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circFAT1 in Tumorigenesis and Cancer Progression: Functional Heterogeneity and Clinical Translational Potential

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Abstract. Circular RNAs are a class of endogenous noncoding RNAs characterized by covalently closed loop structures, high stability, tissue-specific expression, and diverse regulatory functions. Among them, circFAT1 has attracted increasing attention because of its abnormal expression and functional involvement in multiple human cancers. Current studies suggest that circFAT1 participates in tumor proliferation, invasion, migration, metastasis, chemoresistance, stemness maintenance, and immune regulation mainly through competing endogenous RNA mechanisms, RNA-binding protein interactions, and possible epigenetic regulation. However, its biological role is highly context-dependent. In most cancers, including breast cancer, cervical cancer, glioma, hepatocellular carcinoma, lung adenocarcinoma, non-small cell lung cancer, melanoma, osteosarcoma, and cutaneous squamous cell carcinoma, circFAT1 generally acts as an oncogenic regulator. In contrast, studies in gastric cancer and esophageal squamous cell carcinoma indicate that circFAT1 may exert tumor-suppressive effects. This functional heterogeneity may be related to differences in circFAT1 splice variants, tumor-specific microRNA profiles, subcellular localization, molecular subtypes, and tumor microenvironment. This review summarizes the structural characteristics, regulatory mechanisms, cancer-specific functions, current limitations, and potential clinical value of circFAT1, aiming to provide a theoretical basis for future biomarker development and targeted therapeutic strategies.

Keywords: circFAT1, circular RNA, cancer, functional heterogeneity, biomarker

1. Background

In the human genome, protein-coding genes account for only approximately 2%, while more than 70% of sequences are transcribed into noncoding RNAs (ncRNAs) [1, 2]. Noncoding RNAs play core roles in a variety of biological processes, including post-transcriptional regulation, epigenetics, chromatin modification and cell cycle. Their aberrant expression is closely associated with the occurrence and progression of numerous human diseases, especially malignant tumors [2, 3]. Based on length, ncRNAs are classified into small noncoding RNAs (≤ 200 nt) and long noncoding RNAs (> 200 nt). As a special type of endogenous closed-loop noncoding RNA, circular RNAs (circRNAs) are mostly 200–2000 bp in length with an average size of about 500 bp. They are mainly transcribed

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by RNA polymerase II and formed via back-splicing, which generates a covalently closed circular structure by linking the upstream 5' splicing site with the downstream 3' splicing site [4-6].

CircRNAs possess distinctive molecular characteristics. Their closed-loop structure enables resistance to RNase R degradation, granting them markedly higher stability than their linear counterparts. With high abundance in body fluids, evolutionary conservation and tissue- and cell-specific expression patterns, circRNAs are regarded as promising biomarkers for disease diagnosis and potential therapeutic targets [7-9]. According to their origins and structures, circRNAs are categorized into exonic circRNAs (ecircRNAs), exon-intron circRNAs (EIciRNAs), circular intronic RNAs (ciRNAs) and tRNA intronic circRNAs (tricRNAs). Among them, ecircRNAs make up over 80% of all identified circRNAs [10, 11]. The major biological functions of circRNAs include acting as microRNA (miRNA) sponges to sequester miRNAs, binding to RNA-binding proteins (RBPs) to regulate transcription and translation. Some circRNAs can also encode functional small peptides via open reading frames (ORFs) and internal ribosomal entry sites (IRESs). They exert critical regulatory effects on tumor proliferation, invasion, metastasis, chemoresistance and immune escape [9, 11-13].

CircFAT1 is a pivotal circular RNA that has been widely identified in various diseases in recent years. Its dysregulated expression is closely linked to malignant tumor progression, diabetic complications and vascular lesions. Accumulating studies have verified that circFAT1 is abnormally expressed in a wide range of malignancies such as breast cancer, colorectal cancer, lung cancer, glioma and osteosarcoma. It modulates multiple oncogenic signaling pathways through the miRNA-mRNA axis, and participates in the regulation of malignant phenotypes including cell proliferation, migration, invasion, apoptosis, stemness maintenance and chemoresistance [14-17]. Meanwhile, circFAT1 also functions in non-neoplastic diseases such as diabetic nephropathy, diabetic retinopathy and abnormal proliferation of vascular smooth muscle cells, serving as a key node connecting ncRNA regulatory networks and disease mechanisms [18, 19]. Currently, the molecular mechanisms, clinical values and targeting potential of circFAT1 have become a research hotspot in the field of noncoding RNAs. A systematic summary of its structural features and biological functions can provide novel theoretical foundations and experimental evidence for disease diagnosis and targeted therapy.

