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Emerging roles of CircRNA-miRNA networks in cancer development and therapeutic response

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ABSTRACT

The complex interplay of epigenetic factors is essential in regulating the hallmarks of cancer and orchestrating intricate molecular interactions during tumor progression. Circular RNAs (circRNAs), known for their covalently closed loop structures, are non-coding RNA molecules exceptionally resistant to enzymatic degradation, which enhances their stability and regulatory functions in cancer. Similarly, microRNAs (miRNAs) are endogenous non-coding RNAs with linear structures that regulate cellular biological processes akin to circRNAs. Both miRNAs and circRNAs exhibit aberrant expressions in various cancers. Notably, circRNAs can function as sponges for miRNAs, influencing their activity. The circRNA/miRNA interaction plays a pivotal role in the regulation of cancer progression, including in brain, gastrointestinal, gynecological, and urological cancers, influencing key processes such as proliferation, apoptosis, invasion, autophagy, epithelial-mesenchymal transition (EMT), and more. Additionally, this interaction impacts the response of tumor cells to radiotherapy and chemotherapy and contributes to immune evasion, a significant challenge in cancer therapy. Both circRNAs and miRNAs hold potential as biomarkers for cancer prognosis and diagnosis. In this review, we delve into the circRNA-miRNA circuit within human cancers, emphasizing their role in regulating cancer hallmarks and treatment responses. This discussion aims to provide insights for future research to better understand their functions and potentially guide targeted treatments for cancer patients using circRNA/miRNA-based strategies.

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1. Introduction

Non-coding RNA molecules are recognized as promising therapeutic targets in cancer. Despite not encoding proteins, they play crucial roles in cellular processes, influencing gene expression and contributing to disease development, including cancer. MiRNAs, for instance, are small endogenous RNA molecules that regulate gene expression by inhibiting translation or promoting mRNA degradation. The discovery of miRNAs began with Lin-4 in *Caenorhabditis elegans* [1,2], which was pivotal in understanding postembryonic development, followed by let-7, another miRNA involved in developmental timing regulation [3]. Since then, thousands of miRNAs have been identified across various organisms, with humans alone having up to 700 miRNAs identified and more continuing to be discovered [4–7]. In the nucleus, RNA polymerase II or III transcribes primary miRNA, which undergoes processing into precursor miRNA and then is exported to the cytoplasm via exportin 5. There, Dicer, an RNase III enzyme, cleaves it into a mature 22-nucleotide miRNA. This mature miRNA integrates into the RNA-induced silencing complex (RISC), where it exerts its regulatory functions [7–10]. MiRNAs have garnered significant attention in cancer research due to their potential roles in carcinogenesis and tumor malignancy. They can function as either oncogenes or tumor suppressors, influencing crucial aspects of cancer such as growth, metastasis, and response to treatment. Increasing evidence supports their ability to enhance or suppress tumor progression by affecting cellular proliferation and metastatic processes [11–13]. Importantly, miRNAs are considered "druggable targets", meaning anticancer therapies can specifically target them to modulate cancer progression [14]. However, miRNAs are not the sole regulators of tumor biology; their expression levels can also be influenced by other non-coding RNAs like long non-coding RNAs (lncRNAs) and circRNAs [15,16]. This review focuses specifically on circRNAs, exploring how they regulate cancer progression by modulating miRNA expression as downstream targets. Understanding these interactions could pave the way for novel therapeutic strategies in cancer treatment.

2. CircRNAs in cancer: an overview

CircRNAs, discovered around 40 years ago, were initially thought to be byproducts of pre-mRNA splicing errors [17]. Though similar to linear RNA transcripts, circRNAs are now recognized as important regulatory factors [18–20]. Their roles in carcinogenesis, proliferation, invasion, and therapy resistance are well-documented [21]. Unlike mature miRNAs, which are typically less than 20 nucleotides long, circRNAs can range from hundreds to thousands of nucleotides in length. They are formed by back-splicing of pre-mRNA transcripts or back-fusion of linear RNAs, resulting in circular structures with covalently linked 3′ and 5′ ends. This circular configuration provides circRNAs with greater stability compared to linear RNA molecules like lncRNAs and miRNAs [18,19]. CircRNAs can be classified into three types based on their genomic origin: exonic circRNAs (the most abundant type), intronic circRNAs, and exon-intron circRNAs. Their stability makes them valuable in cancer diagnosis. One key function of circRNAs is their ability to act as molecular sponges for miRNAs, binding to and sequestering miRNAs, thus preventing them from interacting with their target mRNAs [22]. This sponging mechanism allows circRNAs to regulate the availability and activity of miRNAs, influencing various cellular processes and pathways involved in cancer progression [23]. For example, circ-000780 is downregulated in 80 % of 82 gastric cancer patients, correlating with tumor size, stage, and invasion. CircRNAs also interact with other molecular pathways in cancer [24]. The circRNA PLCE1, for instance, promotes colorectal cancer progression by increasing invasion and stimulating glycolysis and the EMT mechanism via M2 macrophage polarization [25]. While most studies have focused on circRNAs' regulation of tumor progression through miRNAs [26–28], specific examples include circ-0001823, which promotes proliferation and metastasis in cervical cancer by inhibiting miR-613, thereby affecting RAB8A expression [29]. Similarly, CircVPRBP sponges miR-106 b-5p to increase TRIM3 expression, suppressing growth and invasion in cervical cancer [30], and Circ-0003006 sponges miR-542–3p to elevate HIF-1A expression, promoting hepatocellular carcinoma (HCC) progression [31]. The upcoming sections will delve into the role

Table 1
The role of circRNAs in human cancers.

Human cancer	CircRNA	Remark	Reference
–	Circ-hnRNPU	Circ-hnRNPU downregulates NONO-induced c-Myc transactivation that is necessary for the glycosylation and tumorigenesis	[32]
Gastric cancer	Hsa_circ_0001479	Hsa_circ_0001479 induces carcinogenesis and immune evasion	[33]
Bladder cancer	Circ0000235	Circ0000235 sponges miR-330–5p to regulate MCT4 in enhancing glycolysis	[34]
Pancreatic cancer	Hsa_circ_0007919	Hsa_circ_0007919 promotes LIG1 transcription through binding to FOXA1/TET1 in promoting DNA damage repair and mediating gemcitabine resistance	[35]
Colorectal cancer	Circ0001821	Circ0001821 affects the miR-339–3p/CST1 axis to enhance growth, invasion, and stemness	[36]
Cervical cancer	Circ0006646	Circ0006646 upregulates RRM2 to promote proliferation and invasion	[37]
Colorectal cancer	Circ0084,188	Circ0084,188 sponges miR-654–3p to affect Kruppel-like factor 12 in enhancing tumorigenesis	[38]
Colorectal cancer	circRNA ZNF800	circRNA ZNF800 affects stemness and proliferation	[39]
Gastric cancer	Exosomal hsa_circ_000200	Exosomal hsa_circ_000200 promotes metastasis of gastric cancer	[40]
Colorectal cancer	Circ0071,589	Circ0071,589 downregulates miR-296–5p to promote proliferation, angiogenesis, and invasion	[41]
Cervical cancer	circRNAcirc_0000119	Increase in proliferation and metastasis through affecting miR-433–3p/PAK2 axis	[42]
Lung cancer	Circ-0006528	Circ-0006528 sponges miR-892a to enhance tumorigenesis	[43]
Colorectal cancer	Circ-MALAT1	Circ-MALAT1 promotes growth and EMT	[44]
Breast cancer	Circ0069,094	Circ0069,094 sponges miR-136–5p to mediate paclitaxel resistance	[45]
Colorectal cancer	Circ0087,862	Circ0087,862 sponges miR-296–3p to increase PGK1 expression in glycolysis induction	[46]
Ovarian cancer	Hsa_circ_0001535	Hsa_circ_0001535 sponges miR-593–3p to increase PTEN expression in tumorigenesis suppression	[47]
Colorectal cancer	Hsa_circ_0071,589	Hsa_circ_0071,589 sponges miR-133 b to increase SOX13 levels	[48]
Colorectal cancer	circRNA (circ) _0053,277	Involvement in enhancing proliferation, angiogenesis, metastasis, and glycolysis	[49]
Pancreatic cancer	Circ-STK39	Circ-STK39 sponges miR-140–3p to increase TRAM2 in EMT induction	[50]

of the circRNA/miRNA axis in regulating tumor progression and treatment response. Table 1 provides an overview of circRNAs in human cancers, while Table 2 summarizes the role of the circRNA/miRNA axis in tumorigenesis.

3. CircRNA-miRNA axis in cancers

3.1. Brain tumors

Brain tumors, including gliomas, are among the most common and deadly forms of brain cancer. Gliomas are known for their aggressive nature and difficulty in treatment. The circRNA-miRNA axis plays a crucial role in these tumors, where circRNAs function as molecular "sponges" by binding to miRNAs and preventing them from interacting with their target mRNAs. This sponging mechanism influences various cellular processes and pathways essential for tumor progression. The regulation of brain tumor progression by circRNAs is vital, especially in gliomas, as they can significantly impact glioma development. Traditional treatments such as surgery and radiochemotherapy have proven insufficient for glioma, with overall patient survival rates reported to be less than 15 months [60,61]. The heterogeneous cell populations of glioma stem cells (GSCs) contribute to tumor progression due to their ability to self-renew and differentiate into multiple cell lineages [62]. GSCs are also implicated in the proliferation, recurrence, and therapy resistance of glioma cells [63]. Recent experiments have demonstrated that circRNAs regulate GSCs in gliomas. For instance, ISL2 is overexpressed in gliomas and is associated with a poor prognosis. ISL2 increases the expression of VEGF-A, promoting angiogenesis, proliferation, and migration. In gliomas, U2AF2 enhances the expression and stability of circ-ARF1, which upregulates ISL2 expression by inhibiting miR-342–3p, thereby promoting glioma progression [64].

