Mechanism underlying circRNA dysregulation in the TME of digestive system cancer

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Circular RNAs (circRNAs) are a new series of noncoding RNAs (ncRNAs) that have been reported to be expressed in eukaryotic cells and have a variety of biological functions in the regulation of cancer pathogenesis and progression. The TME, as a microscopic ecological environment, consists of a variety of cells, including tumor cells, immune cells and other normal cells, ECM and a large number of signaling molecules. The crosstalk between circRNAs and the TME plays a complicated role in affecting the malignant behaviors of digestive system cancers. Herein, we summarize the mechanisms underlying aberrant circRNA expression in the TME of the digestive system cancers, including immune surveillance, angiogenesis, EMT, and ECM remodelling. The regulation of the TME by circRNA is expected to be a new therapeutic method.

KEYWORDS
- circular RNAs, tumor microenvironment, molecular mechanism, digestive system cancer, chemotherapy resistance

Introduction

Cancer of the digestive system (DSC) has the highest mortality rate among invasive cancers worldwide. Although current treatments, including surgery, radiotherapy, and immunotherapy are improving, the average survival time of patients with advanced DSC remains low due to the cryptic, rapid, and aggressive nature of early symptoms (1–4). In recent years, numerous studies have reported that the tumor microenvironment (TME) plays a critical role in the genesis and development of digestive tumors (5–8). The TME represents the immediate ecological environment for tumor growth and is composed of multiple cell types that collectively participate in complex regulation (9, 10). These
cellular interactions are conducive to tumor progression, immune escape, angiogenesis, and metastasis (11), and play crucial roles in the chemoresistance of cancer. (Figure 1)

Recently, many circRNAs in eukaryotic cells have been characterized by high-throughput RNA sequencing and new bioinformatics algorithms, and have crucial roles in different types of cancers (12–15). In terms of microstructure, circRNAs have been found to be ncRNAs with covalently closed structures, transcribed by RNA polymerase II, without 5’-3’ polar or polyadenylne tails (16, 17). This covalently closed circular structure makes circRNA less susceptible to exonuclease digestion than linear RNA (15, 18, 19). Therefore, aberrant expression of circRNA may accumulate in cells, which can lead to cancer progression (20). CircRNAs mainly participate in and regulate the progression of DSC by influencing immune cells, energy metabolism, signal transduction, angiogenesis, and lymphatic duct formation in the TME (18, 21, 22). In addition, numerous studies have shown that circRNAs play a key role in human DSCs as diagnostic markers, prognostic targets, and therapeutic agents (9, 23–26).

At present, the crosstalk between circRNAs and various components in the TME has attracted great attention. The role of circRNAs in the TME may become another emerging direction for cancer treatment. Recent studies on circRNAs mainly focus on their impact on cancer biological behavior, but lack a systematic summary of the tumor microenvironment, especially in digestive system tumors.

In this review, we summarize the clinical features and biological functions of DSCs affected by circRNAs and the regulatory mechanisms in the TME. CircRNAs will be a potentially useful tool for the diagnosis and therapeutic targeting of DSC. Finally, we also discussed the messenger role of exosomal circRNAs in the TME of digestive system cancers, and revealed the vital role of exosomal circRNAs in signal transmission.

Biogenesis, regulation and degradation of CircRNAs

It was once thought that the translation mechanism of eukaryotic cells could not translate circRNAs due to the circRNA’s unique ring structure (27). However, the discovery of internal ribosome entry sites and m6A completely overturned this thinking (28–32). These mechanisms promote the independent initiation of translation at the 5’ end of circRNA and enable circRNA to exert a strong influence on translation control through its sponge function to form a new mRNA family (33–36) (Figure 2).

Most current studies have reported that circRNAs are the products of back-splicing of the precursor mRNA of the exon, and its downstream 5’ splice site is connected with the upstream 3’ splice site by a 3’-5’ phosphodiester bond at the junction site (37, 38). The formation of circRNA mainly includes three back-splicing models: exon-skipping, intron pairing, and RNA-binding protein interactions, and the three models contain different mechanisms (39). The first model is exon hopping, which results in the loss of one or more exons of a mature mRNA. In this model, the lariat-driven circularization proceeds as two nonadjacent exons join together, finally producing an mRNA with skipped exons, a circular RNA transcript and a lariat structure. This circularization can achieve a more efficient circle production (40).

The second model is intron pairing-driven circularization. In this biogenesis mechanism, two introns flanking the pre-mRNA exon/exon have one structure capable of interlinking. Flanking introns are close to each other, forming a secondary conformation that allows reverse splicing of the splice site. Most intron pairing patterns are promoted by ALU repeats. The longer the intron length is, the greater the chance that they will have more ALU elements, thereby enhancing exon circularization.

Third, the main mechanism of this mode is through RNA-binding proteins (RBPs). RBPs are able to bind to pre-mRNA and link flanking introns together, this process is induced by protein dimerization, which creates an RNA loop.

The expression level of homeostatic circRNAs can be regulated at three stages. First, the biogenesis of circRNA begins with the transcription and binding of Pol II to the pre-mRNA that produces circRNA (41); second, cis and trans regulators can further affect the efficiency of back-splicing catalyzed by spliceosomal mechanisms (42, 43); and finally, circRNA turnover also plays an important role in expression levels (44).

At present, circRNAs mainly regulate downstream targets through high expression in cancer, so it is critical to understand the degradation and inactivation of circRNAs for future targeted therapy (45). Three main types of nucleases are involved in RNA decay: 5’ exonuclease, 3’ exonuclease, and endonuclease, which cleave RNA from the inside. However, due to the unique closed-loop structure of circRNA, the degradation of circRNA should be mediated by nicking endonucleases (42, 46, 47). The first mode of endonuclease induced circRNA degradation is mediated by Ago2, which relies on endogenous guide RNAs, such as miRNAs, to execute its function (48). miRNA first binds to circRNA in base pairing and directs Ago2-dependent cleavage. For instance, circAGO2 interacts with HuR, resulting in reduced AGO2 binding and the promotion of tumorigenesis and invasiveness (49–51). Moreover, miR1224 splices circFilip1L to regulate chronic inflammatory pain in an Ago2-dependent manner by targeting Ubr5 (52). However, Ago2-dependent circRNA degradation does not work for circRNAs that have no specific miRNA target (53). It is at this point that the role of m6A modification comes into focus. The important role of m6A modification in circRNA regulation has been reported in many recent articles (54–56). m6A modified
DNA generates circRNA precursors by transcribing local exons, and mature circRNAs are formed by reverse splicing. CircRNA degrades in two ways: 1) RNA degradation mediated by AGO2 protein, in which MiRNA binds to circRNA first and then guides AGO2 to perform dependent cleavage; and 2) m6A modification, and CircRNA can be cleaved by endonuclease after m6A modification. Mature circRNA functions in three ways: as a miRNA sponge to regulate downstream targets, translate proteins, and enhance protein reactions.
circRNA is also cleaved by endoribonuclease via the YTHDF2-HRSP12-RNase P/MRP axis (57); however, the number of circRNA degradations mediated by m6A modification reported thus far remains limited, and further studies are needed in this area. In addition to the above, adenosine deaminase 1 acting on RNA (ADAR1), as a dsRNA-binding protein, can inhibit the intron pairing process of circRNA formation by reducing the pairing activity of the ALU repeat series, thus preventing the formation of circRNA. On the other hand, ADAR1 can interrupt miRNA processing, thus regulating the formation of circRNA. A deeper understanding of circRNA biosynthesis, regulation and degradation can facilitate further targeted therapies against cancers caused by circRNA dysregulation.

Biological functions of circRNAs

Current studies have shown that circRNAs perform their biological functions in four main ways: miRNA sponge, transcriptional regulation, coding for proteins and peptides, functions with RNA-binding proteins (54, 58, 59).

miRNA sponge

Most of circRNAs involved in this review can regulate downstream targets by acting as miRNA sponges to affect the TME in digestive system cancers. Although circRNA has a unique closed-loop structure, it still contains miRNA binding sites, which endows it with potential as a miRNA sponge (60–62). This property suggests that circRNAs can inhibit the activity of mature miRNAs, increase the level of endogenous targets, and inhibit miRNAs to regulate the expression of downstream genes (63, 64). For example, CIRS-7, which contains more than 70 miRNA seed regions, is considered a ceRNA and plays an important role in a variety of cancers (65, 66). In esophageal cancer, CIRS-7 upregulates the expression of HOXB13 by sponging miR-7, thereby promoting the proliferation, invasion and metastasis of tumor cells (67). In gastric cancer, CIRS-7 promotes cancer cell proliferation and invasion through the miR-7/PTEN/P13K/AKT pathway (68). These effects are achieved by CIRS-7 acting as a molecular sponge.

CircRNA functions with RNA-binding proteins

In addition to sponging miRNAs, circRNAs also bind to different RBPS with different potential roles: to inhibit protein function (protein bait), to promote protein complex formation and to allow interactions between different proteins (69). First the protein bait, CircMbl (70), as a highly expressed and evolutionarily conserved circRNA, contains multiple binding sites for the MBL protein as well as part of the MBL open reading frame, and has been shown to be translatable (71). There was a good correlation between circMbl and MBL levels, suggesting that circMbl biosynthesis could be adjusted according to MBL protein levels (72). Second, circRNA forms a complex with protein. As a circRNA closely related to cell cycle progression, circ-foxo3 binds to cell division protein kinase 2 (CDK2) and cyclin-dependent kinase inhibitor 1 (OR P21) to form ternary complex (73). CDK2 can promote the cell cycle, while P21 inhibits cell cycle progression, and eventually the formation of this ternary complex prevents CDK2 function and blocks cell cycle progression.

