The functional roles of the circRNA/Wnt axis in cancer

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Abstract
CircRNAs, covalently closed noncoding RNAs, are widely expressed in a wide range of species ranging from viruses to plants to mammals. CircRNAs were enriched in the Wnt pathway. Aberrant Wnt pathway activation is involved in the development of various types of cancers. Accumulating evidence indicates that the circRNA/Wnt axis modulates the expression of cancer-associated genes and then regulates cancer progression. Wnt pathway-related circRNA expression is obviously associated with many clinical characteristics. CircRNAs could regulate cell biological functions by interacting with the Wnt pathway. Moreover, Wnt pathway-related circRNAs are promising potential biomarkers for cancer diagnosis, prognosis evaluation, and treatment. In our review, we summarized the recent research progress on the role and clinical application of Wnt pathway-related circRNAs in tumorigenesis and progression.

Keywords: circRNA, Wnt, cancer, Biomarker, Mechanism

Background
Cancer is one of the main causes of death today and has become a serious public health problem worldwide [1–5]. It is a complex disease that involves changes in a variety of processes, including genetic and epigenetic characteristic changes [6–8]. The molecular changes in cancer genes and related signaling pathways could provide information for cancer diagnosis and targeted therapy [9–11]. This information could contribute to improvements in cancer diagnosis and treatment.

Human genome sequence data indicate that more than 98% of the genome is noncoding genes [12–14]. The transcripts of these genes lack protein-coding ability and are recognized as noncoding RNAs (ncRNAs) [15–18]. ncRNAs were once considered byproducts of transcription [19–21]. With the development of high-throughput sequencing technology, ncRNA features have gradually been revealed. ncRNAs comprise various types of RNA species, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs) [22–24]. CircRNA is a single-stranded, covalently closed ncRNA without 5’ end caps or 3’ end poly (A) tails [25–28]. It is generated from its precursor mRNA by noncanonical splicing [29–31] and is widely expressed in a wide range of species ranging from viruses to plants to mammals [32, 33]. circRNAs may act as transcription modulators, miRNA sponges, or protein decoys to exert their function in cancer progression [34–36]. In addition, circRNAs are obviously associated with many clinical characteristics [37–41], which could provide important guidance for the accurate diagnosis and treatment of cancer. Accumulating evidence indicates that circRNAs play a pivotal role in the process of cancer and have the potential to be biomarkers in cancer diagnosis, prognosis, and treatment [42–46].

The Wnt pathway is an evolutionarily conserved pathway [47–49]. It plays a critical role in embryonic development, tissue renewal and regeneration [50–52]. The Wnt pathway can be divided into three classes: Wnt/β-catenin
signaling, Wnt/planar cell polarity (PCP) signaling, and Wnt/Ca signaling [47, 53, 54]. Aberrant activation of the Wnt pathway is significantly correlated with a series of cancers, such as lung cancer [55–57], colorectal cancer [58, 59], bladder cancer [60, 61], osteosarcoma [62, 63], glioma [64, 65], and chronic lymphocytic leukemia [66, 67]. Accumulating evidence indicates that circRNAs regulate a series of cellular biological functions by interacting with the Wnt pathway in the cancer process [68–70]. These studies provided novel perspectives into cancer diagnosis and treatment. circRNAs related to the Wnt pathway have been the focus of many cancer research studies [63, 69, 71–73]. In this review, we summarized the recent research progress regarding the molecular mechanisms and functional roles of circRNAs related to the Wnt pathway in tumorigenesis and tumor progression.

**The wnt pathway in tumorigenesis**

The Wnt gene was first identified in mouse mammary tumors in 1982 [74–76]. At that time, it was designated as int1 [75, 77]. Because of the high homology between the mouse int1 gene and the Drosophila Wingless gene, the researchers merged Wingless with Int1 and assigned the name Wnt gene [78, 79]. The Wnt gene, localized at 12q13, mediates physiological effects in a paracrine and autocrine manner [78, 80]. The signaling pathways regulated by the Wnt gene are collectively termed the Wnt pathway. The Wnt signaling pathway is highly conserved from Drosophila to humans. The pathway [81–83] is critical for a wide variety of cellular functions, such as cell polarity, movement, proliferation, asymmetric division, and muscle tissue development. Wnts are a family of secreted, lipid-modified proteins that bind to Frizzled receptors to activate signaling cascades [84, 85]. The Wnt pathway can be divided into three classes: Wnt/β-catenin signaling, Wnt/PCP signaling, and Wnt/Ca signaling [86–89] (Fig. 1). Wnt/β-catenin signaling, a canonical Wnt signaling pathway, is involved in the regulation of gene expression [90–92]. Wnt/planar cell polarity signaling regulates cell polarity and directional cell movements [83, 93, 94]. Wnt/Ca signaling is obviously

![Fig. 1](image-url)  
**Fig. 1** Wnts are a family of secreted, lipid-modified proteins that bind to Frizzled receptors to activate signaling cascades. The Wnt pathway can be divided into three classes: Wnt/β-catenin signaling, Wnt/PCP signaling, and Wnt/Ca signaling.
associated with the release of intracellular calcium [95, 96]. Dysregulation of the Wnt pathway has a strong relevance to cancer.

**Wnt/β-catenin signaling**

The Wnt/β-catenin signaling pathway is characterized by the cellular redistribution and nuclear accumulation of the β-catenin gene [97, 98]. Wnt protein combines with Frz and LRP5/6 on the cell surface to form a trimer, which transmits the signal and activates the protein Disheveled [Dsh/DVL] [99, 100]. This leads to the disassociation of the β-catenin degradation complex adenomatous polyposis coli (APC)/Axin/GSK-3β (glycogen synthase kinase 3β) and increases the cytoplasmic levels of β-catenin [101, 102]. Then, upregulated β-catenin is transferred into the nucleus. Nuclear β-catenin interacts with T cell transcription factor (TCF)/lymphoid enhancer factor (LEF) and finally activates the expression of downstream target genes [98, 103–105]. The Wnt/β-catenin signaling pathway participates in the cancer process by acting as an important modulator [106–108] of cell proliferation, metastasis, and differentiation. Overexpression of the Wnt gene or mutation in one of the components that causes β-catenin degradation leads to activation of the Wnt/β-catenin pathway.

**Wnt/PCP signaling**

In the Wnt/PCP signaling pathway, Wnt binds to frizzled transmembrane receptors and then activates the protein Disheveled (Dsh/DVL), leading to a series of cell signaling cascades [109–112]. DSH is connected to the downstream effectors Rho and ROCK (Rho-associated kinase) through Daam1. RAC is directly activated by Dsh, and Dsh further activates JNK by activating mitogen-activated protein kinases (MAP3Ks) and MAP2Ks [113, 114]. The PCP pathway is associated with cell polarity, cell alignment and cell migration.