Table 2
A summary of the circRNA/miRNA axis in the regulation of tumorigenesis in human cancer.

Cancer type	Molecular pathway	Remarks	Reference
Colorectal cancer	Circ-0026416/miR-346/NFIB	Circ-0026,416 sponges miR-346 to increase NFIB expression and promote tumorigenesis	[51]
Cervical cancer	Circ-0084927/miR-142–3p/ARL2	Circ-0084,927 enhances tumorigenesis by decreasing miR-142–3p expression and upregulating ARL2	[52]
Colorectal cancer	Circ0005927/miR-942–5p/BATF2	Downregulation of miR-942–5p by circ-0005927 to increase BATF2 expression and impair tumorigenesis	[53]
Prostate cancer	Hsa_circ_0007494/miR-616/PTEN	Circ-0007494 sponges miR-616 in increasing PTEN expression and suppressing tumorigenesis	[54]
Gastric cancer	Circ0027599/miR-21–5p/RUNX1	Circ0027,599 reduces miR-21–5p expression to enhance RUNX1 expression and promote carcinogenesis	[55]
Colorectal cancer	Circ-ACAP2/miR-143–3p/FZD4	Circ-ACAP2 sponges miR-143–3p to increase FZD4 expression in cancer suppression	[56]
Colorectal cancer	Circ0067835/miR-296–5p/IGF1R	Upregulation of IGFR1 by circ-0067,835 through miR-296–5p sponging in reducing radiosensitivity	[57]
Colorectal cancer	Hsa_circ_001680/miR-340/BMI1	Oncogenic function of circ-001680 in enhancing tumor progression	[58]
Lung cancer	Hsa_circ_100395/miR-1228/TCF21	Circ-100395 upregulates TCF21 expression through miR-12228 sponging in reducing tumor progression	[59]

Additionally, circ-0030,018 prevents apoptosis and promotes glioma cell growth and metastasis by inhibiting miR-1297, leading to the upregulation of RAB21 and furthering glioma development and carcinogenesis [65].

One of the critical molecular signaling pathways in gliomas is PTEN signaling [66]. Downregulation of PTEN by the ANCR/EZH2 axis can inhibit apoptosis and promote tumor cell progression [67]. The circRNA/miRNA axis plays a significant role in regulating PTEN signaling in glioma cells. For example, exosomal circ-BTG2 can suppress glioma progression by inhibiting miR-25–3p, which in turn increases PTEN expression, resulting in reduced tumor growth both *in vitro* and *in vivo* [68]. Similarly, circ NALCN impairs glioma progression by sponging miR-493–3p, thereby enhancing PTEN expression and inhibiting cancer cell growth and metastasis [69]. The downstream target of PTEN signaling is the PI3K/Akt pathway, and PTEN exerts its tumor-suppressive effects by inhibiting this pathway in cancer. Circ-0014,359 promotes glioma progression by sponging miR-153, which induces PI3K signaling [70]. Additionally, circ-PIP5K1 A is overexpressed in gliomas and induces EMT. It enhances glioma cell proliferation and metastasis by inhibiting miR-515–5p and activating the TCF12/PI3K/Akt axis [71].

Regulation of PI3K/Akt signaling by the circRNA/miRNA axis is crucial for influencing therapy response in brain tumors. For instance, circ-PTN stimulates cisplatin resistance in glioblastomas by decreasing miR-542–3p expression, thereby activating PI3K/Akt signaling and triggering resistance to cisplatin [72]. Recent research has shown that overexpression of SOX10 can enhance glioma progression. Circ-EPHB4 sponges miR-637 to increase SOX10 expression, promoting stemness and the growth rate of glioma cells [73]. Conversely, circ-PTK2 suppresses glioma progression by preventing the maturation of miR-23a [74]. Additionally, circ-0001730 promotes glioma progression by sponging miR-326, which increases the expression of Wnt7B [75]. Circ-0029,426 sponges miR-197 to promote glioblastoma progression and is associated with poor survival and unfavorable prognosis [76]. Collectively, these studies demonstrate that the circRNA/miRNA axis plays a significant role in brain tumors by regulating progression and other cancer hallmarks critical to the treatment of malignancies [77–83].

Another brain tumor influenced by the circRNA/miRNA axis is medulloblastoma. For instance, circ-SKA3 enhances tumorigenesis by decoying miR-326, which in turn increases ID3 expression [84]. Additionally, circRNA_103,128 downregulates miR-129–5p, leading to increased SOX4 levels and promoting the progression of medulloblastoma [85].

3.2. Gastrointestinal tumors

Gastrointestinal cancers, including gastric (stomach) cancer, colorectal cancer, and HCC (liver cancer), are among the most common and lethal malignancies worldwide. Gastric cancer is the third leading cause of cancer-related death globally. The circRNA-miRNA axis plays a crucial role in regulating the progression of these cancers by influencing cellular processes such as proliferation, invasion, and metastasis [86]. Due to recurrence and metastasis, the prognosis for patients with gastric cancer is often poor [87,88]. The circRNA/miRNA axis significantly impacts the progression of gastric cancer. For example, circ-0004872 impairs gastric cancer progression by sponging miR-224, which in turn increases the levels of Smad4 and p21 [89]. Conversely, oncogenic circRNAs are upregulated in gastric cancer. Circ-006100 promotes proliferation and invasion by inhibiting miR-195, thereby increasing the expression of GPRC5A, preventing apoptosis, and inducing EMT, which promotes metastasis [90]. VEGFA is a potential therapeutic target in gastric cancer, as its overexpression can lead to angiogenesis. STAT3 acts as an upstream mediator of this process [91]. MiR-205–5p inhibits angiogenesis and cancer progression by decreasing VEGFA expression [92], while miR-4316 also downregulates VEGFA to inhibit growth and

metastasis [93]. Overexpression of VEGFA, on the other hand, promotes metastasis [94]. Circ-RanGAP1 sponges miR-877–3p to increase VEGFA expression, thus promoting invasion. Circ-RanGAP1 is overexpressed in the plasma exosomes of gastric cancer patients and can serve as a biomarker [95]. Additionally, circ-002059 impairs gastric cancer progression by sponging miR-182, which increases MTSS1 expression and promotes growth and invasion [96]. Circ-0000039 and circ-0001023 downregulate miR-1292–5p and miR-409–3p, respectively, thereby promoting the progression of gastric cancer [97,98]. These examples highlight the significant role of the circRNA/miRNA axis in the development and progression of gastrointestinal cancers.

Colorectal cancer is a serious malignancy that poses a significant threat to lives globally. Treatment options include surgery, chemotherapy, radiotherapy, and adjuvant therapy [86,99,100]. However, metastasis remains a major cause of death in colorectal cancer patients, leading to poor prognosis at advanced stages [101]. Molecular markers are potential therapeutic targets for colorectal cancer [102–105]. In colorectal cancer, EIF4A3 promotes the production of circ-0084,615, which acts as a sponge for miR-599. By binding to miR-599, circ-0084,615 prevents it from inhibiting its target, ONECUT2, leading to increased ONECUT2 levels that promote tumor growth and malignancy [106]. Another oncogenic factor in colorectal cancer is MACC1 [107], which is associated with lymph node metastasis and stimulates β-catenin signaling in tumorigenesis [108]. Circ-0101,805 sponges miR-1236–3p, resulting in increased MACC1 expression, thereby promoting colorectal cancer growth and metastasis [109]. Similarly, circ-0006174 is upregulated in colorectal cancer and enhances MACC1 expression by sponging miR-138–5p, which increases proliferation, and invasion, and inhibits apoptosis in tumor cells [110].

HCC is a leading cause of death characterized by liver fibrosis and cirrhosis [111,112]. Despite treatments like surgery and liver transplantation, the overall survival rate remains low [113]. Exosomal circ-MMP2 promotes HCC metastasis by sponging miR-136–5p, thereby increasing MMP2 expression. Conversely, circ-ITCH inhibits miR-224–5p to increase MafF expression, preventing HCC progression [114]. SOX12 is a significant target in cancer, with its overexpression linked to growth and metastasis in colorectal cancer and poor prognosis [115]. SOX12 is a significant target in cancer, with its overexpression linked to growth and metastasis in colorectal cancer and poor prognosis [116]. SOX12 is a significant target in cancer with its overexpression linked to growth and metastasis in colorectal cancer and poor prognosis [117,118]. Silencing SOX12 impairs growth and metastasis, while epigenetic factors like miRNAs can reduce SOX12 expression, suppressing cancer [119,120]. In HCC, circ-0006789 increases SOX12 expression by sponging miR-1324, promoting tumor cell proliferation and metastasis [121]. Similarly, circ-SNX27 accelerates HCC progression by inhibiting miR-637 to increase FGFR1 expression [122]. Thus, targeting the circRNA/miRNA axis holds promise for HCC treatment [123,124].

3.3. Gynecological tumors

Gynecological cancers encompass various malignancies that arise within the female reproductive system, with the most prevalent types being ovarian, cervical, and endometrial (uterine) cancers. Ovarian cancer, known for its lethality, is often diagnosed at a late stage and has a high recurrence rate. Cervical cancer, frequently associated with human papillomavirus (HPV) infection, continues to be a major cause of death despite improvements in screening and vaccines. Endometrial cancer, the most common among gynecological cancers in developed nations, affects postmenopausal women. A deep understanding of the molecular dynamics behind these cancers is vital for crafting effective treatments. Specifically, ovarian cancer, primarily the epithelial type which accounts for 90 % of cases, ranks as the fifth leading cause of cancer-related deaths among women [125–130]. Treatment typically involves cytoreductive surgery and platinum-based chemotherapy [131,132]. CircRNAs play a significant role in the onset and progression of ovarian cancer. For instance, Circ-0007444 is known to inhibit ovarian cancer by sponging miR-570–3p to enhance PTEN expression, thereby hindering tumor growth [133]. Conversely, circ-0015,756 promotes the progression of ovarian cancer by reducing miR-942–5p levels, leading to increased expression of CUL4B [134].