Coding for proteins and peptides

Although circRNAs were originally defined as noncoding RNAs, they still have the ability to encode proteins, depending on their specific structures, such as the presence of internal ribosome entry site (IRES) (74), and N6-methyladenosine (m6A)-mediated initiation (75, 76). Even in the absence of the 5’ cap and related cap-binding protein factors, circRNAs can recruit ribosomal 40S subunits to initiate translation via specialized sequences in the 5’ noncoding region and then produce small proteins and micropeptides (16).

Transcriptional regulation

In addition, circRNA also plays a role in transcriptional regulation, and by regulating two key steps, circRNA can enhance transcription at the transcriptional level (77). The first step is the initiation step, and circRNAs are only involved in the formation of preinitiation complexes. The last step is during the elongation phase, CircRNAs accumulate at their site of transcription and increase parental gene transcription elongation by interacting with RNA polymerase II (78, 79). Additionally, the biogenesis of circRNAs via exon skipping can be seen as a passive function of circular transcripts (41).

Aberrant circRNA expression regulates the clinical features and cell biological functions of DSCs

A range of abnormally expressed circRNAs have been proven to be associated with the progression of DSC, which may lead to the development of a new understanding of the clinical application of circRNAs. In this section, we summarize the association between abnormal circRNA expression and...
biological functions (Table 1) and clinicopathological features (Table 2).

Hepatocellular carcinoma

In patients with HCC, a series of circRNAs have been demonstrated to be closely related to the tumorigenesis and development of HCC. (Figure 3) For example, high expression of circ0003410, circUBAP2, and circFBXO11 was positively related to tumor size (80–82). Low expression of circ110102 and high expression of circSORE were associated with low survival rates, of which circSORE was also negatively correlated with recurrence-free survival (83, 84). As tumor suppressor factors, low expression of circ0007456 and circDLC1 is associated with poor prognosis, tumor stage, lymph node metastasis stage, microvascular invasion, and macrovascular invasion (85, 86). Furthermore, upregulated circUBAP2 and circ0003288 were positively correlated with distant metastasis and invasion (87, 88). High expression of circTMEM181 and circUHRF1 enhances anti-PD1 resistance, causing reduced overall survival, early recurrence, and a high rate of microvascular invasion (89, 90). In terms of biological function, high expression of circ0003410, circ00074854, and circDLC1 could promote HCC cell proliferation and motility in vivo and in vitro (80, 86, 91). CircUBAP2 and circ0001806, as tumor promoters, promote distant metastasis of cancer cells in vivo by enhancing the migration and invasion abilities of cells (87, 92). Circ110102, as a tumor suppressor, can attenuate invasion and thus weaken the metastatic ability of tumor cells (83). CircFBXO11 and circSORE promote malignant proliferation by inhibiting apoptosis (82, 84). CircTMEM181 and circUHRF1 attenuate the immune response signal to promote the immune escape of HCC cells and prevent the killing ability of immune cells (89, 90). In contrast, circ0007456 has been shown to increase the sensitivity of natural killer (NK) cells to tumor cells and thus enhance the killing effect of immune cells (85).

Pancreatic cancer

Given the highly metastatic nature of pancreatic cancer cells, distant metastasis, especially lymphatic metastasis, occurs in the early stage of pancreatic cancer. Relevant studies have shown that high expression of circ0074298, circCCT3, and circ0001666 in pancreatic cancer is closely related to lymph node metastasis (93–95), while low expression of circNFIB1 and circ0092367 is related to advanced TNM stage, lymph node metastasis, and overall survival (96, 97). High expression of circZNF91 promotes chemotherapy resistance in pancreatic cancer cells and is inversely proportional to overall survival (98). In terms of cellular activities, downregulation of circ0074298 has been shown to significantly inhibit the malignant phenotype and promote apoptosis and chemotherapy resistance of pancreatic cancer in vitro and in vivo (95). High expression levels of circZNF91 and circCCT3 promote the migration and invasion of pancreatic cancer cells, and increase tumor volume and weight in vivo (93, 98). Overexpression of circNFIB1 inhibits lymphangiogenesis of PDAC in vitro and LN metastasis of PDAC in vivo (96). As a tumor suppressor, overexpression of circ0092367 inhibits xenograft tumor growth, cell invasion, epithelial-mesenchymal transformation (EMT), and gemcitabine resistance (97).

Gastric carcinoma

In GC, high expression of circSHKB1 and circRANGAPI plays a role in promoting cancer, which is closely associated with lymph node metastasis and advanced TNM staging. Low expression of circCUL2, a tumor suppressor, is positively correlated with the above cancer characteristics (99–101). Upregulation of circ0000620 was shown to be negatively correlated with overall survival of GC (102). In terms of drug resistance, upregulated circPVT1 mediates CIS resistance, and high expression of circARVCF, circ0000260 and low expression of circMCTP2 are closely related to CDDP resistance, thus reducing the efficacy of chemotherapy (103–106). Moreover, Evb-circLMP2A has been shown to promote the invasion and metastasis of GC cells, while high expression of circOXCT1 inhibits lymph node metastasis and pathological stage, which is positively associated with the 5-year survival rate (107, 108). In terms of cellular function, circ0000620 and evb-circLMP2A enhance the tube formation capacity and angiogenesis (102, 107), and upregulation of circ0005556, circSHKB1, circRANGAPI, and circ6orf132 increase the invasion and migration ability (99, 100, 109, 110). CircOXCT1 overexpression was reported to suppress cell migration and invasion, and circ0081143 promotes GC cell invasion and metastasis by promoting EMT (108, 111). CircMCTP2 overexpression and circARVCF knockdown promote apoptosis of CDDP-resistant GC cells, thereby reducing cell proliferation (104, 106). Overexpression of circCUL2 and circPVT1 knockdown have been shown to inhibit autophagy and prevent chemotherapy resistance (101, 103).

Colorectal cancer

In CRC, the expression of all associated circRNAs was upregulated and was associated with poor prognosis. For instance, high expression of circ133 and circCSFP1 is associated with clinical tumor metastasis (112, 113), while overexpression of circMYH9, circ0303998, circEIF3K, and circSLC7A6 is associated with shorter overall survival and advanced stages (Stages III and IV) (114–117). Moreover, circ0007031 was
| Cancer type | CircRNA | Role in cancer progression | Cell Function | Axis | Refs. |
|-------------|---------|----------------------------|---------------|------|-------|
| HCC         | circ0003410 | promoter                  | promote HCC cell proliferation and migration | circ0003410/miR-139-3p/CCCL5 Axis | (80) |
| HCC         | Circ0110102 | suppressor                | suppress HCC cell growth, migration, and invasiveness | circ0110102/miR-580-3p/PARP1/CCCL2 | (83) |
| HCC         | circ0074854 | promoter                  | promote HCC cell proliferation and inhibit apoptosis; knockdown of circ0074854 suppress migration, invasion and EMT | / | (91) |
| HCC         | circTMEM181 | promoter                  | CD39 attenuate the immune response signal stimulated by eATP in tumor microenvironment | circTMEM181/miR-488-3p/CD39 | (89) |
| HCC         | circUHRF1   | promoter                  | immune evasion | circUHRF1/miR-449c-3p/TIM-3 | (90) |
| HCC         | circ0007456 | suppressor                | increase NK cell sensitivity to tumor cells | circ0007456/miR-6852-3p/ICAM-1 | (85) |
| HCC         | circUBAP2   | promoter                  | promote HCC cell migration | circUBAP2/miR-4756/IFIT1/IFIT3 axis | (87) |
| HCC         | circDLC1    | suppressor                | overexpression of circDLC1 inhibits the proliferation and motility of HCC cells in vitro and in vivo | circDLC1/miR-488/CD39 | (86) |
| HCC         | circUBAP2   | promoter                  | promote the migration, invasion, and proliferation of HCC cells | circUBAP2/miR-194-3p/MMP9 | (81) |
| HCC         | circ0001806 | promoter                  | knockedown circ0001806 suppressed the proliferation, migration, and invasion of HCC cells | circ0001806/miR-193a-3p/MMP16 | (92) |
| HCC         | circ_0003288 | promoter                  | promote EMT, migration, and invasion of HCC | circ0003288/miR-145/PD-L1 | (88) |
| HCC         | circFBXO11  | suppressor                | circFBXO11 overexpression alleviated the cycle arrest and apoptosis, circFBXO11 knockdown repressed the tumor growth in vivo | circFBXO11/miR-605/FOXO3/ABCB1 | (82) |
| HCC         | circSORE    | promoter                  | circRNASORE knockdown increased apoptosis in sorafenib-resistant cells | circSORE/miR-103a-2-5p/miR-660-3p/β-catenin signaling | (84) |
| GC          | Circ0006620 | promoter                  | circ0000620 knockdown reduced cell viability, colony formation, migration, invasion and tube formation capacity | circ0000620/miR-671-5p/CDH1 | (102) |
| GC          | circ005556  | promoter                  | circ005556 knockdown can inhibit the migration and invasion, and arrest the cell cycle in the G2/M phase | circ005556/miR-4270/MMP19 | (109) |
| GC          | circSHKBP1  | promoter                  | promote GC cell proliferation, migration and invasion | circSHKBP1/miR-582-3p/HIF1/VEGF | (99) |
| GC          | circRANGAP1 | promoter                  | circRANGAP1 silencing suppressed tumor growth and metastasis in vivo, decreased GC cell invasion and migration in vitro | circRANGAP1/miR-877-3p/VEGFA | (100) |
| GC          | ebv-circLMP2A | promoter              | promoted hypoxia-induced tube formation, migration, and angiogenesis | ebv-circLMP2A/KHSRP/VHL/HIF1/VEGFA | (107) |
| GC          | circC6orf132 | promoter                 | promote cell proliferation, migration, and invasion of gastric cancer cells | circC6orf132/miR-873-5p/PKRAA1 | (110) |
| GC          | circ-OXCT1  | suppressor                | circ-OXCT1 overexpression suppressed cell migration and invasion | circ-OXCT1/miR-136-5p/SMAD4 | (108) |
| GC          | circ088143 | promoter                  | migration, invasion, and EMT | circ088143/miR-497-5p/EGFR | (111) |
| GC          | circMCTP2   | suppressor                | promote apoptosis of CDDP resistant GC cells in response to CDDP treatment, and reducing cell proliferation | circMCTP2/miR-99a-3p/MTMR3 | (106) |
| GC          | circCUL2    | suppressor                | overexpression of circCUL2 inhibited autophagy, and inhibited cell proliferation, migration and invasion | circCUL2/miR-142-3p/ROCK2 | (101) |
| GC          | circPVT1    | promoter                  | circPVT1 knockdown repressed DDP resistance in DDP-resistant GC cells by inducing apoptosis and inhibiting autophagy | circPVT1/miR-30A-5p/YAP1 | (103) |
| GC          | circARVCF   | promoter                  | promote cell invasion and metastasis, inhibit apoptosis | circARVCF/miR-1205/FGFR1 | (104) |

