CircWHSC1 (CircNSD2): A Novel Circular RNA in Multiple Cancers

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ABSTRACT: Circular RNAs (circRNAs) are a type of non-coding RNA (ncRNA) that possesses a unique single-stranded circular structure. They are primarily formed through alternative splicing of pre-mRNA (messenger RNA). The primary biological function of circRNAs is to regulate gene expression at both the transcriptional and post-transcriptional levels. Recent studies have increasingly demonstrated a close association between the dysregulation of circRNAs and the progression of diverse cancers, where they can function as either tumor suppressors or oncogenes. circWHSC1 (circNSD2) is a circular ncRNA that originates from the first 2 exons of the Wolf-Hirschhorn syndrome candidate gene (WHSC1). As Chen 2019 discovery that circWHSC1 (circNSD2) functions as a sponge for miRNAs and promotes cancer, this circRNA has garnered significant interest among researchers. circWHSC1 (circNSD2) has been found to be up-regulated in various malignant tumors, including nasopharyngeal carcinoma, lung cancer, breast cancer, liver cancer, colorectal cancer, ovarian cancer, cervical cancer, and endometrial cancer. It exerts its effects on cancer by either inhibiting or promoting the expression of related genes through direct or indirect pathways, ultimately affecting cancer proliferation, invasion, and prognosis. This article provides a comprehensive review and discussion of the biological roles of circWHSC1 (circNSD2) and its target genes in various cancers, as well as the latest research progress on related molecular biological regulatory mechanisms. Furthermore, the potential significance of circWHSC1 (circNSD2) in future clinical applications and transformations is thoroughly analyzed and discussed.

KEYWORDS: CircRNA, circWHSC1 (circNSD2), miRNA sponge, ceRNA, cancers, therapy

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Introduction

According to the Global Cancer Statistics 2020, approximately 19.3 million new cases of cancer and nearly 10 million cancer-related deaths are reported worldwide.[1] Neoplastic diseases are the result of a complex, multi-step process that involves a variety of factors, including gene mutations, the interaction of various signaling molecules and pathways, and the eventual loss of control over cell growth regulation. These factors work together to create an environment where cells grow and divide uncontrollably, leading to the development of cancerous tumors.[2] In recent decades, significant progress has been made in the treatment of cancer through various methods such as surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Despite these advancements, the overall effectiveness of cancer treatment remains limited, and cancer continues to present a significant threat to human life and health, remaining the leading cause of mortality worldwide.[3] For an extended period, research in the field of tumor biology has primarily concentrated on protein-coding genes, which make up less than 2% of the entire human genome.[4] ncRNA is a class of RNA molecules transcribed from genes. It was previously thought that it does not have the ability to encode proteins.[5] However, in recent years, evidence for ncRNA as a protein template is accumulating.[6-8] It includes various types, such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA).[9] circRNA, a type of ncRNA, was first observed by Sanger et al[10] in 1976 using electron microscopy in plant viroids and the Sendai virus. In 1979, scientists further extracted and observed the existence of circRNA from the cytoplasm of several eukaryotic cells.[11] However, due to technical limitations at the time, circRNA was initially considered a byproduct of RNA splicing errors and was not attributed to significant biological functions. As a result, it did not receive much attention.[12,13] In recent years, the function of circRNA has garnered increasing attention, thanks to the advancements in high-throughput sequencing and bioinformatics technology (Figure 1). Studies have shown that approximately 20% of active genes have the capacity to generate circRNA, further highlighting the significance of this molecule in biological processes.[14] Circular RNA is recognized for its crucial role in a

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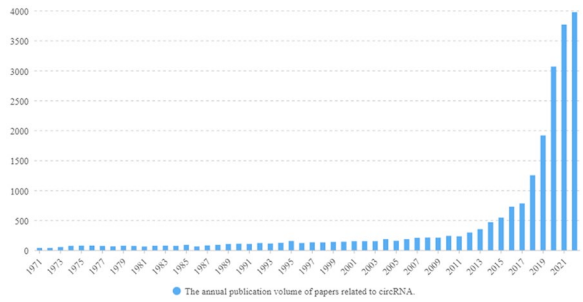

Figure 1. The annual publication volume of papers related to circRNA.

range of cellular and biological processes, including cell proliferation, differentiation, pluripotency, and epithelial-mesenchymal transition (EMT).[15] Moreover, emerging evidence indicates substantial variations in circRNA expression across a range of diseases, including cardiovascular diseases, nervous system disorders, and neoplastic conditions.[16-18] These findings underscore the potential of circRNA as a diagnostic and therapeutic target for a broad range of pathological conditions. The aforementioned discoveries have sparked significant interest among researchers, prompting further investigation into this area. circWHSC1 (circNSD2), also referred to as hsa_circRNA_001387[19] or circNSD2, is a cancer-associated circRNA that has been discovered in recent years and shows potential as a therapeutic target. In 2019, it was first identified that the expression of circWHSC1 (circNSD2) was significantly increased in colorectal cancer tissues, highlighting its potential as a diagnostic and therapeutic tool for this type of cancer.[20] It has been widely reported that circWHSC1 (circNSD2) plays a significant role in the progression of various malignant tumors as a cancer-promoting circRNA. This review aims to describe the role and mechanism of circWHSC1 (circNSD2) in human-related diseases and to discuss possible downstream molecular mechanisms. Further research is expected to provide new insights into the diagnosis and treatment of tumor diseases and other human-related diseases.