Cervical cancer is a prevalent gynecological malignancy and the second leading cause of death among women aged 20–39 years [135]. Despite advancements such as hysterectomy and radiotherapy, which have improved survival, it remains incurable [136–138]. CircRNAs are key regulators in the progression and malignancy of cervical cancer, exhibiting diverse functions and expression levels [139]. For example, Circ-00005215 is highly expressed in cervical cancer and enhances cancer cell survival by blocking miR-326, which in turn increases ELK1 expression, preventing apoptosis [140]. Further studies of cervical cancer cells and tissues have identified circ-0003221 as overexpressed, and its silencing can hinder proliferation and invasion, inhibit the EMT mechanism, and induce cell cycle arrest. Circ-0003221 achieves this by repressing miR-758–3p to upregulate CPEB4, thereby facilitating cervical cancer progression [141]. Additionally, circRNAs can influence multiple miRNAs in regulating cervical cancer; hsa-circ-0107,593, for instance, sponges miR-20a-5p, miR-93–5p, and miR-106 b-5p to curb metastasis and growth in cervical cancer cells [142].

3.4. Urological tumors

Urological cancers encompass malignancies that impact the urinary system and male reproductive organs, with bladder cancer, prostate cancer, and kidney cancer being the most prevalent types. Bladder cancer, a common urinary tract malignancy, occurs more frequently in men than in women. It is typically detected at an early stage; however, its tendency to recur poses significant challenges for long-term management. Urothelial carcinoma, which develops from the bladder's lining cells, is the most usual form of bladder cancer. Prostate cancer ranks as one of the top cancers affecting men globally. It usually progresses slowly and is identified during routine screenings, such as PSA tests, though more aggressive forms can spread quickly and require intensive treatment. Kidney cancer, also known as renal cell carcinoma, arises from the kidneys. Clear cell carcinoma is its most common subtype. Often symptomless in its initial stages, kidney cancer may be discovered during imaging for unrelated conditions. Detailed reviews on urological cancers are available in the literature [143–148].

Bladder cancer is a prevalent malignancy of the urological tract, with approximately 549,000 new cases and 200,000 deaths reported in 2018. The epidemiology of bladder cancer varies geographically [149–154]. Gender significantly influences bladder cancer risk, with men being four times more likely than women to develop metastasis [86]. This disparity suggests a crucial role for sex steroids in the cancer's development and progression [155]. Estrogen receptors (ERs), which are pivotal in many cancers, play diverse roles in bladder cancer [156,157]. ERα inhibits cancer progression, while ERβ facilitates malignancy [158,159]. Specifically, ERα reduces the expression of circ-0023,642, critical for upregulating miR-490–5p, which in turn downregulates EGFR and suppresses bladder cancer [160]. Autophagy is another key factor in bladder cancer, supporting tumor cell survival and promoting migration [161–163], making it a potential therapeutic target [164,165]. For instance, circ-007813 enhances IGF2R expression by sponging miR-361–3p to induce autophagy, thereby aiding bladder tumor progression [166]. Conversely, miR-1231, which has oncogenic properties in bladder cancer, is targeted by circ-0137,606 that sponges miR-1231 to inhibit tumor cell proliferation and invasion [167]. Overall, these findings underscore the significant role of circRNAs in regulating molecular pathways involved in tumor progression through miRNA sponging, with a focus on oncogenic circRNAs in the research [52,168–170].

Prostate cancer poses a significant threat to men's health, with rising

incidence rates observed in China and various other countries [171]. Age and lifestyle are recognized risk factors for developing prostate cancer. Innovations in diagnostic technologies, such as nanostructures, have substantially enhanced early detection capabilities [172,173]. Recent research has also highlighted the importance of epigenetic factors in prostate cancer's development. For example, circ-0006404 has been shown to boost the expression of CFL2 by inhibiting miR-1299, thereby promoting the progression of prostate tumors both *in vitro* and *in vivo* [56]. Additionally, the activation of Akt signaling is a known pathway that facilitates prostate cancer progression. However, circ-0004417 impedes this progression by sponging miR-1228, which leads to decreased Akt expression [174]. Furthermore, circ-0007494 enhances the expression of PTEN, a negative regulator of PI3K/Akt signaling, through the inhibition of miR-616, thus helping to curb the progression of prostate cancer (Fig. 1) [54].

These discussions underscore the crucial role of the circRNA/miRNA axis in regulating several types of human cancers. Here is a summary of the key points:

CircRNAs are vital in glioma by controlling apoptosis, growth, and metastasis. For example, circ-0030,018 accelerates glioma progression by suppressing miR-1297, leading to RAB21 upregulation. GSCs, known for their role in therapy resistance and recurrence, are regulated by circRNAs like exosomal circ-BTG2 and circ-PIP5K1 A, which affect pivotal pathways such as PTEN and PI3K/Akt

In gastric and colorectal cancers, circRNAs play significant roles. Circ-0004872 hinders gastric cancer progression by targeting miR-224, whereas circ-006100 enhances metastasis through miR-195 inhibition. In colorectal cancer, circRNAs like circ-0084,615 and circ-0006174 modulate tumor growth and metastasis via miRNA interactions.

CircRNAs also influence HCC progression. For instance, exosomal circ-MMP2 and circ-ITCH regulate miRNAs such as miR-136–5p and miR-224–5p, affecting metastasis and therapy responses. Targeting the circRNA/miRNA axis could be a promising therapeutic strategy in HCC treatment.

In ovarian cancer, circ-0007444 suppresses tumor growth by sponging miR-570–3p, while circ-0015,756 promotes progression by reducing miR-942–5p levels. Cervical cancer also sees significant regulation from circRNAs like circ-00005215 and circ-0003221, which modulate apoptosis, proliferation, and EMT through various miRNA interactions.

Lastly, in bladder and prostate cancers, circRNAs such as circ-007813 and circ-0137,606 in bladder cancer, and circ-0006404 and circ-0004417 in prostate cancer, crucially influence tumor behaviors by sponging miRNAs and impacting pathways like Akt signaling and PTEN expression

4. CircRNA-miRNA axis in proliferation and metastasis

Proliferation and metastasis are critical hallmarks of cancer, heavily influenced by the circRNA/miRNA axis. Programmed Cell Death 4 (PDCD4) is a key tumor suppressor that helps curb tumor growth and spread by inhibiting protein translation and inducing apoptosis [175–177]. Decreased levels of PDCD4 are linked to worse outcomes in various cancers, such as colorectal and lung cancer. Detailed discussions on PDCD4 are available in recent reviews [178,179]. TRIM27, a contrasting oncogene, facilitates tumor growth and metastasis by acting as an E3 ubiquitin ligase that targets suppressor proteins like PDCD4 for degradation through the ubiquitin-proteasome pathway. This reduction in PDCD4 levels aids in cancer progression and malignancy, with its effects notably documented in ovarian and endometrial cancers [180]. A study involving 289 patients demonstrated that low PDCD4 expression correlates with poor prognosis in colorectal cancer [181]. Conversely, blocking PDCD4 degradation by DTL has shown potential in suppressing lung cancer [182]. The circRNA/miRNA axis plays a significant role in

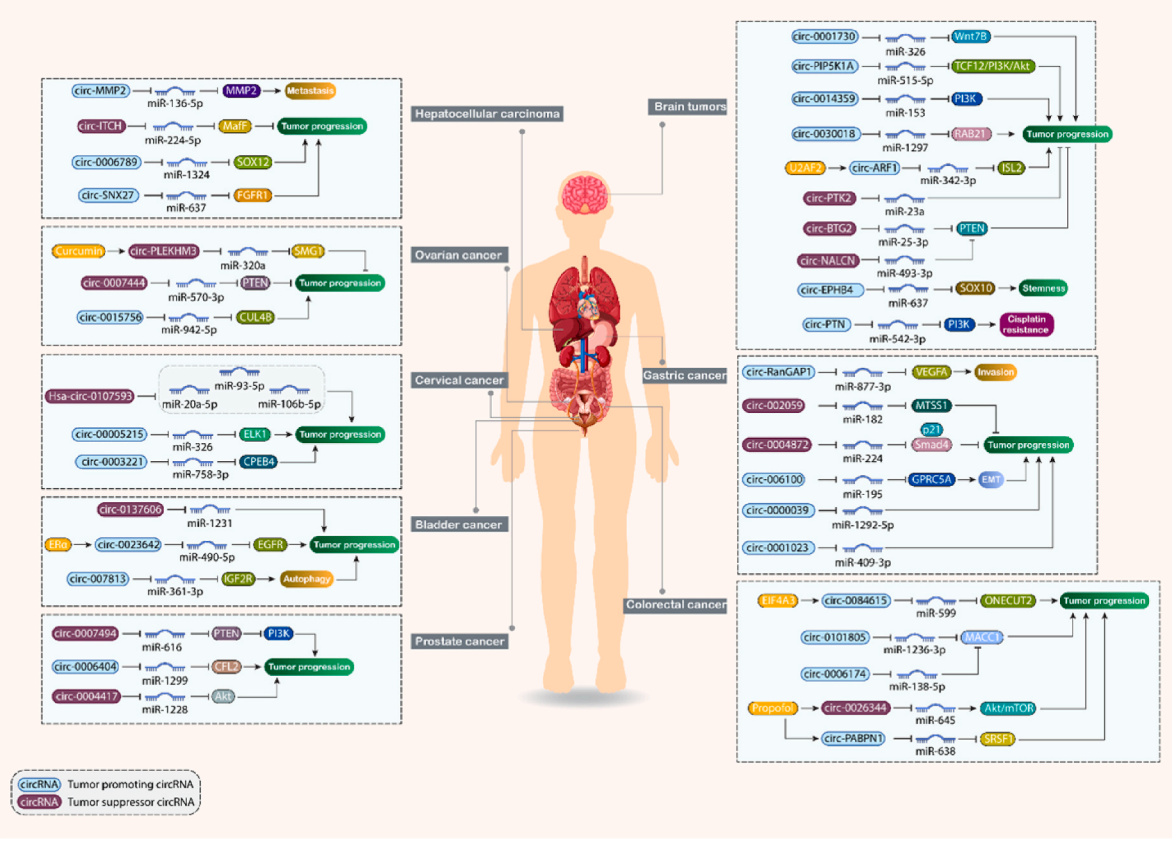

Fig. 1. An overview of the role of the circRNA/miRNA axis in various tumors.

regulating PDCD4 expression across various cancers. For instance, circ-0026,344 helps restrain gastric cancer by sponging miR-590–5p to boost PDCD4 expression, associated with reduced lymph node metastasis and lower tumor stages [183]. In osteosarcomas, both circ-0008259 and PDCD4 are underexpressed, while miR-21–5p is overexpressed. Circ-0008259 suppresses osteosarcoma growth and metastasis by inhibiting miR-21–5p, thereby elevating PDCD4 levels [184]. Furthermore, miR-936 acts as a tumor suppressor by targeting the ERBB4/Akt pathway, reducing gastric cancer growth and metastasis [185]. However, in gliomas, circ-0001162 lowers miR-936 expression, which is crucial for cancer development, leading to increased ERBB4 levels and promoting glioma proliferation and metastasis. These interactions underscore the complex regulatory networks involving circRNAs and miRNAs in cancer progression [186].