(Continued)
| Cancer type | CircRNA | Role in cancer progression | Cell Function | Axis | Refs. |
|-------------|---------|---------------------------|---------------|------|-------|
| GC          | circ0000260 | promoter                | circ0000260 knockdown inhibited proliferation, migration, invasion and adhesion of CDDP-resistant GAC cells | circ0000260/miR-129-5p /MMP11 | (105) |
| PC          | circ0000977 | promoter                | HIF1A mediated immune escape of PC cells, ADAM10 led to low reactivity of NK cells | circ0000977/miR-153/HIF-1A/ADAM10 | (184) |
| PC          | circZNF91   | promoter                | increase tumor size | circZNF91/miR-23b-3p/HIF-1/3 | (98) |
| PC          | circCCT3    | promoter                | promote the migration, invasion of PC cells, and tumor volume and weight | circCCT3/miR-613/VEGF/VEGFR2 | (93) |
| PC          | circNFIB1   | suppressor              | overexpression of circNFIB1 inhibited lymphangiogenesis of PDAC in vitro, inhibited LN metastasis of PDAC in vivo | circNFIB1/miR-486-5p/PK3R1/VEGF-C | (96) |
| PC          | circ0001666 | promoter                | knockdown of circ_0001666 inhibited the proliferation of PC cells, represses EMT in PC | circ0001666/miR-1251/SOX4 | (94) |
| PC          | circ0092367 | suppressor              | overexpression of circ0092367 inhibited xenograft tumor growth, cell invasion, EMT, and gemcitabine resistance | circ0092367/miR-1206/ESR1 | (97) |
| PC          | circ0074298 | promoter                | downregulation of circ0074298 significantly inhibited cell proliferation, migration, invasion, colony formation and promoted cell cycle arrest, apoptosis and chemoresistance of pancreatic cancer in vitro and vivo | circ0074298/miR-518/SMOC | (95) |
| PC          | circ0001666 | promoter                | circ0001666/miR-1251/SOX4 | (94) |
| PC          | circ0074298 | promoter                | circ0074298/miR-518/SMOC | (95) |
| CRC         | circSLC7A6  | promoter                | promote cell proliferation and invasion, and decreased apoptosis | / | (117) |
| CRC         | circEJF3K   | promoter                | promote cell proliferation, enhance cell colony formation | circEJF3K/miR-214/PD-L1 axis | (116) |
| CRC         | circ0136666 | promoter                | Treg-mediated immune escape | circ0136666/miR-497/PD-L1 | (126) |
| CRC         | circMMPI    | promoter                | circMMPI knockdown inhibits the growth and metastasis of CRC in vivo, suppresses the proliferation and invasion of CRC cell in vitro | circMMPI/miR-1238/MMP1/MM2/PMP9 | (123) |
| CRC         | circ005963  | promoter                | enhance glycolysis and drug resistance to increase the size of drug-resistant tumors in vivo | circ005963/miR-122/PKM2 | (119) |
| CRC         | circ0062682 | promoter                | enhance the proliferation and colony formation of CRC cells | circ0062682/miR-940/PHGDH | (120) |
| CRC         | circMYH9    | promoter                | promoted cell cycle and increased cell cycle proteins | circMYH9/miR-53 | (114) |
| CRC         | circ0030998 | promoter                | promoted tumor proliferation and angiogenesis in vitro | circ0030998/miR-567/VEGFA | (115) |
| CRC         | circUBAP2   | promoter                | circUBAP2 knockdown inhibited CRC cell migratory and invasive abilities | circUBAP2/miR-199a/VEGFA | (121) |
| CRC         | circ0056618 | promoter                | promoted cell proliferation, migration and angiogenesis | circ0056618/CXCR4/VEGF-A | (124) |
| CRC         | circ-ERBIN  | promoter                | accelerate the proliferation, migration, invasion and metastasis of CRC cells in vitro and in vivo | circ-ERBIN/miR-125a-5p-5p/miR-138-5p/4EBP-1/HIF-1/3 | (122) |
| CRC         | circ-133    | promoter                | increased cell migration capacity | circ-133/GEF-H1/RhoA | (112) |
| CRC         | circCCDC66  | promoter                | circCCDC66 knockdown reduced viability, migration and invasion, and enhanced the apoptosis of hypoxia-exposed CRC cells | circCCDC66/miR-3140/autophagy | (125) |
| CRC         | circCSPP1   | promoter                | circCSPP1 promoted CRC cell migration and invasion in vitro, promoted tumor cell liver metastasis in vivo, promoting the progression of EMT | circCSPP1/miR-193a-5p/COL1A1 | (113) |
| CRC         | circ0007031 | promoter                | circ0007031 knockdown repressed CRC cell proliferation, migration and invasion and enhanced 5-FU sensitivity | circ0007031/miR-133b/ARCC5 | (118) |
| ESCC        | circOGDH    | promoter                | accelerated proliferation, metastasis, and invasion of ESCC cells | circOGDH/miR-615-5p/PDIX1 | (127) |
| OSCC        | circ0000140 | suppressor              | overexpression of circ0000140 blocked the proliferation, migration, and invasion of OSCC cells | circ0000140/miR-182-5p/CDC73 | (128) |
| TSCC        | circ000003  | promoter                | circ000003 knockdown significantly inhibited cell invasion and migration, overexpression of circ000003 promoted cell proliferation | circ000003/miR-330-3p/GNS axis | (129) |
| Cancer type | CircRNA | Expression | Clinical features | Refs. |
|------------|---------|------------|-------------------|-------|
| HCC        | circ0003410 | overexpression | tumor size | (80) |
| HCC        | circ110102 | low-expression | survival rate | (83) |
| HCC        | circ00074854 | overexpression | / | (91) |
| HCC        | circTMEM181 | overexpression | anti-PD1 therapy resistance, early recurrence, microvascular invasion | (89) |
| HCC        | circUHRF1 | overexpression | increase tumor size and microvascular invasion, reduce overall survival | (90) |
| HCC        | circ0007456 | low-expression | primary tumor stage, lymph node metastasis | (85) |
| HCC        | circUBAP2 | overexpression | promote tumor migration and metastasis | (87) |
| HCC        | circDLC1 | low-expression | advanced tumor stage, TNM stage and BCLC stage, microvascular invasion, macrovascular invasion | (86) |
| HCC        | circUBAP2 | overexpression | tumor size and high tumor recurrence rate | (81) |
| HCC        | circ0001806 | overexpression | / | (92) |
| HCC        | circ0003288 | overexpression | migration and invasion | (88) |
| HCC        | circFBXO11 | overexpression | tumor size | (82) |
| HCC        | circSORE | overexpression | recurrence free survival and overall survival | (84) |
| GC         | circ0000620 | overexpression | overall survival | (102) |
| GC         | circ0005556 | overexpression | / | (109) |
| GC         | circSHKBP1 | overexpression | advanced pathological staging and poor survival | (99) |
| GC         | circRANGAP1 | overexpression | advanced TNM stage, lymph node metastasis, and poor survival | (100) |
| GC         | ebv-circLMP2A | overexpression | tumor invasion and metastasis | (107) |
| GC         | circC6orf132 | overexpression | / | (110) |
| GC         | circOXT1 | low-expression | lymphatic node metastasis, pathological stages, 5-year overall survival | (108) |
| GC         | circ0081143 | overexpression | / | (111) |
| GC         | circMCTP2 | low-expression | CDDP chemosensitivity, tumor size, TNM stage | (106) |
| GC         | circCUL2 | low-expression | Cisplatin resistance, late-stage GC (stage III+IV), lymph node metastasis, poor differentiation and poor overall survival | (101) |
| GC         | circPVT1 | overexpression | CIS resistance | (103) |
| GC         | circARVCF | overexpression | DDP resistance | (104) |
| GC         | circ0000260 | overexpression | CDDP resistance | (105) |
| PC         | circ0000977 | overexpression | / | (184) |
| PC         | circZNF91 | overexpression | promoted chemoresistance, overall survival | (98) |
| PC         | circCCT3 | overexpression | Vascular invasion, peritoneal metastasis, lymph node metastasis and clinical progression | (93) |
| PC         | circNFIβ1 | low-expression | lymphatic metastasis and high pathological TNM stage | (96) |
| PC         | circ0001666 | overexpression | overall survival, lymphatic metastasis | (94) |
| PC         | circ0092367 | low-expression | advanced tumor stage, lymph node metastasis | (97) |
| PC         | circ0074298 | overexpression | tumor diameter, lymphatic metastasis, and pathological grade | (95) |
| CRC        | circSCL7A6 | overexpression | overall survival, advanced stages (Stage III and IV) | (117) |
| CRC        | circEIF3K | overexpression | overall survival, advanced stages | (116) |
| CRC        | circ0136666 | overexpression | / | (126) |
| CRC        | circMMP1 | overexpression | / | (123) |
| CRC        | circ0005963 | overexpression | Enhancing oxaliplatin resistance | (119) |
| CRC        | circ0062682 | overexpression | Tumor stage | (120) |
| CRC        | circMYH9 | overexpression | overall survival, tumor size, distant metastasis, lymph node metastasis, TNM stage, and p53 status | (114) |
| CRC        | circ0030998 | overexpression | Lymph node metastasis and TNM stage, shorter survival | (115) |

