

# Circular RNA Controls Tumor Occurrence and Development via Cell Cycle Regulation

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**Abstract:** Circular RNAs (circRNAs) participate in the occurrence and development of various diseases through different mechanisms, such as by acting as a microRNA (miRNA) sponge, interacting with RNA-binding proteins, and regulating gene transcription and protein translation. For example, the abnormal expression of specific circRNAs in tumor cells can alter key regulatory factors and the cell cycle network, resulting in cell cycle disorders and the development and metastasis of tumors. Here, we summarize the mechanisms involved in the circRNA-mediated processes that lead to uncontrolled cell cycle and tumor cell proliferation. Extensive studies investigating the abnormal expression of circRNAs in different cancer types have been conducted. The unique characteristics of circRNAs and their ability to regulate the cell cycle through diverse mechanisms is extremely valuable in tumor diagnosis, treatment, and prognosis. Our review may assist in further understanding the circRNA-mediated regulation of the cell cycle in tumors and provide insights for research on circRNA-based therapeutic strategies and biological diagnosis for cancer.

**Keywords:** circRNA, cancer, cyclins, CDKs, CKIs, p53

## Introduction

With the development of advanced molecular technologies, such as circular RNA (circRNA) microarray screening and high-throughput sequencing, extensive research on circRNAs has been performed, revealing their biological function and potential therapeutic and diagnostic value.<sup>1</sup>

Unlike linear RNAs, circRNAs possess special covalent bond ring structures, which ensures high stability. They can be differentially expressed in tissues and cells, especially in accessible body fluids such as saliva, plasma, and blood. These characteristics make this class of RNA molecules promising cancer biomarkers.<sup>2</sup> Li et al found that hsa\_circ\_0001649 is expressed at low levels in gastric cancer (GC) tissues, plotted its associated receiver operating characteristic (ROC) curve, and evaluated its diagnostic value in gastric cancer.<sup>3</sup> Circular RNAs are differentially expressed in a variety of cancers, and their clinical significance as potential diagnostic markers has been shown for different malignancies, such as liver cancer,<sup>4</sup> colorectal cancer,<sup>5</sup> glioblastoma,<sup>6</sup> and head and neck squamous cell carcinoma.<sup>7</sup> In addition, many studies have used survival analysis to evaluate the relationship between the expression level of circRNAs in different tumors and the survival rates of patients, reflecting the value of circRNAs in judging tumor prognosis.<sup>8–10</sup> Circular RNAs primarily play a role in tumors by acting as competing endogenous RNA (ceRNA) sponge miRNAs to attenuate the miRNA repression of target genes.<sup>11</sup> In addition, circRNAs can also participate in tumorigenesis and development by interacting with proteins, acting as transcriptional regulators, and participating in protein translation.<sup>11–13</sup> The regulation of circRNA expression can have an impact on many diseases, including cancer, in which abnormally expressed circRNAs play a critical function in activating carcinogenic or tumor suppressor effects during tumor development and progression.<sup>13,14</sup>

The cell cycle involves a strict regulatory process facilitating DNA replication and cellular reproduction.<sup>15</sup> Hence, cell cycle disorders play a vital role in tumor proliferation, metastasis, and prognosis. In eukaryotic cells, the cell cycle

consists of gap 1 (G1, pre-DNA synthesis), synthesis (S, DNA synthesis), gap 2 (G2, pre-division), and mitosis (M, cell division) phases.<sup>15</sup> Cell cycle progression is mainly driven by the complexes formed by cyclins (CCN) and cyclin-dependent kinases (CDKs).<sup>16</sup> The four main types of CCNs in mammalian cells, CCNA, CCNB, CCND, and CCNE, form complexes with various CDKs, such as CDK1, CDK2, CDK4, and CDK6.<sup>16</sup> Simultaneously, cell cycle progression is regulated by the CCN-dependent kinase inhibitors (CKIs), including the INK4 and Cip/Kip families.<sup>17</sup> These inhibitors can block specific CCN/CDK complexes, thereby terminating the cell cycle at certain points.<sup>16,17</sup> Normal cell cycle operation is also inseparable from the regulatory network involving the retinoblastoma protein (pRb) and p53 pathways.<sup>17,18</sup> Hence, cell cycle dysregulation is often a marker of the transformation of normal cells into tumor cells.<sup>15</sup> Aberrantly expressed circRNAs in tumors can affect tumor cell proliferation by regulating key cell cycle regulators, including p53, pRB, CDKs, CDK inhibitors (CKIs), and cyclins.<sup>19</sup> In addition, circRNAs can play a role in tumor invasion, metastasis, the tumor lymph node metastasis (TNM) stage, the histological grade, malignant phenotypes, and chemotherapy drug sensitivity by affecting the aforementioned cell cycle factors.<sup>20–24</sup> Table 1 lists the functions of cyclin/CDK complexes in various phases of the cell cycle. Figure 1 depicts cell cycle regulation in cancer involving circRNA targets.

Circular RNAs can regulate the aforementioned key proteins in the cell cycle in a variety of ways. For example, circRNAs can form a circRNA/miRNA/messenger RNA (mRNA) axis through the adsorption of miRNA and regulate the expression of downstream cell cycle-associated target genes. CircRNAs can also modulate cell cycle processes by regulating the key regulatory factors of phosphatidylinositol-3 kinase (PI3K)/AKT/FOXO, Wnt/ $\beta$ -catenin, and other signaling pathways, altering cell proliferation by directly forming complexes with cell cycle-related factors, and binding to RNA-binding proteins to regulate CCNs.<sup>25–31</sup> Interestingly, circRNAs can also be controlled by cell cycle regulators, forming a regulatory feedback loop directing cell cycle progression.<sup>32,33</sup> Figure 2 shows the regulatory mechanism of the cancer-associated circRNA-mediated cell cycle.

Here, we summarize the mechanisms involved in the circRNA-mediated processes that lead to uncontrolled cell cycle and tumor proliferation through an extensive review of the abnormal expression of circRNAs in different cancer types. We found that circRNAs are extremely valuable for the diagnosis, treatment, and prognosis of tumors.