The Characterization of the circRNAs

circRNAs are a type of non-coding RNA (ncRNA) characterized by a closed circular structure, which are mainly formed by alternative splicing (AS) or alternative back-splicing of pre-RNA.[21] Alternative splicing and alternative back-splicing involve various mechanisms, such as exon skipping (ES), alternative 3′ splicing site (A3SS), alternative 5′ splicing site (A5SS), and intron retention (IR).[22-24] Furthermore, an atypical splicing mechanism, reminiscent of tRNA splicing, has been discovered in the unfolded protein response (UPR) pathway following endoplasmic reticulum (ER) stress. The protein kinase and site-specific ribonuclease known as inositol-requiring protein-1 (IRE1) plays a crucial role in this process. Inositol-requiring protein-1 identifies and cleaves the RNA target sequence on the mRNA (messenger RNA) at 2 specific sites, subsequently linking the resulting fragments together via a specialized tRNA ligase. This process leads to the generation of circular IRE-type RNA.[25,26] Compared with other linear RNAs, circRNA stands out for its distinctive feature of lacking a 5´m7G cap and 3´poly(A) tail structure. This unique structure grants it inherent resistance to RNase R and exoribonuclease. Consequently, circRNA exhibits superior stability and an extended half-life compared with other linear RNA variants.[27-29] Studies have revealed that circRNAs are predominantly found in the cytoplasm of eukaryotes, although a small fraction can also be located in the nucleus. Based on their origin and sequence composition, circRNAs can be broadly categorized into the following types:

1. Exonic circRNAs (EcircRNAs): These circRNAs are primarily located in the cytoplasm and represent the most prevalent type. Their main function is to serve as miRNA sponges, effectively sequestering miRNAs and modulating their activity.[30,31]
2. Circular intronic RNAs (ciRNAs): These circRNAs are formed from intronic regions and adopt a cable-sleeve structure. They are derived from pre-mRNA introns.[32]
3. Exon-intron circular RNAs (ElciRNAs): ElciRNAs are composed of both exonic and intronic sequences.[33]
4. Intergenic circRNAs: It contains 2 intronic circRNA fragments flanked by GT-AC splicing signals acting as the splice donor and acceptor of the circular junction while forming an integrated circRNA.[34]

ElciRNAs and ciRNAs are primarily localized in the nucleus, where they predominantly function as transcriptional regulators to fulfill their biological roles. These distinct types of circRNAs play diverse roles in cellular processes and contribute to the complexity of gene regulation.[35,36]

In addition, it has been reported that the viral RNA genome, transfer RNA (tRNA), ribosomal RNA (rRNA), and small nuclear RNA (snRNA) can undergo cyclization to form circRNA.[37] Furthermore, it should be noted that the expression of circRNA in organisms is not static; instead, it exhibits significant time, spatial, and disease-specific patterns.[38]

Functions of circRNAs

Effect of miRNA sponges

This is the most crucial biological function of circRNA, making it a current research hotspot. Circular RNA possesses a wealth of miRNA binding sites, also referred to as "miRNA response elements (MREs)."[39] Based on the principle of complementary base pairing, circRNA can bind to single or multiple miRNA targets through these MREs.[31,40,41] This interaction allows circRNA to function as a "molecular sponge," competitively binding to the corresponding miRNA. As a result, the inhibitory effect of miRNA on its downstream target gene expression is alleviated, leading to a decrease in functional miRNA levels and an increase in the expression of the target gene.[42-44] This mechanism is commonly referred to as the competitive endogenous RNA (ceRNA) mechanism.[45] Under normal circumstances, circRNA is expressed at low levels. However,

Table 1. The expression and roles of circWHSC1 (circNSD2) in cancers.

CANCER TYPE	EXPRESSION IN CANCERS	RELATED MIRNAS AND GENES	FUNCTIONAL ROLES	REFERENCES
Nasopharyngeal cancer	Up-regulated	miR-338-3p/ELAVL1	Promoting cell proliferation, invasion, migration, and reducing radio-sensitivity. Reducing radio-sensitivity.	Li et al, 2022; Shuai, et al 2020.
Non-small-cell lung cancer	Up-regulated	miR-296-3p/AKT3 miR-7/TAB2 miR-590-5p/SOX5	Exhibiting oncogenic activity. Promoting cell invasion and tumor growth. Promoting cell proliferation, invasion, and migration.	Shi et al, 2021; Guan et al, 2021; Wu et al, 2023.
Breast cancer	Up-regulated	miR-195-5p/FASN miR-212-5p/AKT3	Promoting cell proliferation, invasion, migration, and inhibiting cell apoptosis; promoting cell glycolysis; boosting xenograft tumor growth in nude mice.	Chen et al, 2022; Ding et al, 2021.
Liver cancer	Up-regulated	miR-142-3p/HOXA1	Promoting cell proliferation, invasion, and migration.	Lyu et al, 2021.
Colorectal cancer	Up-regulated	miR-199b-5p/DDR1/ JAG1miR-130a-5p/ ZEB1	Promoting the migration, invasion, and metastasis of CRC in vitro or in vivo. Promoting the migration, invasion, and metastasis of CRC in vitro or in vivo	Chen et al, 2019; Shi et al, 2023.
Ovarian cancer	Up-regulated	miR-1182/hTERT miR-145/MUC1	Increasing cell proliferation, migration, and invasion. Inhibiting cell apoptosis. Exosomal circWHSC1 can be transferred to peritoneal mesothelial cells and promoted peritoneal dissemination.	Zong et al, 2019.
Cervical cancer	Up-regulated	miR-532-3p/LTBP2	Promoting the proliferation, metastasis, and invasion of tumor cells and inhibiting apoptosis.	Li et al, 2022.
Endometrial cancer	Up-regulated	miR-646/NPM1	Promoting the proliferation, migration, and invasion of endometrial cancer cells and decreasing apoptosis.	Liu et al, 2020.