(Continued)
associated with anti-5-fu chemotherapy (118), and upregulated circ0005963 enhances glycolysis and oxaliplatin resistance to increase the size of drug-resistant tumors in vivo (119). In terms of biological function, circSLC7A6, circ-133, circEIF3K, circ0062682, circUBAP2, circ-ERBIN, circCSPP1, and circ0007031 promote cell proliferation and colony formation, and increase migration and invasion (112, 113, 116–118, 120–122). CircMMP1 knockdown inhibits the growth and metastasis

### TABLE 2 Continued

| Cancer type | CircRNA | Expression | Clinical features | Refs. |
|-------------|---------|------------|-------------------|-------|
| CRC         | circUBAP2 | overexpression | /                 | (121) |
| CRC         | circ0056618 | overexpression | /                 | (124) |
| CRC         | circ-ERBIN | overexpression | /                 | (122) |
| CRC         | circ133   | overexpression | metastasis        | (112) |
| CRC         | circCCDC66 | overexpression | /                 | (125) |
| CRC         | circCSPP1 | overexpression | overall survival, metastasis | (113) |
| CRC         | circ0007031 | overexpression | anti-5-fu chemotherapy | (118) |
| ESCC        | circOGDH  | overexpression | promote tumor growth | (127) |
| OSCC        | circ0000140 | low-expression | lymph node metastasis | (128) |
| TSCC        | circ0000003 | overexpression | advanced TNM stage and increased tumor size | (129) |

FIGURE 3

Circ0003410 and circ110102 upregulate CCL5 and CCL2 by sponging miR-139-3p and miR-580-5p, respectively, thereby promoting the polarization of M2 macrophages and promoting cell proliferation and invasion. CircTMEM181 and circUHRF1 promote depletion of CD8+ T and NK cells through the miR-488-3p/CD39 and miR-499-5p/TIM-3 axis, thus inhibiting apoptosis of cancer cells. Circ0007456 upregulates CAM-1 by sponging miR-6852-3p, which increases the lethality of NK cells to cancer cells and promotes tumor cell apoptosis. CircFBXO11 increases the expression of ABCB1 protein on the surface of cancer cells by upregulating FOXO3 and enhancing drug resistance. Circ0003288 promotes EMT through Mir-145/PD-L1. ECM remodeling is mediated by the upregulation of MMP1 and MMP9 by circUBAP2 and circDLC1, thereby promoting metastasis. The role of circRNAs above promotes the occurrence and deterioration of HCC.

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of CRC in vivo and suppresses the proliferation and invasion of CRC cells in vitro (123). CircMYH9 has been shown to promote the cell cycle and increase cell cycle proteins to regulate proliferation (114). Circ0030998 and circ0056618 have been shown to promote angiogenesis in vitro and aid in invasion and metastasis (115, 124). CircCCDC66, as a cancer promoter, is highly expressed in CRC and circCCDC66-knockdown has been shown to reduce viability, migration, and invasion, and promote apoptosis (125). Overexpression of circ0005963 has been shown to enhance glycolysis and drug resistance to increase the size of drug-resistant tumors in vivo (119). Circ0136666 was reported to function as a tumor promoter by mediating Treg-mediated immune escape (126).

Other types of tumors

In addition to the mentioned DSC with high morbidity and malignancy, there are several cases of circRNAs involved in other types of DSC, such as esophageal squamous carcinoma (ESCC), oral squamous cell carcinoma (OSCC), and tongue squamous cell carcinoma (TSCC). For instance, circOGDH is upregulated in ESCC and its overexpression is closely related to tumor size and poor prognosis. In terms of cell activities, circOGDH can promote tumor growth by promoting proliferation, metastasis, invasion, and glutamine metabolism (127). As a tumor suppressor, low expression of circ00000140 is closely associated with poor prognosis of lymph node metastasis in OSCC, and cell function testing showed that overexpression of circ00000140 blocked the proliferation, migration, and invasion of OSCC cells (128). High expression of circ00000003 in ESCC was reported to be correlated with advanced TNM stage and increased tumor size. Overexpression of circ00000003 has been shown to promote cell proliferation, whereas circ00000003 knockdown significantly inhibited cell invasion and migration (129).

Functional mechanisms of circRNAs in the TME

The deterioration of cancers relies on the recruitment and reprogramming of tumor cells to the surrounding normal cells (130). Therefore, in the TME, the crosstalk between tumor cells, immune cells, normal cells, extracellular matrix and various signaling molecules becomes a critical factor (9, 131, 132). As mentioned above, most circRNAs have aberrant expression levels in diverse DSCs, and these dysregulations are caused by different mechanisms. In the following sections, we will focus on the functional mechanisms of circRNA in the TME (Table 3).

CircRNAs regulate the immune system

Macrophages are released into the blood as immature monocyte precursors from bone marrow and migrate to different tissues for corresponding differentiation (133). Different forms of macrophages play different roles in the development of cancer (134). Macrophages can be classified into classical M1 macrophages and alternate M2 macrophages due to different activation procedures (135). Although tumor-associated macrophages (TAMs) are different from the M1 and M2 subtypes, they are generally similar to M2 macrophages and promote tumor growth by inducing immunosuppression (135–137). Previous studies have shown that macrophages play a dual role in cancer, promoting tumor growth and metastasis in addition to inhibiting tumor growth and escape (138–140). In most cases, TAMs promote cancer deterioration and resistance to treatment by providing nutrition and nutritional support to malignant cells (141).

Recent studies have shown that circRNAs promote or inhibit cancer progression in digestive system cancers by regulating macrophage polarization (142). For example, circ0003410, which is highly expressed in liver cancer, promotes the development of HCC by regulating the expression of macrophages. The carcinogenic effect of circ0003410 is mainly reflected in enhancing the proliferation and migration ability of liver cancer cells (80). As a highly expressed chemokine in the TME, CCL5 mainly activates and recruits M2 macrophages, induces extracellular matrix remodelling and enhances tumor cell metastasis and other pro-cancer effects (143, 144). Additionally, the experimental results proved that high expression of circ0003410 could downregulate the anticancer effect of miR-139-3p and upregulate the expression of CCL5 to recruit M2 macrophages and increase the proportion of M2/M1 macrophages to promote cancer progression (80). The chemokine CCL2 is elevated in HCC and is connected with malignant activities and poor prognosis (145, 146), playing an essential role in promoting cancer progression by activating M2 macrophages (147). CCL2 can bind to CCR2 on the macrophage cytomembrane to increase the chemotaxis of TAMs (145). Therefore, lowering the expression level of CCL2 is likely to play a vital role in cancer suppression. Circ0110102, as a tumor suppressor, has low expression in HCC, and its downstream miR-580-5p is associated with poor outcomes, which function to upregulate the expression of CCL2 by decreasing the expression of PPARα. Thus, circ0110102 may function as a sponge of miR-580-5p to decrease the expression of CCL2 through the activation of PPARα in HCC cells (83). Additionally, some studies indicate that exosome-mediated macrophage activation plays an important role in cancer progression (148, 149). Exosomes can transmit signals between cancer cells and...
### TABLE 3 Role of circRNAs in the tumor microenvironment of digestive system tumors.