Angiogenesis is a crucial process that facilitates the progression of various cancers by promoting the growth of new blood vessels. In gastric cancer, angiogenesis is stimulated by calmodulin 2 through the activation of the STAT3/HIF-1A/VEGF-A pathway, enhancing tumor cell progression [187]. In prostate cancer, N-Myc elevates TEM8 expression to induce angiogenesis, furthering cancer progression and contributing to therapy resistance. Thus, targeting angiogenic mechanisms is vital for effective cancer therapy [188]. Experimental studies, such as one involving the silencing of circ-0058,058, have shown that inhibiting specific circRNAs can impair angiogenesis and halt the progression of multiple myeloma. In this instance, circ-0058,058 boosts tumor progression and angiogenesis by promoting ATG14 expression through miR-338–3p sponging [189]. Additionally, circRNAs play a role in helping cancer cells evade apoptosis. For example, the knockdown of circ-0012,152 in acute myeloid leukemia triggers apoptosis and disrupts disease progression. Circ-0012,152 facilitates the growth of leukemia cells and inhibits apoptosis by increasing SOX12 expression via the inhibition of miR-625–5p. These findings underscore the significant roles circRNAs play in cancer biology, influencing both the survival and proliferation of cancer cells [190].

Abnormal energy metabolism is a hallmark of cancer, where instead of relying on oxidative phosphorylation, cancer cells predominantly utilize glycolysis, known as the Warburg effect, to produce energy [191–193]. This metabolic shift not only supports tumor growth but also facilitates metastasis [194,195]. Increasing evidence points to the significant roles of circRNAs and miRNAs in regulating glycolysis in cancer cells [196–200]. For instance, circ-03955 enhances pancreatic cancer carcinogenesis and progression by promoting HIF-1α expression through the sponging of miR-3662, thereby inducing glycolysis [201]. Besides the well-documented role of HIF-1α in glycolysis [195], Akt3 is also crucial in driving the Warburg effect. Circ-WHSC1 stimulates glycolysis and increases breast cancer progression by upregulating Akt3 expression via the suppression of miR-212–5p [202]. HMGA1 is another key regulator of tumor glycolysis, enhancing c-Myc expression in gastric cancer [203]. Caveolin-1 raises HMGA1 levels, leading to increased GLUT3 expression and glycolysis, thus driving colorectal cancer progression [204]. Additionally, circ-0035,483 boosts HMGA1 expression through the inhibition of miR-31–5p, promoting glycolysis and renal cancer progression [205]. Similarly, hsa-circ-0069,004 elevates HMGA1 levels by sponging miR-661, enhancing glycolysis and contributing to breast cancer proliferation while inhibiting apoptosis [206]. Therefore, the circRNA/miRNA axis emerges as a pivotal regulator of glycolysis, influencing tumor proliferation and malignancy [207–210].

Cancer cell progression is significantly influenced by a process known as epithelial-to-mesenchymal transition (EMT). EMT involves the transformation of cells from an epithelial phenotype to a mesenchymal phenotype, a change that underlies key cancer attributes such as metastasis, stemness, and resistance to therapy [211–213]. EMT is characterized as a transformation involving distinct epithelial and mesenchymal cell states [211,214]. The regulation of EMT in various cancers is controlled by the circRNA/miRNA axis. For instance, in colorectal cancer, circ-0006732 plays a pivotal role by sponging miR-127–3p to elevate Rab3D expression, thereby inducing EMT and enhancing metastasis [215]. This demonstrates how EMT is central to colorectal cancer's aggressiveness, prompting extensive research into the circRNA/miRNA axis's role in this cancer type. Another example is circ-0000467, which promotes colorectal cancer progression by upregulating EN2 expression through the inhibition of miR-382–5p, thereby inducing EMT [216]. Additionally, the Wnt7B pathway is another crucial regulator of the EMT process. Circ-0082,375, for example, sponges miR-485–5p to boost Wnt7B expression, thus promoting EMT and aiding the progression and invasion of glioma [217]. While many studies focus on the circRNA/miRNA axis's role in promoting growth and invasion in cancers, such as circ-0103,232 in melanoma, which enhances metastasis by inducing EMT and increasing cell proliferation through the upregulation of RAB3D by inhibiting miR-661 [218]. These investigations underscore the critical role of the circRNA/miRNA axis in cancer progression and highlight its potential as a target for effective cancer therapy (Fig. 2) [219–221].

5. Role of circRNA-miRNA-mRNA in drug resistance

The role of the circRNA/miRNA axis in regulating drug resistance is complex and involves various molecular pathways. Research across multiple cancer types indicates that drug resistance is not confined to any specific type of cancer and that precision medicine may enhance drug sensitivity across a broad spectrum of cancers. Understanding the interactions between circRNAs and miRNAs is crucial because these circRNAs are becoming significant targets in cancer therapy, particularly for their influence on chemosensitivity and the development of new therapeutic strategies. For instance, oncogenic circRNAs like circ-0000376 exacerbate drug resistance, which promotes cancer cell growth and invasion. Specifically, circ-0000376 reduces miR-384 expression to facilitate metastasis and growth in lung cancer while also contributing to drug resistance [222]. Similarly, in myeloma, circ-0007841 and JAG1 are upregulated, with a corresponding downregulation of miR-129–5p. The knockdown of circ-0007841 not only reduces tumor growth and progression both *in vitro* and *in vivo* but also enhances drug sensitivity by diminishing JAG1 expression, mediated through the sponging of miR-129–5p, thereby countering bortezomib resistance [223]. Moreover, targeting circRNAs like circ-0031,242, which is known to confer cisplatin resistance in hepatoma, can impede tumor progression and increase drug responsiveness. Circ-0031,242 sponges miR-924 to upregulate POU3F2, promoting cisplatin resistance. Therefore, the inhibition of such circRNAs is critical in bolstering tumor sensitivity to chemotherapy [224].

MiR-370 is gaining attention as a promising target in cancer therapy, particularly for enhancing drug sensitivity, as demonstrated in various cancers. It is notably downregulated in lymphoma, where it reduces MGMT expression, thereby enhancing sensitivity to temozolomide [225]. Additionally, miR-370 lowers FoxM1 expression, induces apoptosis, and increases drug sensitivity in leukemia [226]. In the context of osteosarcoma, circ-0003496 is typically overexpressed and associated with promoting doxorubicin resistance. MiR-370, which exhibits tumor-suppressive properties, is downregulated by circ-0003496, leading to increased expression of KLF12 and subsequently, drug resistance in osteosarcomas [227]. Furthermore, the downregulation of miRNAs with anticancer activities often leads to drug resistance. For example, circ-0002770 is implicated in promoting cell division, growth, and metastasis in melanoma by reducing miR-331–3p expression, which in turn increases the levels of DUSP5 and TGFBR1, contributing to the cancer's progression [228]. Although prior studies may not have specifically focused on the role of the circRNA/miRNA axis in drug resistance, they clearly illustrate how this axis regulates key cancer hallmarks that contribute to resistance. This highlights the potential of targeting the circRNA/miRNA interactions as a strategy to overcome drug resistance in cancer therapy.