## CircRNA-Mediated Regulation of Cell Cycle via CDKs

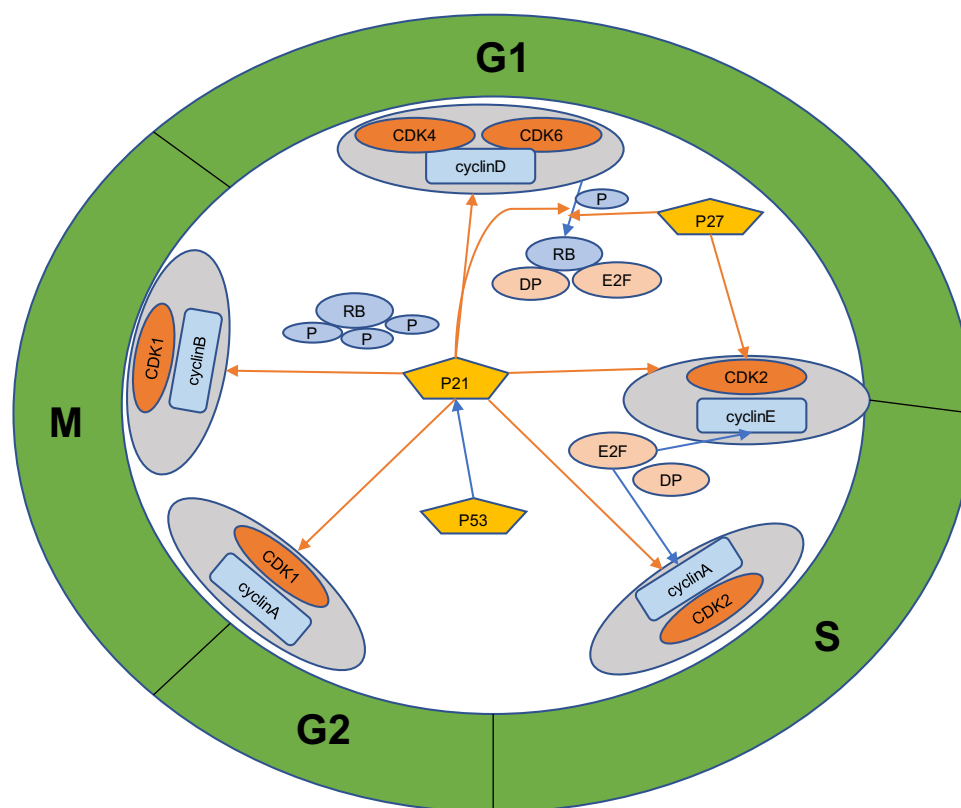
The main driving force of cell cycle progression is the sequential activation of CDKs, a group of serine/threonine kinases that form complexes with CCNs, which stably activate and phosphorylate CDKs at specific stages.<sup>15</sup> CCN/CDK formation also can regulate cell cycle progression through the phosphorylation of pRB. The dysregulation of CDKs primarily leads to the development of many diseases, including cancer.<sup>17,34</sup>

### Cdk1

Generally, CDK1 facilitates the G2/M transition and M phase progression by forming a complex with CCNA and CCNB.<sup>15</sup> In tumor cells, the abnormal expression of circRNAs can affect CDK1 expression through miRNA sponging. For example, the estrogen-induced circPGR, which is highly expressed in estrogen receptor (ER)-positive breast cancer (BrC) cell lines and clinical BrC tissue samples, regulates the cell cycle-associated proteins CDK1 and CDK6 by

**Table 1** Functions of the Cyclin/CDK Complexes in Cell Cycle Phases

Cyclin CDK	Cyclin/CDK Complexes Cell Cycle Phase
CyclinD1, 2, 3 CDK4, 6	Cyclin D-CDK4/6 G1 phase
CyclinE CDK2	Cyclin E-CDK2 G1 phase to S phase
CyclinA CDK2	Cyclin A-CDK2 S phase
CyclinA CDK1	Cyclin A-CDK1 G2 phase to M phase
CyclinB CDK1	Cyclin B-CDK1 M phase

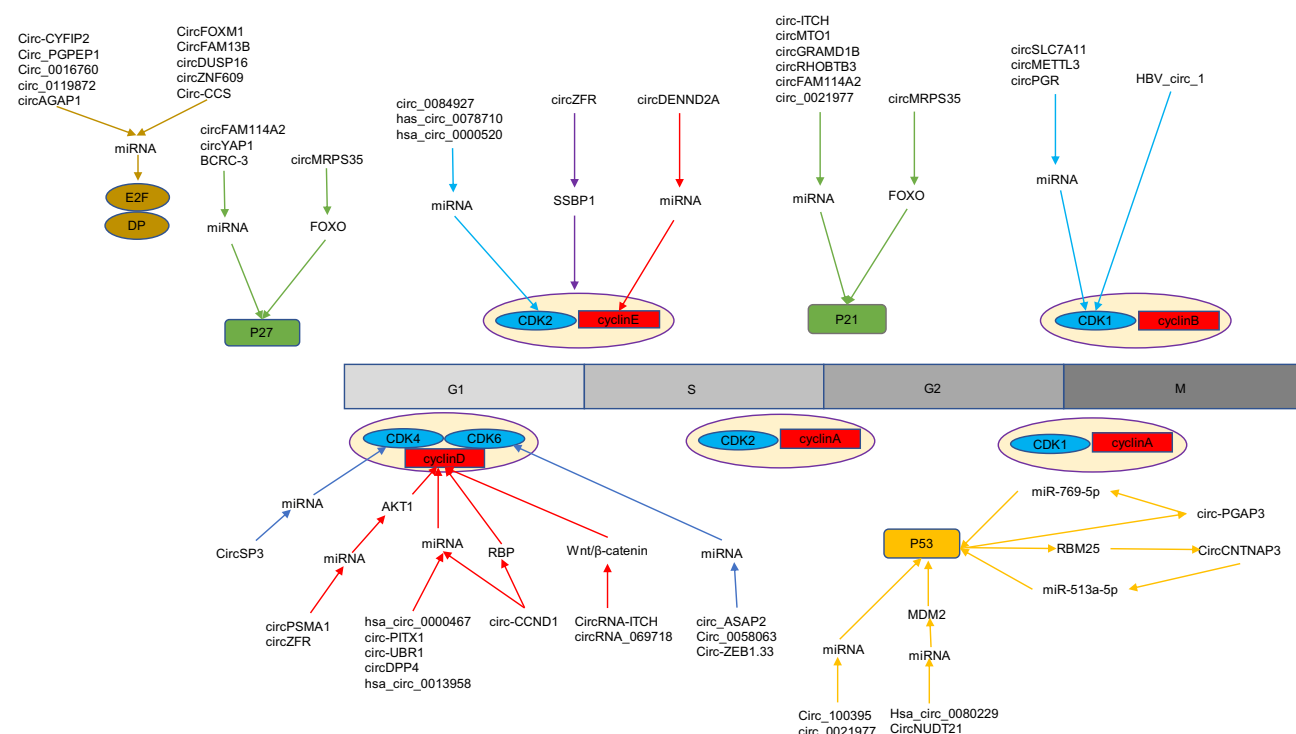


**Figure 1** Schematic diagram of cell cycle regulation in cancer involving circular RNA targets. Orange arrow – inhibition, blue arrow – promotion.