2. Structural characteristics of circFAT1

Derived from the FAT1 gene and generated via alternative back-splicing, circFAT1 is a typical exonic circular RNA (ecircRNA) [20, 21]. Similar to most functional circRNAs, the biogenesis of circFAT1 is regulated by inverted complementary repeat sequences (Alu elements) in flanking introns as well as RNA-binding proteins. It forms a stable covalently closed circular structure through intron pairing-driven circularization or lariat-driven circularization. Without a 5' cap and a 3' poly(A) tail, circFAT1 is resistant to exonuclease degradation and maintains stable existence in cells and body fluids (Figure 1) [22-24].

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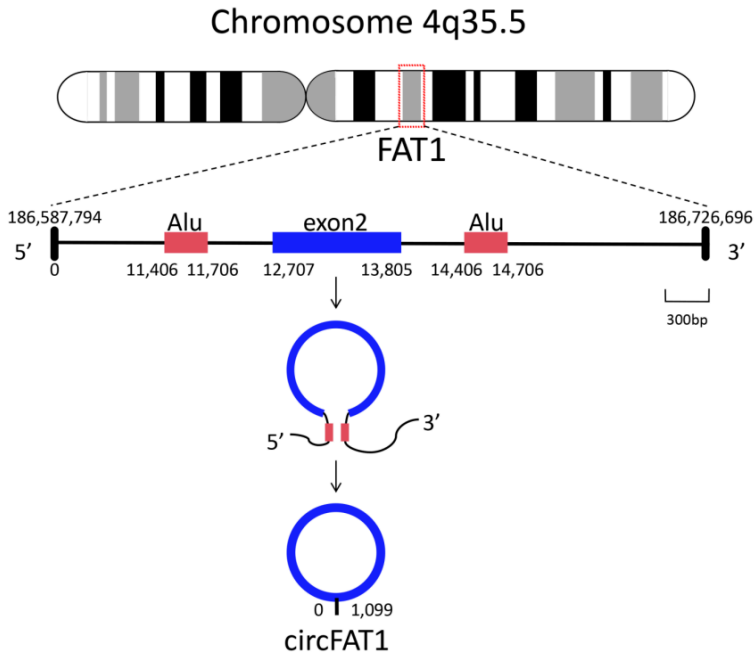


Figure 1. Schematic diagram of the 4q35.5 locus of the FAT1 gene and the formation mechanism of circFAT1

This figure illustrates the localization of the FAT1 gene at the 4q35.5 region of chromosome 4 and the biogenesis process of circFAT1. Blue boxes represent exons and black lines represent introns. circFAT1 is produced by back-splicing of exons from the FAT1 gene. circFAT1 is predominantly localized in the cytoplasm, while a small number of its isoforms are distributed in the nucleus. Such subcellular localization determines its functional patterns. In the cytoplasm, circFAT1 acts mainly as a competing endogenous RNA (ceRNA) to sponge microRNAs (miRNAs) and relieve the inhibitory effect of miRNAs on downstream target genes. In the nucleus, circFAT1 binds to nuclear proteins and participates in transcriptional regulation [20, 25, 26]. Multiple transcripts of circFAT1 have been identified so far. Among them, circFAT1 (e2), which originates from exon 2, is the major functional isoform and has been widely investigated in tumor and disease models [27].

With a moderate length, this circular RNA possesses the typical structural features of circRNAs. It has a highly conserved sequence and is widely expressed in various human tissues. Containing multiple miRNA binding sites, it can sequester several miRNAs simultaneously and establish the circFAT1-miRNA-mRNA regulatory axis. Certain circFAT1 transcripts harbor potential open reading frames, indicating their capacity to encode proteins. The structural stability, unique subcellular localization and multi-target binding ability enable circFAT1 to serve as a hub regulator in disease networks, which constitutes the structural basis for its involvement in the progression of tumors and non-neoplastic disorders [28-30].

3. Roles of circFAT1 in various tumors

3.1. Breast cancer (BC)

circFAT1 is involved in regulating oxaliplatin (OX) resistance and malignant progression of breast cancer, and its expression pattern and mechanism are correlated with treatment response and patient prognosis. Current studies indicate that this circular RNA mainly functions via the competing

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endogenous RNA (ceRNA) regulatory pathway to mediate downstream signaling cascades, thereby affecting drug resistance, migration and invasion of tumor cells.

