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Review Article

Unraveling the crosstalk: circRNAs and the wnt signaling pathway in cancers of the digestive system

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ABSTRACT

Circular RNA (circRNA) is a unique type of noncoding RNA molecule characterized by its closed-loop structure. Functionally versatile, circRNAs play pivotal roles in gene expression regulation, protein activity modulation, and participation in cell signaling processes. In the context of cancers of the digestive system, the Wnt signaling pathway holds particular significance. Anomalous activation of the Wnt pathway serves as a primary catalyst for the development of colorectal cancer. Extensive research underscores the notable participation of circRNAs associated with the Wnt pathway in the progression of digestive system tumors. These circRNAs exhibit pronounced dysregulation across esophageal cancer, gastric cancer, liver cancer, colorectal cancer, pancreatic cancer, and cholangiocarcinoma. Furthermore, the altered expression of circRNAs linked to the Wnt pathway correlates with prognostic factors in digestive system tumors. Additionally, circRNAs related to the Wnt pathway showcase potential as diagnostic, therapeutic, and prognostic markers within the realm of digestive system tumors. This comprehensive review outlines the interplay between circRNAs and the Wnt signaling pathway in cancers of the digestive system. It seeks to provide a comprehensive perspective on their association while delving into ongoing research that explores the clinical applications of circRNAs associated with the Wnt pathway.

1. Introduction

Tumors of the digestive system are among the leading global causes of death, exhibiting high prevalence and the ability to affect various digestive system parts [1]. Gastric cancer remains one of the most common digestive system tumors worldwide [2,3]. According to the World Health Organization reports, approximately one million people are diagnosed with gastric cancer each year [4]. Colorectal cancer (CRC) is also prevalent in digestive system tumors, with higher incidence in developed countries and comparatively lower rates in developing nations [5–7]. These tumors impose a significant burden on public health. Effective management of digestive system tumors necessitates prevention and early screening. Ongoing scientific research strives to unveil more efficient prevention and treatment strategies to enhance the prognosis for individuals afflicted by digestive system tumors.

circRNAs were initially regarded as splicing errors or transcription byproducts and have gained recognition through technological advancements and extensive research. These molecules possess substantial biological functions and play pivotal roles in gene regulation, cellular functions, and disease processes [8,9]. Further investigations have substantiated their involvement in cell signaling, protein interactions, miRNA sponges, and other essential biological processes, solidifying the understanding of their biological significance [9]. However, emerging evidence suggests that some circRNAs may possess coding potential and exert functional roles through peptide encoding [10–12]. These findings further support the notion that circRNAs play a diverse and multifaceted role in cellular regulation. circRNAs contribute to the development of various diseases, including cancer, cardiovascular disease, and neurological disorders [9,13–19]. Circular RNAs (circRNAs) exert their influence on disease progression through diverse mechanisms, such as gene expression regulation, modulation of cellular signaling pathways, and miRNA sequestration [20–22]. Regulating alternative splicing and affecting mRNA stability are two important aspects of circRNA function. CircRNA regulates the occurrence of alternative splicing events by interacting with splicing factors or other regulatory proteins, consequently influencing the production of gene transcripts [23]. Additionally, circRNA can impact mRNA stability through interactions with mRNA, thus modulating gene expression levels [24]. In-depth study of

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circRNA mechanisms in diseases promises to enhance comprehension of disease onset and progression, potentially unveiling novel insights and targets for disease diagnosis and treatment strategies.

The Wnt signaling pathway, a conserved signaling axis, is found in numerous organisms and is integral to the development and maintenance of complex structures [25–27]. It plays a pivotal role in multicellular organisms, regulating diverse biological processes [28]. During embryonic development, the Wnt pathway is crucial for tissue and organ development, encompassing systems including the nervous, muscular, and skeletal systems [29,30]. In adulthood, this pathway continues to maintain normal tissue structure and function, overseeing processes such as cell renewal, tissue repair, and regeneration to ensure tissue homeostasis [28]. Wnt signaling pathways are broadly categorized into β-catenin-dependent and independent signaling types, with the former being the most prevalent [31]. The main effector, β-catenin, assumes a key role in this signaling. Abnormal activation or dysregulation of the Wnt/β-catenin pathway is closely linked to the occurrence and progression of various diseases [32–35]. Several circular RNAs (circRNAs) associated with the Wnt pathway have been identified as prognostic factors in digestive system tumors. These circRNAs directly or indirectly influence the Wnt pathway, thus regulating cell proliferation, apoptosis, and metastasis, consequently impacting tumor growth and metastatic potential. Due to these connections with the Wnt pathway, circRNAs are emerging as potential candidates for tumor diagnosis, treatment, and prognosis assessment. Therefore, this review aims to summarize the interaction between circRNAs and the Wnt signaling pathway, offering an overview of circRNAs linked to the Wnt pathway in digestive cancers. Additionally, we explore the clinical applications and research related to circRNAs associated with the Wnt pathway in digestive cancers.

2. The basic mechanism of the Wnt pathway

The wingless gene was initially discovered during studies involving *Drosophila melanogaster* [36–38]. It belongs to the Wnt signaling pathway and plays a critical part in animal embryonic development and cell fate determination by encoding the Wnt protein [39,40]. The human Wnt family comprises 19 cysteine-rich glycoproteins, serving as ligands that interact with over 15 receptors or co-receptors [41–43]. These diverse Wnt ligands and receptors form intricate signaling networks that are pivotal in biological processes such as embryonic development, tissue repair, and the maintenance of adult physiological functions [28,44,45]. Wnt signaling pathways are typically categorized into β-catenin-dependent (classical) and independent (nonclassical) signaling types. In β-catenin-dependent signaling, the activated Wnt protein binds to the Frizzled receptor and LDL receptor-associated protein (LRP5/6) on the cell membrane, leading to phosphorylation of LRP5/6 [46–50]. This process triggers the activation of β-catenin, enabling it to evade cytoplasmic enzyme complex degradation and enter the nucleus. Inside the nucleus, β-catenin binds to Tcf/Lef transcription factors, promoting the transcription of target genes and thereby regulating biological processes such as cell proliferation, differentiation, and survival. Independent (nonclassical) signaling operates through non-β-catenin-dependent mechanisms. In non-classical signaling, Wnt proteins activate diverse signaling pathways, including calcium ions, small GTPase, and protein kinase C, which regulate processes such as cell polarity, migration, and morphology [25,51].

3. Role of Wnt pathway in cancers of the digestive system

The Wnt signaling pathway assumes a crucial role in digestive system cancer. Abnormal activation of this pathway is a key driver in the development of digestive system cancer [52–54]. In CRC, this pathway becomes abnormally activated, leading to the stabilization and accumulation of β-catenin. This, in turn, promotes the proliferation and survival of cancer cells [55]. In gastric cancer cells, the components of the Wnt signaling pathway often exhibit gene mutations or abnormal expression, resulting in the stabilization and nuclear translocation of β-catenin [56,57]. This enhances the proliferation and invasion of tumor cells. Diseases such as chronic liver disease, hepatitis, and cirrhosis can foster abnormal activation of the Wnt signaling pathway, ultimately culminating in liver cancer [58,59]. The abnormally activated Wnt pathway can alter hepatocyte proliferation, apoptosis, and differentiation, thereby promoting tumor formation. Abnormal activation of the Wnt signaling pathway is also associated with the onset and metastasis of pancreatic cancer [60,61]. These observations underscore the pivotal role of the Wnt signaling pathway in digestive system cancers. Further research holds the promise of revealing precise mechanisms underlying this signaling pathway's involvement in cancer development, offering novel targets for therapeutic strategies targeting the Wnt pathway.