| Category             | Target | CircRNA | Cancer type | Expression | Function to target                                                                 | Refs. |
|----------------------|--------|---------|-------------|------------|------------------------------------------------------------------------------------|-------|
| **Immune system**    |        |         |             |            |                                                                                    |       |
| macrophages          |        | circ003410 | HCC         | up         | promote polarization of M2 macrophages                                            | (80)  |
| macrophages          |        | circ110102 | HCC         | down       | mediate chemotaxis of monocytes and TAM                                            | (83)  |
| macrophages          |        | circ00074854 | HCC         | up         | knockdown of circ00074854 suppressed macrophage M2 Polarization                   | (91)  |
| macrophages          |        | circTMEM181 | HCC         | up         | interfere with the proliferation of CD8+ T cell and induce exhaustion             | (89)  |
| NK cells             |        | circUHRF1  | HCC         | up         | induce natural killer cell exhaustion                                              | (90)  |
| NK cells             |        | circ0009977 | PC          | up         | evade immune surveillance and NK cell-mediated lysis                               | (184) |
| NK cells             |        | circ0007456 | HCC         | down       | increase NK cell sensitivity to tumor                                              | (85)  |
| CAFs                 |        | circSLC7A6 | CRC         | up         | promote CRC tumorigenesis                                                         | (117) |
| CAFs                 |        | circUBAP2  | HCC         | up         | promotes HCC cell migration                                                        | (87)  |
| CAFs                 |        | circEIF3K  | CRC         | up         | upregulate PD-L1 and promote tumorigenesis                                         | (116) |
| Treg                 |        | circ0136666 | CRC         | up         | Treg-mediated immune escape                                                       | (126) |
| **ECM**              |        | MMP1     | CRC         | up         | degrade fibrous collagen                                                          | (123) |
| MMP1                 |        | circDLC1  | HCC         | down       | degrade fibrous collagen                                                          | (86)  |
| MMP2                 |        | circ0008620 | GC          | up         | degrade type II and IV collagen                                                    | (102) |
| MMP9                 |        | circURAP2  | HCC         | up         | degrade type I and IV collagen                                                    | (81)  |
| MMP16                |        | circ0001806 | HCC         | up         | degrade type II fibrous collagen                                                   | (92)  |
| MMP19                |        | circ0005556 | GC          | up         | /                                                                                  | (109) |
| **metabolism**       |        | glycolysis |              |            |                                                                                   |       |
| glycolysis           |        | circ0001400 | OSCC        | down       | reduce glycolysis                                                                  | (128) |
| glycolysis           |        | circ005963  | CRC         | up         | enhance glycolysis                                                                | (119) |
| glutamine metabolism |        | circZNF91  | PC          | up         | enhance glycolysis                                                                | (98)  |
| glutamine metabolism |        | circ0008003 | TSCC        | up         | promote glutamine catabolism, α-KG production, and ATP production                 | (129) |
| serine metabolism    |        | circOOGDH  | ESCC        | up         | elevated glutamine metabolism                                                     | (127) |
| serine metabolism    |        | circ0062682 | CRC         | up         | promote serine metabolism                                                         | (120) |
| serine metabolism    |        | circMYH9   | CRC         | up         | promote serine metabolism                                                         | (114) |
| **Angiogenesis**     |        | VEGF-A    | CRC         | up         | promote angiogenesis                                                              | (115) |
| VEGF-A               |        | circ0039998 | CRC         | up         | promote angiogenesis                                                              | (121) |
| VEGF-A               |        | circURAP2  | CRC         | up         | promote angiogenesis                                                              | (124) |
| VEGF-A               |        | circ0056618 | CRC         | up         | promote angiogenesis                                                              | (93)  |
| VEGF-A               |        | circCCT3   | PC          | up         | promote angiogenesis                                                              | (99)  |
| VEGF-A               |        | circSHKBP1 | GC          | up         | promote angiogenesis                                                              | (100) |
| VEGF-C               |        | circRANGAP1 | GC          | up         | promote angiogenesis                                                              | (96)  |
| VEGF-C               |        | circNFB1   | PC          | down       | inhibit lymphangiogenesis                                                         |       |
| **Hypoxia**          |        | HIF-1α     | CRC         | up         | increase HIF-1α expression to promote angiogenesis                               | (122) |
| HIF1α/VEGFA          |        | ebv-circLMP2A | GC         | up         | increase HIF-1α expression to promote angiogenesis                               | (107) |
| RhoA                 |        | circ-133   | CRC         | up         | reduce E-cadherin                                                                | (112) |
| autophagy            |        | circCCDC66  | CRC         | up         | promote autophagy                                                                | (125) |
| PRKAA1               |        | circC6orf132 | GC          | up         | promotes glycolysis                                                              | (110) |
| **EMT**              |        | COL1A1     | CRC         | up         | promote EMT                                                                     | (113) |
| SOX4                 |        | circ0016666 | PC          | up         | promote EMT                                                                     | (94)  |
| PD-L1                |        | circ0003288 | HCC         | up         | promote EMT                                                                     | (88)  |
| SMAD4                |        | circOXCT1  | GC          | down       | promote EMT                                                                     | (108) |
| EGFR                 |        | circ0081143 | GC          | up         | promote EMT                                                                     | (111) |
| ESRP1                |        | circ0092567 | PC          | down       | promote EMT                                                                     | (97)  |
| **Chemotherapy resistance** | | drug efflux protein | | | promote EMT                                                                     | (82)  |
TAMs, thus influencing tumor progression (150, 151). Circ00074854 is another tumor promoter in HCC, and circ00074854 knockdown mediates its inhibitory effects by reducing the protein stability of an RNA-binding protein called HuR and exosomes with downregulated circ00074854, which can be delivered to macrophages to inhibit macrophage M2 polarization in vitro (91).

Cancer immunotherapy was once regarded as the key node of cancer treatment; however, due to the existence of immune checkpoints such as PD1, PDL1, and CTLA-4, cancer immunotherapy is limited to a certain extent (152–154). Therefore, inhibitors that target the abovementioned immune checkpoints could change the limitations of current tumor drug resistance and have revolutionized cancer therapy (155–157). In the tumor immune microenvironment, PD1 and its ligand PDL1 can induce tumor resistance to immune-induced apoptosis, thus resisting immunotherapy and promoting cancer progression (158). PD1/PDL1 immunotherapy can block recognition between PD1 and PDL1, thus restoring normal T cell function to recognize tumor cells and prevent tumor escape (159). Overexpression of exosomal circTMEM181 derived from HCC cells targets macrophages, reshapes the immune microenvironment, and induces immunosuppression, specifically by interfering with the viability of CD8+ T cells and inducing depletion. CD39, a pivotal enzyme secreted by macrophages can activate the ATP-adenosine pathway (160, 161), and is upregulated by the circTMEM181/miR-488-3p/CD39 axis. Upregulation of CD39 can impair the signaling of extracellular ATP-stimulated immune responses in the TME, thereby impairing antitumor immunity (162, 163). For instance, CD39 and CD73 can activate the ATP-adenosine pathway through synergistic action to weaken antitumor immunity (164). The interaction between tumor cells and macrophages activates the ATP-adenosine pathway leading to hyposensitivity to anti-PD1 therapy (165, 166). Therefore, abnormal CD39 expression targeting macrophages is expected to be developed as a treatment strategy to reverse resistance to PD1.

Additionally, the depletion of CD39 or macrophages has been verified in vivo to inhibit HCC progression and promote CD8+ T cell exhaustion (89, 144). In addition to macrophages, NK cells are involved in PD1-mediated tumor immunity and drug resistance (167). Extracellular circUHRF1 produced by HCC cells may be a key factor in reducing the immune evasion by impairing NK cell-associated functions. CircUHRF1 suppresses the activity of miR-449c-5p to upregulate TIM-3 expression, which functions as an inhibitory receptor on NK cells to reduce antitumoral immunity (168, 169). Therefore, reducing circUHRF1 expression may be developed as a novel approach to recover sensitivity to anti-PD1 therapy (90).

Cancer immunosurveillance is an important process for the immune system to monitor, recognize, and destroy tumor cells, including elimination, balance, and escape (170–172). In the first stage, innate immune cells kill cancer cells through tumor cell recognition and proinflammatory cytokines. In the second stage, the cancer cells develop resistant clones that cannot be eliminated; at this point, if the cancer cells cannot be eliminated by other means, they will enter the final stage - escape (173, 174). As a highly immunosuppressive subgroup of CD4+ T cells, Tregs regulate the expression of the transcription factor FoxP3 (175), which is positively related to poor outcomes in various cancers by downregulating antitumor immune responses (176).

In CRC, upregulation of circ0136666 promotes PD-L1 and Treg activation by sponging miR-497. Studies have shown that silencing circ0136666 reduces CD4+ and FOXP3+, and upregulates CD8+ Tregs, thereby facilitating immune escape mediated by Tregs through the miR-497/PD-L1 pathway (126). In addition to the abovementioned Tregs, NK cells also play an essential role in immune escape. As the major effector in congenital immunity, NK cells can kill tumor cells in the initial stage (177) and suppress tumor metastasis. When NK cells are inhibited by tumor-derived molecules or related factors, their ability to target tumor cells quickly and effectively will be impaired, ultimately abolishing the process of cancer progression and immune escape (178, 179).
circ0007456 acts as a sponge of miR-6852-3p, which can affect ICAM-1, a cell surface glycoprotein and an adhesion receptor that can regulate tumor development and metastasis (180). ICAM-1 can increase the effect of NK cells on tumor cells, while its downregulation is a key mechanism by which cancer cells evade NK cell attack (181). circ0007456 upregulates ICAM-1 by sponging miR-6852-3p in HCC, and overexpression of ICAM-1 has been shown to increase the sensitivity of tumor cells to NK cells (85). Thus, circ0007456 may represent a promising biomarker of HCC, and targets for immune avoidance. In the TME of pancreatic cancer, hypoxia induces the overexpression of circ0000977, increases the expression of HIF1A and ADAM10, enables tumor cells to avoid immune surveillance and suppresses the lethal effect of NK cells on pancreatic cancer cells (182, 183). However, studies have shown that knocking down circ0000977 attenuates the inhibition of miR-153, whereas high expression of miR-153 attenuates the lethal effect and reduces HIF1A-mediated immune escape (184). The circ0000977/miR-153/HIF1A/ADAM10 axis may be used as an immune sensitizer to treat and/or prevent cancer. Therefore, circRNA-mediated tumor immune surveillance and immune escape in the TME may be vital breakthrough directions for future immunotherapy research.

Cancer-associated fibroblasts and cancer deterioration

CAFs are multifunctional fibroblasts in the TME, whose functions include matrix remodelling, signal transduction with cancer cells, and crosstalk with infiltrating leukocytes and diverse chemokines (185–188). CAFs regulate cancer metastasis and influence angiogenesis and therapeutic response through synthesis and remodelling of the extracellular matrix (ECM) and production of growth factors (189–192). Therefore, if the above cancer-promoting characteristics of CAFs can be targeted for treatment, it will optimize current cancer treatment strategies.