sponging miR-301a-5p and promotes the growth and tumorigenesis of ER-positive BrC cells.<sup>35</sup> In addition, this study also found that an anti-sense oligonucleotide targeting circPGR could effectively inhibit the growth of breast cancer cells, providing a new approach for the treatment of ER-positive breast cancer. Li et al discovered that circ-METTL3, which was also highly expressed in BrC, acted as a ceRNA of miR-31-5p and upregulated its target CDK1, facilitating cell proliferation, migration, and invasion in BrC.<sup>36</sup> Huang et al found that circSLC7A11 is significantly overexpressed in tissue and cells of hepatocellular carcinoma (HCC) and that its expression level is positively correlated with the tumor size, microvascular invasion, and TNM stage.<sup>37</sup> Survival analysis showed that HCC patients with high expression of circSLC7A11 usually have worse prognoses, and the results indicated that circSLC7A11 has the potential to become a prognostic marker for HCC. Huang et al further investigated the mechanism of action of circSLC7A11 in HCC cells and found that it accelerates HCC progression and metastasis by dampening the inhibitory effect of miR-330-3p on CDK1.<sup>37</sup> Aside from sponging miRNAs, circRNAs can also directly bind to CKD1. For example, another study found that HBV\_circ\_1, produced by hepatitis B virus (HBV), is significantly more abundant in HBV-related HCC tissues than in adjacent tissues.<sup>38</sup> In addition, the survival rates of HBV\_circ\_1-positive patients is significantly lower than that of HBV\_circ\_1-negative patients. The role of HBV\_circ\_1 in HBV-related HCC was further discovered via RNA pull-down and cell function assays; specifically, HBV\_circ\_1 was found to directly interact with CDK1 and upregulate CDK1 expression in HBV-related HCC tissues, thereby stimulating tumor proliferation, migration, and invasion.<sup>38</sup>

## Cdk2

CDK2 normally facilitates G1/S transition and S phase progression by forming a complex with CCNE and CCNA.<sup>15</sup> Similar with CDK1, circRNAs mainly regulate the level of CDK2 via miRNA sponging. For instance, Zheng et al assessed the expression of hsa\_circ\_0000520 in 52 pairs of cervical cancer (CC) tissues and their corresponding adjacent normal tissues using RT-qPCR. The expression of hsa\_circ\_0000520 in CC was found to be higher than that in normal tissues.<sup>39</sup> Furthermore, the overexpression of hsa\_circ\_0000520 was determined to promote the proliferation of CC cells. Zheng et al further investigated the downstream mechanism of hsa\_circ\_0000520. That study found that



**Figure 2** Circular RNA (circRNA)-mediated regulation of the cell cycle phases influencing tumor proliferation and the specific mechanisms involved. The different colors in the figure represent different key regulators of the cell cycle (including p53, E2Fs, CDKs, CKIs, and cyclins). Aberrantly expressed circRNAs in tumors can mediate cell cycle regulation by affecting the aforementioned cell cycle factors. Blue represents circRNAs involved in cell cycle regulation by affecting CDKs. Red represents circRNAs involved in cell cycle regulation by affecting cyclin. Purple represents circRNAs involved in cell cycle regulation by affecting the CDK/cyclin complex. Brown represents circRNAs involved in cell cycle regulation by affecting E2Fs. Green represents circRNAs involved in cell cycle regulation by affecting CKIs such as P21 and P27. Orange represents circRNAs involved in cell cycle regulation by affecting P53.

hsa\_circ\_0000520 promotes cell proliferation and cell cycle progression by inhibiting miR-1296 and upregulating CDK2 expression, and in vivo experiments were performed to verify this conclusion.<sup>39</sup> This study suggests potential strategies for the treatment of CC. Similarly, circ\_0084927, which is upregulated in CC tissues and cells, sponges miR-1179 to promote tumor cell proliferation and adhesion by regulating CDK2 expression.<sup>23</sup> Xie et al found that has\_circ\_0078710, which was upregulated in HCC, enhanced cell proliferation, migration, and invasion and promoted tumor growth by sponging miR-31 and activating CDK2 expression.<sup>40</sup>

## Cdk3

In mammals, CDK3 can participate in cell cycle progression by promoting the transition of cells from G1 to S phase, and even play a role in tumor progression.<sup>20,41</sup> CDK3 reportedly also promotes the G0/G1 transition by interacting with the non-CDK8-associated pool of CCNC for pRB phosphorylation, which is required for cells to efficiently exit from the G0 phase.<sup>42</sup> CDK3 is overexpressed in several cancer cell lines and may play an important role in cell proliferation and malignant transformation.<sup>43</sup> Liu et al reported that circRNA\_141539 was significantly upregulated in patients with esophageal squamous cell carcinoma (ESCC), which in turn upregulated the CDK3 expression level by sponging miR-4469, which is significantly associated with TNM stage, differentiation, and poor prognosis.<sup>20</sup>

## Cdk4

CDK4 and its homolog CDK6 are classic cell cycle kinases that facilitate the progression of cells through the early G1 phase by forming complexes with D-type CCNs, specifically D1, D2, and D3.<sup>44</sup> The CDK4/6/CCND complexes enable the phosphorylation of the RB protein family members, resulting in the release of E2F transcription factors from RB-mediated inhibition. Subsequently, E2F-dependent gene activation facilitates the G1/S transition and DNA synthesis.<sup>44</sup> Previous studies have reported that miR-198 is abnormally expressed in various cancers, including HCC, and that it is

associated with the initiation and progression of various cancers.<sup>45–48</sup> Li et al used bioinformatics analysis to predict that circSP3 might sponge miR-198 and the miR-198-target gene *CDK4* and further verified this prediction.<sup>49</sup> A series of in vitro and in vivo experiments was further conducted to study the expression and function of circSP3 in HCC. The results showed that high expression of circSP3 in HCC could promote the growth of HCC cells by inducing the expression of CDK4 by sponging miR-198.<sup>49</sup>

## Cdk6

CDK6 commonly interacts with CDK4 and CCND to form a complex during the G1 phase of the cell cycle.<sup>15</sup> A recent study found that the expression level of circ-ZEB1.33 in HCC tissues and serum is higher than that in normal tissue.<sup>50</sup> Gong et al further analyzed the clinical value of circ-ZEB1.33 in HCC by generating Kaplan–Meier curves, and the survival rates of patients with high expression were found to be significantly reduced. This result indicated that circ-ZEB1.33 could be used as a biomarker for HCC diagnosis and prognosis. Furthermore, Gong et al explored the biological function of circ-ZEB1.33 in HCC cells and found that it promotes HCC cell proliferation by attenuating the down-regulation of CDK6 expression mediated by the sponge miR-200a-3p.<sup>50</sup> A previous report revealed that the expression levels of circ\_ASAP2 and CDK6 were increased in gastric cancer (GC) tissues and cells, whereas the expression of miR-770-5p was decreased. Specifically, circ\_ASAP2 sponged miR-770-5p and consequently altered CDK6 expression, thereby boosting cell cycle progression in GC cells.<sup>51</sup> In addition, circ\_0058063 is significantly overexpressed in bladder cancer (BCa) tissues and promotes tumor progression by sponging miR-145-5p and regulating CDK6 expression.<sup>52</sup>

## CircRNA-Mediated Regulation of Cell Cycle via Cyclins

The normal progression of the cell cycle greatly depends on the CCN family proteins and the subsequent activation of CDKS.<sup>53</sup> In turn, the kinase activity of CDKs is positively regulated by the binding of specific CCNs.<sup>15</sup>