Exosomes are tiny vesicular structures released by eukaryotic cells

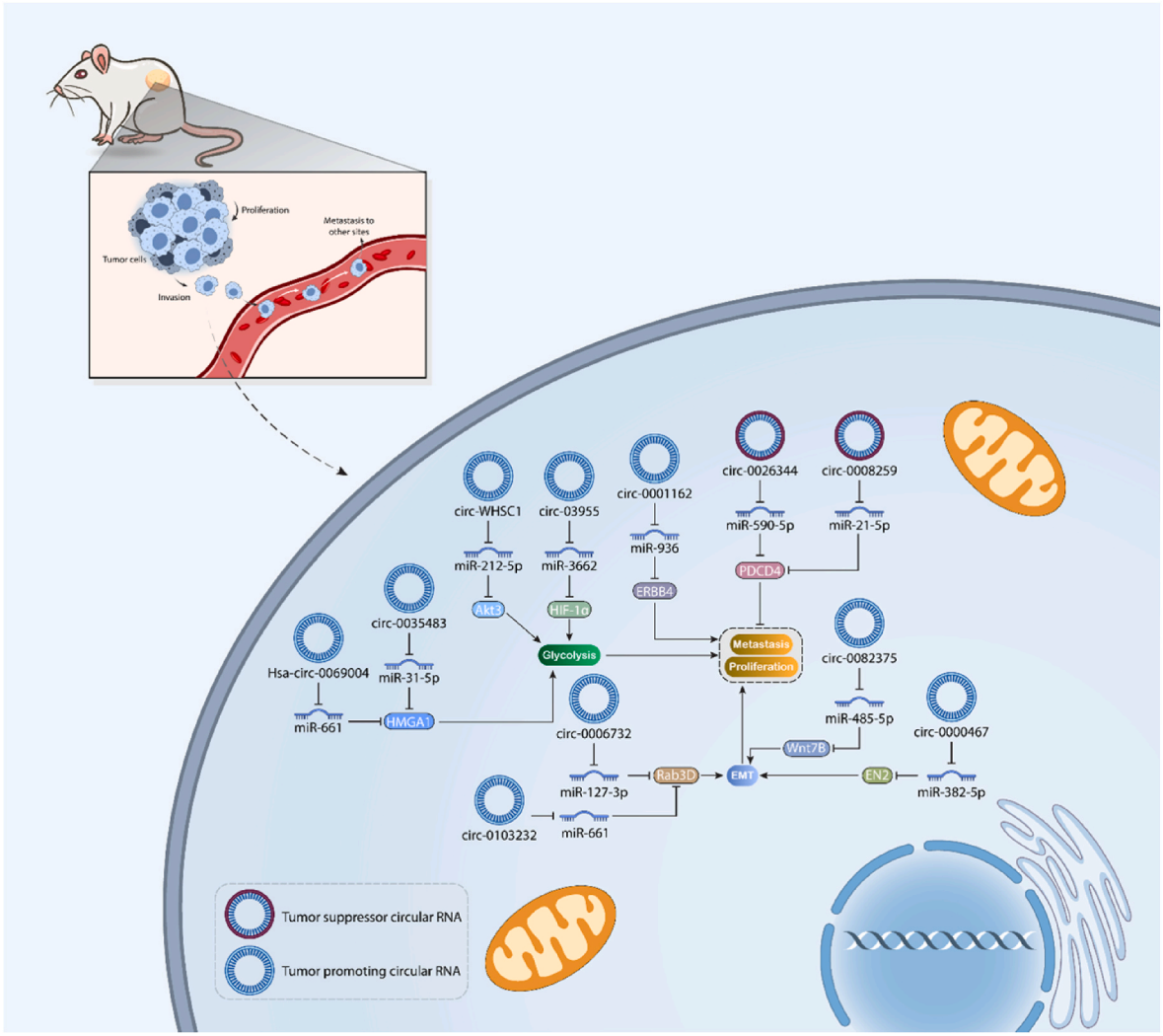

Fig. 2. CircRNA/miRNA axis in regulating growth and invasion.

into the extracellular matrix. Upon merging with the cell membrane of a target cell, exosomes can discharge their contents, which include proteins, lipids, and nucleic acids, facilitating communication and affecting the biological activities of the recipient cells [229–232]. In the realm of cancer treatment, exosomal circRNAs have become a focal point of research. For example, the transfer of circ-0000338 via exosomes leads to the suppression of miR-217 and miR-485–3p, contributing to resistance against 5-fluorouracil in colorectal cancer [233]. Additionally, exosomal ciRS-122 has been shown to foster drug resistance in colorectal cancer by promoting glycolysis. Found in high concentrations in exosomes from colorectal tumor cells, ciRS-122 sponges miR-122, enhancing the expression of PKM2 and thus stimulating glycolysis in the cancer cells [234].

Docetaxel (DTX) belongs to the taxane class of drugs and has proven effective in treating various cancers, especially lung cancer [235,236]. DTX has been shown to curb the progression of lung cancer and enhance patient survival [237–239]. The most prevalent type of lung cancer, non-small cell lung cancer (NSCLC), poses a significant risk to both men and women [240]. Unfortunately, about 67.9 % of NSCLC patients are diagnosed at advanced stages, where drug resistance complicates treatment efforts [241,242]. Circ-0014,130 plays a role in promoting DTX resistance in NSCLC by facilitating tumor cell progression. The silencing of circ-0014,130 has been found to reduce NSCLC cell growth and invasion and decrease colony formation. This circRNA boosts YAP1 expression by sponging miR-545–3p, thereby inducing DTX resistance in lung cancer [243]. In the context of gastric cancer, Circ-LDLRAD3 contributes to the development of cisplatin resistance. It is overexpressed in cisplatin-resistant gastric cancer cells, and the inhibition of miR-588 leads to increased SOX5 expression, which mediates cisplatin resistance [244]. Overall, the circRNA/miRNA axis plays a crucial role in drug resistance, a topic thoroughly explored in various studies [245–248] and is summarized in Table 3 and Fig. 3.

The current discussions emphasize the pivotal role of the circRNA/miRNA axis in regulating tumorigenesis and therapy resistance, summarized as follows:

Proliferation and metastasis, fundamental characteristics of cancer, are influenced by the circRNA/miRNA axis. PDCD4, a vital tumor suppressor, is upregulated by circRNAs like circ-0026,344 and circ-0008259, which inhibit specific miRNAs, thereby hindering cancer progression. For example, circ-0026,344 suppresses miR-590–5p, elevating PDCD4 levels and restraining gastric cancer growth. Similarly, circ-0008259 targets miR-21–5p to boost PDCD4 in osteosarcoma. In contrast, circ-0001162 sponges miR-936 to increase ERBB4 expression, accelerating glioma progression.

Angiogenesis, crucial for tumor expansion, is also controlled by circRNA/miRNA interactions. Circ-0058,058 enhances angiogenesis in multiple myeloma by sponging miR-338–3p to upregulate ATG14. Additionally, circ-0012,152 increases SOX12 expression via miR-625–5p inhibition, which prevents apoptosis in leukemia, thereby supporting tumor growth.

Table 3
Role of CircRNA/miRNA axis in regulating drug resistance in cancer.

CircRNA	Molecular pathway	Cancer type	Drug	Outcome	Reference
CircUBE2D2	MiR-512–3p/CDCA3	Breast cancer	Doxorubicin	CircUBE2D2 increases CDCA3 expression by inhibiting miR-512–3p, causing increased proliferation and invasion and triggering drug resistance	[249]
Circ-SCMH1	MiR-338–3p/LIN28B	Oral cancer	Cisplatin	Circ-SCMH1 sponges miR-338–3p in increasing LIN25B expression and triggering drug resistance	[250]
Circ-0000260	MiR-129–5p/MMP11	Gastric cancer	Cisplatin	Circ-0000260 enhances MMP11 expression by sponging miR-129–5p to trigger cisplatin resistance	[251]
Circ-0004674	MiR-342–3p/FBN1	Osteosarcoma	Doxorubicin	Circ-0004674 promotes FBN1 expression via inhibition of miR-342–3p to induce Wnt/β-catenin signaling and mediate drug resistance	[252]
Circ-0004015	MiR-198/KLF8	Non-small cell lung cancer	Cisplatin	Circ-0004015 enhances the expression of KLF8 via miR-198 sponging in the induction of cisplatin resistance	[253]
Circ-SNAP47	MiR-625–5p/WEE1	Lung cancer	Cisplatin	Circ-SNAP47 promotes WEE expression via miR-625–5p sponging in cisplatin resistance	[254]
Circ-0005198	MiR-198/TRIM14	Glioma	Temozolomide	Circ-0005198 promotes glioma progression and mediates drug resistance via miR-198 sponging and overexpression of TRIM14	[255]
Circ-0001667	MiR-4458/NCOA3	Breast cancer	Adriamycin	Circ-0001667 increases NCOA3 expression via miR-4458 sponging in mediating adriamycin resistance	[256]
Circ-0048,856	MiR-98–5p/MiR-193a-5p/ABCC1	Lung cancer	Cisplatin	Circ-0048,856 sponges miR-98–5p and miR-193a-5p in increasing ABCC1 expression and mediating drug resistance	[257]
Circ-0000199	MiR-206/613/PI3K/Akt/mTOR	Breast cancer	Cisplatin, adriamycin, paclitaxel and gemcitabine	Circ-0000199 sponges miR-206 and miR-613 in inducing PI3K/Akt/mTOR axis and mediating drug resistance	[258]
Circ-0081,001	MiR-494–3p/TGM2	Osteosarcoma	Methotrexate	Circ-0081,001 promotes TGM2 expression via miR-494–3p sponging in inducing drug resistance	[259]
Circ-0017,639	MiR-1296–5p/SIX1	Non-small cell lung cancer	Cisplatin	Circ-0017,639 increases SIX1 expression via miR-1296–5p sponging in triggering drug resistance	[260]
Circ-0000567	MiR-377–3p/ZFX	Lung cancer	Gefitinib	Circ-0000567 promotes ZFX expression via miR-377–3p sponging in triggering drug resistance	[261]
Circ-0006168	MiR-194–5p/JMJD1C	Esophageal cancer	Taxol resistance	Circ-0006168 promotes JMJD1C expression via inhibition of miR-194–5p in triggering drug resistance	[262]
Circ-0011,292	MiR-433–3p/CHEK1	Lung cancer	Paclitaxel	Circ-0011,292 promotes CHEK1 expression via miR-433–3p inhibition in paclitaxel sensitivity	[263]
Circ-0003998	MiR-326	Lung cancer	Docetaxel	Circ-0003998 induces docetaxel resistance through miR-326 inhibition	[264]
Circ-001546	MiR-421/ATM/Chk2/p53	Gastric cancer	Oxaliplatin	Circ-001546 sponges miR-421 to induce ATM/Chk2/p53 axis to increase drug sensitivity	[265]
Circ-0000735	MiR-7	Prostate cancer	Docetaxel	Circ-0000735 sponges miR-7 in increasing docetaxel sensitivity	[266]
Circ-0008450	MiR-338–3p/SMAD5	Nasopharyngeal cancer	Cisplatin	Circ-0008450 stimulates cisplatin resistance by inhibiting miR-338–3p and overexpressing SMAD5	[267]
Circ-0058,357	MiR-361–3p/ABCC1	Lung cancer	Cisplatin	Circ-0058,537 promotes ABCC1 expression by inhibiting miR-361–3p, triggering drug resistance	[268]
Circ-0000277	MiR-873–5p/SOX4	Esophageal cancer	Cisplatin	Circ-0000277 promotes SOX4 expression through miR-873–5p inhibition in the development of drug resistance	[269]
Circ-CEP128	MiR-432–5p/MCL1	Cervical cancer	Paclitaxel	Circ-CEP128 promotes MCL1 expression via miR-432–5p sponging in mediating drug resistance	[270]
Circ-0005273	MiR-133 b	Cervical cancer	Cisplatin	Circ-0005273 stimulates drug resistance via miR-133 b sponging	[271]
Circ-CCT3	MiR-223–3p/BRD4	Multiple myeloma	Bortezomib	Circ-CCT3 increases BRD4 expression via miR-223–3p sponging in triggering drug resistance	[272]
Circ-0030,998	MiR-1323/PDCD4	Lung cancer	Cisplatin	Circ-0030,998 promotes PDCD4 expression via miR-1323 inhibition in triggering drug sensitivity	[273]
Circ-0011,292	MiR-379–5p/TRIM65	Lung cancer	Paclitaxel	Circ-0011,292 increases TRIM65 expression by sponging miR-379–5p in triggering drug resistance	[274]
Circ-0004585	MiR-874–3p/CCND1	Colorectal cancer	5-flourouracil	Circ-0004585 increases CCND1 expression by sponging miR-874–3p, triggering drug resistance	[275]
Circ-LPAR3	MiR-634/PDK1	Ovarian cancer	Cisplatin	Circ-LPAR3 promotes PDK1 expression through miR-634 inhibition in triggering drug resistance	[276]
Circ-0011,298	MiR-486–3p/CRABP2	Lung cancer	Taxol	Circ-0011,298 increases CRABP2 expression by inhibiting miR-486–3p, resulting in glycolysis induction, inhibition of apoptosis, and drug resistance	[277]
Curc-MTHFD1L	MiR-615–3p/RPN6	Pancreatic cancer	Gemcitabine	Circ-MTHFD1L promotes RPN6 expression by sponging miR-615–3p in triggering drug resistance	[278]
Circ-0020,123	MiR-140–3p/HOXB5	Lung cancer	Cisplatin	Circ-0020,123 sponges miR-140–3p to upregulate HOXB5 in triggering drug resistance	[279]
Circ-CDR1as	MiR-641/HOXA9	Lung cancer	Cisplatin	Circ-CDR1as promotes HOXA9 expression by inhibiting miR-641 in triggering drug resistance	[280]
Circ-101277	MiR-370/IL-6	Colorectal cancer	Cisplatin	Circ-101277 increases IL -6 expression through miR-370 sequestration in triggering chemoresistance	[281]
Circ-DONSON	MiR-802/BMI1	Gastric cancer	Cisplatin	Circ-DONSON increases BMI1 expression by sponging miR-802 in mediating drug resistance	[282]
Circ-001275	MiR-370–3p/Wnt7a	Esophageal cancer	Cisplatin	Circ-001275 increases Wnt7a expression by sponging miR-370–3p in triggering drug resistance	[283]