Chemokines have become important participants in the tumorigenesis process (193). CXCL13 and its homologous receptor CXCR5 have demonstrated outstanding abilities to regulate tumor growth, and play crucial roles in inflammation, cancer, and immune responses (194, 195). Matrine, as an alkaloid extracted from traditional Chinese medicine, has anticancer effects (196, 197). In CRC, it inhibits cancer development by inhibiting the secretion of the exosomal circSLC7A6 from CAFs (117). In vitro experiments showed that CXCR5 overexpression reversed the inhibitory effect of matrine on invasion and apoptosis to promote cancer progression. The interaction of exosomal circSLC7A6 with the miR-21, miR-107, and miR-200 families may be a miRNA-dependent means to regulate CXCR5 (198, 199). CXCL11 is another CAF-derived chemokine ligand that participates in the progression of various cancers and mediates the recruitment of T cells, NK cells, and macrophages, predominantly through the receptor CXCR3 (200, 201). The mRNA expression level of CXCL11 is highly expressed in HCC tissues, especially in metastatic HCC compared to the nonmetastatic. Moreover, CXCL11 endows HCC cells with stronger metastasis and cell proliferation ability (202). Bioinformatic analysis and cell experiments confirmed that tumor metastasis regulated by CXCL11 is mediated by circUBAP2. Additionally, circUBAP2 participates in the functions of CXCL11 derived from CAFs via the circUBAP2/miR-4756/IFIT1/IFIT3 axis (87). Hypoxia in the TME is also an important factor in stimulating circRNA secretion by CAFs (203). By culturing CAFs in a hypoxic environment, Yang et al. found that CAFs can secrete exosomes, some of which can secrete circEIF3K. circEIF3K has been shown to promote CRC progression in patients and exerted an oncogenic role in animal and clinical studies by downregulating its downstream effector miR-214 to attenuate the invasion of hypoxia-mediated CRC cells and downregulate PD-L1 expression. Therefore, circEIF3K secreted by CAFs stimulated by hypoxia blocks the expression of its anticancer effects via the miR-214/PD-L1 axis (116). Since circRNA can regulate tumor metastasis by regulating CAFs, it may open up a new strategy for targeted therapy against CAFs.

CircRNAs regulate energy metabolism in the TME

Cancer cells undergo metabolic reprogramming to maintain bioenergetics, redox states, cell signaling, and biosynthesis, which are often poorly vascularized, nutrition-deficient microenvironments (204). Recently, energy metabolism has been regarded as a new hallmark of cancer, which has shifted the research focus toward tumor metabolism (205, 206). In the TME, the crosstalk between complex substance metabolism and circRNAs greatly affects host metabolism and dynamic balance, thus affecting cancer progression. Some circRNAs can influence these behaviors by regulating metabolism (207).

Glucose is the main energy source for almost all cells, including cancer cells, and increased glucose uptake is associated with the proliferation and metastasis of cancer cells (208). Although cancer cells consume a large amount of glucose, they have a strong ability to convert it into lactic acid due to disproportionate oxygen intake (209), and hypoxic tumor glycolysis is more likely to promote metastasis (210). Circ0000140 has been shown to have low expression in OSCC, and overexpressed circ0000140 has been shown to inhibit glycolysis in OSCC cell lines by significantly inhibiting GLUT1 and LDHA protein levels. The above inhibitory effect was caused by sponging miR-182-5p and upregulating CDC73 (128). Circ0000140 has been shown to hinder glycolysis metabolism via the miR-182-5p/CDC73 axis to affect proliferation, migration, and invasion. In addition to influencing tumor
invasion and metastasis by regulating glucose metabolism in the TME, circRNA plays a significant role in chemical resistance \((211)\). Malignant tumors often produce ATP rapidly through glycolysis, which facilitates the rapid proliferation of tumor cells and the generation of chemotherapy resistance \((212)\). The M2 isoform of pyruvate kinase (PKM2) plays a significant role in catalyzing glycolysis \((213)\). Circ0005963 has been proven to function as a sponge for miR-122 to target PKM2. A previous study demonstrated that overexpression of circ0005963 and PKM2 protein in sensitive cells played a vital role in accelerating glycolysis and promoting drug resistance. Additionally, the inhibition of circ0005963 attenuated glycolysis and reversed chemoresistance to oxaliplatin via the circ0005963/miR-122/PKM2 axis \((119)\). The high expression level of circZNF91 secreted by pancreatic cancer cell exosomes in a hypoxic environment significantly promoted chemical resistance. Mechanistically, circZNF91 binds to miR-23b-3p and inhibits the suppression of miR-23b-3p on SIRT1. Moreover, overexpression of SIRT1 leads to the increased glycolysis and GEM chemoresistance by enhancing the stability of HIF-1α \((98)\). Additionally, high expression of circC6orf132 in hypoxic GC cells promotes cell proliferation and glycolysis through the miR-873-5p/PRKAA1 axis \((110)\).

Amino acid metabolism is involved in the development of tumors, and the maladjustment of glutamate metabolism not only promotes the growth of tumor cells but also promotes tumor invasion and metastasis \((204, 214)\). Glutamine is a major nutrient in plasma, and glutaminase can convert glutamine into α-KG to participate in the TCA cycle, carbon and nitrogen metabolism in cells, and provide energy for cells \((215–218)\). Additionally, other studies have shown that glutamine metabolism promotes the malignant proliferation of cancer cells by participating in macromolecular biosynthesis and regulating REDOX homeostasis and signaling pathways \((219)\). In TSCC, circ0000003 upregulates the expression of GLS to promote glutaminase expression and cell proliferation by sponging miR–330–3p. Meanwhile, the miR–330–3p inhibitor has been shown to reverse the above downgrading effects \((129)\). Similarly, circ-OGDH has been shown to elevate glutamine metabolism by sponging miR-615-5p to release PDX1. Further studies showed that increased miR-615-5p decreased glutamine consumption, α-KG production, and ATP content, all of which were inhibited by PDX1 \((127)\).

Beyond that, the serine biosynthesis pathway represents the key point in glucose conversion \((220)\). Serine from synthetic and exogenously ingested glycolysis branches can be converted to glycine and provides a one-carbon unit for one-carbon metabolism \((221)\). The one-carbon unit can regulate the proliferation of cancer cells by affecting nucleotide synthesis, methylation pathways, and redox balance \((222, 223)\). Circ0062682 exerts its carcinomatus functions by sponging miR-940, which targets PHGDH \((120)\). As the first step rate-limiting enzyme in the serine biosynthetic pathway, PHGDH promotes cancer cell proliferation through overexpression in various cancers \((224)\). Studies proved that circ0062682 knockdown could decrease the expression of serine and glycine, scale down NADPH/NADP+ and GSH levels by downregulating PHGDH, thus inhibiting the proliferation of CRC cells. Further research showed that cancer cells can adapt to nutrient stress conditions by increasing serine biosynthesis. The expression of circ0062682 and PHGDH was increased under serum starvation. Serine deprivation could induce the expression of circ0062682, then upregulated PHGDH expression via the miR-940/PHGDH axis \((120)\). In the same way, circMYH9 promoted serine and glycine metabolism through p53–mediated upregulation of PHGDH \((114, 225)\). The results proved that circMYH9 could regulate REDOX homeostasis by inhibiting p53 via m6A modification and upregulating the downstream target PHGDH \((114)\). As a feature of rapid proliferation of tumor cells, circRNAs can meet the high metabolic demand of tumor cells by regulating glycolysis, serine metabolism and glutamine metabolism. Further research in this field may help us to obtain the key to decipher the malignant proliferation of tumor cells.

### Angiogenesis

Tumor cells have very high nutrient requirements to maintain their anabolic demand and energy production efficiency. Tumor angiogenesis can meet the current stringent energy requirements by increasing the uptake of extracellular nutrients \((207)\). Due to the lack of vasculature, tumor growth is limited when the tumor size exceeds 2–3 mm. Here, the angiogenesis switch is triggered to enable survival and promote the invasion and metastasis of cancer cells \((226)\). Angiogenic factors and cytokines in the TME promote tumor angiogenesis \((227)\). In the TME, circRNA plays a critical role in proangiogenic and antiangiogenic signaling networks.

VEGFA is a major factor driving tumor vascular bed dilation. As a part of the growth factor family, VEGFA has a strong ability to promote the angiogenic environment, such as by increasing microvascular density and vascular permeability, finally, leading to tumor resistance to angiogenic therapy \((228, 229)\). Overexpression of circ0030998 can promote angiogenesis by sponging miR-567 to increase VEGFA expression. High expression of VEGFA further promotes cell cycle progression and HUVEC tubular structure formation \((115)\). The latest research shows that circUBAP2 promotes CRC cell progression and angiogenesis via the miR-199a/VEGFA axis. miR-199a directly interacts with VEGFA and significantly suppresses its expression level, which can be reversed by upregulation of circUBAP2 \((121)\). Circ0056618 has been shown to promote angiogenesis by sponging miR-206 and upregulating CXCR4 and VEGFA \((124)\). CircCCT3 functions as a miR-613 sponge to upregulate the expression of VEGFA and
VEGFR2 to promote angiogenesis (93). Additionally, knockdown of circCCT3 reversed the above carcinogenic effects. CircSHKBP1 is an upregulated circRNA in GC tissue that can be efficiently delivered into the circulation by exosomes. CircSHKBP1 sponges miR-582-3p and increases HUR levels (99), to prevent rapid mRNA degradation in the circulation and promote high and stable VEGFA expression by stabilizing VEGFA mRNA expression (230). Additionally, circSHKBP1 directly binds to HSP90 and inhibits the ubiquitination of STUB1 to HSP90. Tumorigenesis of circSHKBP1 can be blocked by anti-VEGF antibodies and HSP90 inhibitors (99). Wang et al. reported that circ-RANGAP1 acted as a sponge for miR-877-30 to promote GC angiogenesis through the miR-877-3p/VEGFA axis (100).