when circRNA is highly expressed, it can actively contribute to the development and progression of tumor cells by engaging in the aforementioned molecular mechanisms, including tumor occurrence, proliferation, invasion, and migration.[46] Table 1 shows the miRNAs and target genes regulated by circWHSC1 (circNSD2) in multiple cancers.

Interaction between circRNAs and proteins

Currently, it is widely believed that the interaction between circRNA and proteins is the second most substantial biological function of circRNA. RNA-binding proteins (RBPs) belong to a specific class of proteins that exert control over the maturation, transportation, and translation of RNA molecules subsequent to their transcription. circRNAs function as RBP sponging and they modulate the function of RBPs, thereby influencing the stability and splicing pattern of mRNA molecules.[47] In addition, the interaction between circRNA and proteins may have a bidirectional effect. On one hand, this interaction can influence the expression and functionality of proteins.[48] On the other hand, it can also regulate the synthesis and degradation of circRNA, creating a reciprocal relationship between the two.[49] Furthermore, circRNA serves as a dynamic molecular scaffold, facilitating the interaction between 2 or more proteins.[50,51]

Regulations of gene transcription

Unlike ecircRNA, which is primarily localized in the cytoplasm, ElciRNA and ciRNA derived from the nucleus do not act as miRNA sponges. However, studies have shown that they can regulate the expression and transcription of their parental genes through RNA-RNA interactions.[52] It primarily involves 2 mechanisms:

1. Circular intronic RNA interacts with RNA polymerase II (Pol-II) in the nucleus, enhancing the expression of its parent gene.
2. Exon-intron circular RNA forms a complex with U1 small ribonucleoprotein (U1 snRNP) in the nucleus. This complex then binds to the Pol-II transcription complex located on the promoter of the parent gene, promoting transcription of the parent gene.[36]

Translations

In 1986, Kos et al made a groundbreaking discovery by demonstrating that circRNA derived from the hepatitis virus can be translated into a 122-amino acid polypeptide. This discovery marked the beginning of a new understanding that circular ncRNA can exhibit protein translation

capabilities like those of linear RNA. Subsequent studies have further supported this notion.[53,54] Due to the unique covalent ring structure of circRNA, it is inherently incapable of being translated through the m7G cap-dependent scanning mechanism, which is commonly employed by eukaryotic mRNA.[55] Up to now, several translation mechanisms of circRNA have been identified. These mechanisms include the following:

1. Internal ribosome entry site (IRES)-mediated translation: IRES is a sequence located 150 to 250 bp upstream of the ATG start codon of circRNA. It can be recognized by eIF4G and facilitate the translation of circRNA into proteins.[56] However, endogenous IRES is not common in eukaryotic transcriptomes. Internal ribosome entry site-like elements are a class of consensus motifs rich in AU, which are significantly enriched in human circRNAs. Some RBPs can promote cap-independent translation of circRNAs by directly identifying these short IRES-like elements. This novel model of circRNA translation initiation differs from the classical IRES mechanism.[57]
2. Adenosine-to-inosine (A-to-I) editing: A-to-I editing is a post-transcriptional modification of RNA, which can change the sequence, coding potential, and secondary structure of RNA.[58] Justin Ralph Welden et al[59] pointed out that the 12→10 circRNA produced by the microtubule-associated protein tau (*MAPT*)gene lacked the start codon and could not be translated into protein. A-to-I editing can change an AUA (isoleucine) in the 12→10 circRNA sequence to an AUI (initiation codon), thereby initiating the translation of 12→10 circRNA without initiation codon. Therefore, it is believed that A-to-I editing is a circRNA translation mechanism.
3. Untranslated region (UTR) translation activation element-mediated translation: In certain cases, circRNAs are generated through reverse cleavage of pre-mRNA, resulting in the circRNA with the same UTR sequence as its pre-mRNA. The UTR region can recruit ribosomes and drive circRNA translation into proteins.[60]
4. M6A modification-mediated translation: Yang et al[61] discovered a conserved m6A sequence in the UTR of certain circRNAs. This modification can influence the translation of circRNAs into proteins. This methylated UTR sequence can be recognized by the YTHDF3 protein, which plays a crucial role in circRNA translation. On recognition, YTHDF3 protein interacts with the translation initiation factor eIF4G2, facilitating the recruitment of translation initiation factors eIF4A and eIF4B. Together, they form the translation initiation complex eIF4, which initiates the translation process of circRNAs.
5. Exon junction complex (EJC)-mediated mechanism: EJC is a RBP complex that is assembled and deposited on mRNA during splicing.[62] It is known that EJC can promote mRNA translation by interacting with ribosomes. In addition, Lin et al[6] research in 2023 showed that EJC plays an important role in the cap-independent translation of circRNA.