## CCNDs

CircRNAs indirectly regulate the expression of CCNDs by sponging miRNAs. For example, Zhu et al found that hsa\_circ\_0013958 expression is upregulated in lung adenocarcinoma (LAC) tissues, cells, and plasma.<sup>54</sup> Furthermore, hsa\_circ\_0013958 levels were found to be associated with the TNM stage and lymphatic metastasis. The diagnostic value of circ-SHPRH for LAC was evaluated by generating an ROC curve, and the area under the curve was 0.815, the sensitivity was 0.755, and the specificity was 0.796, indicating that hsa\_circ\_0013958 has high accuracy, specificity, and sensitivity and can be used as a new diagnostic biomarker for LAC. Through in vitro experiments, hsa\_circ\_0013958 was found to play a tumor-promoting role in LAC cells by upregulating CCND1 levels via the sponging of miR-134.<sup>54</sup> Similarly, a previous study reported that circ-PITX1, which was highly expressed in NSCLC, formed the circ-PITX1/miR-1248/CCND2 regulatory axis that promoted tumor proliferation, migration, and invasion.<sup>21</sup> Yang et al also showed that the overexpression of circDPP4 induced the expression of CCND1 by acting as a ceRNA for miR-195 and enhanced the proliferation, migration, invasion, and cell cycle progression of prostate cancer cells.<sup>55</sup> In addition, hsa\_circ\_0000467 expression is higher in GC tissues than in controls and may play a carcinogenic role in tumor progression by regulating the associated miR-326-3p/CCND1 axis.<sup>56</sup> In BrC, the upregulation of circ-UBR1 expression increases the expression of CCND1 by sponging miR-1299 and promotes tumor cell proliferation.<sup>57</sup> Interestingly, the interaction of circRNAs with RNA-binding proteins can prevent the inhibition of CCND expression. A circRNA derived from CCND1, circ-CCND1, is significantly upregulated in laryngeal squamous cell carcinoma and positively correlates with aggressive clinical features, resulting in poor prognosis and enhanced tumorigenesis.<sup>31</sup> Zang et al analyzed the survival curve and found that patients with high circ-CCND1 expression had a shorter survival time and that it could be a biomarker for the prognosis of laryngeal squamous cell carcinoma. The mechanism underlying the effects of circ-CCND1 in laryngeal squamous cell carcinoma was further explored. Circ-CCND1 can directly interact directly interacts with the human antigen R protein to increase the stability of CCND1 mRNA. In addition, as an effective sponge for miR-646, circ-CCND1 reduces the miR-646-mediated inhibition of CCND1 and further elevates its expression.<sup>31</sup>

CircRNAs can also regulate the expression of CCND1 by targeting the PI3K/AKT pathway. Akt is a serine-threonine kinase that can be regulated following activation of phosphatidylinositol 3-kinase (PI3K),<sup>58</sup> which inhibits FOXO



transcription factors via phosphorylation and contributes to cell survival, growth, and proliferation.<sup>58</sup> FOXOs, which regulate numerous cell cycle-related proteins, can induce cell cycle arrest by suppressing CCND1 and CCND2 expression.<sup>58,59</sup> In addition, AKT promotes cell cycle progression by inactivating GSK-3 $\beta$  and promoting the accumulation of  $\beta$ -catenin, activating the Wnt/ $\beta$ -catenin signaling pathway, and increasing the expression of its target, CCND1.<sup>60–63</sup> Yang et al demonstrated that circZFR expression was elevated in HCC tissues and cells and promoted tumor progression by downregulating miR-511 expression, activating AKT1 signaling, and upregulating CCND1 expression.<sup>60</sup> The circPSMA1 overexpression observed in triple-negative BrC (TNBC) cells and their exosomes attenuated the miR-637-mediated inhibition of AKT1, elevated the expression of CCND1, and enhanced the tumorigenesis, metastasis, and immunosuppression of tumor cells.<sup>64</sup> Yang et al performed Kaplan–Meier analysis to further explore the relationship between the circPSMA1/miR-637/Akt1 axis and the clinical outcomes of TNBC patients; the results showed that high Akt1 expression and low miR-637 expression were closely associated with poor outcomes for TNBC patients with lymphatic metastases.<sup>64</sup> Taken together, these findings suggest that circPSMA1 might serve as a potential prognostic biomarker for TNBC and provide a new research direction for TNBC immunotherapy. circRNAs regulate CCND1-mediated cell proliferation by modulating the Wnt- $\beta$ /catenin signaling pathway.<sup>25</sup> In cancer, aberrant Wnt/ $\beta$ -catenin signaling facilitates stem cell renewal, cell proliferation, and cell differentiation, thus playing crucial roles in tumorigenesis and showing potential for therapy.<sup>61</sup> In particular, the abnormal regulation of the transcription factor  $\beta$ -catenin, a pivotal component of the Wnt signaling pathway, leads to early events in carcinogenesis.<sup>61</sup> In the canonical Wnt cascade,  $\beta$ -catenin is the key effector responsible for signal transduction to the nucleus that triggers the transcription of Wnt-specific genes determining cell fate.<sup>62</sup> Without a Wnt signal, cytoplasmic  $\beta$ -catenin is ubiquitinated and degraded by the APC complex and cannot enter the nucleus, consequently blocking the transcription of Wnt/ $\beta$ -catenin target genes.<sup>62</sup> Normally, Wnt signaling blocks the activity of the destruction complex, resulting in increased levels of cytoplasmic  $\beta$ -catenin that are translocated to the nucleus.<sup>62</sup> In the nucleus,  $\beta$ -catenin interacts with T cell-specific factor (TCF)/lymphoid enhancer-binding factor (LEF) and other co-activators and induces the transcription of Wnt target genes, such as *c-Myc*, *CCND1*, and *CDKN1A*, which in turn upregulate the expression of TCF/LEF target genes.<sup>61,62</sup> Zhang et al revealed that the expression of circRNA\_069718 in TNBC tissues and cell lines was significantly correlated with advanced TNM stage, lymph node metastasis, and poor overall survival in cancer patients.<sup>63</sup> Notably, circRNA\_069718 upregulated the expression of Wnt/ $\beta$ -catenin pathway-related genes (eg  *$\beta$ -catenin*, *c-Myc*, and *CCND1*), subsequently promoting TNBC cell proliferation and invasion in vitro.<sup>63</sup> These findings provide a theoretical basis for developing new diagnostic markers and treatment strategies for TNBC. By contrast, circRNA-ITCH expression was downregulated in HCC tissues. CircRNA-ITCH can reduce the expression of CCND1 by inhibiting the Wnt/ $\beta$ -catenin pathway, affecting the occurrence and development of tumors.<sup>65</sup> In addition, hsa\_circ\_0005615 (circ5615) is significantly upregulated in colorectal cancer (CRC) tissues,<sup>25</sup> and exhibits oncogenic function as a ceRNA of miR-149-5p. In addition, CRC patients with high levels of circ5615 have shorter overall survival, and multivariable analysis confirmed that circ5615 could serve as an independent prognostic biomarker for CRC patients. Tankyrase (TNKS), a regulator of  $\beta$ -catenin stabilization, was identified as the potential miR-149-5p target by a series of experiments. Circ5615 can serve as a miR-149-5p sponge to upregulate TNKS levels, activate the Wnt/ $\beta$ -catenin pathway, and upregulate the expression of  $\beta$ -catenin and cyclin D1 to promote CRC.<sup>25</sup>

