-resistant CRC cells[116]. Similarly, the traditional Chinese medicine formula Pien Tze Huang can effectively overcome multidrug resistance and inhibit EMT *via* suppression of the TGF-β pathway in the 5-FU-resistant CRC cell line HCT-8/5-FU[117]. Moreover, (1*S*,2*S*,3*E*,7*E*,11*E*)-3,7,11,15-Cembratetraen-17,2-olide (LS-1), a marine cembrenolide diterpene from *Lobophytum* sp., can restore TGF-β signaling pathway activity and induce apoptosis in fluorouracil-resistant human colon cancer SNU-C5/5-FU cells[118].

Various other Chinese herbs have been reported to exert antitumor or synergistic antitumor effects *via* TGF-β signaling pathway-mediated mechanisms. Oxymatrine, an alkaloid extracted from the Chinese herb *Sophora flavescens* Ait, can exert antimetastatic and anti-invasive effects through the inhibition of Smad2 phosphorylation and the formation of Smad2/3/4 in colorectal carcinoma RKO cells[119]. Garcinol, a natural compound extracted from *Gambogic genera*, can inhibit EC metastasis in vitro and *in vivo* by dose-dependent suppression of p-Smad2/3 expression in the nucleus[120]. In addition, a glycoprotein from the green alga *Capsosiphon fulvescens* was shown to suppress the proliferation and migration of AGS GC cells by downregulating integrin expression *via* inhibition of the TGF-β1-activated FAK/PI3K/AKT pathways[121]. However, combination therapy with 5-FU and thymoquinone, which is the main bioactive compound derived from *Nigella sativa*, enhanced antitumor effects in a preclinical rat model of colorectal tumorigenesis partly by upregulating the expression of TGF-β1, TβRII, and Smad4[122].

TGF-β SIGNALING AND EMT IN GI CANCER DRUG RESISTANCE

TGF-β secreted from tumor cells is involved in paracrine signaling cascades that promote EMT and activate CAFs. CAFs, in turn, secrete more TGF-β that further drives EMT. Extracellular TGF-β binds to its receptor, resulting in the expression of key EMT genes. Furthermore, TGF-β can promote non-Smad pathways to accelerate EMT progression[16]. It has been reported that fibronectin, a marker of EMT progression, induced EMT through Smad3/4-mediated TGF-β signaling[123]. Therefore, TGF-β is an important inducer of EMT. SW837 rectal cancer cells treated with a TβR inhibitor or transfected with TβRII siRNA exhibited downregulation of mesenchymal markers, such as N-cadherin and vimentin and EMT regulators, including Snail, Twist, Slug, and Zeb1[124]. Ginsenoside Rb2, the bioactive component in ginseng, inhibited EMT in CRC cells by inhibiting the expression of Smad4 and p-Smad2/3[125]. Similarly, eribulin significantly inhibited EMT by downregulating the TGF-β/Smad pathway in GC[126]. The EMT phenotype has been observed in GC cell lines resistant to 5-FU and AZD4547 and CRC cell lines resistant to BGJ398, PD173074, and OXA[84,111,127]. Anticancer drugs can activate the TGF-β signaling pathway and further induce EMT, which is closely associated with chemotherapy resistance and evasion of immune surveillance[10,128]. Dox treatment of HCT116 colon cancer cells was found to increase TGF-β1 and p-Smad2/3 expression and induce an EMT phenotype, exemplified by a reduction in E-cadherin and the upregulation of vimentin and N-cadherin. The changes ultimately resulted in the acquisition of Dox resistance. Furthermore, silencing Smad4 by stable RNA interference reversed the EMT process and increased the sensitivity of HCT116 cells to Dox[103]. In EAC cells, EMT has been identified as a chemoradiation resistance mechanism in which EMT is mediated by the autocrine production of TGF-β in response to chemoradiation. Neutralization of TGF-β ligands effectively counteracted chemoradiation-induced EMT by reversing the mesenchymal phenotype[129]. EAC cells incubated with trastuzumab and

pertuzumab can secrete ligands for the TGF-β receptor and induce EMT-related changes, including reduced expression of epithelial markers (CD24, CD29, and CDH1) and increased expression of mesenchymal markers (CXCR4, VIM, ZEB1, SNAI2, and CDH2), resulting in drug resistance. However, combining the drugs with a TGF-β receptor inhibitor caused the cells to regain an epithelial phenotype[106].

TGF-β SIGNALING AND CSC IN GI CANCER DRUG RESISTANCE

Emerging evidence indicates that CSCs are the main factor underlying therapeutic failure, and chemotherapeutic resistance. The TGF-β pathway has been identified as a major stem cell-associated signaling pathway. ESCC has been found to arise from CSCs. Zhao *et al*[130] showed that the TGF-β signaling pathway contributed to the lymphoid enhancer-binding factor 1-mediated CSC-like phenotype in ESCC cells. In EC, the TGF-β1 inhibitor SB525334 significantly suppressed the migration and invasion of sphere-forming stem-like cells, which possess key traits of CSCs, including chemoresistance[131]. EMT is a critical process for the generation and maintenance of CSCs and the invasive front of ESCC. Moreover, the EGFR inhibitors erlotinib and cetuximab can both markedly suppress CSCs enrichments *via* TGF-β1-mediated EMT in ESCC[132]. In mouse GC cells, activation of the TGF-β pathway downregulated the expression of Sca-1, which has been identified as a potential CSC enrichment marker. High expression of Sca-1 was related to increased resistance to cisplatin/fluorouracil-based chemotherapy[133]. In addition, TGF-β enhanced the anticancer effect of docetaxel by inducing the differentiation of gastric CSCs[99].

TGF-β SIGNALING AND TUMOR MICROENVIRONMENT IN GI CANCER DRUG RESISTANCE

TGF-β is a pleiotropic cytokine with potent immunosuppressive effects. TGF-β downregulates CD8^{+} and CD4^{+} T cell activation and stimulates the differentiation of immune-suppressive regulatory T (Treg) cells[10,114]. CRC cells secrete anti-inflammatory cytokines, including TGF-β, which can affect the dendritic cell (DC) phenotype and support tumor escape from immune surveillance[134]. However, the TGF-β receptor inhibitor SB-431542 can induce potent phenotypic and functional maturation of DCs and trigger an antitumor immune response[135]. In ESCC, TGF-β1 was shown to partially contribute to the downregulation of CD16 on natural killer (NK) cells, resulting in NK cell dysfunction[136].

TGF-β signaling pathway activation plays an important role in immune evasion and contributes to immune checkpoint therapy failure[137,138]. Enabling immune infiltration by blocking TGF-β signaling renders tumors susceptible to anti-PD-1-PD-L1 checkpoint-based therapy[115]. Moreover, the TGF-β neutralizing monoclonal antibody 1D11 markedly enhanced the abscopal effects and the overall treatment efficacy in conjunction with an anti-PD-1 plus anti-CD137 mAb combination in large MC38 colorectal tumors[114]. In ESCC, myeloid-derived suppressor cell-derived TGF-β increased PD-1 expression on CD8^{+} T cells, which led to resistance to PD-1/PD-L1 blockade in the tumor microenvironment. Dual PD-1/PD-L1 and TGF-β pathway blockades restored the function and antitumor ability of CD8^{+} T cells[139]. Furthermore, combined treatment with cyclophosphamide and interleukin (IL)-12-expressing adenovirus, which might be a valid immunotherapeutic strategy for advanced GI cancer, was shown to revert the Treg immunosuppressive phenotype by blocking the secretion of IL-10 and TGF-β, resulting in loss of their DC inhibitory activity[140].

CAFs are the most abundant cell type in the tumor microenvironment. One of the main sources of CAFs is endothelial cells undergoing EMT, which is mainly promoted by TGF-β[141]. CAFs can confer TGF-β1-mediated ESCC cell resistance to several chemotherapeutic drugs, including cisplatin, taxol, irinotecan, 5-FU, carboplatin, docetaxel, pharmorubicin, and vincristine. Inhibition of CAF-secreted TGF-β1 signaling *via* treatment with the TβRI inhibitor LY2157299 significantly enhanced chemosensitivity[142]. Moreover, TGF-β secreted by miR-27-induced CAFs induced chemoresistance to cisplatin in EC[91]. In CRC, Snail-expressing 3T3 fibroblasts exhibit CAF properties that support 5-FU and PTX chemoresistance *via* TGF-β/NF-κB-mediated CCL1 secretion[143]. Tang *et al*[144] found that, in CRC, hypoxia-inducible factor 1α (HIF-1α) and CAF-secreted TGF-β2 synergistically induced the expression of

Table 2 Studies evaluating the relationship between miRNAs and drug resistance related to the transforming growth factor-β signaling pathway in gastrointestinal cancer

miRNA	Tumor type	Target	Effect on drug resistance	Ref.
miR-21	CRC cell line HCT-116	Downregulation of TβRII	Induction of stemness	Yu *et al*[148], 2012
miR-552	CRC tissues of patients, CRC cell lines SW-480 and SW-620	The 3'-UTR of Smad2	Reduction 5-FU resistance	Zhao *et al*[150], 2019
miR-34a	CRC cell line HT29	Downregulation of the TGF-β/Smad4 signaling pathway	Acquired chemoresistance to oxaliplatin	Sun *et al*[149], 2017
miR-455-3p	ESCC cell lines Eca109 and Kyse30	Enhanced expression level of p-Smad2	Resistance to DDP and docetaxel	Liu *et al*[151], 2017
miR-27	ESCC cell line TE10	TGF-β secreted from CAF-like fibroblasts	Resistance to DDP	Tanaka *et al*[91], 2015
miR-187	DDP-resistant GC cells SGC7901/DDP	Downregulated TGF-β1 and p-Smad4	Alleviates DDP-resistance	Zhu *et al*[153], 2019
miR-204	GC cell lines AGS and SGC-7901	Target TβRII	Sensitizes GC cells to 5-FU	Li *et al*[154], 2018

5-FU: 5-fluorouracil; CAF: Cancer-associated fibroblast; CRC: Colorectal cancer; DDP: Cisplatin; ESCC: Esophageal squamous cell carcinoma; GC: Gastric cancer; miRNA: Microribonucleic acid; TGF-β: Transforming growth factor-β.