These translation mechanisms highlight the diverse ways in which circRNAs can be translated, expanding our understanding of their functional roles in cellular processes.

Functions in Exosomes

Exosomes, also known as intracavitary vesicles (ILVs), are a subset of extracellular vesicles (EVs) with a diameter of 30 to 150 nm.[63] In 1986, Johnstone et al first observed and harvested exosomes during sheep reticulocyte culture. But at that time, it was generally believed that these exosomes were a kind of cell waste, and more of their role was to discard unwanted molecular components.[64] However, in recent years, it has been found that almost all mammalian cells secrete and absorb exosomes, and cancer cells usually produce more exosomes than normal cells.[65] The main molecular components include proteins, DNA, lipids, mRNA, lncRNA, miRNA, and circRNA. These molecular components, which can be packaged into exosomes, are delivered to local or systemic cells to provide intercellular communication.[63] This mode of transportation enables circRNAs to transmit biological information and substances to target cells. Moreover, it has been observed that circRNAs can disrupt the stability of the endothelial barrier and influence various cellular processes, including cell growth, EMT, and angiogenesis. These mechanisms are believed to contribute to the acquisition of tumor cell proliferation, invasion, migration, and resistance to chemotherapy.[66] In addition, these exosome particles have been isolated from body fluid circulation, such as blood, urine, saliva, and breast milk.[67] Consequently, further investigation into exosomal circRNA holds promise for the identification of novel oncological markers that could improve the clinical diagnosis of neoplastic diseases.

In conclusion, the study of circRNA has garnered significant attention in the field of RNA research due to its pivotal role in the onset and progression of various human diseases, particularly in tumorigenesis. The significance of circWHSC1 (circNSD2) in the realm of ncRNA and its potential mechanisms in tumor development have prompted the need to consolidate existing knowledge, thereby facilitating further investigations in this domain. This chapter aims to provide a comprehensive overview of the current clinical relevance of circWHSC1 (circNSD2) in human tumor formation and progression, elucidating its associated molecular mechanisms. Moreover, we endeavor to explore its potential for clinical translation, with the ultimate goal of harnessing circWHSC1 (circNSD2) as a novel therapeutic target for the diagnosis and treatment of malignant tumors.

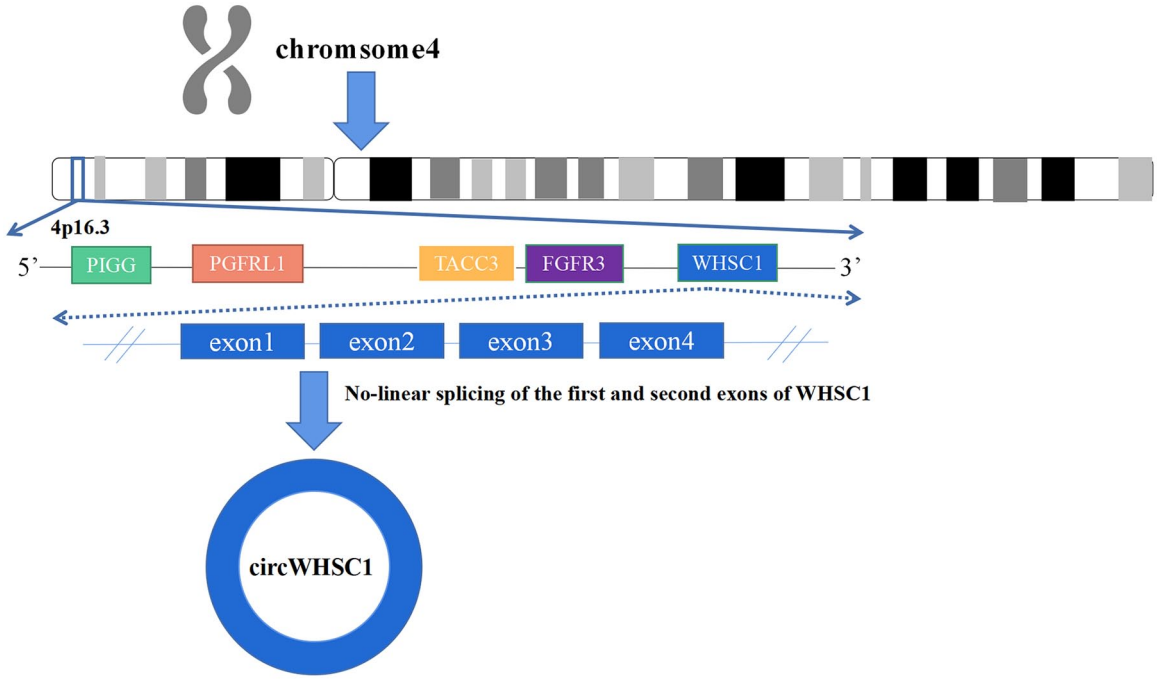

Figure 2. Schematic representation of the formation of circWHSC1 (circNSD2).