## CCNBs

The Cyclin B-CDK1 complex formed by CCNB and CDK1 is the key to triggering and promoting mitosis.<sup>53</sup> In normal cells, the CCNB1/CDK1 complex rapidly accumulates in the nucleus after activation in the cytoplasm, thereby inducing the cell to enter mitosis.<sup>28,53</sup> CircRNAs can regulate cell cycle progression by altering the CCNB level in the nucleus. In HCC tissues, the low hsa\_circ\_0079929 expression influences cell proliferation by regulating the expression of nuclear CCNB1.<sup>28</sup>

## CCNEs

CircRNAs can also alter the expression of CCNE via sponging miRNA. One study discovered that circDENND2A was abnormally expressed in NSCLC samples, which induced the expression of CCNE1 after miR-34a sponging and promoted the proliferation, migration, and invasion of tumor cells.<sup>27</sup>

## CircRNA-Mediated Regulation of Cell Cycle via CDK/Cyclin Interactions

Cell cycle regulators are considered to be promising targets in cancer therapy since cell proliferation depends on the progression of the cell cycle phases regulated by several CDKs acting in complex with their CCN partners.<sup>67</sup> CircRNAs also can regulate cell cycle progression by altering the expression of CCN/CDK complexes. At the end of G1 phase, the accumulation of CCNE activates CDK2 to form a CCNE/CDK2 complex, which can promote G1/S transition.<sup>66</sup>

In addition, the activation of the CDK2/CCNE1 complexes can induce pRB phosphorylation, thus releasing the transcription factor E2F1, which induces the expression of its downstream target genes (eg *CCNA2*, *CCNB1*), thereby promoting cell cycle progression.<sup>66,68</sup> CircRNAs can enhance the formation of the CDK2/CCNE complex by interacting with single-stranded DNA binding proteins (SSBPs). In cervical cancer, the significantly upregulated hsa\_circ\_0072088 (circZFR) recruits and activates the CDK2/CCNE1 complex by interacting with SSBP1 to promote cervical cancer proliferation.<sup>68</sup> In addition, an evaluation of circZFR by ROC analysis indicated that it has good predictive value for the diagnosis of cervical cancer.<sup>68</sup> CCNA replaces CCNE as the partner of CDK2 during the cell cycle to control DNA replication in the S phase and is subsequently associated with CDK1 to promote entry into the M phase.<sup>15</sup> CircRNAs can also directly form a complex with CDKs to hinder cell cycle progression. Interestingly, the high ectopic expression of circ-Foxo3 in non-cancer cells results in the formation of a ternary complex with CDK2 and p21.<sup>30</sup> The formation of the circ-Foxo3/p21/CDK2 complex hijacks CDK2 and p21 together and blocks the formation of the CCNE/CDK2 and CCNA/CDK2 complexes, thereby inhibiting cell cycle progression.<sup>30</sup> Important tumor suppressors involved in cell cycle regulation (eg pRB and p53), which are mainly regulated by post-translational modifications (eg phosphorylation, sumoylation, and acetylation), are functionally related and can form a complex regulatory network.<sup>69</sup> The abnormal regulation of these tumor suppressors alters the expression of cell cycle regulators and leads to tumor occurrence and development.

## CircRNA-Mediated Regulation of Cell Cycle via pRb-E2Fs

As a tumor suppressor, RB loses its function in various cancers; thus, RB has an inseparable relationship with tumor formation.<sup>70</sup> As a product of a tumor suppressor gene found in hereditary retinoblastoma, pRB plays a central role in G1/S transition.<sup>69,70</sup> The dynamic regulation of pRB phosphorylation by the CCN/CDK complex triggers the cell to exit the G0 phase, cross the G1 phase, and enter the S phase.<sup>68</sup> In the early G1 phase, pRB is phosphorylated by the CCND/CDK4/6 complex to release the transcription factor E2F, which positively regulates the transcription of certain genes, such as *CCNA* and *CCNE*, that are necessary for cells to enter the S phase.<sup>17,68</sup> CircRNAs directly influence the expression of RB via sponging its related miRNAs. For instance, circRNA\_100782, which exhibits low expression in GC cells, regulates the proliferation and metastasis of GC cells by regulating RB expression via miR-574-3p sponging.<sup>71</sup> The transcription factor E2F binds to the promoter regions of genes that are required for S phase entry, including DNA polymerase subunits, CCNA, and CCNE.<sup>17,68</sup> Lin et al used quantitative real-time PCR to evaluate the expression of circCYFIP2 in GC tissues and adjacent normal tissues, and the results showed that its expression was significantly increased in GC tissues.<sup>72</sup> Furthermore, high levels of circCYFIP2 were found to be positively correlated with International Union for International Cancer Control (UICC) stages, pathological T stages, lymphatic metastasis, distant metastasis, and grades.<sup>72</sup> Lin et al identified the diagnostic and prognostic value of circCYFIP2 in GC by generating ROC curves and by Kaplan–Meier analysis. Subsequently, through a series of in vitro and in vivo experiments, it was found that circCYFIP2 increases E2F1 expression via miR-1205 sponging and accelerates tumor cell proliferation and invasion.<sup>72</sup> These findings provide potential biomarkers and prognostic indicators to reflect the deadly disease status of and develop more therapeutic targets for GC. Likewise, in GC tissues and cell lines, the significantly upregulated circ\_PGPEP1 elevates E2F3 expression via miR-1297 sponging and enhanced the proliferation of tumor cells.<sup>73</sup> In addition, circ\_0016760 is upregulated in NSCLC and acts as a sponge for miRNA-4295, consequently enhancing the expression of E2F3 and promoting cell proliferation.<sup>74</sup> In malignant melanoma, circ\_0119872 encourages cell

proliferation by relieving the inhibitory effect of miR-582-3p on E2F3 via sponging.<sup>75</sup> Another study reported that circAGAP1 (circ0058792) expression was significantly upregulated in clear cell renal cell carcinoma (ccRCC) tissues compared to that in adjacent non-tumor tissues. In particular, circAGAP1 played a carcinogenic role in ccRCC progression by regulating the miR-15-5p/E2F3 axis.<sup>76</sup> CircFAM13B, which is highly expressed in HCC, serves as a sponge of miR-212 and enhances tumor progression by upregulating E2F5.<sup>77</sup> Furthermore, circFOXM1, which is highly expressed in glioblastoma tumor tissues and cells, alleviates targeted inhibition of E2F5 by miR-577 by competing with miR-577 and upregulates its expression to promote tumor cell proliferation.<sup>78</sup> Similarly, in CRC tissues, the upregulated circDUSP16 elevates the expression of E2F6 by competitively binding with miR-432-5p and promotes tumor progression.<sup>79</sup> In CC tissues and cell lines, the increased expression of circ-ZNF609 significantly promotes the viability, migration, and invasion of tumor cells by acting as a ceRNA of miRNA-197-3p and reducing its inhibitory effect on E2F6.<sup>80</sup> In lung cancer, the upregulated expression of circ-CCS can be used to predict poor prognosis. Circ-CCS indirectly increases the expression of E2F7 by sponging miR-383 and promotes cancer progression.<sup>81</sup>