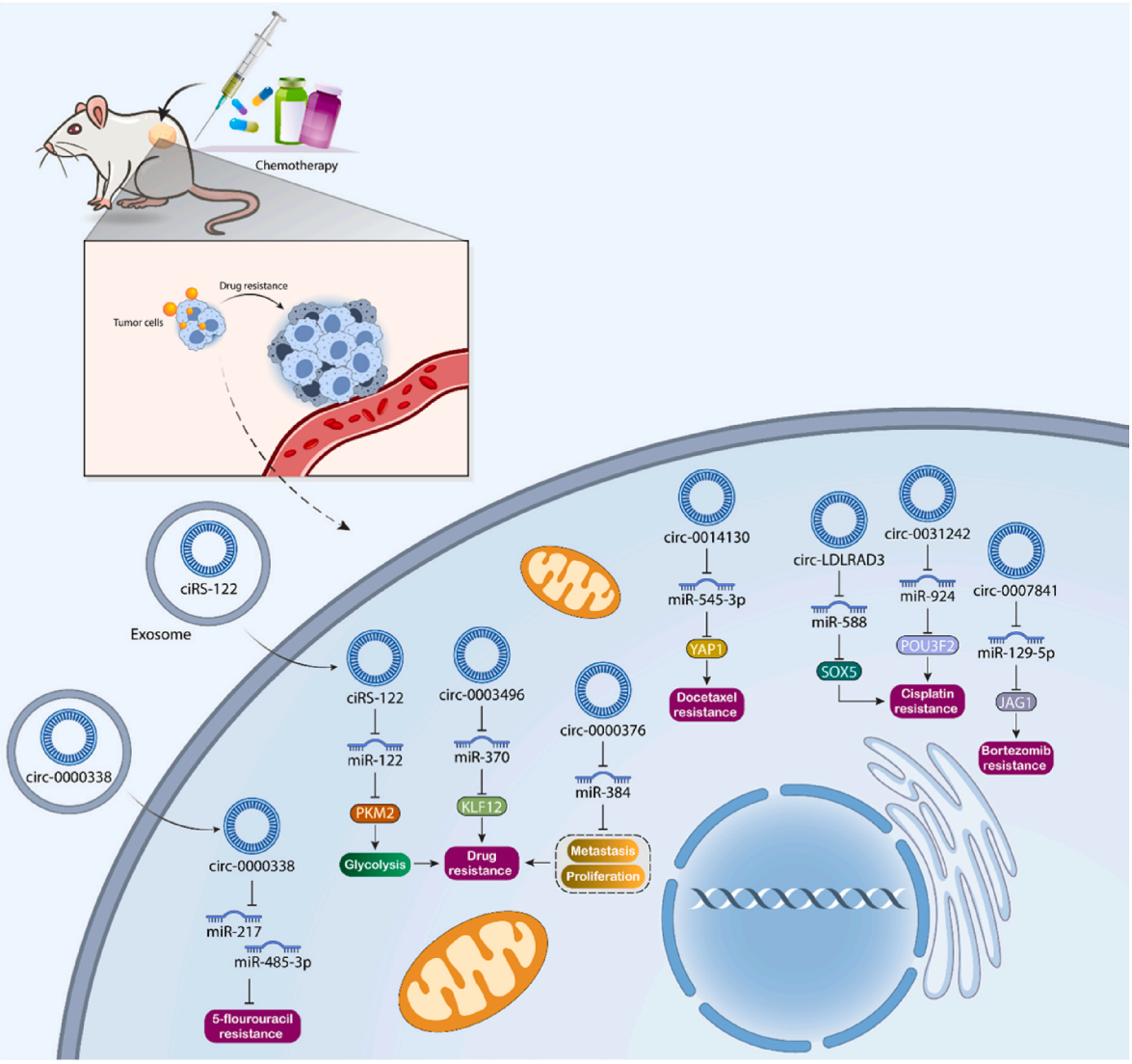

Fig. 3. Role of CircRNA/miRNA axis in drug resistance.

Cancer cells often rely on enhanced glycolysis, known as the Warburg effect, for energy. CircRNAs like circ-03955 and circ-WHSC1 promote this metabolic pathway by suppressing miRNAs such as miR-3662 and miR-212–5p, leading to increased expression of glycolysis-promoting genes like HIF-1α and Akt3.

The EMT, a process where epithelial cells gain mesenchymal properties, is essential for cancer metastasis. CircRNAs such as circ-0006732 and circ-0082,375 influence EMT by sponging miRNAs (e.g., miR-127–3p and miR-485–5p) to upregulate genes like Rab3D and Wnt7B, facilitating invasion and metastasis in colorectal and glioma cancers.

Lastly, the circRNA/miRNA axis is crucial in cancer drug resistance. CircRNAs like circ-0000376 and circ-0007841 enhance resistance by downregulating miRNAs (e.g., miR-384 and miR-129–5p), activating oncogenic pathways. For example, circ-0007841 sponges miR-129–5p to upregulate JAG1, promoting bortezomib resistance in myeloma. Additionally, circ-0031,242 induces cisplatin resistance in hepatoma by inhibiting miR-924, which increases POU3F2 expression. Exosomal circRNAs, such as circ-0000338 and ciRS-122, transfer resistance traits among tumor cells, enhancing drug resistance through mechanisms like miRNA sponging and glycolysis induction. CircRNAs like circ-0014,130 and circ-LDLRAD3 also contribute to resistance against treatments such as docetaxel and cisplatin in lung and gastric cancers, respectively.

6. Role of circRNA-miRNA-mRNA in radioresistance

The development of radioresistance in cancer remains a significant challenge, often leading to treatment failures in clinical settings despite extensive efforts to counteract this phenomenon. The influence of molecular signaling pathways in fostering radioresistance cannot be overstated, with Dll 1-induced Notch signaling playing a critical role through its interactions with cancer-associated fibroblasts to promote radioresistance [284]. In gastric cancer, miR-4537 enhances radiosensitivity by reducing ZNF587 expression, which induces apoptosis and curbs proliferation [73]. Additionally, the loss of mitochondrial membrane potential is recognized as a contributing factor to radioresistance [285]. In lung cancer, the NEDD8-conjugating enzyme E2 UBE2F helps cells evade apoptosis, further enhancing radioresistance [286]. The circRNA/miRNA axis is also pivotal in driving radioresistance in various cancers. For instance, Circ-100367 in esophageal cancer enhances tumor proliferation, invasion, and the EMT, promoting radioresistance by upregulating Wnt3 expression through the inhibition of miR-217 [287]. Furthermore, Circ-CBL.11 curtails colorectal tumor cell proliferation by sponging miR-67778–5p, which increases YWHAE expression. Notably, miR-6778–5p acts as an oncogene in colorectal cancer, with its expression decreasing post-irradiation to inhibit tumor progression [76].