GLI2, which promoted chemoresistance.

Mesenchymal stem cells (MSCs), an important part of the tumor environment, contribute to the development of drug resistance[145]. In GC cells, TGF-β1 secretion by MSCs activated Smad2/3 and induced expression of the lncRNA MACC1-AS1 that promoted FA oxidation-dependent stemness and chemoresistance to 5-FU and OXA [146].

TGF-β SIGNALING AND MIRNA IN GI CANCER DRUG RESISTANCE

Emerging evidence indicates that some miRNAs can regulate the resistance of GI cancers to a variety of chemotherapeutic drugs through the TGF-β signaling pathway, as summarized in Table 2. In HT-29 colon cancer cells, overexpression of miR-146a was found to be associated with various processes in the cancer microenvironment, including enhancement of 5-FU and irinotecan resistance and promotion of TGF-β secretion[147]. MiR-21 was shown to increase both stemness and the overall proportion of CSCs in colon cancer cells by downregulating TβRII, a direct target of miR-21, and by activating the Wnt/β-catenin pathway[148]. MiR-34a was found to mediate OXA resistance in CRC cells by inhibiting macroautophagy *via* regulation of the TGF-β/Smad4 pathway[149]. However, the expression levels of miR-552 were negatively correlated with resistance to 5-FU-based chemotherapy in CRC cells. Mechanically, miR-552 directly targeted the 3'-UTR of Smad2, and stable knockdown of Smad2 reversed miR-552 deficiency-induced 5-FU resistance[150]. Overexpression of miR-455–3p conferred resistance to cisplatin and docetaxel in ESCC cells, whereas miR-455–3p antagonism reversed chemoresistance and reduced the number of CD90^{+} and CD271^{+} tumor-initiating cells *via* the suppression of multiple stemness-associated pathways, including TGF-β signaling[151]. Moreover, miR-27 has shown to play a role in cisplatin resistance in EC through the transformation of normal fibroblasts into CAFs and the induction of TGF-β secretion from the CAFs[91]. In GC, overexpression of miR-577 contributed to TGF-β-mediated EMT and stemness by forming a positive feedback loop, resulting in chemoresistance to OXA[152]. However, overexpression of miR-187 in GC cells alleviated cisplatin resistance by inhibiting the TGF-β/Smad signaling pathway[153]. Furthermore, overexpression of miR-204 was found to sensitize 5-FU-resistant GC cells through the suppression of TβRII-mediated EMT [154].

CONCLUSION

Drug resistance, which leads to unfavorable clinical outcomes and treatment failure, remains a considerable challenge in the treatment of GI cancers. The TGF-β signaling
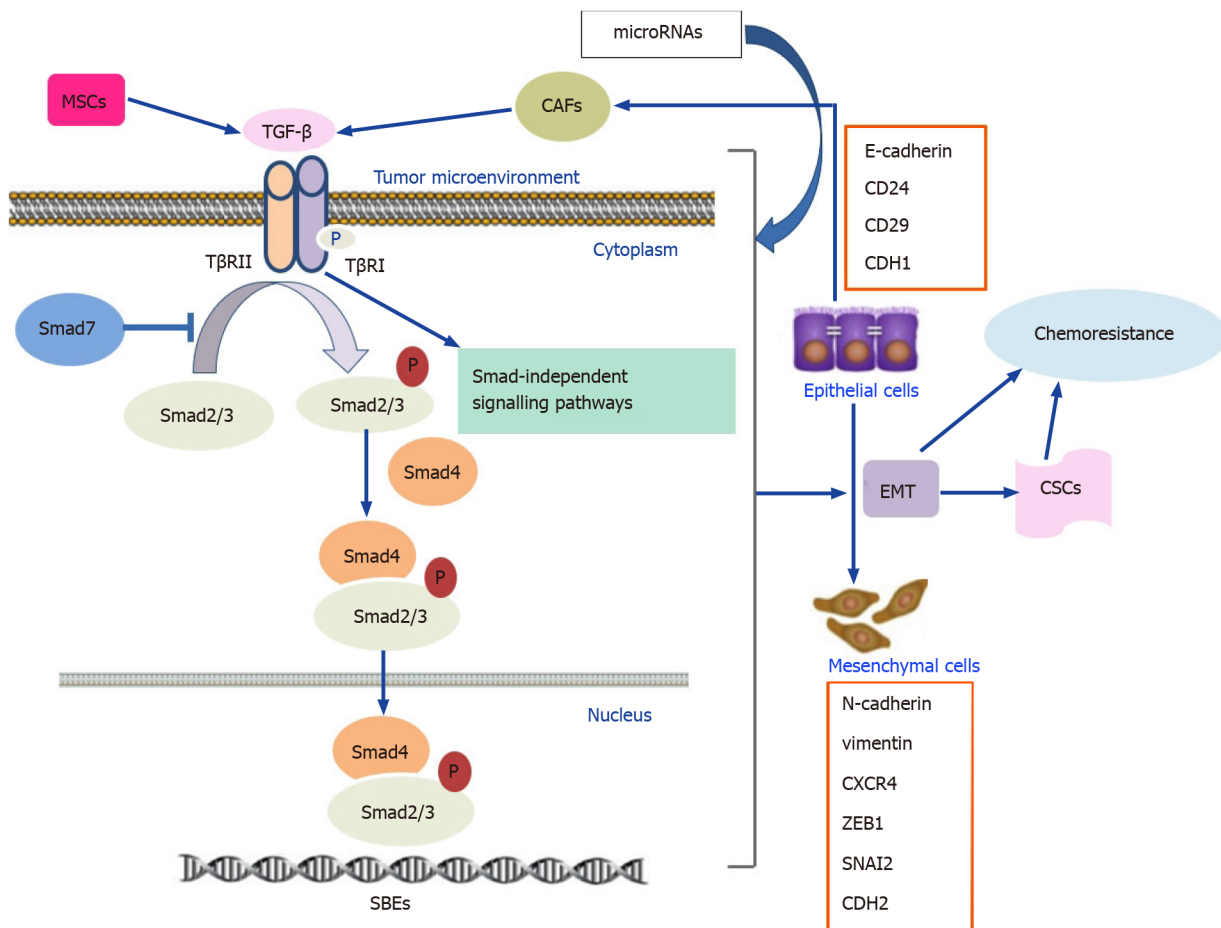
Figure 1 Mechanisms of transforming growth factor-β signaling and involvement in gastrointestinal cancer chemoresistance. CAFs: Cancer-associated fibroblasts; CSCs: Cancer stem cells; EMT: Epithelial-mesenchymal transition; MSCs: Mesenchymal stem cells; TβRI: TGF-β Type 1 receptor; Tβ RII: TGF-β Type 2 receptor.

pathway plays an important role in the regulation of the drug responses to conventional chemotherapy, targeted therapy, immunotherapy, and traditional medicine. Furthermore, TGF-β-mediated drug resistance in GI cancers is closely associated with several processes, including EMT, CSC development, alteration of the tumor microenvironment, and miRNA biogenesis (Figure 1).

Despite improvements in treatment strategies, EC, GC, and metastatic CRC have a poor prognosis, with 5-year OS rates of 15%–25%, 29.3%, and 14%, respectively[2,155, 156]. The key obstacle to therapeutic success is the development of drug resistance, highlighting the urgency driving the development of alternative treatments for GI cancers. Many reports indicate the benefits of combining antitumor agents with agents that suppress TGF-β signaling. However, the findings require further verification by additional clinical studies. The use of some small-molecule inhibitors of TGF-β signaling is currently being investigated in both preclinical and clinical trials[60,157]. As TGF-β possesses paradoxical activities, the identification of potential biological markers related to the response to TGF-β inhibitors would have important clinical implications and would help select patients most likely to benefit from their use.