Yao et al. (2021) found that knockdown of circFAT1 significantly promoted apoptosis of oxaliplatin-resistant breast cancer cells, reduced the half-maximal inhibitory concentration (IC_{50}) of oxaliplatin, and suppressed the migration and invasion capacities of tumor cells [31]. Mechanistically, circFAT1 acts as a molecular sponge for miR-525-5p (Figure 2) and relieves the inhibitory effect of this microRNA on spindle and kinetochore associated complex subunit 1 (SKA1). Upregulated SKA1 further activates the Notch and Wnt signaling pathways, two classic pathways governing tumor cell survival, drug resistance and epithelial-mesenchymal transition (EMT). In a relevant review, Khalaji et al. (2025) further validated this regulatory axis. They demonstrated that SKA1 knockdown downregulated the expression of β-catenin, Notch2 and glycogen synthase kinase-3β (GSK-3β), suggesting that these molecules play core roles in circFAT1-mediated oxaliplatin resistance in breast cancer [32].

In conclusion, existing evidence reveals that circFAT1 participates in breast cancer progression and chemoresistance through the circFAT1-miR-525-5p-SKA1 axis (Figure 2). Targeting circFAT1 may provide a novel strategy to overcome oxaliplatin resistance and inhibit tumor metastasis in breast cancer. Nevertheless, its value as a therapeutic target and prognostic biomarker requires further verification in clinical samples.

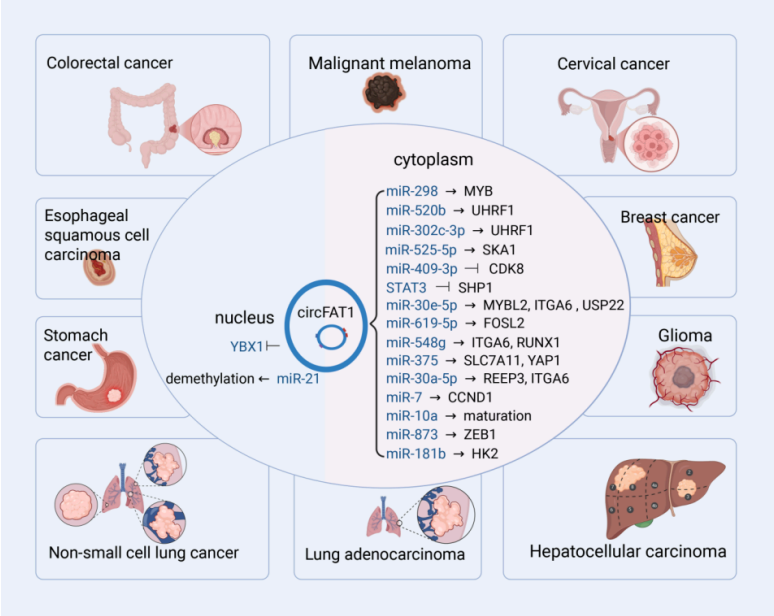


Figure 2. Overview of the expression and functions of circFAT1 in human tumors

circFAT1 is dysregulated in a variety of human tumors, including gastrointestinal, gynecological, pulmonary, hepatic and biliary malignancies. It exerts oncogenic or tumor-suppressive effects by modulating key cellular processes such as cell proliferation, migration, invasion and apoptosis.

3.2. Cervical cancer (CC)

Accumulating studies have shown that circFAT1 plays an oncogenic role in cervical cancer. It regulates the proliferation, migration, invasion and apoptosis of cervical cancer cells, and its biological effects are closely linked to the ERK1/2 and p38 MAPK signaling pathways. Aberrant

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expression of circFAT1 is one of the drivers of malignant phenotypes in cervical cancer, making it a potential therapeutic target.

In vivo and in vitro experiments by Zhou et al. (2021) showed that circFAT1 overexpression promoted the proliferation, migration, and invasion of cervical cancer cells. It also inhibited cell apoptosis. By contrast, circFAT1 silencing inactivated the ERK1/2 and p38 MAPK pathways and clearly suppressed tumor growth in animal models [33]. In terms of mechanism, circFAT1 works through the miR-409-3p/CDK8 axis. circFAT1 sponges miR-409-3p and reduces its inhibitory effect on CDK8. CDK8 then activates the ERK1/2 and p38 MAPK pathways, which are important for cell cycle progression and tumor metastatic potential. In addition, the circFAT1-miR-619-5p-CDK8 auxiliary regulatory pathway was also proposed (Figure 2). This further supports the central role of CDK8 in cervical cancer progression driven by circFAT1.

In short, current studies confirm that circFAT1 plays an oncogenic role in cervical cancer. It does this by regulating the miR-409-3p/CDK8 axis and activating the ERK1/2 and p38 MAPK pathways. Targeting circFAT1 or the components of its downstream signaling pathways may provide new research directions for cervical cancer treatment.