4. Circular RNA: Special RNA molecular structure

While circRNA was initially discovered in the 1970s, it was often dismissed as splicing errors or artifacts resulting from low expression [22,62]. Only in recent years, with advancements in high-throughput sequencing and bioinformatics analysis, did scientists begin to widely recognize and investigate circRNA [63]. A series of studies unveiled its significant role in gene regulation, cellular functions, and disease processes [8,21,64,65]. circRNA is a distinct type of non-coding RNA molecule characterized by its closed-loop structure [8,9]. In contrast to linear RNA, circRNA forms a continuous loop by joining the 5′ and 3′ ends through reverse splicing [66,67]. This unique structure contributes to its enhanced stability and resistance to degradation. Major subtypes of circRNA include exonic circRNA, intronic circRNA, exon-intron circRNA, and linear exon-skipping products [68,69]. These subtypes have distinct formation mechanisms and compositions, leading to the diversity and functional versatility of circRNAs. Each subtype has specific functions and regulatory mechanisms that play pivotal roles in cellular processes and disease pathways [70–72]. CircHIPK3, an exonic circRNA derived from the HIPK3 gene, plays multifunctional roles by interacting with miRNAs in cardiovascular disease (CVD) [73]. The intronic circRNA, circ-ITCH, plays a crucial role in cancer by exerting a tumor-suppressive effect. It regulates gene expression to influence cell proliferation and metastasis in cancer cells [74,75]. Circular RNAs such as circ-EIF3J and circ-PAIP2, which contain both exonic and intronic sequences, have been observed to enhance gene expression by binding with U1 snRNP and interacting with RNA Pol II [76]. Mitochondria-encoded circRNAs (mecciRNA) is a recently discovered subclass of circRNA [77–79]. It is a circular RNA enriched in mitochondria, and its primary functions are associated with mitochondrial biosynthesis and the regulation of apoptosis. MecciRNA can interact with various mitochondrial proteins and play a role in the crucial biological processes within mitochondria. However, ongoing research aims to explore the formation mechanisms and functional implications of these circRNA subtypes further. circRNA formation primarily involves mechanisms such as the sliding model ("backsplicing"), leapfrogging ("lariat-driven circularization"), and "reverse transcription-mediated circularization" [63,80]. Among these, "backsplicing" is the most common, involving the formation of a ring structure during transcription as the 5′ end of one exon joins the 3′ end of another exon within the same gene [10,81]. These mechanisms can vary across cell types, tissues, or physiological states. The circRNA formation process continues to be investigated, necessitating further experimentation and analysis to comprehend its occurrence under diverse conditions. circRNA exhibits diverse biological characteristics and functions, which contribute to our understanding of cell biology and disease pathogenesis. As a novel RNA molecule, circRNA possesses unique stability and plays pivotal roles in various biological processes including cell growth, differentiation, and apoptosis. It achieves these functions by regulating transcription processes, influencing gene expression, and modulating cell signal transduction pathways [16,20,22]. One important aspect is circRNA's involvement in protein synthesis as a translation template for mRNA

[82–84]. This challenges the traditional notion that only linear mRNA can undergo translation. By serving as a template, circRNA directly participates in protein synthesis, giving rise to functional protein products. This discovery provides us with a fresh perspective on the mechanisms underlying cellular protein synthesis. Another significant role played by circRNA is its participation in nuclear export. Nuclear export involves the transportation of transcribed RNA molecules from the nucleus to the cytoplasm for subsequent translation or other functional activities [85,86]. Certain circRNAs possess the ability to undergo nuclear export through interactions with proteins associated with this process. This capability allows circRNAs to influence cell metabolism and signal transduction pathways. It also functions as a miRNA sponge, inhibiting miRNA's regulatory effect on other target genes and consequently affecting gene expression [64,87]. Furthermore, circRNAs interact with proteins to influence cell signaling and regulation [10]. They can also interact with transcription factors, modulating gene transcription processes. Recent evidence indicates that certain circRNAs may have the capability to encode peptides and perform specific functions through this mechanism. circRNA FBXW7 contains an internal ribosome entry site (IRES) and encodes a 21 kDa protein. A recent functional study has revealed the inhibitory role of the FBXW7 protein in the malignant phenotype of human glioblastoma [88]. The discovery of circRNA-encoded peptides holds great promise for therapeutic interventions. It has been discovered that circRNA is also subject to regulation by the intracellular RNA degradation machinery. Certain RNases and microRNAs are believed to be involved in the degradation of circRNAs. Additionally, intracellular stress conditions can impact the rate of circRNA degradation. Despite its reputation for stability, there is increasing interest in understanding the mechanisms underlying circRNA degradation [89–92]. A deeper understanding of circRNA degradation will contribute to a better comprehension of its role in cellular biology and disease pathogenesis. These unique molecules have the potential to be targeted for drug development, offering new opportunities for precision medicine approaches [10–12,93]. These versatile mechanisms contribute to circRNA's significant influence on cell function and disease development.

5. Interaction of circRNA and the Wnt signaling pathway in cancers of the digestive system

Recent evidence highlights the involvement of numerous circRNAs in the Wnt signaling pathway [94]. Research indicates the significant role of circRNAs associated with the Wnt pathway in the development of digestive system tumors (Fig. 1). circRNAs linked to the Wnt pathway exhibit significant dysregulation in esophageal cancer, gastric cancer, liver cancer, CRC, pancreatic cancer, and cholangiocarcinoma (CCA). Additionally, these circRNAs have been correlated with prognostic factors in digestive system tumors (Table 1). They directly or indirectly affect the Wnt pathway, regulating cell proliferation, apoptosis, and metastasis, thus influencing tumor growth and metastatic potential (Table 1). Consequently, circRNAs associated with the Wnt pathway show potential for application in tumor diagnosis, treatment, and prognosis assessment, establishing them as a prominent research focus within the realm of digestive system tumors. This section specifically delves into the role of circRNAs in the Wnt pathway within digestive system tumors, synthesizing evidence from human studies, cellular-level research, and animal models.