REFERENCES

1   **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2   **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: 32133645 DOI: 10.3322/caac.21601]

3   **Piawah S**, Venook AP. Targeted therapy for colorectal cancer metastases: A review of current methods of molecularly targeted therapy and the use of tumor biomarkers in the treatment of

metastatic colorectal cancer. *Cancer* 2019; **125**: 4139-4147 [PMID: 31433498 DOI: 10.1002/cncr.32163]

4   **Chu JN**, Choi J, Ostvar S, Torchia JA, Reynolds KL, Tramontano A, Gainor JF, Chung DC, Clark JW, Hur C. Cost-effectiveness of immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer. *Cancer* 2019; **125**: 278-289 [PMID: 30343509 DOI: 10.1002/cncr.31795]

5   **Adlard JW**, Richman SD, Seymour MT, Quirke P. Prediction of the response of colorectal cancer to systemic therapy. *Lancet Oncol* 2002; **3**: 75-82 [PMID: 11902527 DOI: 10.1016/s1470-2045(02)00648-4]

6   **Roselló S**, Papaccio F, Roda D, Tarazona N, Cervantes A. The role of chemotherapy in localized and locally advanced rectal cancer: A systematic revision. *Cancer Treat Rev* 2018; **63**: 156-171 [PMID: 29407455 DOI: 10.1016/j.ctrv.2018.01.001]

7   **Shen L**, Shan YS, Hu HM, Price TJ, Sirohi B, Yeh KH, Yang YH, Sano T, Yang HK, Zhang X, Park SR, Fujii M, Kang YK, Chen LT. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol* 2013; **14**: e535-e547 [PMID: 24176572 DOI: 10.1016/S1470-2045(13)70436-4]

8   **Wei L**, Wang X, Lv L, Zheng Y, Zhang N, Yang M. The emerging role of noncoding RNAs in colorectal cancer chemoresistance. *Cell Oncol (Dordr)* 2019; **42**: 757-768 [PMID: 31359293 DOI: 10.1007/s13402-019-00466-8]

9   **Zheng HC**. The molecular mechanisms of chemoresistance in cancers. *Oncotarget* 2017; **8**: 59950-59964 [PMID: 28938696 DOI: 10.18632/oncotarget.19048]

10   **Colak S**, Ten Dijke P. Targeting TGF-β Signaling in Cancer. *Trends Cancer* 2017; **3**: 56-71 [PMID: 28718426 DOI: 10.1016/j.trecan.2016.11.008]

11   **Ikushima H**, Miyazono K. TGFbeta signalling: a complex web in cancer progression. *Nat Rev Cancer* 2010; **10**: 415-424 [PMID: 20495575 DOI: 10.1038/nrc2853]

12   **Chruścik A**, Gopalan V, Lam AK. The clinical and biological roles of transforming growth factor beta in colon cancer stem cells: A systematic review. *Eur J Cell Biol* 2018; **97**: 15-22 [PMID: 29128131 DOI: 10.1016/j.ejcb.2017.11.001]

13   **Katz LH**, Likhter M, Jogunoori W, Belkin M, Ohshiro K, Mishra L. TGF-β signaling in liver and gastrointestinal cancers. *Cancer Lett* 2016; **379**: 166-172 [PMID: 27039259 DOI: 10.1016/j.canlet.2016.03.033]

14   **Hong L**, Han Y, Yang J, Zhang H, Zhao Q, Wu K, Fan D. MicroRNAs in gastrointestinal cancer: prognostic significance and potential role in chemoresistance. *Expert Opin Biol Ther* 2014; **14**: 1103-1111 [PMID: 24707835 DOI: 10.1517/14712598.2014.907787]

15   **Sonbol MB**, Ahn DH, Bekaii-Saab T. Therapeutic Targeting Strategies of Cancer Stem Cells in Gastrointestinal Malignancies. *Biomedicines* 2019; **7** [PMID: 30857342 DOI: 10.3390/biomedicines7010017]

16   **Yeldag G**, Rice A, Del Río Hernández A. Chemoresistance and the Self-Maintaining Tumor Microenvironment. *Cancers (Basel)* 2018; **10** [PMID: 30487436 DOI: 10.3390/cancers10120471]

17   **Zheng X**, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, Wu CC, LeBleu VS, Kalluri R. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* 2015; **527**: 525-530 [PMID: 26560028 DOI: 10.1038/nature16064]

18   **Singh A**, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene* 2010; **29**: 4741-4751 [PMID: 20531305 DOI: 10.1038/onc.2010.215]

19   **Zheng H**, Liu Z, Liu T, Cai Y, Wang Y, Lin S, Chen J, Wang J, Wang Z, Jiang B. Fas signaling promotes chemoresistance in gastrointestinal cancer by up-regulating P-glycoprotein. *Oncotarget* 2014; **5**: 10763-10777 [PMID: 25333257 DOI: 10.18632/oncotarget.2498]

20   **Polyak K**, Weinberg RA. Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. *Nat Rev Cancer* 2009; **9**: 265-273 [PMID: 19262571 DOI: 10.1038/nrc2620]

21   **Saxena M**, Stephens MA, Pathak H, Rangarajan A. Transcription factors that mediate epithelial-mesenchymal transition lead to multidrug resistance by upregulating ABC transporters. *Cell Death Dis* 2011; **2**: e179 [PMID: 21734725 DOI: 10.1038/cddis.2011.61]

22   **Fletcher JI**, Haber M, Henderson MJ, Norris MD. ABC transporters in cancer: more than just drug efflux pumps. *Nat Rev Cancer* 2010; **10**: 147-156 [PMID: 20075923 DOI: 10.1038/nrc2789]

23   **Fletcher JI**, Williams RT, Henderson MJ, Norris MD, Haber M. ABC transporters as mediators of drug resistance and contributors to cancer cell biology. *Drug Resist Updat* 2016; **26**: 1-9 [PMID: 27180306 DOI: 10.1016/j.drup.2016.03.001]

24   **Das M**, Law S. Role of tumor microenvironment in cancer stem cell chemoresistance and recurrence. *Int J Biochem Cell Biol* 2018; **103**: 115-124 [PMID: 30153480 DOI: 10.1016/j.biocel.2018.08.011]

25   **Raziq K**, Cai M, Dong K, Wang P, Afrifa J, Fu S. Competitive endogenous network of lncRNA, miRNA, and mRNA in the chemoresistance of gastrointestinal tract adenocarcinomas. *Biomed Pharmacother* 2020; **130**: 110570 [PMID: 32763816 DOI: 10.1016/j.biopha.2020.110570]

26   **Aguda BD**. Modeling microRNA-transcription factor networks in cancer. *Adv Exp Med Biol* 2013; **774**: 149-167 [PMID: 23377973 DOI: 10.1007/978-94-007-5590-1_9]

27   **Qiu H**, Fang X, Luo Q, Ouyang G. Cancer stem cells: a potential target for cancer therapy. *Cell Mol Life Sci* 2015; **72**: 3411-3424 [PMID: 25967289 DOI: 10.1007/s00018-015-1920-4]

28   **Stem J**, Flickinger JC Jr, Merlino D, Caparosa EM, Snook AE, Waldman SA. Therapeutic targeting

of gastrointestinal cancer stem cells. *Regen Med* 2019; **14**: 331-343 [PMID: 31025613 DOI: 10.2217/rme-2018-0146]

29   **Bekaii-Saab T**, El-Rayes B. Identifying and targeting cancer stem cells in the treatment of gastric cancer. *Cancer* 2017; **123**: 1303-1312 [PMID: 28117883 DOI: 10.1002/cncr.30538]

30   **Boroughs LK**, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. *Nat Cell Biol* 2015; **17**: 351-359 [PMID: 25774832 DOI: 10.1038/ncb3124]

31   **Guerra F**, Arbini AA, Moro L. Mitochondria and cancer chemoresistance. *Biochim Biophys Acta Bioenerg* 2017; **1858**: 686-699 [PMID: 28161329 DOI: 10.1016/j.bbabio.2017.01.012]

32   **Wang Y**, Lu JH, Wang F, Wang YN, He MM, Wu QN, Lu YX, Yu HE, Chen ZH, Zhao Q, Liu J, Chen YX, Wang DS, Sheng H, Liu ZX, Zeng ZL, Xu RH, Ju HQ. Inhibition of fatty acid catabolism augments the efficacy of oxaliplatin-based chemotherapy in gastrointestinal cancers. *Cancer Lett* 2020; **473**: 74-89 [PMID: 31904482 DOI: 10.1016/j.canlet.2019.12.036]

33   **Manoochehri Khoshinani H**, Afshar S, Najafi R. Hypoxia: A Double-Edged Sword in Cancer Therapy. *Cancer Invest* 2016; **34**: 536-545 [PMID: 27824512 DOI: 10.1080/07357907.2016.1245317]

34   **Landskron G**, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res* 2014; **2014**: 149185 [PMID: 24901008 DOI: 10.1155/2014/149185]