**Wnt/Ca2+ signaling**

In the Wnt/Ca2+ pathway, the Wnt protein is mainly composed of Wnt1, Wnt5A and Wnt11 and binds to the Frizzled transmembrane receptor on the cell surface [115, 116]. The combination of the Wnt protein and Frizzled activates Disheveled, which activates PLC through the G protein [117, 118]. These cellular processes could finally promote the release of intracellular Ca2+. The activation of Disheveled could also activate the cGMP-specific phosphodiesterase PDE6 and reduce intracellular cGMP, which leads to an increase in the intracellular Ca2+ concentration [119–123]. Elevated cytoplasmic Ca2+ concentrations can stimulate the nuclear factor NFAT and other transcription factors [124, 125]. These processes trigger the activation of downstream pathways and a series of altered cell functions. The Wnt/Ca2+ pathway is essential for early embryonic development, interneural communication and the inflammatory response [126, 127].

**CircRNA in the Wnt pathway**

CircRNAs, first found in the 1890s [128], remain enigmatic owing to technological limitations and limited existing knowledge. In 2013, Hansen TB et al. first proposed and confirmed that circRNAs function as miRNA sponges [129]. This finding started a new era in circRNA research [32, 42, 130–133]. Unlike linear RNAs, circRNAs are single-stranded, covalently closed noncoding RNAs without 5’ end caps or 3’ end poly (A) tails [25–28]. CircRNAs are not affected by RNA exonuclease, and their expression is more stable [134, 135]. CircRNAs are formed by reverse splicing events [29–31]. A mechanistic model argued that the RNA is partially folded during the transcription of pre-RNA. Initially, nonadjacent exons are pulled closer by RNA folding, and exon skipping occurs. The spanned region forms a circular RNA intermediate, and then circRNAs are formed by further splicing. Another model suggests that the reverse complement sequence located in the intron region causes the intron region to pair and mediate reverse splicing to form circRNA [136–140].

CircRNAs act mainly through four molecular mechanisms. In regulating gene expression, circRNAs affect the expression of parental gene mRNA by interacting with RNA binding proteins [141–143]. Competitive complementary pairing between introns can strike a balance with linear RNAs during the formation of circRNAs. CircRNAs can also exert their functions by acting as competing endogenous RNAs (ceRNAs) of miRNAs [144–147]. In addition, circRNAs are involved in the immune response [29, 148, 149]. Endogenous circRNAs play a role in the antiviral response, while exogenous circRNAs can stimulate immune signaling in mammalian cells by activating the pattern recognition receptor RIG-L [150–153]. Moreover, although circRNAs are noncoding RNAs, a few circRNAs can also perform regulatory functions by encoding peptides [154–156]. Several previous studies have shown that circRNAs play an important role in tumorigenesis and tumor progression. CircRNA_403658 facilitates aerobic glycolysis and cell growth by upregulating LDHA expression in bladder cancer [157]. CircRNA_103809 functions as an oncogene in the progression of hepatocellular carcinoma [158].

Both circRNAs and the Wnt pathway play a critical role in cancer development and progression. CircRNAs negatively or positively regulate cancer initiation, promotion, and progression by directly or indirectly interacting with the Wnt pathway. The interaction of circRNAs and
the Wnt pathway has a noticeable impact on cell growth, metastasis, and other malignant cell behaviors in cancer. The majority of circRNAs act as sponges of miRNAs to activate or inactivate the Wnt pathway. With the deepening of research, more action modes between circRNAs and the Wnt pathway will be found. Related studies are expected to provide new insights for the diagnosis and treatment of cancer.

The role of the circRNA/Wnt axis in cancer
CircRNAs related to the Wnt pathway are aberrantly expressed in many cancers. Emerging evidence suggests that a range of clinical characteristics have been associated with circRNAs related to the Wnt pathway (Table 1). Moreover, the circRNA/Wnt axis contributes to cancer progression by modulating many cell biological functions. In this section, we will introduce the expression, corresponding clinical features, functions and mechanisms of the circRNAs/Wnt axis (Table 2).

Digestive tumors

Esophageal cancer
Elevated levels of circRNA_100367 were observed in radioresistant esophageal cancer cell lines [192], while the expression of circ-ITCH was downregulated in esophageal squamous cell carcinoma (ESCC) tissues [193] (Fig. 2). The expression of circ-ITCH is positively associated with linear ITCH in ESCC. Functionally, colony formation and Cell Counting Kit-8 (CCK-8) assays showed that circ-ITCH could inhibit ESCC tumor growth through the regulation of cell proliferation. Knockdown of circRNA_100367 attenuates cell proliferation, migration, and radioresistance in esophageal cancer [192]. circRNA_100367 decreases radiation sensitivity by regulating the miR-217/Wnt3 pathway. CircRNA_100367 could also affect esophageal cancer cell growth under irradiation in vivo. Using bioinformatics tools, Su et al. [234] found that a large number of circRNAs were closely related to cancer progression. Further studies on these molecules are still required.

Gastric cancer
Some Wnt pathway-related circRNAs (circ0005654, circ-SFMBT2, circ_SMAD4, circRNA_0044516, and circHIPK3) are markedly upregulated in gastric cancer [73, 159, 161, 195, 197]. The expression of circ0005654, circ_SMAD4, circHIPK3, and circheckd1 are positively associated with a poor prognosis in patients with gastric cancer [73, 159–161]. Functionally, these circRNAs all contribute to promoting tumor cell proliferation in gastric cancer [73, 159, 161, 194, 195, 197]. Additionally, circ0005654, circRNA_ASAP2, circ-SFMBT2, and circHIPK3 obviously promote gastric cancer cell migration and invasion. Circ-SFMBT2 upregulation indicates higher levels of oxidative stress in gastric cancer [195]. Mechanistically, in vitro and in vivo studies demonstrated that circ0005654 functions as a ceRNA of miR-363 to upregulate sp1 in the process of gastric cancer [159]. The level of CTNNB1 is regulated by circ-SFMBT2, a sponge of miR-1276 [73]. Circ-SFMBT2 activates the Wnt/β-catenin pathway by upregulating CTNNB1 expression. CircRNA_0044516 affects cancer progression by regulating the miR-149/Wnt1/β-catenin axis [197].

Interestingly, some researchers found that the expression of circCNIH4, circ-ITCH, and circ_0001649 was significantly downregulated in gastric cancer tissues and cells [160, 196, 198]. circ-ITCH is closely related to lymph node metastasis and patient prognosis [160]. CircCNIH4, circ-ITCH, and circ_0001649 markedly reduced cell proliferation, invasion, and migration in gastric cancer cell lines. CircCNIH4 and circ_0001649 also contribute to gastric cancer progression through the regulation of cell apoptosis [196, 198]. CircCNIH4 inhibits the Wnt/β-catenin pathway by upregulating DKK2 and FRZB levels (Fig. 3). Similarly, circ-ITCH reduce miR-17 levels to inactivate the Wnt/β-catenin pathway. Circ_0001649 inhibits the ERK and Wnt/β-catenin signaling pathways by sponging miR-20a.