In addition to spreading directly through the blood to other tissues and organs, cancer cells can also spread through the lymphatic system (231). Tumors trigger lymphatic growth and remodelling by secreting lymphangiogenic growth factors such as VEGF-C (232, 233). VEGF-C can bind with VEGFR3 and activate related signaling pathways, promoting lymphatic endothelial cell proliferation and vascular permeability (234). CircNFIB1 is crucial for inhibiting LN metastasis in PDAC. Mechanistically, miR-486-5p promotes lymphangiogenesis in PDAC cells, whereas circNFIB1 directly binds to miR-486-5p to inhibit its expression. PIK3R1, a regulatory subunit of PI3K, suppresses the activation of the PI3K/Akt pathway and inhibits cancer progression (235, 236). miR-486-5p degrades PIK3R1 by targeting its 3’UTR, whereas circNFIB1 reverses the negative regulation of miR-486-5p on PIK3R1 expression by inhibiting the phosphorylation of Akt and increasing the expression of PI3K/ Akt pathway and inhibits cancer progression (235, 236). miR-486-5p degrades PIK3R1 by targeting its 3’UTR, whereas circNFIB1 reverses the negative regulation of miR-486-5p on PIK3R1 expression by inhibiting the phosphorylation of Akt and increasing the expression of PI3K/ Akt pathway and inhibits cancer progression (235, 236).

In conclusion, circRNAs promote angiogenesis primarily by mediating the VEGFA family, creating a favorable microenvironment for nutrient requirements and metastasis of tumor cells. Therefore, targets against circRNAs have great potential as future inhibitors of angiogenesis.

**Hypoxia regulates circRNA production in the TME**

Rapid and unrestricted proliferation limits oxygen and blood supplementation and induces hypoxia, which is a representative microenvironmental feature of almost all solid tumors (237). Rapid tumor proliferation can also stimulate the generation of new vascular systems. In this case, the vasculature becomes disordered and the distance between capillaries increases beyond the ability of oxygen diffusion, which is not conducive to the transport of oxygenated blood (238). As tumor cells adapt to hypoxia, they result in a more malignant and therapeutic resistant tumor phenotype (239).

During this process, the overexpression of HIF-1α is a significant marker. HIF-1α enhances the activity of Snail and Twist and then reduces E-cadherin expression, thereby promoting invasion, a cancer stem cell-like phenotype, and chemoresistance (240). Recently, circRNA has also been shown to be regulated by hypoxia in the TME (112, 122). Hypoxia and TGF-β stimulate the expression of circERBIN, which promotes HIF-1α through a protein called 4EBP-1, which plays a vital role in HIF1-α translation (241). Further studies have shown that 4EBP-1 is a common downstream target for both miR-125a-5p and miR-138-5p, with a negative and positive correlation with circERBIN, respectively. These results suggest that circERBIN increases HIF-1α expression via the miR-125A-5p/miR-138-5p/ 4EBP-1 signaling pathway (122). HIF1α has been shown to upregulate ebv-circLMP2A under hypoxia to enhance angiogenesis, while ebv-circLMP2A stabilizes HIF1α by reducing VHL (242). Mechanistically, ebv-circLMP2A interacts with KHSRP to enhance the degradation of VHL mRNA, thereby activating the HIF1α/VEGFA axis to promote angiogenesis. HIF1α and ebv-circLMP2A under hypoxia promote the increased expression of each in the form of positive feedback (107). In the case of hypoxia, adaptive reprogramming is mediated by the HIF-1 protein in most cases. Hypoxia contributes to the upregulation of circCCDC66 in CRC. Upregulated circCCDC66 can increase the viability of CRC cells in the hypoxic environment, enhance invasion and migration ability, and inhibit apoptosis. While circCCDC66 knockdown can completely reverse its carcinogenic effect by decreasing the inhibition of miR-3140, the increased miR-3140 resulted in the expression of autophagy regulator Beclin1 to inhibit cancer progression by inhibiting autophagy (125). The interior of solid tumors can be roughly divided into hypoxic and normoxic cancer cells (243). After incubation with hypoxic-derived exosomes, prometastatic signals can be transmitted to normoxic cancer cells, resulting in overexpressed GEF-H1/RhoA and increased cell migration capacity. GEF-H1 and RhoA can be directly targeted by miR-133a and negatively regulated. Circ-133 can be delivered into relatively normoxic cells and targeted to GEF-H1/RhoA by sponging miR-133a, which serves to decrease the expression of E-cadherin on the surface to enhance the migration capacity of cancer cells (112). Therefore, hypoxia can regulate the expression of circRNAs, and thereby indirectly promote angiogenesis, invasion and metastasis in which circRNAs are involved.

**CircRNA induces EMT and tumor cell migration**

EMT is a cellular phenomenon that allows stationary polarized epithelial cells to undergo various morphological changes resulting in a migratory, invasive mesenchymal phenotype (244–246). Activation of EMT under pathological
The TME mainly consists of stromal cells and ECM components. The TME is secreted by cells to provide structural and biochemical support and has a significant role in cell proliferation, differentiation, and maintenance of tissue homeostasis (250–252). Collagen and fibronectin, as the most important components of ECM proteins, are regulated by the MMP family of proteins (253, 254). Recent studies have shown that circRNA abnormally regulates the MMP family to cause remodeling of the ECM matrix, thus supporting tumor cell invasion into the basement membrane and stroma, vascular infiltration and metastasis (255–257).

CircMMP1 is highly expressed in CRC and can enhance MMP1, MMP2, and MMP9 by sponging miR-1238 to promote remodeling of the ECM matrix and metastasis of cancer cells (123). CircDLC1 is a tumor suppressor with low expression in HCC, and the overexpression of MMP1, MMP2, MMP3, and MMP10 remarkably appeared in circDLC1-knockdown cells. Mechanistically, circDLC1 impaired mRNA stability and translation by competitively binding to the mRNA stabilizing protein HuR, thus downregulating the expression level of MMP1. In conclusion, these data suggest that circDLC1 can inhibit HCC metastasis through the HUR-MMP1 axis (86). Circ0000620 is upregulated as a carcinogen in GC tissues, while circ0000620 acts as a sponge for miR-671-5p to upregulate MMP2 expression, thereby promoting metastasis and angiogenesis (102). MMP9 acts primarily as collagenase and mainly degrades type IV collagen (258, 259). CircUBAP2 is upregulated in HCC and upregulates MMP9 by sponging miR-194-3p to promote HCC metastasis (81). Circ0001806 adsorbs miR-193a-5p and negatively modulates its expression to upregulate the expression of MMP16 to degrade type I fibrous collagen (260), which could enhance the proliferation, migration, and invasion of HCC cells (92). Additionally, in GC tissues, overexpression of circ0005556 can accelerate GC progression by increasing MMP19 expression by sponging miR-4270 (109). However, current studies on MMP19 only focus on its functional phenotype, and there are few specific mechanisms for MMP19 to regulate ECM. ECM remodeling occurs in the whole process of tumorigenesis and development, and plays a vital role in supporting tumor cells to invade basement membrane, stroma and vascular penetration. Therefore, the regulation of ECM by circRNA can be used to create the targeted therapy for high tumor aggressiveness.

### CircRNAs regulate chemotherapeutic resistance

Although chemotherapy remains the preferred method of postoperative cancer treatment, a significant proportion of cancer patients still experience local recurrence and distant metastasis due to the development of drug resistance. Chemotherapeutic resistance is an obstacle to patients’ long-term survival (261–263). Cancers use different pathways to evade treatment-induced cell killing and acquire drug resistance in the TME, which is a huge barrier to cancer treatment (264, 265). In recent years, many studies have shown that circRNAs are important players in regulating drug resistance through various mechanisms such as drug efflux proteins, autophagy, and apoptosis (266). Therefore, understanding the regulatory mechanisms of circRNA associated with chemotherapeutic resistance can identify new targets to optimize treatment. (Figure 4)
Among the various drug resistance mechanisms, drug efflux is one of the first methods used in cancer cells. Cancer cells preferentially use ATP-fuel ATP binding box (ABC) transporters to squeeze out chemotherapeutic drugs and block their killing effects by efflux of drugs, leading to the development of drug-resistant phenotypes (267). There is considerable evidence that the expression of the ATP binding box (ABC) transporter, particularly by member 1 of the ABC subfamily B (ABCB1), confers resistance to cytotoxicity and is targeted chemotherapy (268). Qin et al. demonstrated that circFBXO11 promoted tumor progression and OXA resistance in HCC cells. Overexpression of circFBXO11 can upregulate downstream target FOXO3 through sponging miR-605, and overexpression of transcription factor FOXO3 can promote the level of ABCB1 protein in HCC cells, thereby promoting OXA efflux of HCC cells to produce drug resistance (82). It has also been reported that circ0007031 sponges miR-133b to regulate the expression of the downstream target ABCC5. Experiments have proved that circ0007031, which is highly expressed in CRC, promotes the efflux of 5-FU in cancer cells by upregulating ABCC5 and increases the drug resistance of CRC to 5-FU (118). Chen et al. demonstrated that highly expressed circ0074298 regulates the expression of SMOC2 by sponging mir-519d and affects biological behavior such as resistance to gemcitabine in pancreatic cancer. Additionally, knockdown of circ0074298 increased the sensitivity of PANC-1-GEM cells to gemcitabine and downregulated the expression levels of MDR1 and SMOC2 (95). However, the mechanism by which SMOC2 exerts drug resistance in pancreatic cancer remains to be elucidated.