3.3. Colorectal cancer (CRC)

As noted in the nomenclature descriptions, different studies may focus on different splice variants of circFAT1. For this reason, the original names are kept in this section. The role of circFAT1 in colorectal cancer is complex. Several studies have reported both oncogenic and tumor-suppressive functions through different regulatory axes. These studies show that circFAT1 can regulate proliferation, apoptosis, migration, invasion, and glycolysis in colorectal cancer cells. But its specific effects are not fully consistent among different studies.

Ma et al. (2022) showed an oncogenic role of circFAT1. They found that circFAT1 overexpression promoted migration, invasion, and angiogenesis in colorectal cancer cells in vitro. It also reduced cell apoptosis. This effect is mediated by the circFAT1-miR-619-5p-FOSL2 axis. circFAT1 acts as a molecular sponge for miR-619-5p. It then weakens the inhibitory effect of miR-619-5p on the oncogene FOSL2. FOSL2 is a key gene involved in epithelial-mesenchymal transition and tumor metastasis [34]. By contrast, Liu et al. (2021) reported that circFAT1 was highly expressed in colorectal cancer tissues, but it had tumor-suppressive effects. It helped the maturation of miR-10a. In this way, it suppressed the proliferation, invasion, and migration of colorectal cancer cells [35]. Hu et al. (2021) reached similar conclusions about its tumor-suppressive properties. Their results showed that circFAT1 knockdown inhibited cell proliferation, cell cycle progression, and glycolysis. It also induced apoptosis in colorectal cancer cells both in vivo and in vitro. This biological effect is controlled by two parallel axes: circFAT1-miR-520b/UHRF1 and circFAT1-miR-302c-3p/UHRF1. More specifically, circFAT1 upregulates UHRF1 expression by sponging these microRNAs (Figure 2) [36].

These functional differences may be related to several factors. These factors include tumor stage, such as early-stage or advanced-stage disease. They may also include the genetic background of cells and differences in the tumor microenvironment. Such microenvironmental differences include hypoxia and inflammatory factors. The different circFAT1 splice variants studied may also be an important reason. Unfortunately, no study has compared the functional differences among different isoforms in one unified system. No study has compared these effects under different experimental conditions in the same system either. This makes it hard to reach a consistent conclusion.

In short, although the findings are not fully consistent, existing studies still show a clear point. circFAT1 regulates key biological processes in colorectal cancer. It does this through interactions

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with different microRNAs and target genes. Further detailed functional analysis is needed. Future work should be based on tumor classification, including molecular subtypes and clinical stages.

3.4. Esophageal squamous cell carcinoma (ESCC)

Different from its oncogenic role in most malignant tumors, circFAT1 tends to act as a tumor suppressor in esophageal squamous cell carcinoma. The downregulation of circFAT1 can increase the migration and invasion abilities of tumor cells. This change may further promote the malignant progression of ESCC and support tumor spread.

Takaki et al. (2021) found that circFAT1 expression was clearly lower in ESCC tumor tissues than in adjacent normal mucosal tissues. Functional assays showed that circFAT1 knockdown promoted the migration and invasion of ESCC cells. But it had no obvious effect on cell proliferation [37]. Its tumor-suppressive mechanism may involve the targeted regulation of miR-548g. This forms the circFAT1-miR-548g regulatory axis (Figure 2), which helps restrain tumor progression. Although the downstream target genes of miR-548g in this pathway have not been fully clarified, the observed cellular phenotypes still provide useful clues. The inhibition of miR-548g mediated by circFAT1 may take part in regulating epithelial-mesenchymal transition. It may also affect other processes related to cell motility and invasion.

Overall, current evidence suggests that circFAT1 acts as a tumor suppressor in ESCC. It does this by regulating miR-548g and inhibiting tumor cell migration and invasion. The downregulation of circFAT1 in ESCC tissues is related to poor prognosis and higher metastatic potential. This suggests that circFAT1 may serve as a prognostic biomarker. Still, treatment strategies that aim to restore circFAT1 expression need more validation. Further tests are needed in both in vitro and in vivo experiments.

3.5. Gastric cancer (GC)

A specific isoform of circFAT1 shows tumor-suppressive effects in gastric cancer. It regulates several biological behaviors of tumor cells through two mechanisms in the cytoplasm and nucleus. circFAT1 overexpression inhibits the proliferation, migration, and invasion of gastric cancer cells. This indicates that circFAT1 acts as a protective factor against gastric cancer progression.