The Source and Function of the circWHSC1 (circNSD2)

Wolf-Hirschhorn syndrome candidate gene, also known as nuclear receptor binding SET domain-protein 2 (*NSD2)* or multiple myeloma SET domain (*MMSET)*, is a gene located on the short arm of human chromosome 4.[68,69] Its primary biological function is to encode a histone lysine methyltransferase.[70] This enzyme plays a crucial role in gene transcription by modifying histones through methylation.[71] Wolf-Hirschhorn syndrome candidate gene undergoes AS, resulting in 3 main protein subtypes: NSD2 type I (short NSD2, consisting of 647 amino acids), NSD2 type II (long NSD2, consisting of 1365 amino acids), and RE-IIBP (interleukin-5 response element II binding protein, consisting of 584 amino acids).[72] The *WHSC1* gene is widely believed to play a crucial role in early growth and development of newborns. Deletion of this gene has been linked to the development of Wolf-Hirschhorn syndrome, and the clinical manifestations are multi-system developmental disorders such as neonatal heart, bone, reproduction, urine, and immunity.[73,74] Based on available reports, the *WHSC1* gene has been identified with abnormal expression in various types of solid tumors. As an oncogene, it plays a crucial role in promoting the proliferation, invasion, migration, EMT transformation, and chemotherapy resistance of different malignant tumors.[75,76] circWHSC1 (circNSD2), also referred to as hsa_circRNA_001387 or circNSD2,[77] is a novel circRNA discovered in recent years. This circular ncRNA is transcribed from the first 2 exons of the *WHSC1* gene[19] (Figure 2). Recent studies have shown that circWHSC1 (circNSD2) is up-regulated in various malignant tumors, including nasopharyngeal carcinoma (NPC), lung cancer, breast cancer, liver cancer, colorectal cancer, ovarian cancer, cervical cancer, and endometrial cancer (Figure 3). Abnormal expression of circWHSC1 (circNSD2) has been found to affect the malignant process of tumors and the sensitivity of radiotherapy and chemotherapy.[19]

CircWHSC1 (circNSD2) Dysregulation in Human Cancers and Mechanisms

Nasopharyngeal cancer

Nasopharyngeal carcinoma is a prevalent malignant tumor in the head and neck region, with a mortality rate of approximately 3% among all malignant tumors.[78] The leading cause of NPC is believed to be the Epstein-Barr virus infection.[79] Concurrent chemoradiotherapy (CCRT) is often the primary treatment for advanced NPC due to its high sensitivity to radiotherapy and chemotherapy.[80] Shuai et al[77] discovered that circWHSC1 (circNSD2) is significantly up-regulated in both NPC tissues and cell lines. The research team also observed a significant correlation between high circWHSC1 (circNSD2) expression and tumor differentiation, TNM stage, EB virus positivity, and family history of NPC (Table 2). In addition, patients with high circWHSC1 (circNSD2) expression were found to have reduced sensitivity to radiotherapy. Further investigation by Li et al[19] revealed that circWHSC1 (circNSD2) primarily promotes the proliferation, invasion, and migration of NPC cells by regulating the miR-338-3p/embryonic lethal abnormal vision 1 (ELAVL1) axis, thereby affecting the tumor's sensitivity to radiotherapy. ELAVL1 is an RBP that is widely expressed in mammals and primarily functions by binding and stabilizing mRNA. In previous reports, Hu et al[81] have highlighted that ELAVL1 is abnormally highly expressed in both NPC tissues