5.1. Esophageal cancer

Esophageal cancer is a significant global health challenge with substantial morbidity and mortality rates [95,96]. In esophageal cancer, the levels of circABCA13 and circ0000277 are notably upregulated [97,98]. Moreover, the expression of circ001275 was observed to increase in cisplatin-resistant esophageal squamous cell carcinoma (ESCC) tissues [99]. Conversely, circITCH expression was consistently downregulated

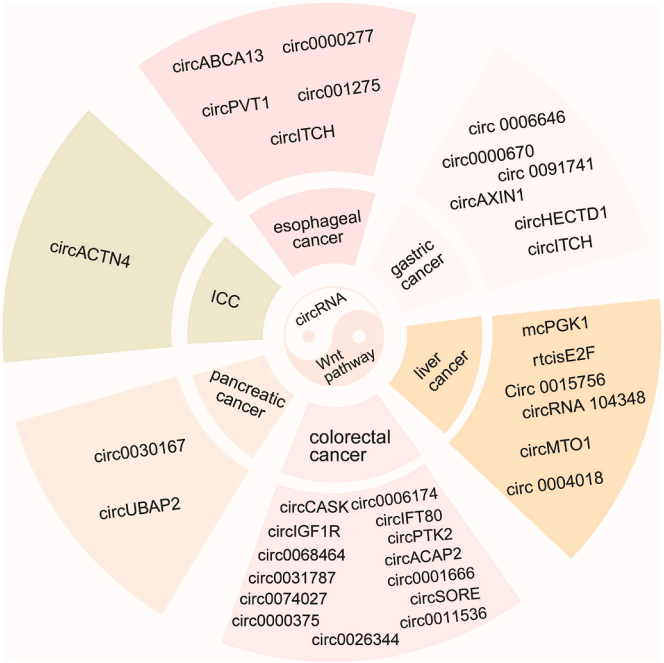

Fig. 1. CircRNAs prominently influence the progression of digestive cancers by engaging with the Wnt pathway.

in ESCC tissues [100]. Furthermore, circABCA13 expression exhibited a positive correlation with lymph node metastases and TNM stage [97]. Similarly, circ0000277 levels were associated with tumor growth, metastasis, and recurrence in patients with ESCC [98]. Notably, patients showcasing elevated circABCA13 and circ0000277 expression experienced improved overall survival rates.

Functionally, depletion of circABCA13 exhibited adverse effects on cell biological functions [97]. Specifically, silencing circ0000277 effectively curtailed cell proliferation and colony formation while promoting cell apoptosis [98]. This knockdown also hindered the transition from the G0/G1 phase to the S phase, effectively halting cell cycle progression. Furthermore, the reduction of circ0000277 increased the susceptibility to DDP treatment, as indicated by the lowered IC50 value, suggesting enhanced drug sensitivity. Moreover, the downregulation of circ0000277 amplified DDP-induced cell apoptosis, highlighting its potential in overcomingto overcome DDP resistance [98]. Notably, heightened expressions of circPVT1 and circ001275 were evident in 5-fluorouracil (5-FU) resistant ESCC cells, indicating their role in sustaining chemoresistance to 5-FU [101]. Suppression of circPVT1 led to reduced cell viability, migration, and invasion, while circ001275 overexpression promoted cell proliferation and invasion while suppressing apoptosis in cisplatin-resistant cells [99,101]. Conversely, silencing circ001275 hindered proliferation and invasion while enhancing apoptosis [99]. In addition, circITCH was found to decrease cell viability and inhibit proliferation in ESCC cells [100]. Overexpression of circABCA13 in ESCC cells leads to increased tumor volume, weight, and expression of the proliferation marker Ki67 in vivo [97]. Knockdown of circ0000277 or treatment with DDP significantly reduces tumor volume and weight compared with the control group [98]. Moreover, downregulating circ0000277 not only diminishes DDP resistance but also effectively curbs DDP-induced tumorigenesis. Suppressing circPVT1 expression effectively inhibits tumor growth and enhances the sensitivity of cancer cells to 5-FU treatment [101]. Combining circPVT1 knockdown with 5-FU treatment demonstrates a synergistic effect in restraining tumor growth. Mice with up-regulated circITCH xenografts exhibit significantly inhibited tumor growth compared with the control group [100].

Mechanistically, circABCA13 functions as a miR-4429 sponge,

Table 1
Role of circRNAs with clinical features in the Wnt pathway.
Table 1 Role of circRNAs regulating the Wnt pathway in cancers of the digestive system.

cancer types	circRNAs	level	clinical feature	functional role	regulatory mechanisms	Targeted pathway	refs
esophageal cancer	circABCA13	up	TNM stage, lymph node metastases, T grade, and overall survival rate	cell proliferation, migration, invasion, anchorage-independent growth	circABCA13, miR-4429, and SRXN1	Wnt/β-catenin pathway	[97]
esophageal cancer	circ0000277	up	tumor stage, metastasis, DDP resistance, recurrence, and overall survival rate	cell proliferation, colony formation, cell cycle, DDP resistance	circ0000277, miR-873-5p, and SOX4	Wnt/β-catenin pathway	[98]
esophageal cancer	circPVT1	up		5-Fluorouracil chemosensitivity	circPVT1, miR-30a-5p, and FZD3	Wnt/β-catenin pathway	[101]
esophageal cancer	circ001275	up		cisplatin resistance, cell proliferation, invasion, and cell apoptosis	circ001275, and miR-370-3p	Wnt/β-catenin pathway	[99]
esophageal cancer	circITCH	down			circITCH, miR-7, miR-17, miR-214, ITCH, and Dvl2	Wnt/β-catenin pathway	[100]
gastric cancer	circ0006646	up	TNM stage, lymph node invasion, and prognosis	cell proliferation, colony formation, migration, invasion, and EMT	circ_0006646, miR-665, and HMGB1	Wnt/β-catenin pathway	[104]
gastric cancer	circ0000670	up	smoking history	stemness, and EMT		Wnt/β-catenin pathway	[108]
gastric cancer	circ0091741	up		autophagy, and OXA resistance	circ0091741, miR-330-3p, TRIM14, and Dvl2	Wnt/β-catenin pathway	[107]
gastric cancer	circAXIN1	up		cell proliferation, migration, and invasion		Wnt/β-catenin pathway	[105]
gastric cancer	circHECTD1	up	lymph node metastasis, AJCC stage, and prognosis	cell glutaminolysis, proliferation, migration, and invasion,	circHECTD1, miR-1256, and USP5	Wnt/β-catenin pathway	[106]
gastric cancer	circITCH	down	metastasis			Wnt/β-catenin pathway	[109]
liver cancer	mcPGK1	up		liver TIC self-renewal, OXPHOS, and glycolysis		Wnt/β-catenin pathway	[113]
liver cancer	rtcisE2F	up				Wnt/β-catenin pathway	[114]
liver cancer	circ104348	up	prognosis	cell proliferation, migration, invasion, and apoptosis	circ104348, miR-187-3p, and RTKN2	Wnt/β-catenin pathway	[115]
liver cancer	circMTO1	down		cell proliferation, migration, invasion, and apoptosis	circMTO1, miR-541-5p, and ZIC1	Wnt/β-catenin pathway	[120]
liver cancer	circ0004018	down	tumor size	cell proliferation, and migration	circ0004018, miR-626, and DKK3	Wnt/β-catenin pathway	[119]
colorectal cancer	circCASK	up		cell growth, cell migration, and invasion	circCASK, miR-1271-5p, FOXC2, and SIX1	Wnt/β-catenin pathway	[121]
colorectal cancer	circIGF1R	up	overall survival rate		circIGF1R, miR-362-5p, and HMGB3	Wnt/β-catenin pathway	[122]
colorectal cancer	circIFT80	up		cell proliferation, migration, cell cycle, and cell apoptosis		Wnt/β-catenin pathway	[123]
colorectal cancer	circ0006174	up	tumor diameter, and T stage	cell growth, metastatic potential, and cell apoptosis	circ0006174, and miR-1205	Wnt/β-catenin pathway	[124]
colorectal cancer	circ0068464	up		cell migration, proliferation, apoptosis, tumor growth, and lung metastasis		Wnt/β-catenin pathway	[125]
colorectal cancer	circ0031787	up	TNM stage, and lymph node metastasis	cell proliferation, invasion, and tumor growth		Wnt/β-catenin pathway	[126]
colorectal cancer	circACAP2	up		cell proliferation, migration, invasion, radioresistance, and apoptosis	circACAP2, miR-143-3p, and FZD4	Wnt/β-catenin pathway	[127]
colorectal cancer	circ0074027	up	tumor differentiation, lymph node metastasis, and TMN stage	cell proliferation, metastasis, and EMT	circ0074027, and miR-3p	Wnt/β-catenin pathway	[128]