Fang et al. (2019) identified circFAT1 as a tumor-suppressive circular RNA in gastric cancer. In vitro experiments confirmed that its overexpression clearly suppressed the proliferation, migration, and invasion of gastric cancer cells [20]. Two different subcellular regulatory pathways are involved in its mechanism. In the cytoplasm, circFAT1 works as a molecular sponge for miR-548g (Figure 2). It removes the inhibitory effect of miR-548g on RUNX1, a transcription factor that regulates the cell cycle and cell differentiation. In the nucleus, circFAT1 directly interacts with the proto-oncoprotein YBX1 and inhibits its oncogenic activity. These two mechanisms work together and form the tumor-suppressive phenotype of circFAT1 in gastric cancer.

In conclusion, current studies show that circFAT1 has tumor-suppressive functions in gastric cancer through two modes. It sponges microRNAs in the cytoplasm and interacts with nuclear proteins. The downregulation of circFAT1 in gastric cancer tissues speeds up tumor progression. This suggests that circFAT1 may serve as a prognostic biomarker. But the therapeutic value of restoring circFAT1 expression still needs further evaluation in animal models and clinical samples.

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3.6. Glioma

circFAT1 plays an oncogenic role in glioma. It regulates the proliferation, growth, and metastasis of tumor cells through the miR-30e-5p/MYBL2 signaling axis. Its overexpression is related to malignant phenotypes of glioma. This makes circFAT1 a possible therapeutic target for this malignant brain tumor.

Liu et al. (2025) confirmed that circFAT1 works as a molecular sponge for miR-30e-5p in glioma cells. Silencing circFAT1 inhibits glioma growth and metastasis. It also induces G1-phase cell cycle arrest and promotes cell apoptosis. By contrast, circFAT1 overexpression reverses the pro-apoptotic effect caused by miR-30e-5p mimics [27]. In terms of mechanism, circFAT1 sequesters miR-30e-5p and reduces its inhibitory effect on MYBL2 (Figure 2). MYBL2 is a key transcription factor that controls cell cycle progression and cell survival. This study provides strong evidence to support the above regulatory mechanism.

Overall, current evidence shows that circFAT1 has oncogenic effects in glioma by regulating the miR-30e-5p/MYBL2 axis. Targeting circFAT1 or the components of its downstream pathway may provide new ideas for glioma treatment. Still, large-scale studies based on clinical samples are needed to analyze the relationship between circFAT1 expression and clinical prognosis.

3.7. Hepatocellular carcinoma (HCC)

Studies have shown the oncogenic role of circFAT1 in hepatocellular carcinoma. It promotes the proliferation, invasion, and in vivo tumorigenicity of cancer cells through the miR-30a-5p/REEP3 signaling pathway. The abnormal expression of circFAT1 is one of the driving factors for the malignant progression of HCC. It may also serve as a potential prognostic biomarker and therapeutic target for this disease.

Wei et al. (2020) found that circFAT1 was highly expressed in HCC tissues and cell lines. In vitro assays showed that circFAT1 overexpression promoted the proliferation and invasion of hepatoma cells. In vivo experiments further showed that circFAT1 increased the tumor-forming ability of xenografts in nude mice [38]. In terms of mechanism, circFAT1 sponges miR-30a-5p and removes its inhibitory effect on receptor expression enhancing protein 3 (REEP3) (Figure 2). In addition, REEP3 overexpression could reverse the tumor-suppressive effects caused by circFAT1 knockdown. This proves that REEP3 is a key downstream effector of circFAT1 in HCC. Although the specific biological functions of REEP3 in HCC still need to be fully clarified, its ability to mediate the malignant phenotypes induced by circFAT1 suggests its possible role in cell cycle regulation, epithelial-mesenchymal transition, or extracellular matrix remodeling.

In short, circFAT1 drives HCC progression through the miR-30a-5p/REEP3 pathway. Targeting circFAT1 or REEP3 may have potential therapeutic value. At the same time, the abnormal expression of circFAT1 in HCC suggests its potential as a prognostic biomarker for assessing the risk of disease progression. This still needs to be verified in independent patient cohorts.

3.8. Malignant melanoma (MM)

Current studies show that circFAT1 plays an oncogenic role in malignant melanoma. It promotes the proliferation, invasion, and colony formation of tumor cells through the miR-375/SLC7A11 signaling axis. Its abnormal expression contributes to the malignant phenotypes of melanoma. This makes circFAT1 a potential therapeutic target for this highly metastatic cancer.

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Lu et al. (2023) found that circFAT1 was highly expressed in malignant melanoma cells. Silencing circFAT1 with siRNA plasmids clearly suppressed the proliferation, invasion, and colony-forming ability of melanoma cell lines [39]. In terms of mechanism, circFAT1 works as a molecular sponge for miR-375 and reduces the inhibitory effect of miR-375 on solute carrier family 7 member 11 (SLC7A11) (Figure 2). As a core component of the cystine-glutamate antiporter, SLC7A11 plays an important role in maintaining intracellular redox homeostasis and inhibiting ferroptosis. High expression of SLC7A11 in melanoma cells helps cell survival and proliferation. It also increases invasive ability and strengthens cellular resistance to cell death caused by oxidative stress.