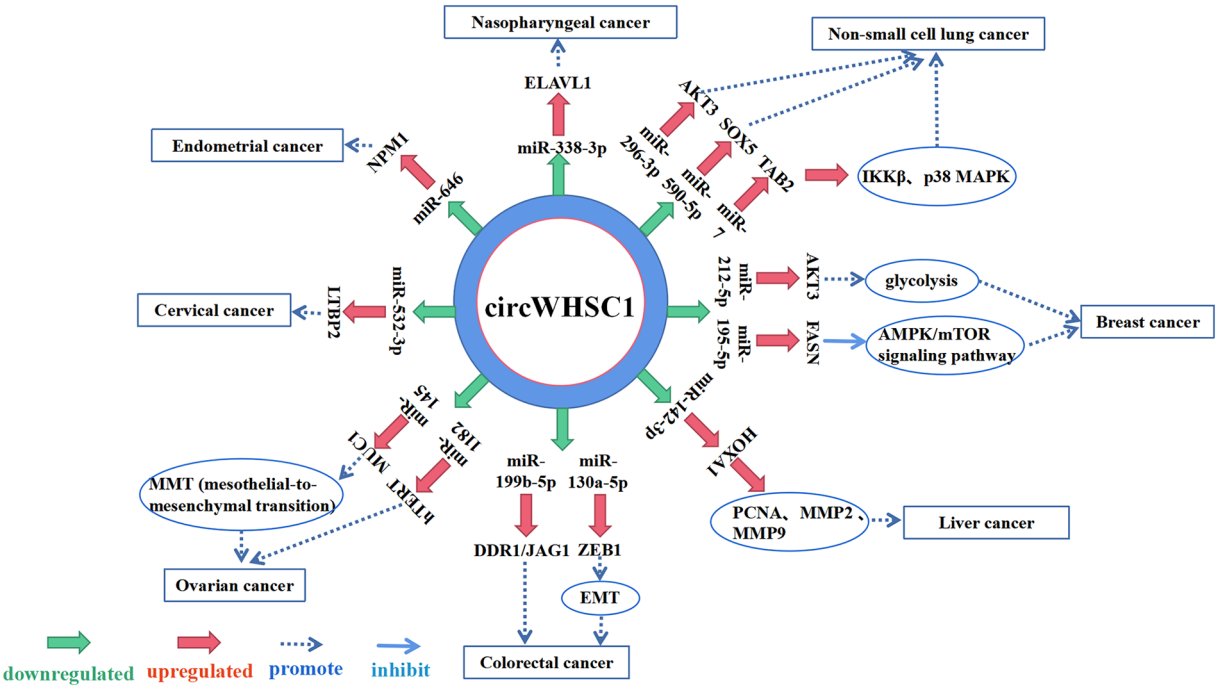

Figure 3. circWHSC1 (circNSD2) participates in various cancers in different ways.

and cell lines when compared to normal human nasopharyngeal tissues. It has been found to be significantly correlated with various malignant tumor cell characteristics such as proliferation, invasion, metastasis, angiogenesis, chemoradiotherapy resistance, and prognosis.[82,83]

Lung cancer

Lung cancer is a major contributor to cancer-related deaths globally,[84] with non-small-cell lung cancer (NSCLC) being the most prevalent pathological subtype, accounting for approximately 80% to 85% of all lung cancer cases.[85] According to Shi et al,[86] circWHSC1 (circNSD2) exhibits high expression levels in both NSCLC tissues and cell lines. Inhibition of circWHSC1 (circNSD2) expression has been shown to impede the proliferation, invasion, and migration of NSCLC cells. This is due to the competitive binding of circWHSC1 (circNSD2) to miR-296-3p, which results in the upregulation of AKT3 protein expression through the ceRNA mechanism. The overexpression of AKT3 further activates the PI3K/AKT signaling pathway, a pivotal regulator of the proliferation, invasion, migration, and anti-apoptotic ability of NSCLC cells. This abnormal activation of the AKT3-mediated PI3K/AKT signaling pathway has been reported to be essential for the progression of NSCLC.[87] According to Guan et al,[88] circWHSC1 (circNSD2) expression is up-regulated in NSCLC tissues and cell lines, and it acts as a molecular sponge of miR-7 to up-regulate the expression of TGFβ-activated kinase 1 (TAK1)-binding protein 2 (TAB2). Subsequent Western blotting (WB) detection revealed that the downstream proteins of TAB2, IKKβ and p38 MAPK were also significantly up-regulated in NSCLC cells overexpressing circWHSC1 (circNSD2). This suggests that circWHSC1 (circNSD2) may promote cancer through the NF-κB and MAPK signaling pathways. TAK1-binding protein 2, as an adaptor protein, can bind to TAK1 and TNF receptor-associated factor 6 (TRAF6) to form a ternary complex, mediating the phosphorylation and activation of TAK1. Phosphorylated TAK1 can further activate the NF-κB and MAPK signaling pathways.[89] Abnormal activation of these pathways has been shown to promote the occurrence and development of various malignant tumors, including NSCLC.[90,91] Similarly, Wu et al also found abnormally high expression of circWHSC1 (circNSD2) in NSCLC tissues and cell lines, and its high expression was related to a low survival rate of patients with NSCLC ($P < .05$). In vitro, knockdown of circWHSC1 significantly reduced the proliferation, migration, and invasion of NSCLC cells. Further experiments revealed that circWHSC1 regulates the malignant characteristics of NSCLC cells through the miR-590-5p/SOX5 axis.[92]

Therefore, it can be concluded that circWHSC1 (circNSD2) serves as an independent prognostic indicator for poor outcomes in patients with NSCLC. Further investigation into the role and underlying mechanism of circWHSC1 (circNSD2) in NSCLC progression is of great significance, as it may lead to the development of novel therapeutic strategies to improve patient prognosis and the overall survival rate.

Breast cancer

Breast cancer is a prevalent and potentially life-threatening cancer that affects women worldwide. It can be classified into 3 types based on the receptors present on the surface of breast

Table 2. Clinical pathological features and prognostic significance of circWHSC1 (circNSD2) in cancers.