(*continued on next page*)

Table 1 (*continued*)

cancer types	circRNAs	level	clinical feature	functional role	regulatory mechanisms	Targeted pathway	refs
colorectal cancer	circSORE	up		sorafenib resistance		Wnt/β-catenin pathway	[130]
colorectal cancer	circ0001666	down		cell proliferation, apoptosis, invasion, and the number of CD133+ cells		Wnt/β-catenin pathway	[131]
colorectal cancer	circ0000375, circ0011536	down		proliferation, migration, and invasion		Wnt/β-catenin pathway	[132]
colorectal cancer	circ0001666	down	TNM stage, lymph node invasion, tumor size, and overall survival rate	cell proliferation, invasion, cell apoptosis, tumor growth, and metastasis	circ0001666, miR-576-5p, and PCDH10	Wnt/β-catenin pathway	[133]
colorectal cancer	circ0026344	down		cell proliferation, migration, and invasion		Wnt/β-catenin pathway	[134]
pancreatic cancer	circ0030167	down		cell invasion, migration, proliferation, and tumor stemness	circ0030167, miR-338-5p, and Wif1	Wnt/β-catenin pathway	[135]
intrahepatic cholangiocarcinoma	circACTN4	up	overall survival rate, and recurrence rate	proliferation, migration, invasion, and angiogenesis	circACTN4, miR-424-5p, YBX1, and FZD7	Wnt/β-catenin pathway	[141]

elevating SRXN1 expression and thereby promoting ESCC cell proliferation, migration, and invasion through Wnt/β-catenin pathway activation (Fig. 2) [97]. Similarly, circ0000277 acts as a miR-873-5p sponge, enhancing SOX4 expression and activating the Wnt/β-catenin signaling pathway through miR-873-5p targeting, affecting tumor progression and DDP resistance [98]. circPVT1 acts as a sponge for miR-30a-5p in ESCC cells, regulating chemosensitivity through the miR-30a-5p/FZD3 axis, influencing the ferroptosis and Wnt/β-catenin pathways [101]. circRNA_001275 functions as a miR-370-3p sponge, targeting and activating Wnt7a [100]. circITCH, on the other hand, acts as a sponge for miR-7, miR-17, and miR-214, leading to increased ITCH expression, culminating in the inhibition of the Wnt/β-catenin pathway. Thus, circITCH emerges as an inhibitory factor in the Wnt pathway [100].

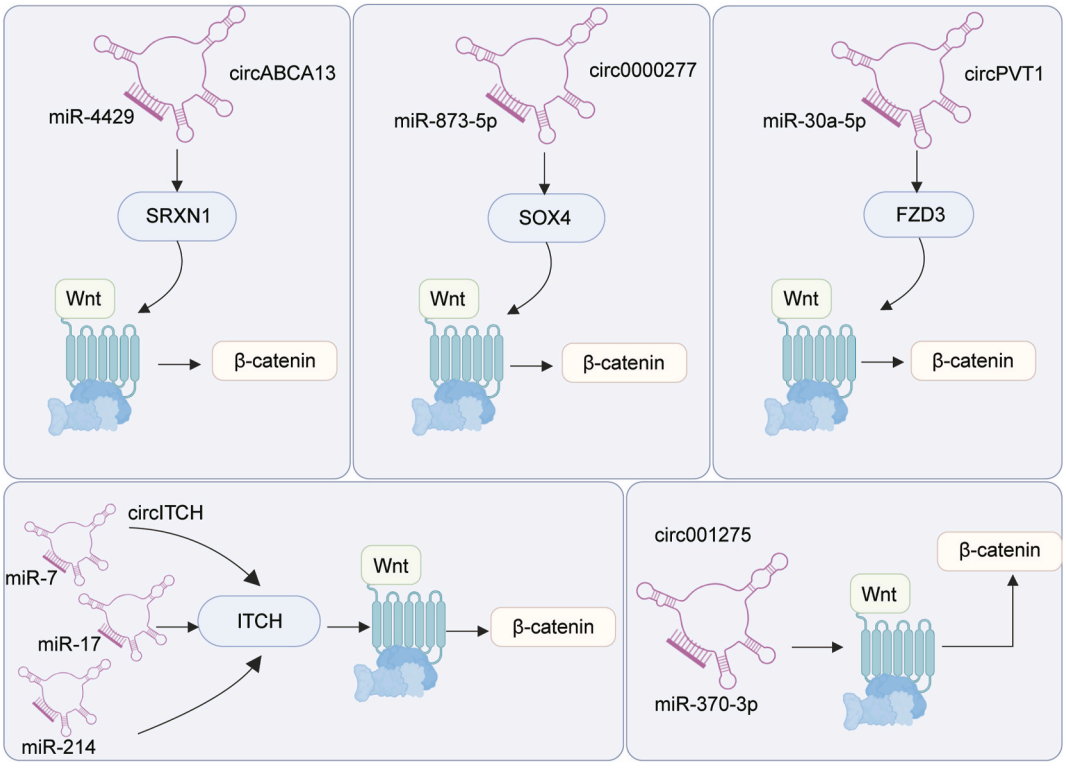

Fig. 2. CircRNAs play a pivotal role in the advancement of esophageal cancer by modulating the Wnt pathway through diverse mechanisms. circABCA13 acts as a miR-4429 sponge, augmenting SRXN1 expression and consequently promoting the progression of esophageal squamous cell carcinoma (ESCC) through Wnt/β-catenin pathway activation. In ESCC cells, circ0000277 functions as a miR-873-5p sponge, elevating SOX4 expression and concurrently activating the Wnt/β-catenin signaling pathway by sequestering miR-873-5p. circPVT1 serves as a miR-30a-5p sponge, influencing chemosensitivity by inhibiting FZD3 expression, thereby modulating chemosensitivity through ferroptosis and the Wnt/β-catenin pathways. circ001275 acts as a miR-370-3p sponge, directly interacting with and activating Wnt7a. circITCH acts as a sponge for miR-7, miR-17, and miR-214, leading to increased ITCH expression that effectively restrains the Wnt/β-catenin pathway.