## CircRNA-Mediated Regulation of Cell Cycle via CKIs

CircRNA can regulate the cell cycle at multiple levels by targeting different molecules. Aside from RB family proteins, CKIs can also negatively regulate CDK activity by binding to either free CDKs or CDK/CCN complexes.<sup>15,17</sup> There are two distinct families of CKIs: the INK4 family, composed of p16 (INK4a), p15 (INK4b), p18 (INK4c), and p19 (INK4d), which specifically inactivate CDK4 and CDK6, thereby preventing their interaction with CCND, and the Cip/Kip family, comprising p21 (Cip1), p27 (Kip1), and p57 (Kip2), which form heterotrimeric complexes with CCND-, CCNE-, and CCNA-dependent kinase complexes, thus inhibiting their activities.<sup>15</sup> CKI dysregulation can cause a variety of diseases, including cancers.<sup>15,82</sup> CircRNAs can also alter the levels of CKIs in tumors and interfere with cell cycle progression.

### p21

P21, a potent universal CKI that belongs to the CIP/Kip family, possesses high binding affinity for CCN/CDK2, CCN/CDK1, and CCN/CDK4/6 complexes, which subsequently prevents the phosphorylation of pRB and blocks cell cycle progression.<sup>82–84</sup> In addition, p21 directly interacts with the E2F complexes and inhibits E2F activity to induce cell cycle arrest.<sup>83</sup> As a tumor suppressor, p21 exerts oncogenic effects and is usually downregulated in several cancer types, contributing to poor prognosis and decreased overall survival in patients.<sup>83</sup> As a critical effector of various intra- and extracellular stress signals, p21 is highly regulated by multiple transcriptional factors, distinct post-transcriptional regulators (eg miRNAs, RNA-binding proteins), and different post-translational modifications.<sup>82</sup> In addition, the p21 gene can be activated by p53.<sup>85,86</sup> Notably, a previous study reported that circMTO1 was significantly downregulated in HCC. CircMTO1 could elevate the expression of p21 by sponging miR-9, thus reducing tumor cell proliferation.<sup>87</sup> In addition, HCC patients with low levels of circMTO1 have shorter survival, suggesting that it could be used to evaluate the survival rate of HCC patients as a predictive prognostic indicator. In GC tissues and cell lines, the downregulated expression of the circGRAMD1B alters the expression of p21 by sponging miR-130a-3p and influences the proliferation, migration, and invasion of tumor cells.<sup>88</sup> In addition, the circRHOBTB3 expression is downregulated in GC. CircRHOBTB3 can act as a tumor suppressor to inhibit the proliferation of tumor cells by acting as a sponge for miR-654-3p to elevate the expression of p21.<sup>89</sup> Circ-ITCH, which is downregulated in BCa tissues and cell lines, regulates the expression levels of p21 by sponging miR-17 or miR-224 and influences the aggressive biological behaviors of BCa.<sup>90</sup> Yang et al included and analyzed the clinicopathological parameters and survival data of BCa patients and found that the level of circ-ITCH expression was positively correlated with the histological grade and that BCa patients with lower cyclic ITCH expression have a shorter overall survival and worse prognosis.<sup>90</sup> Similarly, the circCdr1as, which acts as a tumor suppressor in BCa, has significantly reduced expression in BCa. CircCdr1as can partly upregulate p21 expression by sponging miR-135a and exerts anti-cancer effects.<sup>91</sup> In BrC, the circDDX17 reduces CDK1 and increases p21 expression by sponging miR-605, thereby inhibiting tumor cell proliferation.<sup>92</sup> Circ\_0021977, which acts as a tumor suppressor in CRC, has significantly reduced expression in tumor tissues, plasma, and cell lines. Circ\_0021977 indirectly regulates p21/p53 by acting as a sponge of miR-10b-5p, thus inhibiting the proliferation, migration, and invasion of CRC cells.<sup>93</sup> Previous reports have found that circFAM114A2 levels were decreased in urothelial carcinoma (UC) cell lines and tissues. Furthermore, circFAM114A2 inhibited the proliferation of UC cells in the G1 phase and heightened the sensitivity of UC to cisplatin chemotherapy. Mechanistically, circFAM114A2 directly sponges miR-



222-3p and miR-146a-5p, altering the expression of their downstream target genes *p27* and *p21*, respectively, and thus inhibiting the progression of UC and enhancing the sensitivity of cancer cells to cisplatin chemotherapy.<sup>22</sup> In addition, this study also found that the expression level of circFAM114A2 is positively correlated with the survival rate of patients with UC. Therefore, circFAM1142 has great potential as a prognostic biomarker and therapeutic target for UC. CircRNAs can also regulate the expression of p21 by targeting the AKT/FOXO signaling axis. For example, FOXO is an important target in the PI3K/AKT pathway regulated by AKT phosphorylation.<sup>58</sup> One of its functions is to activate *p21* gene transcription, which plays a key role in G1 arrest.<sup>58,94</sup> Jie et al revealed that circRNAs could directly affect acetylation at the regulatory region of target genes and “unlock” their expression, suggesting that noncoding RNAs play a significant role in the histone modification of gene promoters.<sup>95</sup> Lysine acetyltransferase 7 (KAT7) is a member of the histone acetyltransferase family that regulates histone acetylation and participates in histone modification.<sup>96</sup> Jie et al found that circMRPS35 expression is downregulated in GC.<sup>95</sup> In addition, this study found that the area under the ROC curve of circMRPS35 was 0.6976 and its expression level was closely related to the survival time of patients. This study showed that circMRPS35 has important clinical significance for GC diagnosis and prognosis. A further investigation of the mechanism underlying the effects of circMRPS35 in GC revealed that circMRPS35 increased the H4K5 acetylation associated with the promoter regions of *FOXO1* and *FOXO3a* via recruitment of KAT7, which resulted in the upregulation of FOXO1 and FOXO3a.<sup>95</sup> Notably, FOXO1 and FOXO3a can inhibit cell proliferation and invasion by upregulating the expression of their target genes *p21* and *p27*.<sup>58</sup>