CANCER TYPES	SAMPLES	CLINICOPATHOLOGICAL FEATURES	PROGNOSTIC IMPLICATIONS	REFERENCES
Nasopharyngeal cancer	100 pairs of tissues and adjacent normal tissues from patients with NPC who underwent surgical treatment, none of these patients received radiotherapy prior to surgery. 23 pairs of tissues and adjacent normal tissues.	Lower overall survival ($P = .044$) Lower progression-free survival ($P = .023$) Lymph node metastasis ($P = .033$) Distant metastasis ($P = .043$) TNM stage ($P = .011$)	Poor prognosis	Shuai et al, 2020; Li et al, 2022.
Non-small-cell lung cancer	70 pairs of tissues and adjacent normal tissues. 15 pairs of tissues and adjacent normal tissues. 55 pairs of tissues and adjacent normal tissues from patients with NSCLC who underwent surgical treatment, none of these patients received radiotherapy or chemotherapy prior to surgery.	Lower overall survival ($P < .01$) Lower overall survival ($P < .05$)	Poor prognosis	Shi et al, 2021; Guan et al, 2021; Wu et al, 2023.
Breast cancer	50 pairs of tissues and adjacent normal tissues. 65 pairs of tissues and adjacent normal tissues, including 22 pairs of TNBC tissues.	Lower overall survival ($P = .0055$) Lower overall survival ($P = .0261$) Lymphatic metastasis ($P = .028$) Distant metastasis ($P = .049$) Tumor stage ($P = .0184$) Ki-67 level (%) ($P = .0217$)	Poor prognosis	Chen et al, 2022; Ding et al, 2021.
Liver cancer	50 pairs of tissues and adjacent normal tissues; the serum samples were obtained from 45 patients with HCC and 35 healthy volunteers.	Lower overall survival ($P = .0024$)	Poor prognosis	Lyu et al, 2021.
Colorectal cancer	82 pairs of tissues and adjacent normal tissues.	Tumor area ($P < .05$)	Poor prognosis	Chen et al, 2019; Shi et al, 2023.
Ovarian cancer	79 epithelial ovarian carcinoma samples and 13 normal ovary samples, none of them had undergone chemotherapy or radiotherapy prior to surgery.	Tumor size ($P < .05$)	Poor prognosis	Zong et al, 2019.
Cervical cancer	30 pairs of tissues and adjacent normal tissues.	Lower overall survival ($P = .0110$)	Poor prognosis	Li et al, 2022.
Endometrial cancer	26 normal endometrial tissues and 32 endometrial cancer tissues were confirmed pathologically.	Tumor size ($P < .05$)	Poor prognosis	Liu et al, 2020.

cancer cells: hormone receptor-positive breast cancer, human epidermal growth factor receptor 2 (HER-2)-positive breast cancer, and triple-negative breast cancer (TNBC). Hormone receptor-positive breast cancer is characterized by the presence of estrogen or progesterone receptors, whereas human EGFR 2-positive breast cancer is characterized by the overexpression of HER2 protein. Triple-negative breast cancer, on the contrary, lacks all 3 receptors and is considered the most aggressive subtype of breast cancer.[93,94] Chen et al[95] identified that circWHSC1 (circNSD2) was elevated in breast cancer tissues and cell lines. Notably, a significant correlation was found between high circWHSC1 (circNSD2) expression and factors such as tumor size, advanced tumor stage, lymph and distant metastasis, and Ki-67 expression levels in breast cancer. It was also noted that circWHSC1 (circNSD2) increases the expression of fatty acid synthase (FASN) by competitively binding to miR-195-5p. The overexpression of FASN significantly hastens the advancement of breast cancer by impeding the activation of the AMPK/mTOR signaling pathway. Previous studies have demonstrated that targeting FASN and AMPK in breast cancer cells can effectively suppress cancer cell proliferation, invasion, and migration, while enhancing their sensitivity to radiochemotherapy.[96,97] This study also revealed that inhibiting FASN or activating AMPK can increase the expression of apoptosis-related proteins, including Bax, c-Caspase3, and E-cadherin. This suggests that blocking anti-apoptotic pathways may contribute to the increased sensitivity of breast cancer to radiotherapy and chemotherapy.[95] Furthermore, TNBC is a unique subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) receptors on the surface of

cancer cells. Triple-negative breast cancer carries a heightened risk of distant metastasis and recurrence and has a poor prognosis compared with other types of breast cancer.[98] According to Ding and Xie,[99] the expression of circWHSC1 (circNSD2) is significantly up-regulated in TNBC tissues compared with adjacent tissues. Knockdown of circWHSC1 (circNSD2) not only inhibits the proliferation, invasion, and migration of cancer cells but also significantly reduces their glycolysis level. In TNBC, circWHSC1 (circNSD2) mainly induces the upregulation of its downstream molecule, serine/threonine kinase 3 (AKT3), by sponge adsorption of miR-212-5p, and promotes the malignant progression of breast cancer through these mechanisms. Previous studies have identified AKT3 as an oncogene of breast cancer, and knockdown of AKT3 can significantly inhibit the proliferation of TNBC cells and promote apoptosis.[100]

Hence, delving deeper into the interplay between circRNA and miRNA in breast cancer can yield valuable insights into potential prognostic biomarkers and therapeutic targets for the disease.

Liver cancer

Hepatocellular carcinoma (HCC) is a highly prevalent and deadly form of cancer that affects people all over the world. It is the most common type of primary liver cancer, accounting for approximately 85% of cases.[101] The study by Lyu et al[102] showed that the expression level of circWHSC1 (circNSD2) in liver cancer tissues and cell lines was significantly higher than that in normal tissues. At the same time, the overall survival rate of patients with high circWHSC1 (circNSD2) expression was notably lower than those in the low expression group. Recent research has revealed that circWHSC1 (circNSD2) plays a significant role in the development of HCC by enhancing the expression of HOXA1 protein in HCC cells. This is achieved through its competitive binding to miR-142-3p. Lyu et al[102] also highlighted that knocking down circWHSC1 (circNSD2) resulted in a significant inhibition of HCC cell proliferation, invasion, and migration. In addition, it played a crucial role in promoting HCC cell apoptosis. In subsequent western blot experiments, we observed a significant reduction in the expression of oncogenes such as HOXA1, PCNA, MMP2, MMP9, and other proteins related to cell proliferation and metastasis in the circWHSC1 (circNSD2) knockdown group, as compared to the normal control group. These genes have been previously reported to play a crucial role in the progression of liver cancer. Furthermore, Lyu et al discovered that the expression level of circWHSC1 (circNSD2) in serum exosomes of patients with HCC was significantly elevated compared with the normal control group. This finding suggests that circWHSC1 (circNSD2) may serve as a potential biomarker for the diagnosis and prognosis of HCC.