In summary, existing studies show that circFAT1 drives malignant melanoma progression through the miR-375/SLC7A11 axis. Targeting circFAT1 or SLC7A11 may provide new ideas for melanoma treatment. However, this study was only carried out in cell lines. It still lacks validation from in vivo animal models and clinical samples.

3.9. Lung adenocarcinoma (LUAD)

circFAT1 functions as an oncogene in lung adenocarcinoma. It accelerates tumor cell proliferation and induces cisplatin (DDP) resistance by sponging miR-7 and activating the IRS2-ERK-CCND1 signaling pathway. Its overexpression is related to poor treatment response and aggressive tumor behaviors in LUAD.

Peng et al. (2022) confirmed that circFAT1 was upregulated in LUAD tissues and cells. circFAT1 overexpression promoted the proliferation of lung adenocarcinoma cells both in vitro and in vivo. Functional experiments showed that circFAT1 knockdown increased the sensitivity of tumor cells to cisplatin. This was verified in cellular assays and nude mouse xenograft models. These results indicate that circFAT1 is a key regulator of cisplatin resistance in lung adenocarcinoma cells [25]. In terms of mechanism, circFAT1 sequesters miR-7 and blocks its inhibitory effect on insulin receptor substrate 2 (IRS2). Increased IRS2 expression triggers ERK1/2 phosphorylation and further upregulates cyclin D1 (CCND1), a core molecule that controls cell cycle progression (Figure 2). This signaling cascade promotes cell proliferation, inhibits apoptosis, and finally leads to cisplatin resistance and tumor progression.

Overall, current evidence suggests that circFAT1 has oncogenic effects in lung adenocarcinoma. It also regulates the response to cisplatin through the miR-7-IRS2-ERK-CCND1 axis. Targeting circFAT1 may help improve the effect of cisplatin-based chemotherapy. But its safety and translational potential still need further verification in preclinical models.

3.10. Non-small cell lung cancer (NSCLC)

circFAT1 plays an oncogenic role in non-small cell lung cancer. It regulates tumor cell proliferation, migration, and invasion. It also affects the tumor immune microenvironment. Its interactions with microRNAs and its effects on immune cells may work together to promote NSCLC progression.

Dong et al. (2021) confirmed that circFAT1 was highly expressed in NSCLC tissues and cell lines. circFAT1 knockdown clearly inhibited the proliferation, migration, and invasion of NSCLC cells. In terms of mechanism, circFAT1 acts as a molecular sponge for miR-30e-5p (Figure 2). It then upregulates ubiquitin-specific peptidase 22 (USP22). As a deubiquitinase, USP22 promotes tumor progression by regulating the cell cycle, epithelial-mesenchymal transition, and DNA repair [15]. In addition, Li et al. (2023) reported that circFAT1 expression was positively related to the infiltration of $CD4^+$ T cells and $Foxp3^+$ regulatory T cells in NSCLC tissues. It was also negatively related to $CD8^+$ cytotoxic T cells. This suggests that circFAT1 may change the tumor immune

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microenvironment by regulating immune cell infiltration. In this way, it may promote tumor immune escape and disease progression [40].

In short, circFAT1 promotes NSCLC progression through two different mechanisms. On the one hand, it regulates tumor cell proliferation and metastasis through the circFAT1-miR-30e-5p-USP22 axis. On the other hand, it reshapes the tumor immune microenvironment by changing immune cell infiltration. Targeting circFAT1 may suppress both tumor cell growth and immune escape. Still, the immune-related findings above need further validation through functional experiments. These may include co-culture systems and in vivo immune models.

3.11. Osteosarcoma (OS)

Studies have shown that circFAT1 has oncogenic effects in osteosarcoma. It promotes tumor cell migration, invasion, in vivo tumorigenesis, and proliferation through the miR-375/YAP1 signaling axis. Its overexpression is closely related to the malignant phenotypes of osteosarcoma. This makes circFAT1 a potential therapeutic target for this malignant tumor, which often occurs in children and adolescents.

Liu et al. (2018) confirmed that circFAT1 acts as a molecular sponge for miR-375 in osteosarcoma cells. In this way, it upregulates the expression of Yes-associated protein 1 (YAP1), a core effector of the Hippo signaling pathway (Figure 2) [41]. Inhibiting circFAT1 effectively blocked the migration, invasion, and tumor-forming ability of osteosarcoma cells in vitro. It also clearly suppressed tumor growth in vivo. The Hippo-YAP1 pathway is a classic cascade that regulates cell proliferation, apoptosis, and epithelial-mesenchymal transition. The activation of this pathway driven by circFAT1 is a major factor in osteosarcoma progression. This study fully validated the miR-375/YAP1 axis as the main mechanism behind the function of circFAT1 in osteosarcoma.