5.2. Gastric cancer

Gastric cancer stands as a substantial global health concern, characterized by aggressive progression and unfavorable prognosis [102,103]. Despite advances in diagnostics and treatment, the overall survival rate remains disheartening. Unveiling the molecular mechanisms underpinning gastric cancer is pivotal to devising effective therapeutic interventions. Notably, circ0006646, circ0091741, circAXIN1, and circHECTD1 exhibit marked overexpression in gastric cancer tissues and cell lines [104–108]. In patients with gastric cancer, circ0006646 expression positively correlates with the TNM stage and lymph node invasion [104]. Kaplan-Meier analysis indicates that elevated hsa_circ0006646 levels are linked to lower overall survival rates. Similarly, circAXIN1 shows substantial overexpression in gastric cancer, particularly in advanced tumors [105]. It also correlates with tumor invasion depth and lymph node metastasis, suggesting its potential as a prognostic marker [105]. Furthermore, heightened circHECTD1 expression in gastric cancer is associated with lymph node metastasis, advanced AJCC stage, and poor overall survival, independently predicting adverse outcomes in patients with gastric cancer [106]. Notably, circITCH expression is higher in adjacent normal mucosa compared with gastric cancer samples, and it is significantly elevated in patients without metastasis in contrast to those with metastasis [109].

Functionally, overexpression of circ0006646, circAXIN1, and circHECTD1 facilitates cell proliferation, migration, and invasion in GC cells [104–106]. In addition, circHECTD1 regulates glutaminolysis in GC cells by influencing metabolite levels and key enzymes in the pathway. Downregulating circ0000670 in cigarette smoke-treated exosomes reduces stemness and EMT marker expression in GES-1 cells, impairing cell migration [108]. Conversely, overexpressing circ0000670 in exosomes from gastric cancer cells enhances stemness and EMT marker expression in GES-1 cells, promoting cell migration. These findings underscore the role of circ0006646, circ0000670, circ0091741, circAXIN1, and circHECTD1 in promoting malignant characteristics in ESCC. In contrast, circITCH expression is diminished in AGS and MKN45 cell lines compared to the normal gastric mucosal cell line GES-1 [109]. circ0006646 interacts with miR-665 in GC cells, leading to HMGB1 upregulation by acting as a miR-665 sponge [104]. Exosomal circ_0091,741 acts as a competitive sponge for miR-330-3p, enhancing TRIM14 expression in GC cell-derived exosomes [107]. Facilitated by circ0091741, TRIM14 stabilizes Dvl2 and activates the Wnt/β-catenin signaling pathway. circHECTD1 promotes GC progression by binding miR-1256 and regulating downstream target USP5 [106]. In addition, circITCH overexpression attenuates the cell proliferation, migration, and invasion in GC [109]. It functions as a miR-17 sponge, enhancing linear ITCH expression, thereby inhibiting the Wnt/β-catenin pathway through Dvl targeting. Consequently, gastric cancer cell proliferation, migration, and invasion are suppressed [109]. Suppressing circ0006646 and circ0091741 significantly inhibited GC cell growth in vivo [104,105,107,109]. Tumor volumes and weights were markedly reduced in the knockdown group of circAXIN1 and circHECTD1. Additionally, the administration of siRNA effectively inhibited lung metastasis in mice injected with AGS cells. Moreover, overexpressing circITCH suppressed tumor growth in both tumor xenografts and a patient-derived tumor xenograft model [109].

5.3. Liver cancer

Liver cancer, or hepatocellular carcinoma (HCC), is an aggressive disease characterized by high mortality rates [110–112]. Timely identification and intervention are pivotal for a more favorable prognosis due to the rapid spread of metastasis. Notably, mcPGK1, rtcisE2F, and circ104348 are significantly overexpressed in liver tumor tissues and cell lines [113–115]. rtcisE2F expression is markedly increased in liver tumor-initiating cells (TICs), which constitute a specialized subset within of liver tumors [116–118]. Conversely, the expression of circ0004018 is significantly reduced in Huh7, Bel7402, SNU182, Hep3B, and SNU449 cell lines [119]. The heightened expression of circ104348 is particularly evident in the advanced stages of HCC [115]. rtcisE2F mainly localizes in the cytoplasm as opposed to the nucleus or mitochondria. It is associated with advanced stages, tumor recurrence, and prognosis. Notably, rtcisE2F exhibits high expression in CD133+ tumor-initiating cells (TICs) and spheres, showing a negative correlation with parent genes CYP2C18 and CYP2C19 [114]. Heightened circ104348 expression correlates with tumor size, lymph node involvement, and TNM stage in patients with HCC, and it is associated with lower survival rates [115]. mcPGK1 is linked to clinical stages, tumor volumes, relapse, and survival [113]. It co-expresses with CD133, a marker of tumor-initiating cells (TICs), and is enriched in the mitochondrial fraction of TICs, particularly in sphere cells. Conversely, circMTO1 and circ0004018 demonstrate significantly lower expression levels in liver tumor tissues compared to matched normal tissues, with larger tumor size linked to reduced circ0004018 expression in liver cancer tissues [113,119].

Functionally, TICs possess unique self-renewal capabilities and the ability to initiate new tumor growth. These cells play a pivotal role in driving tumor initiation, progression, metastasis, and conferring resistance to liver cancer therapies. Silencing mcPGK1 and rtcisE2F led to reduced expression of TIC markers, impaired sphere formation, and hindered cell proliferation in liver cells [113,114]. Moreover, specifically targeting mitochondrial mcPGK1 further dampened sphere-forming capacity. Upregulating mcPGK1 and rtcisE2F increased TIC abundance and bolstered their self-renewal, tumor-initiating, and propagating capacities. These findings emphasize the crucial involvement of mcPGK1 in facilitating liver TIC self-renewal [113,114]. Mechanistically, mcPGK1 enhances the interaction between PGK1 and the TOM40 complex, facilitating PGK1 entry and translocation into mitochondria (Fig. 3) [113]. This triggers OXPHOS inhibition, boosts glycolysis through the PGK1-PDK1-PDH pathway, and influences α-ketoglutarate and lactate levels. These changes affect Wnt/β-catenin activation and self-renewal of liver tumor-initiating cells (TICs). By binding to E2F6/E2F3 mRNAs, rtcisE2F stabilizes them and affects the binding of m6A readers IGF2BP2 and YTHDF2 [114]. These molecular mechanisms contribute to the enhanced self-renewal and metastatic potential of liver TICs. Circ104348 modulates HCC cell behavior by controlling the miR-187-3p/RTKN2 axis, thereby influencing key processes such as proliferation, migration, invasion, apoptosis, and potentially the Wnt/β-catenin signaling pathway [115]. Additionally, decreasing circ0004018 and circMTO1 expression promotes proliferation, migration, and invasion while suppressing apoptosis in HCC [120]. circMTO1 acts as a miRNA sponge for miR-541-5p in HCC, inhibiting malignancy by regulating the miR-541-5p/ZIC1 axis [120]. This regulation involves modulation of the Wnt/β-catenin signaling pathway and epithelial-to-mesenchymal transition (EMT). circ0004018 modulates miR-626 expression in HCC cells and regulates DKK3, a direct target of miR-626 [119]. The interaction between circ0004018 and miR-626 inhibits the Wnt/β-catenin signaling pathway. In orthotopic xenograft mouse models, knockdown of circ104348 exhibited slower tumor growth and smaller tumor volume [115]. Furthermore, the knockdown of circ104348 effectively suppressed tumorigenesis and lung metastasis. Treatment of HCC xenografts with circMTO1 and circ0004018 resulted in notable reductions in tumor growth compared with the control group [119,120].