Colorectal cancer (CRC)
CircRNA dysregulation has been discovered to be closely related to the occurrence and progression of CRC. Wnt pathway-associated circRNAs of CRC are shown in Table 1 [70, 162–168, 199–207]. Circ_0082182, circ-PRKDC, circ5615, and circ_0005075 are significantly correlated with advanced tumor-node-metastasis (TNM) stage in CRC [70, 163, 164, 167]. The overexpression of circRASSF2, circ_0082182, circ5615, circct3, circ_0005075, and circRNA_100290 indicates a poor prognosis in CRC patients [70, 162, 163, 165, 167, 168]. Circ-PRKDC is also associated with lymph node metastasis and tumor size [164]. Circ_0005075 expression is correlated with differentiation and the depth of tumor invasion [162, 167]. Functionally, the expression of cis-HOX facilitates the self-renewal of colorectal tumor-initiating cells [201]. Circ-ABCC1 could regulate malignant phenotypes, such as cell sphere formation ability, cell migration, and cell stemness, in CRC [204]. The role of circ-PRKDC in 5-fluorouracil resistance has been reported [164]. Additionally, the other Wnt pathway-associated upregulated circRNAs (Table 1) inhibit CRC cell growth and metastasis [70, 202, 205–207].

Liver cancer
Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer [235–238]. The
expression of circRNA-SORE, circβ-catenin, circZFR, and circ_0067934 is relatively elevated in HCC [71, 172, 173, 210]. In particular, increased circRNA-SORE levels were found in sorafenib-resistant HCC. CircZFR and circ_0067934 levels are significantly associated with the prognosis of patients with HCC [172, 173]. The expression of circ_0067934 is also markedly correlated with tumor TNM stage in HCC [173]. CircRNA-SORE, cZNF292, circβ-catenin, circZFR, and circ_0067934 markedly facilitates cell proliferation [172, 173, 209],