Circ-0008344 plays a crucial role in inducing radioresistance in

gliomas. It is overexpressed in glioma cells during radiation treatment to shield the cells from radiation toxicity [288]. This circRNA promotes the expression of RNF2 by sponging miR-433–3p, which in turn triggers radioresistance in these tumors [288]. Similarly, Circ-VCAN is also found to be overexpressed in gliomas, contributing to their radioresistance. It acts by downregulating miR-1183, thereby enhancing tumor growth and invasion and fostering resistance to radiotherapy [289]. These findings indicate that the circRNA/miRNA axis not only regulates key cancer characteristics like proliferation and invasion but also plays a significant role in the development of radioresistance or sensitivity in various cancers [79].

MiR-338–3p plays a crucial role in cancer progression, influencing tumor cell proliferation, invasion, and response to therapy [290]. In prostate cancer, miR-338–3p inhibits RAB23 expression, thereby preventing carcinogenesis. Additionally, in colorectal cancer, it suppresses MACC1, contributing to its tumor-suppressive effects [291]. Studies indicate that miR-338–3p is commonly downregulated to enhance radioresistance in various cancers. For instance, circ-0001313 suppresses miR-338–3p expression, which promotes colony formation and mediates radioresistance in colorectal cancer. Conversely, silencing circ-0001313 elevates miR-338–3p levels, thereby increasing radiosensitivity [292]. Reducing the expression of tumor suppressor miRNAs like miR-338–3p is a key mechanism underlying radioresistance. In esophageal cancer, circ-0014,879 upregulates CDC25A by inhibiting miR-519–3p, further promoting resistance to radiation [293].

MiR-1256 plays a critical role in inhibiting growth and metastasis in lung cancer by downregulating TCTN1 [294]. In thyroid cancer, it curtails HTR3A expression, thereby suppressing tumor growth and cell cycle progression [295]. MiR-1256 is also a key target for circRNAs that influence tumor progression [296,297]. For example, in gastric cancer,

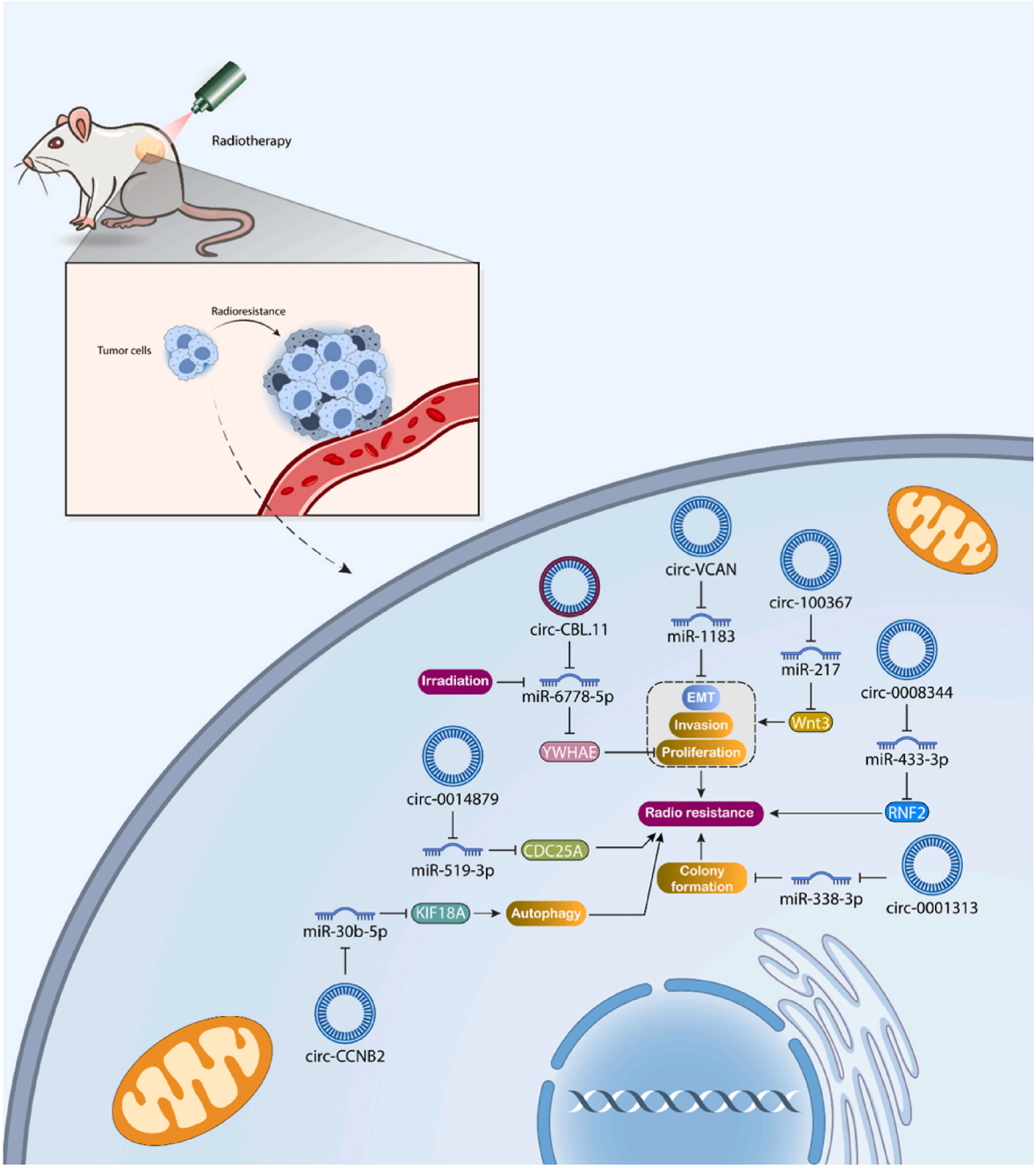

Fig. 4. The role of the circRNA/miRNA axis in radioresistance.

circ-0003506 binds to miR-1256, enhancing the expression of the receptor for bone morphogenic protein type 2, which contributes to radioresistance [298]. In prostate cancer, Circ-CCNB2 triggers radioresistance by inducing autophagy [299]. This process is mediated by the downregulation of miR-30 b-5p, which leads to the overexpression of KIF18A, enhancing resistance to radiation [299]. These findings underscore the role of circRNAs in using miRNA sponging to regulate radioresistance across various cancers (Fig. 4) [289,300–302].

7. Role of circRNA-miRNA in immune evasion

In addition to drug and radioresistance, another significant challenge in cancer therapy is the ability of tumor cells to evade immune detection and inhibit the immune system's response [303]. Several mechanisms contribute to immune evasion in cancer. For instance, TRIB3 in colorectal cancer suppresses the STAT1/CXCL10 pathway, hindering the infiltration of $CD8^+$ T cells and facilitating immune escape [304]. Additionally, phosphorylation of PDHE1α through MAPK signaling is implicated in cancer-related immune evasion [305]. Moreover, extracellular vesicles from colorectal cancer cells promote immune escape by enhancing PD-L1 expression [306]. Other factors like the glycosylation of PD-L2 [307] and overexpression of the glucocorticoid receptor [308] also contribute to immune evasion. Given the significance of immune evasion, the role of the circRNA/miRNA axis in modulating immune resistance is under scrutiny. For example, the overexpression of circ-0020,710 is linked to immune evasion in melanoma, promoting tumor progression by increasing CXCL12 expression through miR-370–3p sponging, which depletes cytotoxic lymphocytes [309]. Circ-keratin 6c is implicated in the development of immune evasion in colorectal cancer by influencing PD-L1 expression [310]. PD-1 is expressed on immune cells like CD8 T and CD4 T cells, with PD-L1 serving as its ligand. PD-L1 acts as an immune checkpoint in human cancers and can also be used as a diagnostic marker [311]. PD-L1 is often overexpressed in cancer cells, and it inhibits anti-tumor immune responses by inducing apoptosis in T cells [312]. Evasion of the immune system promotes tumorigenesis and cancer progression [313]. Circ-keratin 6c contributes to the progression of colorectal cancer and is linked to immune evasion. By sponging miR-485–3p, circ-keratin 6c elevates PD-L1 expression, thereby facilitating immune escape in cancer [310]. In lung cancer, circRNAs impact the regulation of immune evasion by affecting STAT3 and the PD-1/PD-L1 pathway. Specifically, circ-HSP90A enhances tumor proliferation, metastasis, and immune evasion by enlisting USP30 to increase HSP90A stability, thereby activating STAT3 signaling [314]. Furthermore, circ-HSP90A absorbs miR-424–5p, leading to an overexpression of PD-L1, which facilitates immune evasion in lung cancer. In colorectal cancer, hsa-circ-0136,666 plays a pivotal role in immune evasion by promoting PD-L1 expression through the inhibition of miR-497, which supports Treg-induced immune escape [315]. Additionally, circ-0007456 in HCC sponges miR-6852–3p to upregulate ICAM-1, reducing the effectiveness of natural killer cell (Fig. 5) [316].