5.4. Colorectal cancer

In CRC tissues, the expression of circCASK, circIGF1R, circIFT80, circ0006174, circ0068464, circ0031787, circACAP2, and circ0074027 is significantly increased [121–128]. In CRC cell lines, the expression of circIGF1R, circIFT80, circ0006174, circ0068464, circPTK2, circ0031787, circACAP2, and circ0074027 is significantly elevated [121–123,126,127]. A potential link between elevated circIGF1R

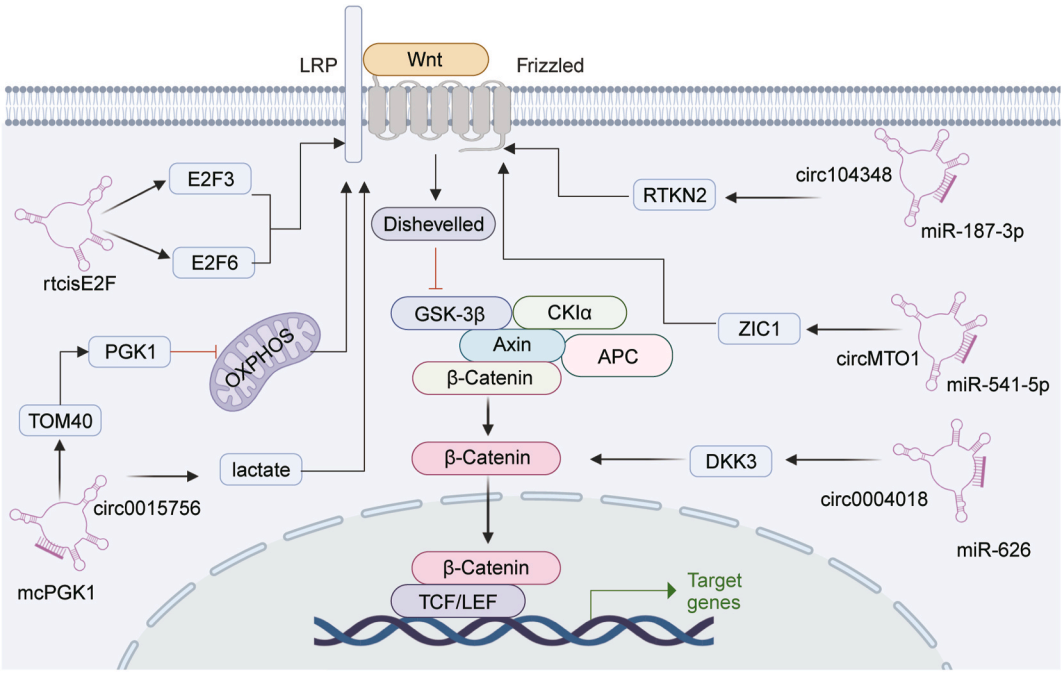

Fig. 3. circRNAs play a pivotal role in the initiation and progression of liver cancer by regulating the Wnt pathway through diverse mechanisms. rtcisE2F binds to E2F6/E2F3 mRNAs, enhancing stability and influencing interaction with m6A readers IGF2BP2 and YTHDF2. mcPGK1 facilitates PGK1 entry into mitochondria by promoting interaction with the TOM40 complex. This inhibition of oxidative phosphorylation fosters glycolysis, affecting Wnt/β-catenin activation and self-renewal of liver tumor-initiating cells (TICs). circ104348 governs HCC cell behavior through the miR-187-3p/RTKN2/Wnt/β-catenin axis. In HCC, circMTO1 acts as a miRNA sponge for miR-541-5p, curtailing malignant progression by modulating the miR-541-5p/ZIC1 axis. circ0004018 regulates miR-626 expression, thereby modulating DKK3 activity and subsequently suppressing the Wnt/β-catenin signaling pathway.

expression and poor prognosis has been noted in patients with CRC [122]. Notably, circ0006174 overexpression is associated with larger tumor diameter and higher T stage in liver cancer [124]. High expression of circ0031787 is positively associated with advanced TNM stage in CRC [126]. Zhang et al. reported significant associations between circ0074027 expression and differential status, N stage, vascular invasion, tumor size, and TNM stage [128]. Moreover, patients with CRC circ0047027 overexpression show a higher incidence of low tumor differentiation, lymph node metastasis, and TNM stage [128]. In CRC blood samples, high expression of circ0004831 is significantly associated with distant metastasis and differentiation grade [129]. Prognostic analysis further indicates that patients with high circ0004831 expression exhibit a poorer prognosis compared with those with low expression [129]. Silencing circCASK, circIGF1R, circIFT80, circ0006174, circ0031787, circACAP2, and circ0074027 resulted in reduced CRC cell proliferation, migration, and invasion, as confirmed by qRT-PCR and functional assays [121–124,126,127]. circSORE consistently showed upregulation in sorafenib-resistant cell lines [130]. Knockdown of circSORE significantly improved the efficacy of sorafenib by promoting apoptosis in CRC cells [130]. Silencing of circACAP2 increased the radiosensitivity of CRC cells, resulting in decreased survival following irradiation [127]. Mechanistically, circCASK acts as a sponge for miR-1271-5p, leading to increased SIX1 expression [121]. Remarkably, overexpression of SIX1 and miR-1271-5p knockdown could reverse the inhibitory effects caused by circCASK knockdown. circCASK activates the Wnt/β-catenin signaling through the miR-1271-5p/SIX1 axis [121]. Knockdown of circIGF1R obstructs the Wnt/β-catenin pathway by promoting miR-362-5p-mediated HMGB3 downregulation [122]. circIFT80 acts as a ceRNA in CRC, binding to miR-142, miR-568, and miR-634, which increases β-catenin levels and activates the Wnt/β-catenin pathway [123]. circ0006174 enhances CCBE1 expression, promoting CRC progression by interacting with miR-1205 [124]. circ0068464 acts as a miR-383 suppressor, regulating the Wnt/β-catenin signaling pathway and exerting oncogenic effects [125]. circACAP2 enhances CRC progression and radioresistance by sequestering miR-143-3p [127]. MiR-143-3p directly targets the 3′ untranslated region (3′-UTR) of FZD4 in CRC cells, and increased FZD4 expression partially mitigates the effects mediated by miR-143-3p. The N6-methyladenosine-modified circSORE acts as a competitive endogenous RNA (ceRNA), sequestering miR-103a-2-5p and miR-660-3p. This ceRNA activity leads to Wnt/β-catenin pathway activation, fostering sorafenib resistance [130].