### Table 1 Expression and characteristic features of cancer-related circRNAs in the Wnt pathway

| Type              | circRNA          | Expression   | Prognostic indicator                  | Clinical feature                                                                 |
|-------------------|------------------|--------------|---------------------------------------|----------------------------------------------------------------------------------|
| Gastric cancer    | circ0005654      | Upregulated  | Overall survival                      |                                                                                  |
| Gastric cancer    | circ_SMAD4       | Upregulated  | Overall survival                      |                                                                                  |
| Gastric cancer    | circITCH         | Downregulated| Overall survival                      |                                                                                  |
| Gastric cancer    | circHIPK3        | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circASSF2        | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circ_0082182     | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circPRKDC        | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circS615         | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circCCT3         | Upregulated  | Overall survival, and disease-free survival |                                                                                   |
| Colorectal cancer | circ_0005075     | Upregulated  | Overall survival                      |                                                                                  |
| Colorectal cancer | circMT01         | Downregulated| Overall survival                      |                                                                                  |
| Colorectal cancer | circRNA_100290   | Upregulated  | Overall survival                      |                                                                                  |
| Liver cancer      | circ_0004018     | Downregulated| Overall survival                      |                                                                                  |
| Liver cancer      | circ_0003418     | Downregulated| Overall survival                      |                                                                                  |
| Liver cancer      | circZFR          | Upregulated  | Overall survival                      |                                                                                  |
| Liver cancer      | circ_0067934     | Upregulated  | Overall survival                      |                                                                                  |
| Liver cancer      | circITCH         | Downregulated| Overall survival                      |                                                                                  |
| Lung cancer       | circ_000984      | Upregulated  | Overall survival, and disease-free survival |                                                                                   |
| Lung cancer       | circ_001569      | Upregulated  | Overall survival                      |                                                                                  |
| Lung cancer       | circ_0001946     | Upregulated  | Overall survival                      |                                                                                  |
| Lung cancer       | circ_0018414     | Downregulated| Overall survival                      |                                                                                  |
| Lung cancer       | circ_0006427     | Downregulated| Overall survival                      |                                                                                  |
| Lung cancer       | circ_0007059     | Downregulated| Overall survival                      |                                                                                  |
| Lung cancer       | circITCH         | Downregulated| Overall survival                      |                                                                                  |
| Glioma            | circ_0001730     | Upregulated  | Overall survival                      |                                                                                  |
| Glioma            | circ_0000177     | Upregulated  | Overall survival                      |                                                                                  |
| Ovarian cancer    | circPLEKH3       | Downregulated| Overall survival, and recurrence-free survival |                                                                                   |
| Endometrial carcinoma | circ_0109046 | Upregulated  | 5-year survival                      |                                                                                  |
| Endometrial carcinoma | circ_0002577 | Upregulated  | Overall survival rate                  | FIGO stage, and lymph node metastasis                                            |
| Osteosarcoma      | circ_0002052     | Downregulated| Overall survival, and progression-free survival |                                                                                   |
| Thyroid cancer    | circITCH         | Downregulated| Overall survival                      |                                                                                  |
| Breast cancer     | circEIF6         | Upregulated  | Overall survival                      |                                                                                  |
| Breast cancer     | circITCH         | Downregulated| Overall survival                      |                                                                                  |
| Breast cancer     | circRNA_069718   | Upregulated  | Overall survival                      |                                                                                  |
| Category         | Type               | circRNA                | Role        | Functions                                      | Targeted molecule                | Refs  |
|------------------|--------------------|------------------------|-------------|------------------------------------------------|-----------------------------------|-------|
| Digestive tumors | Esophageal cancer  | circRNA_100367        | Oncogene    | EMT, proliferation, migration, and radioreistance | miR-217, and Wnt3                | [192] |
|                  | Esophageal cancer  | cir-ITCH               | Tumor suppressor | Cell cycle, and cell proliferation              | miRNA, Wnt                       | [193] |
|                  | Gastric cancer     | circ0005654            | Oncogene    | Proliferation, migration, and invasiveness     | miR-363, SP1, Wnt, and β-catenin  | [159] |
|                  | Gastric cancer     | circRNA_ asap2         | Oncogene    | Proliferation, migration, invasion, and cell apoptosis | Wnt, and β-catenin            | [194] |
|                  | Gastric cancer     | circ-SFMBT2            | Oncogene    | Proliferation, migration, invasion, cell apoptosis, and oxidative stress | miR-885-3p, CHD7, Wnt, and β-catenin | [195] |
|                  | Gastric cancer     | circCNIH4              | Tumor suppressor | Proliferation, migration, invasion, and cell apoptosis | DKK2, FRZB, Wnt, and β-catenin | [196] |
|                  | Gastric cancer     | circ_SMAD4             | Oncogene    | Proliferation, migration, and cell apoptosis | miR-1276, CTNNB1, Wnt, and β-catenin | [73]  |
|                  | Gastric cancer     | circRNA_0044516       | Oncogene    | Proliferation, and cell apoptosis              | miR-149, Wnt, 1, and β-catenin   | [197] |
|                  | Gastric cancer     | cir-ITCH               | Tumor suppressor | Cell proliferation, migration, and invasion | miR-17, Wnt, and β-catenin       | [160] |
|                  | Gastric cancer     | circ_0001649           | Tumor suppressor | Proliferation, migration, invasion, and cell apoptosis | miR-20a, ERK, and Wnt/β-catenin | [198] |
|                  | Gastric cancer     | cirCHIPK3              | Oncogene    | Proliferation, and migration                   | Wnt 1, and β-catenin             | [161] |
|                  | Colorectal cancer  | circ_0038718           | Oncogene    | Cell proliferation, migration, and invasian    | miR-195-5p, Axin2, and Wnt/β-catenin | [199] |
|                  | Colorectal cancer  | circ_0026628           | Oncogene    | Cell proliferation, migration, and stemness    | miR-346, FUS protein, SP1, Wnt/β-catenin, and Sox2 | [200] |
|                  | Colorectal tumor   | cis-HOX                | Oncogene    | Self-renewal, tumorigenesis, and metastatic capacites of TICs | FZD3, Wnt/β-catenin, and kSRP | [201] |
|                  | Colorectal cancer  | circRASSF2             | Oncogene    | Cell proliferation, migration, invasion, and cell apoptosis | miR-195-5p, FZD4, Wnt, and β-catenin | [162] |
|                  | Colorectal cancer  | circSMARCA5            | Tumor suppressor | Cell proliferation, migration, and invasian | miR-552, Wnt, and YAP1         | [202] |
|                  | Colorectal cancer  | circ_0082182           | Oncogene    | Cell proliferation, cell cycle, apoptosis, and metastasis | miR-411, miR-1205, and Wnt/β-catenin | [163] |
|                  | Colorectal cancer  | circAGFG1              | Oncogene    | Cell proliferation, migration, stemness, and apoptosis | miR-4262, miR-185-5p, YY1, CTNNB1, Wnt, and β-catenin | [203] |
|                  | Colorectal cancer  | circ-PRKDC             | Oncogene    | 5-FU resistance, cell proliferation, and invasion | FOXM1, miR-375, Wnt, and β-catenin | [164] |
|                  | Colorectal cancer  | circ5615               | Oncogene    | Cell proliferation, cell cycle, and invasion   | miR-149-5p, TNKS, Wnt, and β-catenin | [165] |