35   **Savant SS**, Sriramkumar S, O'Hagan HM. The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer. *Cancers (Basel)* 2018; **10** [PMID: 30061485 DOI: 10.3390/cancers10080251]

36   **Schirmer M**, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA, Ter Horst R, Jansen T, Jacobs L, Bonder MJ, Kurilshikov A, Fu J, Joosten LAB, Zhernakova A, Huttenhower C, Wijmenga C, Netea MG, Xavier RJ. Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity. *Cell* 2016; **167**: 1125-1136.e8 [PMID: 27814509 DOI: 10.1016/j.cell.2016.10.020]

37   **Garajová I**, Balsano R, Wang H, Leonardi F, Giovannetti E, Deng D, Peters GJ. The role of the microbiome in drug resistance in gastrointestinal cancers. *Expert Rev Anticancer Ther* 2021; **21**: 165-176 [PMID: 33115280 DOI: 10.1080/14737140.2021.1844007]

38   **Kobayashi H**, Enomoto A, Woods SL, Burt AD, Takahashi M, Worthley DL. Cancer-associated fibroblasts in gastrointestinal cancer. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 282-295 [PMID: 30778141 DOI: 10.1038/s41575-019-0115-0]

39   **Massagué J**. TGFbeta in Cancer. *Cell* 2008; **134**: 215-230 [PMID: 18662538 DOI: 10.1016/j.cell.2008.07.001]

40   **Pardali K**, Moustakas A. Actions of TGF-beta as tumor suppressor and pro-metastatic factor in human cancer. *Biochim Biophys Acta* 2007; **1775**: 21-62 [PMID: 16904831 DOI: 10.1016/j.bbcan.2006.06.004]

41   **Shi Y**, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* 2003; **113**: 685-700 [PMID: 12809600 DOI: 10.1016/s0092-8674(03)00432-x]

42   **Kamiya Y**, Miyazono K, Miyazawa K. Smad7 inhibits transforming growth factor-beta family type i receptors through two distinct modes of interaction. *J Biol Chem* 2010; **285**: 30804-30813 [PMID: 20663871 DOI: 10.1074/jbc.M110.166140]

43   **Nakao A**, Afrakhte M, Morén A, Nakayama T, Christian JL, Heuchel R, Itoh S, Kawabata M, Heldin NE, Heldin CH, ten Dijke P. Identification of Smad7, a TGFbeta-inducible antagonist of TGF-beta signalling. *Nature* 1997; **389**: 631-635 [PMID: 9335507 DOI: 10.1038/39369]

44   **Derynck R**, Muthusamy BP, Saeteurn KY. Signaling pathway cooperation in TGF-β-induced epithelial-mesenchymal transition. *Curr Opin Cell Biol* 2014; **31**: 56-66 [PMID: 25240174 DOI: 10.1016/j.ceb.2014.09.001]

45   **Zhang YE**. Non-Smad pathways in TGF-beta signaling. *Cell Res* 2009; **19**: 128-139 [PMID: 19114990 DOI: 10.1038/cr.2008.328]

46   **Jung B**, Staudacher JJ, Beauchamp D. Transforming Growth Factor β Superfamily Signaling in Development of Colorectal Cancer. *Gastroenterology* 2017; **152**: 36-52 [PMID: 27773809 DOI: 10.1053/j.gastro.2016.10.015]

47   **Hao Y**, Baker D, Ten Dijke P. TGF-β-Mediated Epithelial-Mesenchymal Transition and Cancer Metastasis. *Int J Mol Sci* 2019; **20** [PMID: 31195692 DOI: 10.3390/ijms20112767]

48   **Peñuelas S**, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. *Cancer Cell* 2009; **15**: 315-327 [PMID: 19345330 DOI: 10.1016/j.ccr.2009.02.011]

49   **Achyut BR**, Yang L. Transforming growth factor-β in the gastrointestinal and hepatic tumor microenvironment. *Gastroenterology* 2011; **141**: 1167-1178 [PMID: 21839702 DOI: 10.1053/j.gastro.2011.07.048]

50   **Itatani Y**, Kawada K, Sakai Y. Transforming Growth Factor-β Signaling Pathway in Colorectal Cancer and Its Tumor Microenvironment. *Int J Mol Sci* 2019; **20** [PMID: 31756952 DOI: 10.3390/ijms20235822]

51   **Yang L**, Pang Y, Moses HL. TGF-beta and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends Immunol* 2010; **31**: 220-227 [PMID: 20538542 DOI: 10.1016/j.it.2010.04.002]

52   **Calon A**, Espinet E, Palomo-Ponce S, Tauriello DV, Iglesias M, Céspedes MV, Sevillano M, Nadal

C, Jung P, Zhang XH, Byrom D, Riera A, Rossell D, Mangues R, Massagué J, Sancho E, Batlle E. Dependency of colorectal cancer on a TGF-β-driven program in stromal cells for metastasis initiation. *Cancer Cell* 2012; **22**: 571-584 [PMID: 23153532 DOI: 10.1016/j.ccr.2012.08.013]

53 **Tsushima H**, Ito N, Tamura S, Matsuda Y, Inada M, Yabuuchi I, Imai Y, Nagashima R, Misawa H, Takeda H, Matsuzawa Y, Kawata S. Circulating transforming growth factor beta 1 as a predictor of liver metastasis after resection in colorectal cancer. *Clin Cancer Res* 2001; **7**: 1258-1262 [PMID: 11350892]

54 **Ebert MP**, Yu J, Miehlke S, Fei G, Lendeckel U, Ridwelski K, Stolte M, Bayerdörffer E, Malfertheiner P. Expression of transforming growth factor beta-1 in gastric cancer and in the gastric mucosa of first-degree relatives of patients with gastric cancer. *Br J Cancer* 2000; **82**: 1795-1800 [PMID: 10839293 DOI: 10.1054/bjoc.1999.1107]

55 **Ma GF**, Miao Q, Zeng XQ, Luo TC, Ma LL, Liu YM, Lian JJ, Gao H, Chen SY. Transforming growth factor-β1 and -β2 in gastric precancer and cancer and roles in tumor-cell interactions with peripheral blood mononuclear cells in vitro. *PLoS One* 2013; **8**: e54249 [PMID: 23342108 DOI: 10.1371/journal.pone.0054249]

56 **Hawinkels LJ**, Verspaget HW, van Duijn W, van der Zon JM, Zuidwijk K, Kubben FJ, Verheijen JH, Hommes DW, Lamers CB, Sier CF. Tissue level, activation and cellular localisation of TGF-beta1 and association with survival in gastric cancer patients. *Br J Cancer* 2007; **97**: 398-404 [PMID: 17637685 DOI: 10.1038/sj.bjc.6603877]

57 **Hu WQ**, Wang LW, Yuan JP, Yan SG, Li JD, Zhao HL, Peng CW, Yang GF, Li Y. High expression of transform growth factor beta 1 in gastric cancer confers worse outcome: results of a cohort study on 184 patients. *Hepatogastroenterology* 2014; **61**: 245-250 [PMID: 24895830]

58 **Gholamin M**, Moaven O, Memar B, Farshchian M, Naseh H, Malekzadeh R, Sotoudeh M, Rajabi-Mashhadi MT, Forghani MN, Farrokhi F, Abbaszadegan MR. Overexpression and interactions of interleukin-10, transforming growth factor beta, and vascular endothelial growth factor in esophageal squamous cell carcinoma. *World J Surg* 2009; **33**: 1439-1445 [PMID: 19440651 DOI: 10.1007/s00268-009-0070-y]

59 **Ramamoorthi G**, Sivalingam N. Molecular mechanism of TGF-β signaling pathway in colon carcinogenesis and status of curcumin as chemopreventive strategy. *Tumour Biol* 2014; **35**: 7295-7305 [PMID: 24668546 DOI: 10.1007/s13277-014-1840-1]

60 **Villalba M**, Evans SR, Vidal-Vanaclocha F, Calvo A. Role of TGF-β in metastatic colon cancer: it is finally time for targeted therapy. *Cell Tissue Res* 2017; **370**: 29-39 [PMID: 28560691 DOI: 10.1007/s00441-017-2633-9]

61 **Lampropoulos P**, Zizi-Sermpetzoglou A, Rizos S, Kostakis A, Nikiteas N, Papavassiliou AG. TGF-beta signalling in colon carcinogenesis. *Cancer Lett* 2012; **314**: 1-7 [PMID: 22018778 DOI: 10.1016/j.canlet.2011.09.041]

62 **Fleming NI**, Jorissen RN, Mouradov D, Christie M, Sakthianandeswaren A, Palmieri M, Day F, Li S, Tsui C, Lipton L, Desai J, Jones IT, McLaughlin S, Ward RL, Hawkins NJ, Ruszkiewicz AR, Moore J, Zhu HJ, Mariadason JM, Burgess AW, Busam D, Zhao Q, Strausberg RL, Gibbs P, Sieber OM. SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer. *Cancer Res* 2013; **73**: 725-735 [PMID: 23139211 DOI: 10.1158/0008-5472.CAN-12-2706]