## p27

The CKI p27 (or KIP1), one of the members of the Cip/Kip family, can block cell cycle progression via CDK inhibition, with CDK2 as the main target.<sup>97</sup> In addition, p27 can inhibit the CCN-mediated phosphorylation of RB and prevent the separation of E2F from RB, subsequently inhibiting the transcription of genes required for G1/S transition.<sup>97</sup> As the most important pathway involved in the p27 function, PI3K/AKT signaling promotes the G1/S transition by phosphorylating FOXO and downregulating the expression of cell cycle inhibitory genes.<sup>58,97</sup> CircRNAs can regulate cell cycle progression by altering p27 expression via miRNA sponging. For instance, circRNA BCRC-3, which exhibits low expression in BCa tissues and cell lines, acts as a tumor suppressor to inhibit the proliferation of tumor cells through the miR-182-5p/p27 axis. Specifically, circRNA BCRC-3 directly interacts with miR-182-5p, weakening its inhibitory effect on *p27* at the 3'-UTR and resulting in the significant upregulation of p27, preventing tumor cell proliferation.<sup>98</sup> In GC tissues, the expression level of circYAP1 is significantly lower than that in adjacent normal tissues. Furthermore, circYAP1 acts as a tumor suppressor to inhibit the proliferation of GC cells by blocking the miR-367-5p/p27 axis.<sup>99</sup>

## CircRNA-Mediated Regulation of Cell Cycle via p53

The tumor suppressor p53 encoded by the *TP53* gene is also an important part of the cell cycle control mechanism as a transcription factor that specifically binds to DNA and activates the transcription of key genes that induce cell cycle arrest (eg CKI p21 for G1 arrest).<sup>16</sup> Many human tumors carry inactivating missense mutations in *TP53* that disrupt p53 activity, resulting in cell cycle dysregulation and promoting tumor proliferation.<sup>16,100</sup> CircRNAs can directly affect the expression of p53 via sponging its associated miRNAs. For instance, Li et al discovered that circ\_100395 was lowly expressed in ovarian cancer tissues and functioned as a miR-1228 sponge, which altered the p53 expression and influenced tumor progression.<sup>101</sup> CircRNAs can also indirectly modulate p53 expression by changing the levels of p53 antagonists through miRNA sponging. One p53 inhibitor, MDM, creates an autoregulatory feedback loop with p53.<sup>102</sup> In cells containing wild-type p53 and subjected to various stimuli, p53 normally transcribes the *MDM2* gene to produce MDM2 protein, and in turn, the binding of MDM2 to p53 directly inhibits p53 function.<sup>102</sup> Notably, MDM2 expression is abnormally upregulated in different cancer types.<sup>103</sup> In BCa, circNUDT21 is overexpressed in tumor tissues and cell lines. Additionally, MDM2 is a potential downstream target of miR-16-1-3p, and circNUDT21 promotes BCa progression by sponging miR-16-1-3p and activating the miR-16-1-3p/MDM2/p53 axis.<sup>104</sup> Similarly, Zhou et al found that circ\_0080229 expression was upregulated in both glioma tissues and cell lines. Circ\_0080229 relieved the inhibitory effect of miR-1827 on MDM2 via sponging and promoted tumorigenesis and metastasis.<sup>105</sup> The MDM2 homolog MDM4 can also inhibit p53 function through multiple pathways.<sup>103</sup> In CC, MDM4 expression is regulated by circ-0000263 via sponging miR-150-5p, which indirectly downregulates the expression of p53, and consequently promotes cell proliferation and migration and inhibits cell apoptosis.<sup>106</sup>

CircRNAs can also be regulated by p53, forming a regulation feedback loop between the two. For instance, MDM2 is both the direct transcription target and primary negative regulator of p53.<sup>103</sup> Circ-MDM2 was confirmed to be a circRNA derived from MDM2 pre-mRNA, which could promote tumor growth. Interestingly, circ-MDM2 was resistant to RNase R digestion, and its transcription was induced in a p53-dependent manner. Simultaneously, although the specific mechanism underlying the regulation of p53 level remains to be determined, experiments have confirmed that circ-MDM2 can negatively regulate the expression of p53, thus forming a self-regulating negative feedback loop that facilitates tumor cell proliferation.<sup>107</sup> The expression of another circRNA derived from PGAP3, circ-PGAP3, is significantly downregulated in CC tissues, and the low expression of circ-PGAP3 is closely related to a larger tumor size, advanced FIGO stage, and lymph node metastasis.<sup>32</sup> In addition, the survival times of CC patients with low levels of circ-PGAP3 were verified by analyzing survival curves, and they were found to be shorter than those of patients with high levels of circ-PGAP3, indicating that circ-PGAP3 has the potential to be used to judge the prognosis of CC. Jun et al further investigated the biological function and mechanism of circ-PGAP3 in CC cells and found that its overexpression could significantly reduce tumor cell proliferation. Circ-PGAP3 attenuates the miR-769-5p-mediated inhibition of wild-type p53 via sponging and indirectly promotes the expression of p53. In addition, p53 promotes the transcription of circ-PGAP3 by combining with its promoter and subsequently forming a regulatory feedback loop that inhibits CC cell proliferation and invasion.<sup>32</sup> Wang et al reported significantly downregulated circCNTNAP3 expression in ESCC tissues compared to paired normal tissues.<sup>33</sup> CircCNTNAP3 also inhibited the proliferation and increased apoptosis of ESCC cells with wild-type p53 both in vitro and in vivo. On one hand, circCNTNAP3 promoted the expression of p53 by sponging miR-513a-5p. However, p53 could also regulate the expression of circCNTNAP3 by interacting with RNA-binding-motif protein 25 (RBM25), which is a direct transcriptional target of p53 that can bind to circCNTNAP3 and positively regulate its expression.<sup>33</sup> Overall, circCNTNAP3 can inhibit the malignant progression of ESCC through the circCNTNAP3/TP53 positive feedback loop. The roles and specific targets of cancer-associated circular RNAs involved in the cell cycle are summarized in Table 2.

**Table 2** Roles and Specific Targets of Cancer-Associated Circular RNAs Involved in the Cell Cycle

circRNA	Cancer Type	Expression in Cancers	Cell Cycle Target	Functional Roles	Refs
hsa_circ_0005615 (circ5615)	Colorectal cancer	Upregulated	CCND1	Promote tumor proliferation	[25]
circ-UBR1	Breast cancer	Upregulated	CCND1	Promote tumor proliferation	[57]
circRNA_069718	Triple negative breast cancer	Upregulated	CCND1	Promote tumor proliferation	[63]
hsa_circ_0079929	Hepatocellular carcinoma	Downregulated	CCNB1	Inhibit tumor proliferation	[28]
hsa_circ_0000467	Gastric cancer	Upregulated	CCND1	Promote tumor proliferation	[56]
circRNA_141539	Esophageal squamous cell carcinoma	Upregulated	CDK3	Promote tumor proliferation	[20]
circ_ASAP2	Gastric cancer	Upregulated	CDK6	Promote tumor proliferation	[51]
circ-CCND1	Laryngeal squamous cell carcinoma	Upregulated	CCND1	Promote tumor proliferation	[31]
has_circ_0078710	Hepatocellular carcinoma	Upregulated	CDK2	Promote tumor proliferation	[40]

(Continued)