|                  | Colorectal cancer  | circ-ABCC1             | Oncogene    | Cell stemness, sphere formation, and metastasis | Wnt                                       | [204] |
| Category                    | Type      | circRNA           | Role            | Functions                                      | Targeted molecule                     | Refs   |
|-----------------------------|-----------|-------------------|-----------------|-----------------------------------------------|---------------------------------------|--------|
| Colorectal cancer           | circCCT3  | Oncogene          | Cell invasion, and apoptosis | miR-613, Wnt3, miR-613, and VEGFA               | [166]                                 |        |
| Colorectal cancer           | circ _ 0009361 | Tumor suppressor | Cell proliferation, migration, invasion, and EMT | miR-582, Wnt, and β-catenin                   | [205]                                 |        |
| Colorectal cancer           | circ _ 0005075 | Oncogene | Cell proliferation, migration, and invasion | Wnt, and β-catenin                           | [167]                                 |        |
| Colorectal cancer           | circMTDO1 | Tumor suppressor | Cell proliferation, and invasion | Wnt, and β-catenin                           | [70]                                  |        |
| Colorectal cancer           | circ _ 0000523 | Tumor suppressor | Cell proliferation, and apoptosis | miR-31, Wnt, and β-catenin                   | [206]                                 |        |
| Colorectal cancer           | circRNA_100290 | Oncogene | Cell proliferation, migration, and invasion | miR-516b, FZD4, Wnt, and β-catenin            | [168]                                 |        |
| Colorectal cancer           | circ-ITCH | Tumor suppressor | Cell proliferation | Wnt, and β-catenin                           | [207]                                 |        |
| Liver cancer                | circRNA-SORE | Oncogene | Sorafenib resistance, and apoptosis | Wnt, and β-catenin                           | [71]                                  |        |
| Liver cancer                | circ _ 0004018 | Tumor suppressor | Cell proliferation, and migration | miR-626, DKK3, Wnt, and β-catenin             | [169]                                 |        |
| Liver cancer                | circ-ITCH | Tumor suppressor | Cell proliferation, and apoptosis | Wnt, β-catenin, c-Myc, and CyclinD1           | [174, 208]                            |        |
| Liver cancer                | circ _ 0003418 | Tumor suppressor | Cell proliferation, migration, invasion, and cisplatin resistance | Wnt, and β-catenin                           | [170]                                 |        |
| Liver cancer                | circZKSCAN1 | Tumor suppressor | Cell stemness | FMRP, CCAR1, and Wnt                           | [171]                                 |        |
| Liver cancer                | cZNF292 | Oncogene          | Cell proliferation, and cell cycle | Wnt, β-catenin, and SOX9                      | [209]                                 |        |
| Liver cancer                | circβ-catenin | Oncogene | Cell growth, cell cycle, migration, and invasion | Wnt, and β-catenin                           | [210]                                 |        |
| Liver cancer                | circZFR | Oncogene          | Cell proliferation and EMT | Wnt, and β-catenin                           | [172]                                 |        |
| Liver cancer                | circ _ 0067934 | Oncogene | Cell proliferation, migration, invasion, and apoptosis | miR-1324, FZD5, and β-catenin                | [173]                                 |        |
| Liver cancer                | circ-ITCH | Tumor suppressor | Cell invasion, migration, proliferation and stemness | miR-338-5p, Wip1, Wnt 8, and β-catenin        | [174]                                 |        |
| Pancreatic cancer           | circ _ 0030167 | Tumor suppressor | Cell viability, colony formation, cell migration, invasion, and glycolysis metabolism | miR-532-3p, FOXR2, Wnt, and β-catenin        | [211]                                 |        |
| Lung cancer                 | circ-PGC | Oncogene          | Cell proliferation, apoptosis, and cycle arrest | miR-498, YES, Wnt, and β-catenin              | [212]                                 |        |
| Lung cancer                 | circ-ZNF124 | Oncogene          | Cell proliferation, migration and invasion, and apoptosis | miR-4491, Wnt2B, and β-catenin                | [213]                                 |        |
| Lung cancer                 | circ-BIRC6 | Oncogene          | Cell proliferation, migration and invasion, and apoptosis | miR-1182, KIF8, Wnt, and β-catenin            | [214]                                 |        |
| Lung cancer                 | circ _ 0067934 | Oncogene | Cell proliferation, migration, invasion, and apoptosis | Wnt, and β-catenin                           | [175]                                 |        |
| Lung cancer                 | circ _ 000984 | Oncogene | Cell proliferation, migration, invasion, and EMT | Wnt, and β-catenin                           | [176]                                 |        |
| Lung cancer                 | circ _ 001569 | Oncogene | Cell proliferation | Wnt, and β-catenin                           | [177]                                 |        |
| Category                  | Type      | circRNA     | Role       | Functions                              | Targeted molecule                              | Refs  |
|--------------------------|-----------|-------------|------------|----------------------------------------|-----------------------------------------------|-------|
| Lung cancer              | circ_0043256 | Oncogene    | Cell proliferation, and apoptosis | miR-1252, ITCH, and Wnt                     | [216] |
| Lung cancer              | circ-SOX4  | Oncogene    | Cell proliferation, invasion, and migration | miR-1270, PLAGL2, and Wnt                    | [69]  |
| Lung cancer              | circ_0001946 | Oncogene    | Cell proliferation | miR-135a-5p, SIRT1, Wnt, and β-catenin   | [177] |
| Lung cancer              | circ_0018414 | Tumor suppressor | Cell proliferation, stemness, and apoptosis | miR-6807-3p, DKK1, Wnt, and β-catenin         | [178] |
| Lung cancer              | circ_0006427 | Tumor suppressor | Cell proliferation, migration, and invasion | miR-6783-3p, DKK1, Wnt, and β-catenin         | [179] |
| Lung cancer              | circ_0007059 | Tumor suppressor | Cell proliferation, apoptosis, and invasion | miR-378, Wnt, and β-catenin                   | [180] |
| Lung cancer              | cir-ITCH   | Tumor suppressor | Cell proliferation | Wnt, and β-catenin                       | [181] |
| Glioma                   | circ_0001730 | Oncogene    | Cell proliferation, and migration    | Sp1, miR-326, Wnt7B, and β-catenin            | [182] |
| Glioma                   | circKIF4A   | Oncogene    | Cell proliferation, and migration    | miR-139-3p, Wnt, and β-catenin                | [217] |
| Glioma                   | circ_0000177 | Oncogene    | Cell proliferation, and invasion    | miR-638, Fzd7, and Wnt                      | [183] |
| Glioma                   | cZNF292     | Oncogene    | Cell proliferation, cell cycle, and angiogenic potential | miR-638, Fzd7, and Wnt | [218] |
| Prostate cancer          | cir-ITCH   | Tumor suppressor | Cell viability, and invasion | miR-17, Wnt, β-Catenin, PI3K, AKT, and mTOR | [219] |
| Ovarian cancer           | circABCB10  | Oncogene    | Cell proliferation, and cell apoptosis | miR-1271, Capn4, Wnt, and β-catenin          | [220] |
| Ovarian cancer           | circPLEKHM3 | Tumor suppressor | Cell growth, and migration | miR-9, BRCA1, DNAJB6, KLF4, Akt1, Wnt, and β-catenin | [184] |
| Endometrial carcinoma    | circ_0109046 | Oncogene    | Cell proliferation, aggressiveness, and apoptosis | miR105, SOX9, Wnt, and β-catenin             | [185] |
| Endometrial carcinoma    | circ_0002577 | Oncogene    | Cell proliferation, migration, and invasion | miR-197, CTNND1, Wnt, and β-catenin          | [186] |
| Cervical cancer          | circSAMD11  | Oncogene    | Cell proliferation, migration, invasion, and apoptosis | miR-503, SOX4, Wnt, and β-catenin             | [221] |
| Acute myeloid leukemia    | circ_0121582 | Tumor suppressor | Cell proliferation, and cell cycle | miR-224, GSK3β, Wnt, and β-catenin          | [222] |
| Chronic lymphocytic leukemia | circ-CBF8 | Oncogene    | Cell proliferation, cell cycle, and apoptosis | miR-607, Fzd3, Wnt, and β-catenin            | [223] |
| Diffuse large B-cell lymphoma | circ-APC | Tumor suppressor | Cell viability, and cell cycle | Wnt, β-catenin, TET1, and miR-888             | [224] |
| Osteosarcoma             | circUBAP2   | Oncogene    | Cell proliferation, migration, invasion, apoptosis, and cisplatin resistance | miR-506-3p, SEMA4D, Wnt, and β-catenin         | [225] |
| Osteosarcoma             | circMYO10   | Oncogene    | Cell proliferation, and emt | miR-370-3p, RUVBL1, Wnt, and β-catenin       | [63]  |
| Osteosarcoma             | circ_0002052 | Tumor suppressor | Cell proliferation, migration, invasion, and apoptosis | miR1205, APC2, Wnt, and β-catenin             | [187] |
Additionally, cZNF292, circRNA-SORE, and circ_0067934 reduce cell apoptosis [71, 173, 210, 239], while cZNF292 has no apparent effect on apoptosis [209]. The overexpression of circβ-catenin, circZFR and circ_0067934 increased the migration or invasion of HCC cancer cells [172, 173, 210]. High circRNA-SORE levels are important for maintaining HCC sorafenib resistance [71]. Mechanistically, some circRNAs interact with Wnt/β-catenin via other molecules in HCC. Circ_0067934 regulates HCC cell behaviors by activating the miR-1324/FZD5/wnt/β-catenin axis [173]. cZNF292 increases Wnt/β-catenin pathway activity through the upregulation of sex-determining region Y (SRY)-box 9 (SOX9) nuclear translocation [209].