63 **Bellam N**, Pasche B. Tgf-beta signaling alterations and colon cancer. *Cancer Treat Res* 2010; **155**: 85-103 [PMID: 20517689 DOI: 10.1007/978-1-4419-6033-7_5]

64 **Takagi Y**, Koumura H, Futamura M, Aoki S, Ymaguchi K, Kida H, Tanemura H, Shimokawa K, Saji S. Somatic alterations of the SMAD-2 gene in human colorectal cancers. *Br J Cancer* 1998; **78**: 1152-1155 [PMID: 9820171 DOI: 10.1038/bjc.1998.645]

65 **Zhang B**, Zhang B, Chen X, Bae S, Singh K, Washington MK, Datta PK. Loss of Smad4 in colorectal cancer induces resistance to 5-fluorouracil through activating Akt pathway. *Br J Cancer* 2014; **110**: 946-957 [PMID: 24384683 DOI: 10.1038/bjc.2013.789]

66 **Brunen D**, Willems SM, Kellner U, Midgley R, Simon I, Bernards R. TGF-β: an emerging player in drug resistance. *Cell Cycle* 2013; **12**: 2960-2968 [PMID: 23974105 DOI: 10.4161/cc.26034]

67 **Huang S**, Hölzel M, Knijnenburg T, Schlicker A, Roepman P, McDermott U, Garnett M, Grernrum W, Sun C, Prahallad A, Groenendijk FH, Mittempergher L, Nijkamp W, Neefjes J, Salazar R, Ten Dijke P, Uramoto H, Tanaka F, Beijersbergen RL, Wessels LF, Bernards R. MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signaling. *Cell* 2012; **151**: 937-950 [PMID: 23178117 DOI: 10.1016/j.cell.2012.10.035]

68 **Kim JC**, Roh SA, Cho DH, Kim TW, Yoon SN, Kim CW, Yu CS, Kim SY, Kim YS. Chemoresponsiveness associated with canonical molecular changes in colorectal adenocarcinomas. *Anticancer Res* 2009; **29**: 3115-3123 [PMID: 19661324]

69 **Zhou YL**, Zhang WC, Chen XB, Xiao ZF, Qiao Y, Yu DK, Lin DX, Tan W. [The association between polymorphism of transforming growth factor-β1 and radiochemotherapy response and survival in esophageal squamous cell carcinoma patients]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2011; **45**: 583-587 [PMID: 22041558]

70 **Peters GJ**. Novel developments in the use of antimetabolites. *Nucleosides Nucleotides Nucleic Acids* 2014; **33**: 358-374 [PMID: 24940694 DOI: 10.1080/15257770.2014.894197]

71 **Zhang N**, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: mechanisms of resistance and reversal strategies. *Molecules* 2008; **13**: 1551-1569 [PMID: 18794772 DOI: 10.3390/molecules13081551]

72 **Chen J**, Han M, Saif MW. TAS-102 an Emerging Oral Fluoropyrimidine. *Anticancer Res* 2016; **36**: 21-26 [PMID: 26722024]

73   **Boulay JL**, Mild G, Lowy A, Reuter J, Lagrange M, Terracciano L, Laffer U, Herrmann R, Rochlitz C. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. *Br J Cancer* 2002; **87**: 630-634 [PMID: 12237773 DOI: 10.1038/sj.bjc.6600511]

74   **Buess M**, Terracciano L, Reuter J, Ballabeni P, Boulay JL, Laffer U, Metzger U, Herrmann R, Rochlitz C. STRAP is a strong predictive marker of adjuvant chemotherapy benefit in colorectal cancer. *Neoplasia* 2004; **6**: 813-820 [PMID: 15720808 DOI: 10.1593/neo.04307]

75   **Alhopuro P**, Alazzouzi H, Sammalkorpi H, Dávalos V, Salovaara R, Hemminki A, Järvinen H, Mecklin JP, Schwartz S Jr, Aaltonen LA, Arango D. SMAD4 levels and response to 5-fluorouracil in colorectal cancer. *Clin Cancer Res* 2005; **11**: 6311-6316 [PMID: 16144935 DOI: 10.1158/1078-0432.ccr-05-0244]

76   **Papageorgis P**, Cheng K, Ozturk S, Gong Y, Lambert AW, Abdolmaleky HM, Zhou JR, Thiagalingam S. Smad4 inactivation promotes malignancy and drug resistance of colon cancer. *Cancer Res* 2011; **71**: 998-1008 [PMID: 21245094 DOI: 10.1158/0008-5472.CAN-09-3269]

77   **Refaat B**, El-Shemi AG, Kensara OA, Mohamed AM, Idris S, Ahmad J, Khojah A. Vitamin D3 enhances the tumouricidal effects of 5-Fluorouracil through multipathway mechanisms in azoxymethane rat model of colon cancer. *J Exp Clin Cancer Res* 2015; **34**: 71 [PMID: 26205949 DOI: 10.1186/s13046-015-0187-9]

78   **Huang MY**, Lin CH, Huang CM, Tsai HL, Huang CW, Yeh YS, Chai CY, Wang JY. Relationships between SMAD3 expression and preoperative fluoropyrimidine-based chemoradiotherapy response in locally advanced rectal cancer patients. *World J Surg* 2015; **39**: 1257-1267 [PMID: 25561186 DOI: 10.1007/s00268-014-2917-0]

79   **Cheng JC**, Graber MS, Hsu FM, Tsai CL, Castaneda L, Lee JM, Chang DT, Koong AC. High serum levels of vascular endothelial growth factor-A and transforming growth factor-β1 before neoadjuvant chemoradiotherapy predict poor outcomes in patients with esophageal squamous cell carcinoma receiving combined modality therapy. *Ann Surg Oncol* 2014; **21**: 2361-2368 [PMID: 24623035 DOI: 10.1245/s10434-014-3611-z]

80   **Moon JR**, Oh SJ, Lee CK, Chi SG, Kim HJ. TGF-β1 protects colon tumor cells from apoptosis through XAF1 suppression. *Int J Oncol* 2019; **54**: 2117-2126 [PMID: 31081052 DOI: 10.3892/ijo.2019.4776]

81   **Quan Q**, Zhong F, Wang X, Chen K, Guo L. PAR2 Inhibition Enhanced the Sensitivity of Colorectal Cancer Cells to 5-FU and Reduced EMT Signaling. *Oncol Res* 2019; **27**: 779-788 [PMID: 30841957 DOI: 10.3727/096504018X15442985680348]

82   **Romano G**, Santi L, Bianco MR, Giuffrè MR, Pettinato M, Bugarin C, Garanzini C, Savarese L, Leoni S, Cerrito MG, Leone BE, Gaipa G, Grassilli E, Papa M, Lavitrano M, Giovannoni R. The TGF-β pathway is activated by 5-fluorouracil treatment in drug resistant colorectal carcinoma cells. *Oncotarget* 2016; **7**: 22077-22091 [PMID: 26956045 DOI: 10.18632/oncotarget.7895]

83   **Moon SU**, Kang MH, Sung JH, Kim JW, Lee JO, Kim YJ, Lee KW, Bang SM, Lee JS, Kim JH. Effect of Smad3/4 on chemotherapeutic drug sensitivity in colorectal cancer cells. *Oncol Rep* 2015; **33**: 185-192 [PMID: 25370208 DOI: 10.3892/or.2014.3582]

84   **Zhang H**, Ren L, Ding Y, Li F, Chen X, Ouyang Y, Zhang Y, Zhang D. Hyaluronan-mediated motility receptor confers resistance to chemotherapy *via* TGFβ/Smad2-induced epithelial-mesenchymal transition in gastric cancer. *FASEB J* 2019; **33**: 6365-6377 [PMID: 30802150 DOI: 10.1096/fj.201802186R]

85   **Florea AM**, Büsselberg D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers (Basel)* 2011; **3**: 1351-1371 [PMID: 24212665 DOI: 10.3390/cancers3011351]

86   **Haller DG**. Recent updates in the clinical use of platinum compounds for the treatment of gastrointestinal cancers. *Semin Oncol* 2004; **31**: 10-16 [PMID: 15726529 DOI: 10.1053/j.seminoncol.2004.11.006]

87   **Carrato A**, Gallego J, Díaz-Rubio E. Oxaliplatin: results in colorectal carcinoma. *Crit Rev Oncol Hematol* 2002; **44**: 29-44 [PMID: 12398998 DOI: 10.1016/s1040-8428(01)00192-5]

88   **Mao L**, Li Y, Zhao J, Li Q, Yang B, Wang Y, Zhu Z, Sun H, Zhai Z. Transforming growth factor-β1 contributes to oxaliplatin resistance in colorectal cancer *via* epithelial to mesenchymal transition. *Oncol Lett* 2017; **14**: 647-654 [PMID: 28693217 DOI: 10.3892/ol.2017.6209]