On the contrary, downregulated levels of circ0001666, circ0000375, circ0011536, and circ0001666 are observed in CRC tissues and cell lines [131–134]. On the contrary, the expression of circ0001666, circ0000375, and circ0011536 is noticeably diminished in CRC cell lines [131–134]. Patients with lymph node metastasis or advanced TNM stage are more likely to exhibit elevated circ0011536 expression [132]. High expression of circ0001666 is linked with favorable clinical characteristics in patients with CRC, including lower TNM stage, reduced lymph node invasion, and smaller tumor size [133]. Importantly, the levels of circ0000375 and circ0011536 in the serum of patients with CRC are lower than those in healthy controls (HCs) [132]. Post-surgery, their levels increase but remain significantly lower than those in HCs.

Functionally, the decrease in circ0026344 expression facilitates the epithelial-to-mesenchymal transition (EMT) process in CRC cell lines [134]. Furthermore, overexpressing circ0001666 curtails the cancer stemness of CRC cell lines, leading to a significant reduction in the population of CD133+ cells [131]. In CRC cells, circ0001666 regulates miR-1229 expression through CXCR5. It exerts inhibitory effects on CRC cell proliferation, invasion, and stemness by deactivating the Wnt/β-catenin signaling pathway and targeting miR-1229 [131]. Additionally, circ0001666 directly binds to miR-576-5p in CRC cells [133]. The interaction between PCDH10 and miR-576-5p forms the miR-576-5p/PCDH10 axis, contributing to the suppression of cell motility and stemness in vitro. The collaborative action of CCL20 and CXCL8 leads to the reduction of circ0026344 expression [134]. Overexpressing circ0026344 results in Wnt pathway inhibition, and this inhibition can be reversed by a miR-183 mimic. These findings propose

that circ0026344 potentially suppresses CRC cell metastasis by down-regulating miR-183 [134].

5.5. Pancreatic cancer

qRT-PCR analysis indicated a decrease in circ0030167 expression in pancreatic cancer cells [135]. Overexpressing circ0030167 exhibited suppressive effects on pancreatic cancer cell proliferation, metastasis, and invasion. Moreover, it exerted inhibitory effects on the stemness of pancreatic cancer cells [135]. Furthermore, the circUBAP2-mediated ceRNA network regulates immune cell infiltration and functional activities, thereby impacting the progression of pancreatic adenocarcinoma [136]. Mechanistically, exosomal circ0030167 enhances Wif1 expression and inhibits the Wnt8/β-catenin pathway by acting as a sponge for miR-338-5p [135]. This pathway inhibition contributes to the suppression of stemness in pancreatic cancer cells and tumor progression. Exosomes originating from BM-MSCs have the ability to impede tumor progression in vivo, resulting in significantly smaller tumor volumes in the exosome group [135].

5.6. Biliary tract tumor

CCA is a significant subset of liver and biliary tract cancers, originating from the bile duct lining cells [137–140]. Despite its global prevalence, early detection remains challenging due to its aggressive nature and inconspicuous symptoms, resulting in unfavorable prognoses. Notably, elevated levels of circACTN4 are observed in intrahepatic cholangiocarcinoma (ICC) tissues compared to adjacent normal tissues [141]. This heightened expression is associated with poorer 3-year overall survival and increased recurrence rates, underlining its potential as an independent prognostic marker. Additionally, high circACTN4 expression is linked to the heightened risk of both overall survival and recurrence in patients with ICC [141].

Functionally, circACTN4 induces proliferation, migration, invasion, and angiogenesis in RBE cells, while it inhibits these processes in FRH0201 cells [141]. Furthermore, proangiogenic factors originating from the RBE cell supernatant enhance endothelial tube formation, while the supernatant from FRH0201 cells has the opposite effect. Frizzled-7 (FZD7) plays a critical role as a receptor protein in the Wnt signaling pathway, serving as a key component in Wnt signal transduction through its interaction with Wnt proteins and other co-receptors. The activation of the Wnt/β-catenin pathway was positively associated with the expression of circACTN4. Further research has shown that circACTN4 drives ICC progression by elevating YAP1 expression through miR-424-5p sequestration, promoting FZD7 transcription through YBX1 recruitment, and enhancing the interaction between YAP1 and β-catenin, key components in the Hippo and Wnt signaling pathways, respectively [141].

6. Clinical application research of circRNAs associated with the Wnt pathway in cancers of the digestive system

6.1. Clinical potential of circRNA and Wnt pathways in diagnosis

Numerous circRNAs associated with the Wnt pathway have been identified as biomarkers for diagnosing gastric cancer. These circRNAs display dysregulated expression in various types of digestive tumors, including esophageal cancer, gastric cancer, liver cancer, CRC, pancreatic cancer, and CCA. These Wnt pathway-associated circRNA biomarkers offer substantial advantages over existing diagnostic markers, making them highly promising for clinical applications. Additionally, detecting circRNAs associated with the Wnt pathway in body fluids, such as serum and plasma samples, presents a new and non-invasive approach for early cancer diagnosis [142–144]. ROC curve analysis revealed that circABCA13 shows excellent accuracy in detecting ESCC and ESCC with lymph node metastases, with AUC values of 0.8519 and 0.7838, respectively [97]. Further studies suggest that circABCA13 has great potential as a reliable diagnostic biomarker for both ESCC and its lymph node metastases. The levels of circ0000375 and circ0011536 in serum from patients with CRC were significantly lower compared with HCs, indicating their association with CRC tumorigenesis [132]. Post-surgery, the levels of these circRNAs increased but remained significantly lower than those in HCs. Importantly, Yao et al. also demonstrated the robust expression of circ0000375 and circ0011536 across different subtypes of patients with CRC [132]. To validate the usefulness of biomarkers such as circABCA13, circ0000375, and circ0011536, confirming their effectiveness using large-scale clinical samples is crucial. Large-scale studies involving a significant number of patients with ESCC and lymph node metastases would provide more robust evidence regarding the diagnostic accuracy and efficacy of circABCA13, circ0000375, and circ0011536 as biomarkers. This approach ensures that the findings are representative and reliable, supporting the potential translation of circABCA13, circ0000375, and circ0011536 into clinical practice. Therefore, further research using extensive clinical samples is necessary to establish the true clinical value of circABCA13, circ0000375, and circ0011536 as biomarkers.