Radio-resistance and immune evasion pose significant hurdles in human cancer treatment, with the circRNA/miRNA axis playing a pivotal role. Here's a condensed overview of the related discussions: Notch signaling, activated by Dll 1 in conjunction with cancer-associated fibroblasts, contributes to radioresistance. In gastric cancer, miR-4537 targets ZNF587 to enhance radiosensitivity through apoptosis induction and proliferation inhibition. Certain circRNAs, such as circ-100367 and circ-0008344, modulate radiosensitivity by absorbing miRNAs like miR-217 and miR-433–3p, which results in the

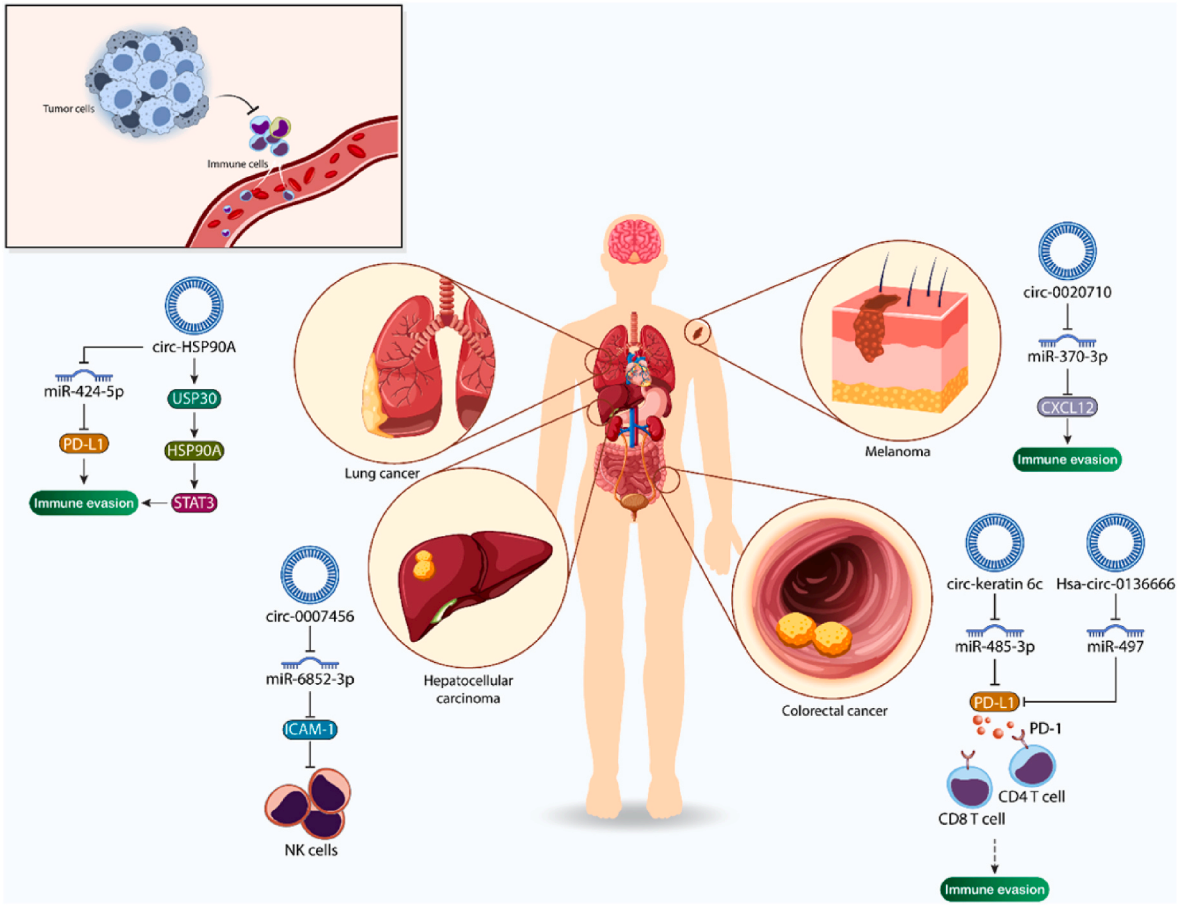

Fig. 5. Role of the circRNA/miRNA axis in cancer immune evasion.

upregulation of genes linked to radioresistance, such as Wnt3 and RNF2. Circ-VCAN suppresses miR-1183, aiding in glioma growth and invasion, thus promoting radioresistance. The decrease in tumor suppressor miRNAs such as miR-338–3p and miR-1256 is crucial for radioresistance development, with circRNAs like circ-0001313 and circ-0003506 blocking these miRNAs, thereby enhancing radioresistance in colorectal and gastric cancers, respectively. Circ-CCNB2 triggers autophagy and promotes radioresistance in prostate cancer by inhibiting miRNAs like miR-30 b-5p, leading to elevated expression of autophagy-related genes such as KIF18A. CircRNAs regulate immune responses by altering miRNA levels, which subsequently impact essential immune-related genes. For example, circ-0020,710 captures miR-370–3p to boost CXCL12 expression, facilitating immune evasion in melanoma. CircRNAs like circ-keratin 6c and circ-HSP90A affect the PD-1/PD-L1 immune checkpoint by sponging miRNAs (e.g., miR-485–3p, miR-424–5p), thus increasing PD-L1 and promoting immune evasion by hindering T cell-mediated anti-tumor responses. Furthermore, circRNAs impact the interaction between cancer cells and immune cells, such as circ-0136,666, which blocks miR-497 to raise PD-L1 expression and foster Treg-mediated immune evasion in colorectal cancer. Similarly, circ-0007456 absorbs miR-6852–3p to upregulate ICAM-1, diminishing natural killer cell toxicity against HCC.

8. CircRNA/miRNA axis as a therapeutic target

CircRNAs are targets for anticancer agents in tumor therapy. Propofol, commonly used in anesthesia, possesses antitumor properties. It inhibits STAT3 signaling to trigger ferroptosis in colorectal cancer [317] and reduces tumor cell invasion by blocking EMT [318]. Propofol also curtails glycolysis, thus diminishing colorectal tumor cell proliferation [319]. Additionally, it increases miR-638 expression by suppressing circ-PABPN1, which in turn inhibits SRSF1 expression, preventing colorectal tumor development [320]. Propofol further enhances circ-0026,344 expression, which suppresses miR-645, thereby inhibiting the Akt/mTOR pathway and slowing colorectal cancer progression [321]. In ovarian cancer therapy, circRNAs are similarly influenced by anticancer drugs. Curcumin, effective in treating ovarian cancer, inhibits tumor proliferation and invasion. It is often used synergistically with other chemotherapeutic agents [322–324]. Curcumin administration upregulates circ-PLEKHM3, leading to the suppression of miR-320a and the overexpression of SMG1, thereby hindering ovarian cancer progression [325]. These findings underscore the significance of the circRNA/miRNA axis as a crucial target in colorectal cancer therapy [326,327]. Recent research has emphasized the potential of targeting the miRNA-circRNA axis for therapeutic purposes, focusing on altering interactions between circRNAs and miRNAs to affect cancer-related activities such as proliferation, invasion, metastasis, and therapy resistance. This section explores the potential of miRNA-circRNA interactions as therapeutic targets and reviews recent advancements and approaches in this evolving area.

9. Conclusion and remarks

Epigenetic factors, alongside environmental influences, exposure to toxic and carcinogenic substances, and lifestyle choices, play a crucial role in the development of cancer. Introducing new concepts in epigenetics can significantly enhance our understanding and lead to the development of effective therapies. Two key epigenetic factors, miRNAs and circRNAs, exhibit abnormal expression patterns during cancer progression, proliferation, metastasis, and therapy resistance. CircRNAs, in conjunction with miRNAs, regulate various molecular signaling pathways involved in cancer development. Notably, circRNAs can regulate miRNAs through sponging mechanisms. This comprehensive review highlights the influence of the circRNA/miRNA axis on various cancer hallmarks. The circRNA/miRNA axis has been found to regulate the progression of multiple tumors, including bladder, prostate, glioblastoma, liver, gastric, and colorectal cancers, making them crucial targets in cancer therapy. Tumor-suppressive miRNAs can inhibit the proliferation and invasion of cancer cells by acting on molecular signaling pathways such as PTEN, PI3K/Akt/mTOR, and p53. Conversely, overexpression of oncogenic circRNAs in tumor cells and tissues can decrease the expression of tumor-suppressor miRNAs through sponging, thereby promoting tumor progression.

The role of the circRNA/miRNA axis extends beyond cancer cell proliferation and metastasis. Growing evidence indicates that this axis plays a key role in regulating drug resistance in cancer. Chemotherapeutic agents like cisplatin, doxorubicin, paclitaxel, and docetaxel are used to treat cancer, but oncogenic circRNAs can induce therapy resistance by attenuating tumor-suppressor miRNAs. Similarly, this axis contributes to radioresistance. In terms of immune evasion, the circRNA/miRNA axis can induce PD-1 signaling, reducing T cell cytotoxicity against tumor cells. Several studies have confirmed that circRNAs regulating miRNA expression can serve as biomarkers for cancer patients. Based on these findings, targeting circRNAs or miRNAs and their downstream pathways is strongly recommended for cancer therapy.

While the role of circRNA-miRNA networks in cancer development and therapeutic response has been extensively studied, several challenges remain for future research. The circRNA-miRNA regulatory networks are highly complex and dynamic. Future studies need to unravel these intricate interactions and understand the context-dependent functions of circRNAs and miRNAs across different cancer types and stages. Although circRNAs and miRNAs hold promise as biomarkers for cancer diagnosis and prognosis, improving the specificity and sensitivity of these biomarkers is essential. This involves identifying circRNAs and miRNAs uniquely expressed in cancerous tissues compared to normal tissues. A significant gap exists in understanding the detailed molecular mechanisms by which circRNA-miRNA interactions influence cancer hallmarks such as proliferation, apoptosis, invasion, autophagy, and EMT. Future research should aim to comprehensively elucidate these mechanisms. Developing effective therapeutic strategies targeting circRNA-miRNA networks is a major challenge. This includes designing and delivering circRNA/miRNA-based therapeutics that selectively target cancer cells without affecting normal cells. Understanding the role of circRNA-miRNA networks in mediating resistance to radiotherapy and chemotherapy is crucial. Future studies should focus on identifying the mechanisms by which these networks contribute to therapeutic resistance and finding ways to overcome this resistance. The interaction between circRNAs, miRNAs, and the immune system is an emerging area of research. More studies are needed to understand how circRNA-miRNA networks contribute to immune evasion by cancer cells and how they can be manipulated to enhance anti-tumor immunity. Bridging the gap between basic research and clinical application is a significant challenge. Future research should focus on validating preclinical findings in clinical settings and developing standardized protocols for the clinical use of circRNA-miRNA-based diagnostics and therapeutics.

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Declaration of competing interest

The authors declare that they have no competing interests.

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