Autophagy is a conserved self-degrading system and a tightly coordinated process. On the one hand, autophagy can suppress tumor progression by removing misfolded proteins and dysfunctional organelles (269–271) On the other hand, autophagy is essential for maintaining cellular homeostasis under stress, and in the later stages of tumor growth, autophagy can be used to survive in the absence of nutrients or oxygen (272, 273). In digestive cancers, autophagy is a significant mechanism of cell survival that is effectively used by tumor cells. Through cell degradation, the recovery of intracellular substrates and damaged organelles can alleviate cellular stress caused by nutrient deprivation, hypoxia, radiation, and cytotoxic agents (240, 274, 275). Recent studies have shown that circRNAs can promote drug tolerance induced by autophagy by regulating related miRNAs and downstream targets (276). For instance, circMCTP2 has been shown to be downregulated in CDDP-resistant GC cells. Mechanistically, circMCTP2 acts as a sponge...
for miR-99a-5p and promotes the expression of the downstream target MTMR3. Upregulated circMCTP2 and MTMR3 have been shown to inhibit autophagy in CDDP-resistant GC cells and induce apoptosis in response to CDDP treatment (106). Circ-PVT1 promotes cancer cell resistance through the miR-30A-5p/YAP1 axis in cisplatin chemotherapy for GC. Circ-PVT1 knockdown repressed DDP resistance by inducing apoptosis and inhibiting autophagy. Overexpression of miR-30a-5p could reduce DDP resistance by suppressing YAP1 (103). Lei et al. reported low expression of circCUL2 as a tumor suppressor in GC tissues. Mechanistically, circCUL2 inhibits autophagy in cisplatin-resistant GC cells through the miR-142-3p/ROCK2 axis (101).

Most cancer treatments eliminate tumor cells by triggering apoptosis, but there are also corresponding antiapoptotic signals in cancer, particularly the activation of antiapoptotic mechanisms, which enable tumor cells to escape apoptosis and conduct uncontrolled malignant proliferation (277). Recently, reports on circRNAs have suggested that circRNAs can mediate the proapoptotic effect of chemotherapy drugs by influencing the expression of apoptosis factors and apoptosis-related signaling pathways through the signaling network (278). CircARVCF has been reported to be upregulated and increase FGFR1 expression by sponging miR-1205 in DDP-resistant GC tissues and cells. CircARVCF inhibition has been shown to decrease the expression of MRPI, MDR1, and Bcl-2, and increase the expression of Bax. Meanwhile, miR-1205 overexpression inhibited DDP resistance by downregulating FGFR1 expression (104). Circ0000260 has been shown to be highly expressed in CDDP-resistant GC cells, and knockdown of circ0000260 enhanced the chemical sensitivity of CDDP and then blocked malignant behavior. Upregulated circ0000260 downregulates CDDP chemical sensitivity in vivo by targeting the miR-129-5p/MMP11 axis (105). Furthermore, MMP-11 promotes tumor development in the early stage by inhibiting apoptosis and promoting the migration and invasion of cancer cells (279). Sorafenib-resistant HCC cells express high levels of circRNA-SORE, and apoptosis of sorafenib-resistant cells has been shown to increase after circRNA-SORE knockout. circRNA-SORE maintains sorafenib resistance by acting as a miRNA sponge for miR-103a-2-5p and miR-660-3p. More importantly, miR-103a-2-5p or miR-660-3p alone or in combination can significantly suppress the Wnt/β-catenin downstream signals (84). Activation of β-catenin to enhance cancer stem cell characterization and drive sorafenib resistance in HCC has also been reported in other articles (280).

Most of the chemotherapeutics currently in clinical use trigger the apoptotic signaling pathway to induce cancer cell apoptosis. Thus, defects in apoptotic pathways may lead to tolerance, which limits the efficacy of treatment. Therefore, better insight into the regulation of circRNAs on the apoptotic signaling pathway may improve the curative effect of chemotherapeutics.

Significance of exosomal circRNA for digestive system tumors

Exosomes were initially thought to be extra waste products produced by cells, and with further research, exosomes have been found to exist in various body fluids and to mediate communications between diverse cells (281). CircRNAs can also play an important role in the TME in the form of exosomes, such as participating in tumor angiogenesis, invasion, metastasis and EMT (247).

In digestive system cancers, circRNAs with carcinogenic effects are usually expressed stably in cancer cells, but they can also be encapsulated by tiny vesicles in exosomes to deliver some vital biological information from the interior of tumor cells and affect the expression of downstream miRNAs, thus affecting the progression of related cancers (282, 283). For example, circ-100338 derived from HCC cell lines can be transferred to adjacent cells by exosomes and promote the proliferation and angiogenesis of surrounding HUVECs, as well as the invasion and metastasis of HCC cells (284). Exosomes secreted by TAM contained highly expressed hsa_circ_0020256, which enters cholangiocarcinoma (CCA) cells and causes upregulation of hsa_circ_0020256, and further upregulates E2F3 by sponging miR-432-5p, thus enhancing the proliferation, invasion and metastasis of CCA cells (285). In addition to promoting cancer progression, exosome circRNA also acts as a tumor suppressor. As a tumor suppressor, when GC cells continuously ingested exosomal circRELL1, the ectopic high expression of circRELL1 can greatly weaken the proliferation and metastasis ability of GC cells. Mechanistically, circRELL1 upregulates EPHB3 by acting as a miRNA sponge for miR-637, thereby reducing inhibition of tumor growth and metastasis in vivo (286). In HCC patients, circ-0051443 is delivered from normal cells to HCC cells by exosomes and inhibits malignant biological behavior by promoting apoptosis and blocking the cell cycle. The above tumor suppressive effects include reducing the weight and volume of xenograft tumors in vivo, mainly through circ-0051443 sponging miR-331-3p and indirectly increasing the expression of downstream target BAK1 (287).

Exosomal circRNA is more abundant than linear RNA in serum exosomes and is more easily detected with higher specificity. Therefore, exosomal circRNA has more potential as a cancer marker (288, 289). For example, circLPA1 is stably encapsulated in exosomes, and with the progression of CRC, circLPA1 with inversely low expression can be significantly detected in exosomes in blood, and the level of circLPA1 in exosomes increases significantly after colorectal cancer resection (290). Hsa_circ_0015286 was significantly up-regulated in plasma exosomes and cancer cells of GC patients, and hsa_circ_0015286 was significantly down-regulated in plasma exosomes 10 days after surgery (291). In addition, highly
expressed exosomal circAKT3 was associated with a higher risk of HCC recurrence and mortality (292). Together, exosomal circRNA can be used as a valuable biomarker to provide some novel insights into the diagnosis, prognosis and treatment of digestive cancer.

Conclusion

In this review, we explored the role of circRNAs in regulating cancer progression in the digestive system tumor TME and the great potential of circRNAs as therapeutic targets and prognostic indicators. In summary, although circRNAs are in the initial stage of the TME, they have shown excellent development prospects. Therefore, it is necessary and urgent to translate circRNA research into clinical application.

Author contributions

WG, SZ, and YH designed and guided the study. ZW, XY, and YH wrote and edited the manuscript. XY helped with reference collection. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

circRNAs Circular RNAs
ncRNAs non-coding RNAs
DSC Cancer of the digestive system
TME tumor microenvironment
pre-mRNAs precursor mRNAs
Pol II RNA polymerase II
miRNAs MicroRNAs
HuR human antigen R
m6A N6-methyladenosine
NK cells natural killer cells
HCC Hepatocellular carcinoma
PC Pancreatic cancer
GC Gastric cancer
CRC Colorectal cancer
ESCC esophageal squamous carcinoma
OSCC oral squamous cell carcinoma
TSCC tongue squamous cell carcinoma
LN lymph node
EMT epithelial-mesenchymal transformation
PDAC pancreatic ductal adenocarcinoma
CIS cisplatin
CDDP cisplatin
eBv Epstein-Barr virus
5-fu 5-fluouracil
Treg Regulatory T cells

Continued

TAM tumor-associated macrophages
CCL2 C-C motif chemokine ligand 2
CCL5 CC chemokine ligand 5
CCR2 C-C chemokine receptor type 2
PPARa Peroxisome proliferator-activated receptor a
PD1 programmed cell death protein 1
PD-L1 Programmed cell death ligand-1
CTLA-4 Cytotoxic T-lymphocyte-associated protein 4
ICAM-1 Intercellular adhesion molecule 1
HIF-1a Hypoxia-inducible factor-1a
CAF Cancer-associated fibroblasts
ECM extracellular matrix
CXCL13 chemokine ligand 13
CXCR5 chemokine receptor 5
REDOX reduction/oxidation
GLUT1 glucose transporter type 1
LDHA lactate dehydrogenase A
PKM2 M2 isoform of pyruvate kinase
TCA cycle the tricarboxylic acid cycle
a-KG a-ketoglutarate
PHGDH phosphoglycerate dehydrogenase
GSH Glutathione
VEGFA vascular endothelial growth factor A
HUVEC human umbilical vein endothelial cells
VEGFR vascular endothelial growth factor receptor
miRSC miRNA induced silencing complex
TGF-b transforming growth factor-b
4EBP-1 eukaryotic translation initiation factor 4E binding protein

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