89   **Kim YH**, Lee SB, Shim S, Kim A, Park JH, Jang WS, Lee SJ, Myung JK, Park S, Kim MJ. Hyaluronic acid synthase 2 promotes malignant phenotypes of colorectal cancer cells through transforming growth factor beta signaling. *Cancer Sci* 2019; **110**: 2226-2236 [PMID: 31102316 DOI: 10.1111/cas.14070]

90   **Yin J**, Wang L, Wang Y, Shen H, Wang X, Wu L. Curcumin reverses oxaliplatin resistance in human colorectal cancer *via* regulation of TGF-β/Smad2/3 signaling pathway. *Onco Targets Ther* 2019; **12**: 3893-3903 [PMID: 31190888 DOI: 10.2147/OTT.S199601]

91   **Tanaka K**, Miyata H, Sugimura K, Fukuda S, Kanemura T, Yamashita K, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M, Wada H, Nakajima K, Takiguchi S, Mori M, Doki Y. miR-27 is associated with chemoresistance in esophageal cancer through transformation of normal fibroblasts to cancer-associated fibroblasts. *Carcinogenesis* 2015; **36**: 894-903 [PMID: 26026166 DOI: 10.1093/carcin/bgv067]

92   **Gelmon K**. The taxoids: paclitaxel and docetaxel. *Lancet* 1994; **344**: 1267-1272 [PMID: 7967989 DOI: 10.1016/s0140-6736(94)90754-4]

93   **Bekaii-Saab TS**, Villalona-Calero MA. Preclinical experience with docetaxel in gastrointestinal

cancers. *Semin Oncol* 2005; **32**: S3-S9 [PMID: 16015550 DOI: 10.1053/j.seminoncol.2005.04.002]

94 **Ojima I**, Das M. Recent advances in the chemistry and biology of new generation taxoids. *J Nat Prod* 2009; **72**: 554-565 [PMID: 19239240 DOI: 10.1021/np8006556]

95 **Koizumi W**, Akiya T, Sato A, Yamaguchi K, Sakuyama T, Nakayama N, Tanabe S, Higuchi K, Sasaki T, Sekikawa T; Tokyo Cooperative Oncology Group (TCOG GI Group). Second-line chemotherapy with biweekly paclitaxel after failure of fluoropyrimidine-based treatment in patients with advanced or recurrent gastric cancer: a report from the gastrointestinal oncology group of the Tokyo cooperative oncology group, TCOG GC-0501 trial. *Jpn J Clin Oncol* 2009; **39**: 713-719 [PMID: 19812061 DOI: 10.1093/jjco/hyp099]

96 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1224-1235 [PMID: 25240821 DOI: 10.1016/S1470-2045(14)70420-6]

97 **Ajani JA**. Docetaxel for gastric and esophageal carcinomas. *Oncology (Williston Park)* 2002; **16**: 89-96 [PMID: 12108902]

98 **Tsukada T**, Fushida S, Harada S, Terai S, Yagi Y, Kinoshita J, Oyama K, Tajima H, Ninomiya I, Fujimura T, Ohta T. Low-dose paclitaxel modulates tumour fibrosis in gastric cancer. *Int J Oncol* 2013; **42**: 1167-1174 [PMID: 23443842 DOI: 10.3892/ijo.2013.1801]

99 **Fujita T**, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. *PLoS One* 2015; **10**: e0130808 [PMID: 26110809 DOI: 10.1371/journal.pone.0130808]

100 **Zhou K**, Shi X, Huo J, Liu W, Yang D, Yang T, Qin T, Wang C. Bone morphogenetic protein 4 is overexpressed in and promotes migration and invasion of drug-resistant cancer cells. *Int J Biol Macromol* 2017; **101**: 427-437 [PMID: 28315766 DOI: 10.1016/j.ijbiomac.2017.03.064]

101 **Matsunaga T**, Kezuka C, Morikawa Y, Suzuki A, Endo S, Iguchi K, Miura T, Nishinaka T, Terada T, El-Kabbani O, Hara A, Ikari A. Up-Regulation of Carbonyl Reductase 1 Renders Development of Doxorubicin Resistance in Human Gastrointestinal Cancers. *Biol Pharm Bull* 2015; **38**: 1309-1319 [PMID: 26328486 DOI: 10.1248/bpb.b15-00176]

102 **Rivankar S**. An overview of doxorubicin formulations in cancer therapy. *J Cancer Res Ther* 2014; **10**: 853-858 [PMID: 25579518 DOI: 10.4103/0973-1482.139267]

103 **Li J**, Liu H, Yu J, Yu H. Chemoresistance to doxorubicin induces epithelial-mesenchymal transition *via* upregulation of transforming growth factor β signaling in HCT116 colon cancer cells. *Mol Med Rep* 2015; **12**: 192-198 [PMID: 25684678 DOI: 10.3892/mmr.2015.3356]

104 **Izutani R**, Kato M, Asano S, Imano M, Ohyanagi H. Expression of manganese superoxide disumutase influences chemosensivity in esophageal and gastric cancers. *Cancer Detect Prev* 2002; **26**: 213-221 [PMID: 12269769 DOI: 10.1016/s0361-090x(02)00059-4]

105 **Cordeiro HG**, de Sousa Faria AV, Ferreira-Halder CV. Vemurafenib downmodulates aggressiveness mediators of colorectal cancer (CRC): Low Molecular Weight Protein Tyrosine Phosphatase (LMWPTP), Protein Tyrosine Phosphatase 1B (PTP1B) and Transforming Growth Factor β (TGFβ). *Biol Chem* 2020; **401**: 1063-1069 [PMID: 32229687 DOI: 10.1515/hsz-2020-0124]

106 **Ebbing EA**, Steins A, Fessler E, Stathi P, Lesterhuis WJ, Krishnadath KK, Vermeulen L, Medema JP, Bijlsma MF, van Laarhoven HWM. Esophageal Adenocarcinoma Cells and Xenograft Tumors Exposed to Erb-b2 Receptor Tyrosine Kinase 2 and 3 Inhibitors Activate Transforming Growth Factor Beta Signaling, Which Induces Epithelial to Mesenchymal Transition. *Gastroenterology* 2017; **153**: 63-76.e14 [PMID: 28286209 DOI: 10.1053/j.gastro.2017.03.004]

107 **Zhou X**, Men X, Zhao R, Han J, Fan Z, Wang Y, Lv Y, Zuo J, Zhao L, Sang M, Liu XD, Shan B. miR-200c inhibits TGF-β-induced-EMT to restore trastuzumab sensitivity by targeting ZEB1 and ZEB2 in gastric cancer. *Cancer Gene Ther* 2018; **25**: 68-76 [PMID: 29302045 DOI: 10.1038/s41417-017-0005-y]

108 **Kawaguchi Y**, Kono K, Mimura K, Mitsui F, Sugai H, Akaike H, Fujii H. Targeting EGFR and HER-2 with cetuximab- and trastuzumab-mediated immunotherapy in oesophageal squamous cell carcinoma. *Br J Cancer* 2007; **97**: 494-501 [PMID: 17622245 DOI: 10.1038/sj.bjc.6603885]

109 **Kawaguchi Y**, Kono K, Mimura K, Sugai H, Akaike H, Fujii H. Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. *Int J Cancer* 2007; **120**: 781-787 [PMID: 17096332 DOI: 10.1002/ijc.22370]

110 **Mimura K**, Kono K, Hanawa M, Kanzaki M, Nakao A, Ooi A, Fujii H. Trastuzumab-mediated antibody-dependent cellular cytotoxicity against esophageal squamous cell carcinoma. *Clin Cancer Res* 2005; **11**: 4898-4904 [PMID: 16000588 DOI: 10.1158/1078-0432.CCR-04-2476]

111 **Grygielewicz P**, Dymek B, Bujak A, Gunerka P, Stanczak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K, Zdzalik D. Epithelial-mesenchymal transition confers resistance to selective FGFR inhibitors in SNU-16 gastric cancer cells. *Gastric Cancer* 2016; **19**: 53-62 [PMID: 25407459 DOI: 10.1007/s10120-014-0444-1]

112 **Shi X**, Mihaylova VT, Kuruvilla L, Chen F, Viviano S, Baldassarre M, Sperandio D, Martinez R, Yue P, Bates JG, Breckenridge DG, Schlessinger J, Turk BE, Calderwood DA. Loss of TRIM33

causes resistance to BET bromodomain inhibitors through MYC- and TGF-β-dependent mechanisms. *Proc Natl Acad Sci U S A* 2016; **113**: E4558-E4566 [PMID: 27432991 DOI: 10.1073/pnas.1608319113]

113   **Llopiz D**, Dotor J, Casares N, Bezunartea J, Díaz-Valdés N, Ruiz M, Aranda F, Berraondo P, Prieto J, Lasarte JJ, Borrás-Cuesta F, Sarobe P. Peptide inhibitors of transforming growth factor-beta enhance the efficacy of antitumor immunotherapy. *Int J Cancer* 2009; **125**: 2614-2623 [PMID: 19530254 DOI: 10.1002/ijc.24656]