On the other hand, the expression of circ_0004018, circ_0003418, and circ-ITCH is significantly down-regulated in HCC [169, 170, 174, 208]. CircZKSCAN1 and circ-ITCH are potential prognostic biomarkers [171, 174]. Circ_0004018 and circ_0003418 are negatively correlated with tumor size [169, 170]. In addition, the expression of circ_0003418 has been reported to be related to TNM stage and HBsAg levels in HCC [170]. Circ_0004018 and circ_0003418 contribute to cancer development and progression by regulating many cell biological functions, including cell proliferation, migration, and invasion. Knockdown of circZKSCAN1 could inhibit the malignant behaviors of HCC cancer stem cells, such as sphere formation, colony formation, cell proliferation, and metastasis. Circ_0004018 modulates the Wnt/β-catenin pathway to accelerate HCC progression by targeting the miR-626/DKK3 axis. CircZKSCAN1 binds with FMRP to increase Wnt signaling activity in HCC.

### Table 2 (continued)

| Category                  | Type            | circRNA          | Role              | Functions                             | Targeted molecule                                      | Refs   |
|---------------------------|-----------------|------------------|-------------------|---------------------------------------|--------------------------------------------------------|--------|
| Endocrine system tumors   | Thyroid cancer  | circRNA_102171   | Oncogene          | Cell proliferation, migration, invasion, and apoptosis. | CTNNBIP1, β-catenin, TCF3, TCF4, LEF1 complex, Wnt, and β-catenin | [226]  |
|                           | Thyroid cancer  | circRNA_NEK6     | Oncogene          | Cell growth, and invasion             | FZD8, Wnt, and miR-370-3p                                | [227]  |
|                           | Thyroid cancer  | circ-ITCH        | Tumor suppressor  | Cell proliferation, invasion, and apoptosis | miR-22-3p, CBL, and β-catenin                          | [188]  |
| Other systems tumors      | Breast cancer   | circ-EF6         | Oncogene          | Cell proliferation, migration, invasion | MYH9, Wnt, β-catenin, and EF6-224aa                      | [189]  |
|                           | Breast cancer   | circARL8B        | Oncogene          | Cell viability, migration, invasion, and fatty acid metabolism | miR-653-5p, PGE2, PI3K, AKT, GSK-3β, Wnt, and β-catenin | [228]  |
|                           | Breast cancer   | circABCC4        | Oncogene          | Cell viability, migration, invasion, and apoptosis | miR-154-5p, NF-kB, Wnt, and β-catenin                    | [229]  |
|                           | Breast cancer   | circ-ITCH        | Tumor suppressor  | Cell proliferation, invasion, and metastasis | miR-214, miR-17, ITCH, Wnt, and β-catenin               | [190]  |
|                           | Breast cancer   | circRNA_069718   | Oncogene          | Cell proliferation, and invasion      | Wnt, and β-catenin                                      | [191]  |
|                           | Breast cancer   | circFAT1         | Oncogene          | Cell apoptosis, migration, invasion, and oxaliplatin resistance | miR-525-5p, SKA1, Notch, and Wnt                       | [230]  |
|                           | Melanoma        | circ_0119872     | Oncogene          | Cell proliferation, and angiogenesis  | miR-622, G3BP1, Wnt, β-catenin, and mTOR                | [231]  |
|                           | Melanoma        | circ-GLI1 (circ_0027247) | Oncogene | Cell metastasis, and angiogenesis | p70S6K2, Hedgehog, GLI1, Cyr61, Wnt, and β-catenin  | [232]  |
|                           | Melanoma        | circ_0084043     | Oncogene          | Cell proliferation, migration, invasion, and apoptosis | miR-429, and homolog 2, Wnt, and β-catenin             | [233]  |
exosomes, attenuates pancreatic cancer cell growth, metastasis, and stemness. Exosomal circ_0030167 activates the WIF1/Wnt8/β-catenin axis by sponging miR-338-5p in pancreatic cancer. An increasing number of Wnt pathway-associated circRNAs have also been found in pancreatic ductal adenocarcinoma [247]. However, the underlying functions and mechanisms still need to be further explored.

**The respiratory system tumor**

**Lung cancer**

Lung cancer is the main cause of cancer-associated mortality worldwide [248–252]. It can be classified into non-small-cell lung cancer (NSCLC) and small-cell lung cancer, and NSCLC accounts for the overwhelming majority of lung cancer cases [253–255]. Wnt pathway-associated circRNAs of NSCLC are shown in Table 1 [69, 175–181, 212–216] (Fig. 4). The overexpression of circ_000984 and circ_001569 is significantly correlated with TNM stage and lymph node metastasis in NSCLC [175, 176]. The circ_0001946 expression profile is obviously associated with TNM stage and tumor size in NSCLC [177]. Additionally, circ_000984, circ_001569, and circ_0001946 upregulation predicts a poor prognosis in patients with NSCLC [175–177]. These upregulated circRNAs in NSCLC could promote cell growth by enhancing cell proliferation [69, 175–177, 212–216]. In vitro asty assay showed that silencing circ_0067934 and circ_000984 could inhibit the epithelial-mesenchymal transition (EMT) process to reduce cell metastasis in NSCLC [175, 215]. Circ-PGC could also hinder cancer progression by suppressing glycolysis metabolism [212]. Mechanistically, the majority of circRNAs interact with miRNAs to activate the Wnt/β-catenin pathway in NSCLC [69, 177, 212–216].

Interestingly, circ_0018414, circ_0006427, circ_0007059, and circ-ITCH are remarkably downregulated in NSCLC [178–181]. Circ_0018414 and circ_0006427 are markedly associated with the overall survival rate [178, 179]. Circ_0006427 and circ_0007059 facilitate cell growth and motility in NSCLC [179, 180]. Circ_0018414 enhances stemness features by promoting
DKK1 expression in NSCLC [178] (Fig. 5). CircRNAs can inhibit NSCLC tumorigenesis and progression by regulating the circ_0018414/miR-6807-3p/dkk1/Wnt/β-catenin, circ_0006427/miR-6783-3p/dkk1/Wnt/β-catenin, and circ_0007059/miR-378/Wnt/β-catenin pathways and the cir-ITCH/miR-7/miR-214/ITCH/Wnt/β-catenin axis.

Nervous system neoplasms

Glioma
Malignant gliomas are the most common primary tumors of the central nervous system [256–259]. Wnt pathway-associated circRNAs have drawn much attention in glioma research in recent years [260–263]. The levels of circ_0001730, circKIF4A, circ_0000177, and cZNF292 are upregulated in glioma [182, 183, 217, 218, 264] tissues versus normal brain tissues. Circ_0000177 is related to clinical stage, and patients with increased circ_0000177 expression have a poor prognosis [183]. Circ_0001730, circKIF4A, and circ_0000177 are all involved in tumor cell growth and metastasis in glioma [182, 183, 217]. cZNF292 promotes cancer development by regulating cell proliferation, the cell cycle, and angiogenesis. Mechanistically, circ_0001730 functions as a sponge of miR-326 to positively regulate Wnt/β-catenin pathways in the pathophysiologic processes of glioma. Circ_0001730 could also be upregulated by SP1 [218]. Overexpression of circ_0000177 increases FZD7 levels to activate Wnt signaling mediated by miR-638 in glioma.

Genitourinary tumors

Prostate cancer (PCa)
PCa refers to an epithelial malignancy that occurs in the prostate [265–269]. The expression of cir-ITCH was significantly downregulated in PCa tissues and cell lines [219]. Further experiments showed that cir-ITCH could attenuate PCa cell viability and invasion. Cir-ITCH hinders PCa development by inactivating the Wnt/β-Catenin and PI3K/AKT/mTOR pathways. Not much is known about Wnt pathway-associated circRNAs in PCa. There is a crucial need for Wnt pathway-associated circRNA research in PCa [219].
Female reproductive system cancers
Cancers that originate in the female reproductive system are called female reproductive cancers [270]. Ovarian cancer (OC), endometrial cancer (EC), and cervical cancer are the three most common gynecological malignancies [271–274]. The expression of circ-ABCB10 is significantly upregulated, while circPLEKHM3 expression is downregulated in OC [184, 220]. Moreover, the level of circPLEKHM3 is positively associated with the overall survival rate in patients with OC [184]. Circ-ABCB10 remarkably facilitates cell proliferation and invasion and reduces cell apoptosis by miR-1271 in OC [220]. Circ-ABCB10 plays a critical role in OC progression via the regulation of Capn4/Wnt/β-catenin. CircPLEKHM3 inhibits cell proliferation and migration by sponging miR-9 and regulating the BRCA1/DNAJB6/KLF4/AKT1/Wnt/β-catenin axis in OC [184]. Circ_0109046 and circ_0002577 are elevated in EC tissues and cell lines [185, 186]. The overexpression of circ_0002577 is positively correlated with advanced FIGO stage and lymph node metastasis in EC. High expression of circ_0109046 and circ_0002577 predicts a poor prognosis in patients with EC. Circ_0109046 activates the Wnt/β-catenin pathway by sponging miR-105 to increase SOX9 levels. Circ_0002577 functions as a sponge of miR-197 to regulate the CTNND1/Wnt/β-catenin axis in EC. CircSAMD11 expression is markedly upregulated in cervical cancer [221]. Silencing of circSAMD11 expression suppressed cell proliferation and metastasis and promoted cell apoptosis in cervical cancer. The circSAMD11/miR-503/sox4/Wnt/β-catenin axis plays an essential role in the progression of cervical cancer [221].