In short, current evidence indicates that circFAT1 acts as a key oncogenic regulator in osteosarcoma through the miR-375/YAP1 axis. Targeting circFAT1 or parts of its downstream signaling pathways may provide new directions for osteosarcoma treatment. Still, this study was published at an early stage. Later independent validation and clinical translational research are still insufficient.

3.12. Cutaneous squamous cell carcinoma (cscc)

It should be noted that the squamous cell carcinoma discussed in this section refers specifically to cutaneous squamous cell carcinoma (cSCC). It is different from cervical squamous cell carcinoma (CC) and esophageal squamous cell carcinoma (ESCC) mentioned above. Squamous cell carcinomas from different anatomical sites have different causes, genetic backgrounds, and microenvironments. These differences may lead to different functions of circFAT1.

circFAT1 plays an oncogenic role in cSCC. It enhances cancer stem cell properties and promotes immune escape by activating the STAT3 signaling pathway. Its ability to increase tumor-initiating potential and weaken anti-tumor immunity makes an important contribution to disease progression and treatment resistance in cSCC.

Jia et al. (2021) found that circFAT1 promoted tumor sphere formation of cSCC cells in vitro and accelerated tumor growth in vivo. This shows its ability to strengthen cancer stem cell traits [42]. In terms of mechanism, circFAT1 inhibits the expression of Src homology 2 domain-containing phosphatase 1 (SHP1) and then activates signal transducer and activator of transcription 3 (STAT3) (Figure 2). As a tyrosine phosphatase, SHP1 inactivates STAT3 through dephosphorylation. Reduced

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SHP1 expression increases STAT3 phosphorylation and activation. This further upregulates stemness-related genes and weakens the innate immunity of tumor cells. The two effects of circFAT1, namely enhancing cancer stem cell characteristics and promoting immune escape, work together to drive malignant phenotypes and resistance to conventional treatment in cSCC.

In short, current evidence shows that circFAT1 has oncogenic effects in cutaneous squamous cell carcinoma by regulating the SHP1-STAT3 axis. This enhances cancer stem cell properties and promotes immune escape. Its overexpression in squamous cell carcinoma tissues is related to poor patient prognosis. This suggests its potential as a prognostic biomarker. But treatment strategies targeting circFAT1 or the STAT3 pathway still need further validation in more preclinical models.

3.13. Endometrial carcinoma (EC)

Growing studies suggest that circFAT1 regulates the stemness of endometrial carcinoma cells. In this way, it affects the malignant progression of the disease. Wu et al. (2022) found that circFAT1 overexpression increased the stemness of endometrial carcinoma cells. This pro-stemness effect could be reversed by miR-21 inhibition [43]. Mechanistic studies showed that circFAT1 upregulates miR-21 expression by inducing demethylation of the miR-21 gene (Figure 2). As a well-known oncogenic microRNA, miR-21 further increases the stemness of endometrial carcinoma cells. It also promotes tumor proliferation and progression. This regulatory pathway shows a functional pattern of circFAT1 in endometrial carcinoma that is independent of the classic ceRNA mechanism. It also provides new ideas about the epigenetic regulatory roles of circular RNAs.

In conclusion, existing evidence indicates that circFAT1 takes part in maintaining cancer stemness and promoting the malignant progression of endometrial carcinoma through epigenetic regulation of miR-21. The relationship between its abnormal expression and the malignancy of endometrial carcinoma still needs to be verified in clinical samples. Its value as a prognostic molecular biomarker also needs further evaluation.

4. Functional heterogeneity of circFAT1

A comprehensive review of existing studies reveals that the roles of circFAT1 vary across different tumor types. In breast cancer, cervical cancer, glioma, hepatocellular carcinoma, lung adenocarcinoma, malignant melanoma, non-small cell lung cancer, osteosarcoma and cutaneous squamous cell carcinoma, circFAT1 predominantly acts as an oncogenic factor. It mainly sequesters specific microRNAs via the competing endogenous RNA (ceRNA) mechanism, relieving the repression of downstream target genes such as SKA1, CDK8, MYBL2, REEP3, IRS2, SLC7A11, USP22 and YAP1. This process further activates signaling pathways including Notch/Wnt, ERK/p38 MAPK and Hippo, thereby promoting tumor cell proliferation, migration, invasion, drug resistance and immune escape. In contrast, circFAT1 functions as a tumor suppressor in gastric cancer and esophageal squamous cell carcinoma. It inhibits tumor cell migration and invasion through miR-548g-related pathways or interactions with proteins such as YBX1 [15, 16, 20, 21, 44].