114   **Rodríguez-Ruiz ME**, Rodríguez I, Mayorga L, Labiano T, Barbes B, Etxeberria I, Ponz-Sarvise M, Azpilikueta A, Bolaños E, Sanmamed MF, Berraondo P, Calvo FA, Barcelos-Hoff MH, Perez-Gracia JL, Melero I. TGFβ Blockade Enhances Radiotherapy Abscopal Efficacy Effects in Combination with Anti-PD1 and Anti-CD137 Immunostimulatory Monoclonal Antibodies. *Mol Cancer Ther* 2019; **18**: 621-631 [PMID: 30683810 DOI: 10.1158/1535-7163.MCT-18-0558]

115   **Tauriello DVF**, Palomo-Ponce S, Stork D, Berenguer-Llergo A, Badia-Ramentol J, Iglesias M, Sevillano M, Ibiza S, Cañellas A, Hernando-Momblona X, Byrom D, Matarin JA, Calon A, Rivas EI, Nebreda AR, Riera A, Attolini CS, Batlle E. TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature* 2018; **554**: 538-543 [PMID: 29443964 DOI: 10.1038/nature25492]

116   **Lai Z**, Yan Z, Chen W, Peng J, Feng J, Li Q, Jin Y, Lin J. Hedyotis diffusa Willd suppresses metastasis in 5fluorouracilresistant colorectal cancer cells by regulating the TGFβ signaling pathway. *Mol Med Rep* 2017; **16**: 7752-7758 [PMID: 28944846 DOI: 10.3892/mmr.2017.7500]

117   **Shen A**, Chen H, Chen Y, Lin J, Lin W, Liu L, Sferra TJ, Peng J. Pien Tze Huang Overcomes Multidrug Resistance and Epithelial-Mesenchymal Transition in Human Colorectal Carcinoma Cells *via* Suppression of TGF-β Pathway. *Evid Based Complement Alternat Med* 2014; **2014**: 679436 [PMID: 25505925 DOI: 10.1155/2014/679436]

118   **Kim EJ**, Kang JI, Kwak JW, Jeon CH, Tung NH, Kim YH, Choi CH, Hyun JW, Koh YS, Yoo ES, Kang HK. The anticancer effect of (1S,2S,3E,7E,11E)-3,7,11, 15-cembratetraen-17,2-olide(LS-1) through the activation of TGF-β signaling in SNU-C5/5-FU, fluorouracil-resistant human colon cancer cells. *Mar Drugs* 2015; **13**: 1340-1359 [PMID: 25786063 DOI: 10.3390/md13031340]

119   **Wang X**, Liu C, Wang J, Fan Y, Wang Z, Wang Y. Oxymatrine inhibits the migration of human colorectal carcinoma RKO cells *via* inhibition of PAI-1 and the TGF-β1/Smad signaling pathway. *Oncol Rep* 2017; **37**: 747-753 [PMID: 27959430 DOI: 10.3892/or.2016.5292]

120   **Wang J**, Wu M, Zheng D, Zhang H, Lv Y, Zhang L, Tan HS, Zhou H, Lao YZ, Xu HX. Garcinol inhibits esophageal cancer metastasis by suppressing the p300 and TGF-β1 signaling pathways. *Acta Pharmacol Sin* 2020; **41**: 82-92 [PMID: 31371781 DOI: 10.1038/s41401-019-0271-3]

121   **Kim YM**, Kim IH, Nam TJ. Capsosiphon fulvescens glycoprotein reduces AGS gastric cancer cell migration by downregulating transforming growth factor-β1 and integrin expression. *Int J Oncol* 2013; **43**: 1059-1065 [PMID: 23934170 DOI: 10.3892/ijo.2013.2055]

122   **Kensara OA**, El-Shemi AG, Mohamed AM, Refaat B, Idris S, Ahmad J. Thymoquinone subdues tumor growth and potentiates the chemopreventive effect of 5-fluorouracil on the early stages of colorectal carcinogenesis in rats. *Drug Des Devel Ther* 2016; **10**: 2239-2253 [PMID: 27468227 DOI: 10.2147/DDDT.S109721]

123   **Câmara J**, Jarai G. Epithelial-mesenchymal transition in primary human bronchial epithelial cells is Smad-dependent and enhanced by fibronectin and TNF-alpha. *Fibrogenesis Tissue Repair* 2010; **3**: 2 [PMID: 20051102 DOI: 10.1186/1755-1536-3-2]

124   **Park JH**, Kim YH, Park EH, Lee SJ, Kim H, Kim A, Lee SB, Shim S, Jang H, Myung JK, Park S, Kim MJ. Effects of metformin and phenformin on apoptosis and epithelial-mesenchymal transition in chemoresistant rectal cancer. *Cancer Sci* 2019; **110**: 2834-2845 [PMID: 31278880 DOI: 10.1111/cas.14124]

125   **Dai G**, Sun B, Gong T, Pan Z, Meng Q, Ju W. Ginsenoside Rb2 inhibits epithelial-mesenchymal transition of colorectal cancer cells by suppressing TGF-β/Smad signaling. *Phytomedicine* 2019; **56**: 126-135 [PMID: 30668333 DOI: 10.1016/j.phymed.2018.10.025]

126   **Kurata T**, Fushida S, Kinoshita J, Oyama K, Yamaguchi T, Okazaki M, Miyashita T, Tajima H, Ninomiya I, Ohta T. Low-dose eribulin mesylate exerts antitumor effects in gastric cancer by inhibiting fibrosis *via* the suppression of epithelial-mesenchymal transition and acts synergistically with 5-fluorouracil. *Cancer Manag Res* 2018; **10**: 2729-2742 [PMID: 30147370 DOI: 10.2147/CMAR.S167846]

127   **Yang AD**, Fan F, Camp ER, van Buren G, Liu W, Somcio R, Gray MJ, Cheng H, Hoff PM, Ellis LM. Chronic oxaliplatin resistance induces epithelial-to-mesenchymal transition in colorectal cancer cell lines. *Clin Cancer Res* 2006; **12**: 4147-4153 [PMID: 16857785 DOI: 10.1158/1078-0432.CCR-06-0038]

128   **Moustakas A**, Heldin P. TGFβ and matrix-regulated epithelial to mesenchymal transition. *Biochim Biophys Acta* 2014; **1840**: 2621-2634 [PMID: 24561266 DOI: 10.1016/j.bbagen.2014.02.004]

129   **Steins A**, Ebbing EA, Creemers A, van der Zalm AP, Jibodh RA, Waasdorp C, Meijer SL, van Delden OM, Krishnadath KK, Hulshof MCCM, Bennink RJ, Punt CJA, Medema JP, Bijlsma MF, van Laarhoven HWM. Chemoradiation induces epithelial-to-mesenchymal transition in esophageal adenocarcinoma. *Int J Cancer* 2019; **145**: 2792-2803 [PMID: 31018252 DOI: 10.1002/ijc.32364]

130   **Zhao Y**, Zhu J, Shi B, Wang X, Lu Q, Li C, Chen H. The transcription factor LEF1 promotes tumorigenicity and activates the TGF-β signaling pathway in esophageal squamous cell carcinoma. *J Exp Clin Cancer Res* 2019; **38**: 304 [PMID: 31296250 DOI: 10.1186/s13046-019-1296-7]

131   **Yue D**, Zhang Z, Li J, Chen X, Ping Y, Liu S, Shi X, Li L, Wang L, Huang L, Zhang B, Sun Y, Zhang Y. Transforming growth factor-beta1 promotes the migration and invasion of sphere-forming stem-like cell subpopulations in esophageal cancer. *Exp Cell Res* 2015; **336**: 141-149 [PMID: 26096658 DOI: 10.1016/j.yexcr.2015.06.007]

132   **Sato F**, Kubota Y, Natsuizaka M, Maehara O, Hatanaka Y, Marukawa K, Terashita K, Suda G, Ohnishi S, Shimizu Y, Komatsu Y, Ohashi S, Kagawa S, Kinugasa H, Whelan KA, Nakagawa H, Sakamoto S. EGFR inhibitors prevent induction of cancer stem-like cells in esophageal squamous cell carcinoma by suppressing epithelial-mesenchymal transition. *Cancer Biol Ther* 2015; **16**: 933-940 [PMID: 25897987 DOI: 10.1080/15384047.2015.1040959]

133   **Park JW**, Park JM, Park DM, Kim DY, Kim HK. Stem Cells Antigen-1 Enriches for a Cancer Stem Cell-Like Subpopulation in Mouse Gastric Cancer. *Stem Cells* 2016; **34**: 1177-1187 [PMID: 26869189 DOI: 10.1002/stem.2329]

134   **Chistiakov DA**, Orekhov AN, Bobryshev YV. Dendritic Cells in Colorectal Cancer and a Potential for their Use in Therapeutic Approaches. *Curr Pharm Des* 2016; **22**: 2431-2438 [PMID: 26845127 DOI: 10.2174/1381612822666160203141740]