Tumors of the blood system
Hematological malignancies, also known as neoplasms of the blood, lymph nodes and bone marrow, include leukemia, lymphoma, and multiple myeloma [275–278]. The common types of leukemia are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic...
lymphocytic leukemia (CLL) [279–282]. Circ_0121582 expression is significantly decreased in AML [222]. Functional experiments demonstrated that the overexpression of circ_0121582 significantly attenuated cell survival and promoted the cell cycle arrest in AML. Circ_0121582 activates Wnt/β-catenin by sponging miR-224 to increase GSK3β expression in AML. The expression of circ-CBFB was upregulated in CLL, and it has been reported as an independent predictive factor for the prognosis of CLL [223]. Circ-CBFB facilitates CLL cell proliferation and inhibits cell apoptosis by sponging miR-607 and upregulating the FZD3/Wnt/β-catenin axis. Diffuse large B-cell lymphoma (DLBCL) is the most common malignant lymphoma subtype [283–285]. The level of circ-APC is significantly decreased in the tissues, cell lines, and plasma of DLBCL patients versus normal controls [224]. circ-APC inactivates the Wnt/β-catenin pathway to suppress cell proliferation in DLBCL through the regulation of the miR-888/APC and TET1/APC axes.

Fig. 5 The mechanisms of Wnt-associated circRNA in lung cancer. A In lung cancer, circ_0018414 inhibits cancer progression by regulating miR-6807-3p/DKK1 and the Wnt/β-catenin pathway. DKK1 is upregulated by circ_0018414, a ceRNA of miR-6783-3p. B Circ_0007059 inhibits the Wnt/β-catenin by acting as a sponge for miR-378. C Cir-ITCH upregulates ITCH expression to inactivate Wnt/β-catenin signaling by sponging miR-7 and miR-214.
Tumors of the musculoskeletal systems

Osteosarcoma (OS)

OS is the most common primary malignant neoplasm of the bone and mainly affects children, adolescents, and young adults [286–289]. The level of circMYO10 is significantly elevated [63], while circ_0002052 expression is downregulated in OS tissues and cell lines [187]. The expression of circ_0002052 is positively associated with overall progression-free survival in patients with OS. circ_0002052 inhibits cell growth and cell motility and enhances cell apoptosis in OS by sponging miR-1205 and modulating the APC2/Wnt/β-catenin axis. CircMYO10 functions as an oncogene in OS progression. The overexpression of circMYO10 facilitates OS cell proliferation and EMT in vitro. CircMYO10 facilitates histone H4K16 acetylation by regulating the miR-370-3p/RUVBL1 axis and activating Wnt/β-catenin signaling in OS. Cisplatin (DDP) is a conventional chemotherapy drug in the treatment of OS [290–293]. Cisplatin resistance is a major challenge for OS chemotherapy application [294, 295]. CircUBAP2 expression is increased in cisplatin-resistant OS tissues and cells [225]. Silencing circUBAP2 inhibits cell proliferation, migration, and invasion and induced apoptosis in OS. CircUBAP2 knockdown also suppresses cisplatin resistance by regulating miR-506-3p/SEMA6D and the Wnt/β-catenin pathway [225].

Tumors of the endocrine system

Thyroid cancer

The incidence rate of thyroid cancer has been increasing throughout the world [296–300]. CircRNA_102171 and circRNA_NEK6 are relatively upregulated [226, 227], while circ-ITCH is downregulated in thyroid cancer tissues and cell lines [188]. The level of circ-ITCH is closely associated with clinical stage, lymph node metastasis, and patient prognosis in thyroid cancer. CircRNA_102171 and circRNA_NEK6 play a promoting role in cell growth and metastasis. CircRNA_102171 activates the Wnt/β-catenin pathway in a CTNNBIP1-dependent way [226]. CircRNA_NEK6 facilitates thyroid cancer progression by sponging miR-370-3p and upregulating the FZD8/Wnt axis [227]. Circ-ITCH exerts its tumor suppressor action by modulating miR-22-3p/CBL/β-catenin in thyroid cancer [188].

Tumors of other systems

Breast cancer is one of the most common malignant malignancies among females worldwide [301–304]. Circ-EIf6, circARL8B, circABCC4, circRNA_069718, and circFAT1 expression levels are obviously upregulated in breast cancer [189, 191, 228–230]. CircRNA_069718 overexpression is positively correlated with TNM stage, lymph node metastasis, and overall survival in patients with breast cancer [191]. These upregulated Wnt-associated circRNAs contribute to cancer progression by promoting cell growth and metastasis. In addition, studies also observed that knockdown of circARL8B could induce a suppressive effect on fatty acid metabolism in breast cancer [228]. CircFAT1 enhances oxaliplatin resistance through the miR-525-5p/SKA1 and Wnt pathways in breast cancer [230]. CircARL8B, circABCC4, and CircFAT1 regulate the Wnt pathway by acting as sponges of miRNAs in breast cancer. EIf6-224aa, encoded by circ-EIf6, activates Wnt/β-catenin by regulating the MYH9/Wnt/beta-catenin pathway [189].

Melanoma is a potentially fatal disease with increasing incidence [305–309]. Circ_0027247 was isolated from circ-GL11 [232]. Circ_0119872, circ_0084043 and circGL11 (circ_0027247) are dramatically upregulated in melanoma tissues and cell lines [231–233]. High levels of circ_0027247 and circ_0084043 can promote cell motility [232], while circ_0119872 has no influence on cell migration and invasion [231]. Circ_0119872 and circ_0027247 are novel negative feedback regulators of angiogenesis in melanoma. Circ_0119872 and circ_0084043 have the same effects on cell proliferation. Circ_0119872 activates the Wnt/β-catenin pathway by interacting with p70S6K2 and upregulates Cyr61 expression in melanoma. The tumorigenesis and progression of melanoma are also regulated by the circ_0119872/ p70S6K2/Wnt/β-catenin and circ_0027247/miR-622/G3BP1/Wnt/β-catenin axes [231].