These functional differences show that the biological roles of circFAT1 depend on cancer type and tissue specificity. The possible reasons are summarized as follows. First, different studies may detect different circFAT1 transcripts. Differences in exon composition and splicing sites can change its ability to bind microRNAs or proteins. Second, microRNA expression profiles and downstream target gene networks are not the same across tumor cells. Because of this, the same circRNA may regulate different pathways in different cellular contexts. Third, the subcellular location of circFAT1 determines how it works. Cytoplasmic circFAT1 mainly works through the ceRNA mechanism,

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while nuclear circFAT1 may take part in protein binding or transcriptional regulation. Fourth, the tumor microenvironment, cellular origin, and driver gene mutation backgrounds may also change the functional direction of circFAT1 [4, 9].

Accordingly, circFAT1 cannot be simply defined as a pure oncogene or tumor suppressor. Future research should first clarify the specific transcript isoform of circFAT1 being investigated, and conduct analyses combined with tumor classification, clinical staging and treatment regimens. In addition, it is necessary to compare the expression patterns and functional differences of various circFAT1 isoforms within a unified experimental system, so as to resolve the contradictory findings among different cancer types and even within the same malignancy. Only after fully elucidating its functional heterogeneity can circFAT1 be further developed into a reliable diagnostic biomarker and therapeutic target.

5. Limitations of current evidence and future perspectives

Although the roles of circFAT1 in various tumors have drawn widespread attention, existing studies still have certain limitations. Firstly, most current evidence is derived from in vitro cellular experiments and xenograft tumor models, with generally small clinical sample sizes. There is a lack of large-sample, multicenter and prospective cohort studies. Hence, the practical value of circFAT1 in tumor diagnosis, prognosis assessment and treatment response prediction remains to be further validated [26].

Secondly, inconsistencies exist in the nomenclature, detection regions and transcript isoforms of circFAT1 across different studies, which may largely account for conflicting research conclusions [45]. Particularly in colorectal cancer and other malignancies, circFAT1 has been reported to exert both oncogenic and tumor-suppressive effects, suggesting that its functions are influenced by tumor type, molecular subtype, disease stage and experimental models [46]. In follow-up studies, researchers should clearly specify primer locations, circularization sites and detailed transcript information in experimental design, so as to improve the reproducibility and comparability of results.

Thirdly, the molecular mechanisms of circFAT1 remain to be fully elucidated. Most existing studies focus on the competing endogenous RNA (ceRNA) regulatory pattern, whereby circFAT1 modulates the expression of downstream target genes by sponging microRNAs. Nevertheless, circRNAs can also function via binding RNA-binding proteins, regulating transcription, modulating protein stability, and even encoding functional small peptides. Researches on whether circFAT1 acts through these non-ceRNA mechanisms are still insufficient [47, 48].

Finally, the research on targeted therapy against circFAT1 is still in the exploratory stage. Antisense oligonucleotides, siRNA and CRISPR-based technologies can theoretically be applied to interfere with circFAT1 expression. However, their delivery efficiency, tissue specificity, safety and off-target effects have not been systematically evaluated [49]. Additionally, the physiological functions of circFAT1 in normal tissues remain unclear, and direct inhibition or overexpression of circFAT1 may bring potential risks. Therefore, more investigations based on animal models, patient-derived organoids and clinical samples are required to verify its safety and efficacy prior to clinical translation.

6. Conclusions

As a circular RNA with great research significance, circFAT1 participates in the occurrence, progression, metastasis, drug resistance and immune regulation of a wide range of tumors. Current

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studies demonstrate that circFAT1 acts predominantly as an oncogenic factor in most tumor types, whereas it serves as a tumor suppressor in gastric cancer and esophageal squamous cell carcinoma, indicating prominent tissue specificity and context dependence of its biological functions. Its major mechanisms include the microRNA sponge effect, regulation of downstream oncogenic or tumor-suppressive signaling pathways, as well as potential protein interaction and epigenetic modulation. Overall, circFAT1 holds great potential to be developed into a diagnostic biomarker, prognostic indicator and therapeutic target for tumors. Nevertheless, relevant findings are mainly limited to basic research, and its clinical translational value needs further verification. Future studies should prioritize addressing the ambiguous definition of transcript isoforms, simplistic mechanistic research, insufficient clinical data and unclear safety of targeted intervention, so as to advance the research on circFAT1 from mechanistic exploration toward clinical application.

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