6.2. Clinical potential of circRNA and Wnt pathways in prognostic assessment

TNM stage, lymph node metastases, tumor size, drug resistance, and overall survival rate represent pivotal factors in determining the prognosis of patients with cancer [145–147]. In various digestive cancers, specific circRNAs associated with the Wnt signaling pathway have emerged as potential prognostic indicators. These circRNAs exhibit relevance to prognosis-related factors across esophageal cancer, gastric cancer, liver cancer, CRC, pancreatic cancer, and CCA. Notably, circ0000277 has been explored concerning its correlation with recurrent tissues in ESCC [98]. The expression level of circITCH was notably elevated in patients with gastric cancer without metastasis in contrast to those with metastasis [109]. Elevated circ0047027 expression in patients with CRC was associated with low tumor differentiation [128]. Among patients with GC diagnosed with AJCC stage III, heightened circHECTD1 expression levels were observed compared with the AJCC stage I/II group [106]. Additionally, circABCA13, circ0000277, circ0006646, circHECTD1, circIGF1R, circ0001666, and circACTN4 expression levels have demonstrated an impact on overall survival in digestive cancers [97,98,104,106,122,133]. These circRNAs provide valuable insights into cancer extent and aggressiveness, enabling healthcare professionals to assess potential outcomes and devise tailored treatment strategies for enhanced patient management. Ongoing research aims to evaluate the prognostic value and clinical implications of circRNAs associated with the Wnt pathway for assessing digestive cancer prognosis.

6.3. Clinical application prospect and challenges with circRNAs associated with the Wnt pathway as a therapeutic target

In the realm of digestive cancers, circRNAs participate in various biological processes, including cell proliferation, invasion, and metastasis, by orchestrating gene expression and signal pathways [6,148,149]. Researchers have identified numerous circRNAs linked to the Wnt pathway that intricately interact with proteins, miRNAs, and DNA to form intricate regulatory networks across esophageal cancer, gastric cancer, liver cancer, CRC, pancreatic cancer, and CCA. These circRNA networks effectively modulate cell proliferation, migration, and invasion, and subsequently impact tumor volume and weight. Targeting circRNAs associated with the Wnt pathway for therapeutic purposes can disrupt their interactions with Wnt signaling pathway components, hinder Wnt signal activation, and thereby restrain cancer cell proliferation and invasion. Additionally, the circRNA/Wnt axis holds the potential to impact treatment resistance directly or indirectly.

Downregulating circ0000277 expression led to reduced DDP IC50 values, indicating heightened susceptibility to DDP treatment [98]. Simultaneous circPVT1 knockdown and 5-FU treatment synergistically suppressed tumor growth [101]. Suppression of circSORE markedly augmented sorafenib sensitivity in CRC cells by enhancing apoptosis [130]. circRNAs associated with the Wnt pathway could prove instrumental in addressing treatment resistance in digestive tumors. The circRNA/Wnt axis may emerge as a novel therapeutic target, enhancing tumor responsiveness to therapeutic drugs or strategies by modulating their expression or function. For example, circ0000277 influenced gastric cancer cell DDP sensitivity and apoptosis pathway by regulating miR-873-5p levels [98]. miR-873-5p inhibitors nullified circ0000277's impact on DDP sensitivity. In ESCC cells, CircPVT1 functions as a miR-30a-5p sponge, influencing chemosensitivity through FZD3 suppression [101]. miR-30a-5p inhibitors affect ESCC cell chemosensitivity via direct FZD3 targeting. Moreover, silencing through siRNA or shRNA can target circRNA sequences, affecting their expression levels and functions. However, clinical application hurdles include the delivery efficiency of siRNA and shRNA [150–152]. Antisense oligonucleotides (ASOs) offer a feasible option, targeting circRNA sequences through complementary binding and promoting degradation via RNase activation. ASOs hold promise as therapeutic agents for circRNA-based treatments [153]. Rigorous large-scale clinical studies are imperative to assess the safety and efficacy of these strategies.

7. Conclusions and perspectives

Initially regarded as splicing anomalies, circRNAs have emerged as pivotal regulators of gene expression and cellular processes. Extensive investigation has unveiled their involvement in a myriad of biological pathways and their linkage to various diseases. Dysregulated circRNA expression and functional alterations significantly contribute to disease progression by modulating gene expression. The Wnt signaling pathway, a conserved cascade across species, plays a central role in diverse biological processes, from embryonic development to adult tissue homeostasis. circRNAs wield significant influence in the Wnt signaling pathway within digestive system tumors. They exhibit aberrant expression in a range of digestive cancers, including esophageal, gastric, liver, colorectal, pancreatic, and CCA. These circRNAs, directly or indirectly, impact cell proliferation, apoptosis, and metastasis by modulating the Wnt pathway, ultimately influencing tumor growth and metastatic potential. Altered circRNAs linked to the Wnt pathway also display correlation with prognostic factors in digestive system tumors. circRNAs associated with the Wnt pathway hold potential for diagnostic, therapeutic, and prognostic applications in digestive system tumors. Notably, detecting Wnt-associated circRNAs in body fluids such as serum and plasma samples offers a non-invasive avenue for early cancer detection. Nevertheless, robust validation through extensive clinical samples is essential to substantiate their efficacy. The validation process is pivotal for ensuring reliability and bolstering the potential clinical utilization of Wnt-associated circRNAs. Due to its high stability, circRNA can be utilized as an immunotherapy agent. For instance, circRNAs can be employed in crafting personalized tumor vaccines aimed at impeding tumor proliferation by stimulating the generation of specific antibodies and T cell responses within the body. Furthermore, circRNAs linked to the Wnt pathway provide pivotal insights into cancer progression and aggressiveness, thus facilitating healthcare professionals in prognostication and the formulation of tailored treatment strategies for effective patient care. The circRNA/Wnt axis presents a promising novel therapeutic target to heighten tumor sensitivity to drugs. However, challenges in clinical implementation include biological stability, low expression levels, lack of effective delivery modalities for circRNA. circRNA possesses high biological stability, which is advantageous for its potential as a therapeutic target. However, this stability also presents challenges in terms of intervention and regulation within cells. Additionally, circRNAs are generally expressed at lower levels compared to linear mRNAs, making their detection and quantification more challenging. The lack of effective delivery methods for circRNAs to tumor tissues is also a hurdle, hindering the utilization of circRNA characteristics in achieving cancer therapy outcomes. Furthermore, the functional mechanisms of many circRNAs remain incompletely understood, limiting our comprehensive understanding of their applications in tumor development and therapy. Despite these challenges, we believe that through further research, these issues will gradually be addressed. The ongoing development of new technologies and methods will aid in overcoming limitations in circRNA application and promote its use in the field of cancer therapy. Future research and innovation will continue to unveil the crucial role of circRNA in tumor development and treatment, offering possibilities for the development of effective therapeutic strategies. Antisense oligonucleotides (ASOs) hold potential as therapeutic candidates for circRNA-based treatments. Rigorous large-scale clinical studies are indispensable to ascertain the clinical utility and efficacy of targeting Wnt-associated circRNAs in cancer treatment.

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CRediT authorship contribution statement

Yu Zhang: Writing – review & editing, Writing – original draft. **Cheng Zhang:** Writing – review & editing. **Chuanhui Peng:** Writing – review & editing. **Junjun Jia:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

All authors declare that there are no competing interests.

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