CircRNA, a potential biomarker in wnt pathway

Despite technological advances, cancer diagnosis and treatment are still a challenge that may require the emergence of new tumor biomarkers [310, 311]. Increasing evidence has revealed that Wnt-associated circRNAs are closely related to cancer progression. Wnt-associated circRNAs may be very promising biomarkers in cancer diagnosis, prognosis, and treatment. In this section, we will further discuss their potential application in clinical practice.

Diagnosis

The early screening and diagnosis of cancer is conducive to the survival of cancer patients [312–316]. Identifying suitable biomarkers has always been a difficult issue in cancer research. Wnt-associated circRNAs may be used to assist early diagnosis in many cancers. They are aberrantly expressed in many kinds of tumors from multiple systems, such as digestive tumors, respiratory system tumors, nervous system neoplasms, genitourinary tumors, musculoskeletal system tumors and endocrine system cancers. Moreover, plasma circ-APC levels are significantly downregulated in DLBCL [224].
discovery indicates a more convenient clinical application of circ-APC as a diagnostic marker. Studies further evaluated the diagnostic potential for cancer by receiver operating characteristic (ROC) curve analysis. Yang et al. found that the AUC value of circ0005654 was 0.781 in gastric cancer [159]. ROC analysis of circRASSF2 expression levels in colorectal cancer tissues and cells accurately discriminated between CRC patients and healthy controls (AUC: 0.9863) [162]. Further experimental verification and research on circRASSF2 in body fluids is necessary. The corresponding AUC value for circ-CBF was 0.80 in chronic lymphocytic leukemia [223].

**Prognosis prediction**

Early prognostic information is important in making treatment decisions [317–321]. A growing amount of evidence shows that Wnt-associated circRNAs can be of important prognostic value. These circRNAs are closely related to overall survival, disease-free survival, recurrence-free survival, 5-year survival rate, and progression-free survival in several cancers. Patients with lower circZKSCAN1 expression have shorter overall and recurrence-free survival in HCC [171]. Li et al. [166] reported that the overexpression of circCCT3 was negatively correlated with the disease-free survival rate in colorectal cancer. Higher circ_0109046 expression predicts a decreased 5-year survival rate in patients with endometrial carcinoma [185]. Such studies have important implications in prognosis evaluation and treatment selection. In addition, Wnt-associated circRNAs are associated with other relevant prognostic factors. For example, downregulated circMTO1 levels predict advanced TNM stage and lymph node metastasis in CRC [70].

**Cancer treatment**

Despite rapidly progressing treatment modalities, cancer therapy remains one of the most challenging issues in the world. CircRNA-based targeted therapeutic strategies shed new light on the evolution of cancer treatment [42, 43, 262, 322, 323]. CircRNAs regulate many cell biological functions by directly or indirectly interacting with the Wnt pathway. CircRNA_NEK6 activated the FZD8/Wnt axis to facilitate thyroid cancer progression by sponging miR-370-3p [227]. Circ_0121582 promotes GSK3β expression to activate the Wnt/β-catenin pathway by sponging miR-224 in AML [222]. Circ-SFMBT2 contributes to the development and tumorigenesis of gastric cancer via regulation of the miR-1276/CTNNB1/Wnt/β-catenin axis [195]. Controlling Wnt-associated circRNA expression may be an effective approach for cancer treatment. The knockdown of circ_SMAD4 blocked gastric cancer progression by negatively regulating cell growth [73]. Silencing circ-ZNF124 expression inhibited malignant phenotypes in NSCLC cells [73]. In addition, Circ-ITCH is a tumor suppressor in many cancers [160, 174, 181, 188, 190, 193, 207, 208, 219]. Wang et al. found that upregulated circ-ITCH expression suppressed cell proliferation and invasion in papillary thyroid cancer [188]. However, the identification of targeted drugs that can stably control the expression of circRNA and transmit this effect is the current difficulty. This requires a deeper understanding of the structure and function of Wnt-associated circRNAs. The majority of circRNAs act as sponges of miRNAs to activate or inactivate the Wnt pathway. Regulating the target miRNAs of Wnt-associated circRNAs may also be feasible. MiR-582 intervention effectively reversed the cell biological functions regulated by circ_0009361 in CRC [205].

**Conclusions and future perspectives**

The Wnt signaling pathway is highly involved in cancer development, and essential for a wide variety of cellular functions, such as cell polarity, movement, proliferation, asymmetric division, and muscle tissue development. Both circRNA and the Wnt pathway play a critical role in cancer development and progression. Emerging data suggest that the circRNA/Wnt axis modulates the expression of cancer-associated genes and then regulates tumor progression. CircRNAs are enriched in the Wnt pathway. Wnt-associated circRNAs are abnormally expressed in digestive tumors, respiratory system tumors, nervous system neoplasms, genitourinary tumors, musculoskeletal system tumors, endocrine system cancers and other cancers. Their aberrant expression indicates their potential as diagnostic markers. However, most related experiments are based on tissue and cell research. Ideal and effective molecular markers should be stably expressed in plasma, serum, and other body fluids. Such molecules have greater potential for clinical applications. Wnt-associated circRNAs are also promising potential biomarkers in the treatment of cancer. CircRNAs negatively or positively regulate cancer initiation, promotion, and progression by directly or indirectly interacting with the Wnt pathway. We could enhance the expression of cancer-promoting circRNAs or inhibit the expression of tumor suppressor circRNAs to control cancer progression. The current goal is to find targeted drugs that can stably control the expression of circRNA and induce this effect. We need to further understand the structure and function of Wnt-related circRNAs. Furthermore, the interaction and the related mechanisms between circRNAs involved in the Wnt pathway need more studies to confirm.

**Abbreviations**

ncRNAs: noncoding RNAs; miRNAs: microRNAs; lncRNAs: long ncRNAs; circRNAs: circular RNAs; PCP: Wnt/planar cell polarity; GSK-3β: glycogen synthase
kinase 3β; TCF: T-cell transcription factor; LEF: lymphoid enhancer factor; ceRNAs: competing endogenous RNAs; ESCC: esophageal squamous cellcarcinoma; CKX-8: Cell Counting Kit-8; CRC: colorectal cancer; TNM: tumor-node-metastasis; HCC: hepatocellular carcinoma; SRY: sex-determining region Y; SOX9: sex-determining region Y-box 9; BM-MSCs: bone marrow mesenchymal stem cells; NSCLC: non-small-cell lung cancer; EMT: epithelial-mesenchymal transition; KPS: Kamofsky Performance Status; OC: ovarian cancer; EC: endometrial cancer; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; OS: osteosarcoma; DDP: cisplatin; ROC: receiver operating characteristic.

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Authors’ contributions
Lanjuan Li and Juan Lu designed and guided the review. Chen Xue, Ganglei Li, and Quxian Zheng wrote and edited the manuscript. Xinyu Gu and Zhengyi Bao helped with reference collection and draw the figures. All authors read and approved the final manuscript.

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