135   **Tanaka H**, Shinto O, Yashiro M, Yamazoe S, Iwauchi T, Muguruma K, Kubo N, Ohira M, Hirakawa K. Transforming growth factor β signaling inhibitor, SB-431542, induces maturation of dendritic cells and enhances anti-tumor activity. *Oncol Rep* 2010; **24**: 1637-1643 [PMID: 21042762 DOI: 10.3892/or_00001028]

136   **Watanabe M**, Kono K, Kawaguchi Y, Mizukami Y, Mimura K, Maruyama T, Izawa S, Fujii H. NK cell dysfunction with down-regulated CD16 and up-regulated CD56 molecules in patients with esophageal squamous cell carcinoma. *Dis Esophagus* 2010; **23**: 675-681 [PMID: 20545975 DOI: 10.1111/j.1442-2050.2010.01073.x]

137   **Zeng D**, Li M, Zhou R, Zhang J, Sun H, Shi M, Bin J, Liao Y, Rao J, Liao W. Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and Immunotherapeutically Relevant Gene Signatures. *Cancer Immunol Res* 2019; **7**: 737-750 [PMID: 30842092 DOI: 10.1158/2326-6066.CIR-18-0436]

138   **Zhou YJ**, Zhu GQ, Lu XF, Zheng KI, Wang QW, Chen JN, Zhang QW, Yan FR, Li XB. Identification and validation of tumour microenvironment-based immune molecular subgroups for gastric cancer: immunotherapeutic implications. *Cancer Immunol Immunother* 2020; **69**: 1057-1069 [PMID: 32100076 DOI: 10.1007/s00262-020-02525-8]

139   **Chen X**, Wang L, Li P, Song M, Qin G, Gao Q, Zhang Z, Yue D, Wang D, Nan S, Qi Y, Li F, Yang L, Huang L, Zhang M, Zhang B, Gao Y, Zhang Y. Dual TGF-β and PD-1 blockade synergistically enhances MAGE-A3-specific CD8^{+} T cell response in esophageal squamous cell carcinoma. *Int J Cancer* 2018; **143**: 2561-2574 [PMID: 29981155 DOI: 10.1002/ijc.31730]

140   **Malvicini M**, Ingolotti M, Piccioni F, Garcia M, Bayo J, Atorrasagasti C, Alaniz L, Aquino JB, Espinoza JA, Gidekel M, Scharovsky OG, Matar P, Mazzolini G. Reversal of gastrointestinal carcinoma-induced immunosuppression and induction of antitumoural immunity by a combination of cyclophosphamide and gene transfer of IL-12. *Mol Oncol* 2011; **5**: 242-255 [PMID: 21515097 DOI: 10.1016/j.molonc.2011.03.007]

141   **Ciszewski WM**, Sobierajska K, Wawro ME, Klopocka W, Chefczyńska N, Muzyczuk A, Siekacz K, Wujkowska A, Niewiarowska J. The ILK-MMP9-MRTF axis is crucial for EndMT differentiation of endothelial cells in a tumor microenvironment. *Biochim Biophys Acta Mol Cell Res* 2017; **1864**: 2283-2296 [PMID: 28893556 DOI: 10.1016/j.bbamcr.2017.09.004]

142   **Zhang H**, Xie C, Yue J, Jiang Z, Zhou R, Xie R, Wang Y, Wu S. Cancer-associated fibroblasts mediated chemoresistance by a FOXO1/TGFβ1 signaling loop in esophageal squamous cell carcinoma. *Mol Carcinog* 2017; **56**: 1150-1163 [PMID: 27769097 DOI: 10.1002/mc.22581]

143   **Li Z**, Chan K, Qi Y, Lu L, Ning F, Wu M, Wang H, Wang Y, Cai S, Du J. Participation of CCL1 in Snail-Positive Fibroblasts in Colorectal Cancer Contribute to 5-Fluorouracil/Paclitaxel Chemoresistance. *Cancer Res Treat* 2018; **50**: 894-907 [PMID: 28934847 DOI: 10.4143/crt.2017.356]

144   **Tang YA**, Chen YF, Bao Y, Mahara S, Yatim SMJM, Oguz G, Lee PL, Feng M, Cai Y, Tan EY, Fong SS, Yang ZH, Lan P, Wu XJ, Yu Q. Hypoxic tumor microenvironment activates GLI2 *via* HIF-1α and TGF-β2 to promote chemoresistance in colorectal cancer. *Proc Natl Acad Sci U S A* 2018; **115**: E5990-E5999 [PMID: 29891662 DOI: 10.1073/pnas.1801348115]

145   **Houthuijzen JM**, Daenen LG, Roodhart JM, Voest EE. The role of mesenchymal stem cells in anti-cancer drug resistance and tumour progression. *Br J Cancer* 2012; **106**: 1901-1906 [PMID: 22596239 DOI: 10.1038/bjc.2012.201]

146   **He W**, Liang B, Wang C, Li S, Zhao Y, Huang Q, Liu Z, Yao Z, Wu Q, Liao W, Zhang S, Liu Y, Xiang Y, Liu J, Shi M. MSC-regulated lncRNA MACC1-AS1 promotes stemness and chemoresistance through fatty acid oxidation in gastric cancer. *Oncogene* 2019; **38**: 4637-4654 [PMID: 30742067 DOI: 10.1038/s41388-019-0747-0]

147   **Khorrami S**, Zavaran Hosseini A, Mowla SJ, Soleimani M, Rakhshani N, Malekzadeh R. MicroRNA-146a induces immune suppression and drug-resistant colorectal cancer cells. *Tumour Biol* 2017; **39**: 1010428317698365 [PMID: 28466779 DOI: 10.1177/1010428317698365]

148   **Yu Y**, Kanwar SS, Patel BB, Oh PS, Nautiyal J, Sarkar FH, Majumdar AP. MicroRNA-21 induces stemness by downregulating transforming growth factor beta receptor 2 (TGFβR2) in colon cancer cells. *Carcinogenesis* 2012; **33**: 68-76 [PMID: 22072622 DOI: 10.1093/carcin/bgr246]

149   **Sun C**, Wang FJ, Zhang HG, Xu XZ, Jia RC, Yao L, Qiao PF. miR-34a mediates oxaliplatin

resistance of colorectal cancer cells by inhibiting macroautophagy *via* transforming growth factor-β /Smad4 pathway. *World J Gastroenterol* 2017; **23**: 1816-1827 [PMID: 28348487 DOI: 10.3748/wjg.v23.i10.1816]

150   **Zhao P**, Ma YG, Zhao Y, Liu D, Dai ZJ, Yan CY, Guan HT. MicroRNA-552 deficiency mediates 5-fluorouracil resistance by targeting SMAD2 signaling in DNA-mismatch-repair-deficient colorectal cancer. *Cancer Chemother Pharmacol* 2019; **84**: 427-439 [PMID: 31087138 DOI: 10.1007/s00280-019-03866-7]

151   **Liu A**, Zhu J, Wu G, Cao L, Tan Z, Zhang S, Jiang L, Wu J, Li M, Song L, Li J. Antagonizing miR-455-3p inhibits chemoresistance and aggressiveness in esophageal squamous cell carcinoma. *Mol Cancer* 2017; **16**: 106 [PMID: 28633632 DOI: 10.1186/s12943-017-0669-9]

152   **Luo Y**, Wu J, Wu Q, Li X, Zhang J, Rong X, Rao J, Liao Y, Bin J, Huang N, Liao W. miR-577 Regulates TGF-β Induced Cancer Progression through a SDPR-Modulated Positive-Feedback Loop with ERK-NF-κB in Gastric Cancer. *Mol Ther* 2019; **27**: 1166-1182 [PMID: 30879950 DOI: 10.1016/j.ymthe.2019.02.002]

153   **Zhu QL**, Li Z, Lv CM, Wang W. MiR-187 influences cisplatin-resistance of gastric cancer cells through regulating the TGF-β/Smad signaling pathway. *Eur Rev Med Pharmacol Sci* 2019; **23**: 9907-9914 [PMID: 31799659 DOI: 10.26355/eurrev_201911_19556]

154   **Li LQ**, Pan D, Chen Q, Zhang SW, Xie DY, Zheng XL, Chen H. Sensitization of Gastric Cancer Cells to 5-FU by MicroRNA-204 Through Targeting the TGFBR2-Mediated Epithelial to Mesenchymal Transition. *Cell Physiol Biochem* 2018; **47**: 1533-1545 [PMID: 29940566 DOI: 10.1159/000490871]

155   **Pennathur A**, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2013; **381**: 400-412 [PMID: 23374478 DOI: 10.1016/S0140-6736(12)60643-6]

156   **Liu N**, Wu Y, Cheng W, Wang L, Zhuang L. Identification of novel prognostic biomarkers by integrating multi-omics data in gastric cancer. *BMC Cancer* 2021; **21**: 460 [PMID: 33902514 DOI: 10.1186/s12885-021-08210-y]

157   **Calone I**, Souchelnytskyi S. Inhibition of TGFβ signaling and its implications in anticancer treatments. *Exp Oncol* 2012; **34**: 9-16 [PMID: 22453142]