**Table 2** (Continued).

circRNA	Cancer Type	Expression in Cancers	Cell Cycle Target	Functional Roles	Refs
circ-PITX1	Non-small cell lung cancer	Upregulated	CCND2	Promote tumor proliferation	[21]
circMETTL3	Breast cancer	Upregulated	CDK1	Promote tumor proliferation	[36]
circPSMA1	Triple negative breast cancer	Upregulated	CCND1	Promote tumor proliferation	[64]
hsa_circ_0013958	Lung adenocarcinoma (LAC)	Upregulated	CCND1	Promote tumor proliferation	[54]
circSP3	Hepatocellular carcinoma	Upregulated	CDK4	Promote tumor proliferation	[49]
circDPP4	Prostate cancer	Upregulated	CCND1	Promote tumor proliferation	[55]
hsa_circ_0000520	Cervical cancer	Upregulated	CDK2	Promote tumor proliferation	[39]
circZFR	Cervical cancer	Upregulated	CDK2/CCNE1	Promote tumor proliferation	[68]
circZFR	Hepatocellular carcinoma	Upregulated	CCND1	Promote tumor proliferation	[60]
circYAP1	Gastric cancer	Downregulated	P27	Inhibit tumor proliferation	[99]
circ-ITCH	Bladder cancer	Downregulated	P21	Inhibit tumor proliferation	[90]
circ_0084927	Cervical cancer	Upregulated	CDK2	Promote tumor proliferation	[23]
circ_0058063	Bladder cancer	Upregulated	CDK6	Promote tumor proliferation	[52]
circ_PGPEP1	Gastric cancer	Upregulated	E2F3	Promote tumor proliferation	[73]
circPGR	ER-positive breast cancer	Upregulated	CDK1, CDK6	Promote tumor proliferation	[35]
circCNTNAP3	Esophageal squamous cell carcinoma	Downregulated	P53	Inhibit tumor proliferation	[33]
circ_0021977	Colorectal cancer	Downregulated	P53, P21	Inhibit tumor proliferation	[93]
circ-PGAP3	Cervical cancer	Downregulated	P53	Inhibit tumor proliferation	[32]
circMRPS35	Gastric cancer	Downregulated	P21, P27	Inhibit tumor proliferation	[95]

(Continued)

**Table 2** (Continued).

<b>circRNA</b>	<b>Cancer Type</b>	<b>Expression in Cancers</b>	<b>Cell Cycle Target</b>	<b>Functional Roles</b>	<b>Refs</b>
circMTO1	Hepatocellular carcinoma	Downregulated	P21	Inhibit tumor proliferation	[87]
circGRAMD1B	Gastric cancer	Downregulated	P21	Inhibit tumor proliferation	[88]
circRNA-Cdr1as	Bladder cancer	Downregulated	P21	Inhibit tumor proliferation	[91]
circRHOBTB3	Gastric cancer	Downregulated	P21	Inhibit tumor proliferation	[89]
circDDX17	Breast cancer	Downregulated	P21, CDK1	Inhibit tumor proliferation	[92]
circFAM114A2	Urothelial carcinoma	Downregulated	P21, P27	Inhibit tumor proliferation	[22]
BCRC-3 (circRNA-3)	Bladder cancer	Downregulated	P27	Inhibit tumor proliferation	[98]
circSLC7A11	Hepatocellular carcinoma	Upregulated	CDK1	Promote tumor proliferation	[37]
HBV_circ_1	HBV-related HCC	Upregulated	CDK1	Promote tumor proliferation	[38]
circRNA_100782	Gastric cancer	Downregulated	RB	Inhibit tumor proliferation	[71]
circ-ZEB1.33	Hepatocellular carcinoma	Upregulated	CDK6	Promote tumor proliferation	[50]
circ_0016760	Non-small cell lung cancer	Upregulated	E2F3	Promote tumor proliferation	[74]
circDUSP16	Colorectal cancer	Upregulated	E2F6	Promote tumor proliferation	[79]
circFOXM1	Glioblastoma	Upregulated	E2F5	Promote tumor proliferation	[78]
circ_0119872	Malignant melanoma	Upregulated	E2F3	Promote tumor proliferation	[75]
circAGAP1	Clear cell renal cell carcinoma	Upregulated	E2F3	Promote tumor proliferation	[76]
circ-ZNF609	Cervical cancer	Upregulated	E2F6	Promote tumor proliferation	[80]
circ_100395	Ovarian cancer	Downregulated	P53	Inhibit tumor proliferation	[101]
circ-0000263	Cervical cancer	Upregulated	P53	Promote tumor proliferation	[106]

(Continued)

**Table 2** (Continued).

circRNA	Cancer Type	Expression in Cancers	Cell Cycle Target	Functional Roles	Refs
circNUDT21	Bladder cancer	Upregulated	P53	Promote tumor proliferation	[104]
hsa_circ_0080229	Gliomas	Upregulated	P53	Promote tumor proliferation	[105]
circCYFIP2	Gastric cancer	Upregulated	E2F1	Promote tumor proliferation	[72]
circRNA-ITCH	Hepatocellular carcinoma	Downregulated	CCND1	Inhibit tumor proliferation	[65]
circFAM13B	Hepatocellular carcinoma	Upregulated	E2F5	Promote tumor proliferation	[77]
circ-CCS	Lung cancer	Upregulated	E2F7	Promote tumor proliferation	[81]

## Conclusion

In recent years, cancer incidence and mortality have been increasing to critical levels.<sup>108</sup> Therefore, it is particularly important to discover effective tumor markers and therapeutic targets. Disorders of the cell cycle are known to play an important role in tumor proliferation, metastasis, and prognosis.<sup>15</sup> Several studies have confirmed that cell cycle progression can be blocked by targeting specific regulators, thereby preventing tumor growth and survival.<sup>70,109</sup> For example, in the treatment of patients with HR+, HER2- breast cancer, the CDK4/6 inhibitor palbociclib can play an important therapeutic role in inhibiting tumor cell proliferation by inhibiting cell cycle progression.<sup>109</sup> In recent years, the dysregulation of circRNA expression has opened a new chapter in the etiology of various human diseases, especially cancer.<sup>110</sup> This review summarizes the mechanism of circRNAs involved in tumor cell cycle regulation and finds that their abnormal expression in tumors not only plays a role in tumor proliferation but also in tumor invasion and metastasis, TNM staging, histological grade, malignant phenotype, sensitivity to chemotherapy drugs and patient survival.<sup>3,5,8,9,25–33,111–114</sup> These findings highlight potential biomarkers for tumor diagnosis and provide an effective reference for developing future tumor treatments involving the regulation of the cell cycle based on circRNA.

## Abbreviations

circRNAs, Circular RNAs; miRNA, microRNA; CCN, cyclins; CDKs, cyclin-dependent kinases; CKI, cyclin-dependent kinase inhibitor; pRb, retinoblastoma protein; BrC, breast cancer; HCC, hepatocellular carcinoma; HCCT, hepatitis B virus (HBV)-related HCC tissues; CC, cervical cancer; GC, gastric cancer; BCa, bladder cancer; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; CRC, colorectal cancer; ccRCC, clear cell renal cell carcinoma.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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