Colorectal cancer

Colorectal cancer ranks as the third leading cause of cancer-related death globally.[103] Liver metastasis is the most frequent complication of colorectal cancer, occurring in approximately 40% to 50% of cases during the course of the disease.[104] According to Chen et al,[20] circWHSC1 (circNSD2) is highly expressed in colorectal cancer cells and has been found to up-regulate the expression of discoidin domain receptor 1 (DDR1) and Jagged 1 (JAG1) proteins by targeting miR-199b-5p. This, in turn, enhances the ability of colorectal cancer cells to metastasize. Discoidin domain receptor 1 is a member of the collagen receptor tyrosine kinase (RTK) family and is known to be an oncogenic gene. Its expression is abnormally up-regulated in various cancers, including breast cancer, ovarian cancer, and colorectal cancer.[105-107] In colorectal cancer cells, the tumor microenvironment (TEM) features high collagen concentrations. This contributes to the binding and phosphorylation of DDR1, which in turn results in its over-activation. Subsequently, this over-activated, phosphorylated DDR1 promotes the EMT of tumor cells by aberrantly activating the Wnt/β-catenin signaling pathway, thereby fostering tumor proliferation.[107,108] Similarly, the abnormal activation of the Notch signaling pathway, mediated by JAG1, plays a significant role in both the emergence and progression of tumors.[109]

Shi et al pointed out in a recent study that expression of circWHSC1 (circNSD2) was up-regulated in colorectal cancer cells compared with normal colon epithelial FHC-1 cell line. Knockdown of circWHSC1 (circNSD2) not only inhibited the proliferation, invasion, and migration of cancer cells and promoted their apoptosis, but also significantly inhibited the process of cell cycle. The results of in vivo experiments also showed that circWHSC1 (circNSD2) silencing significantly reduced the tumor growth of subcutaneous colorectal cancer cells in nude mice. Subsequent studies found that circWHSC1 (circNSD2) up-regulated the expression of its downstream molecule zinc finger E-box binding homeobox 1 (ZEB1) by interacting with miR-130a-5p.[110] The transcription factor ZEB1 is a key inducer of EMT and plays an important role in the invasion and metastasis of tumor cells. It has been found to be significantly correlated with various malignant tumor cell characteristics, such as cell stemness, therapeutic resistance, and immune escape.[111]

Consequently, in-depth studies on the circ-NSD2/miR-199b-5p/DDR1/JAG1, circWHSC1 (circNSD2)/miR-130a-5p/ZEB1 axis and its subsequent pathways could potentially herald a new era in the treatment of patients afflicted with colorectal cancer.

Ovarian cancer

Ovarian cancer ranks as the third most common gynecological tumor globally, surpassed only by cervical cancer and uterine cancer. It is the predominant cause of cancer-related mortality

in women.[112,113] An unfortunate characteristic of this disease is its non-specific clinical symptoms during the early stages. Consequently, ovarian cancer is usually not diagnosed until it has reached an advanced state, resulting in a bleak prognosis.[114] Zong et al[115] initially discovered and examined the expression level of circWHSC1 (circNSD2) in ovarian cancer tissues. The findings revealed a significant upregulation of circWHSC1 (circNSD2) expression in both ovarian cancer tissues and cell lines, in comparison with normal ovarian epithelium. Furthermore, there is a positive correlation observed between the expression level of circWHSC1 (circNSD2) and the malignancy of ovarian cancer. The overexpression of circWHSC1 (circNSD2) has the potential to enhance the expression of downstream target genes such as human telomerase reverse transcriptase protein (hTERT) or mucin 1 (MUC1). This is achieved through the "sponge adsorption" of miR-1182 and miR-145, thereby exerting its cancer-promoting effect. Prior research has indicated that hTERT is highly expressed in the ovarian cancer cell line SKOV3. The suppression of hTER1 can impede cell cycle progression and stimulate the apoptosis of tumor cells.[116] Ma et al[117] have highlighted that MUC1 can induce the expression of EGFR in ovarian cancer cells. Furthermore, the overexpression of EGFR can facilitate the phosphorylation of serine/threonine kinase (AKT). The activation of AKT through phosphorylation can stimulate the proliferation of ovarian cancer cells, impede apoptosis, and induce resistance to chemotherapy in ovarian cancer tissues by activating the AKT signaling pathway. Zong et al[115] have also reported that circWHSC1 (circNSD2) can be secreted in the form of exosomes. On absorption of circWHSC1 (circNSD2) vesicles by peritoneal mesothelial cells, the expression of MUC1 in these cells can be up-regulated. This mechanism promotes the mesothelial-mesenchymal transition (MMT) of peritoneal mesothelial cells, which is associated with the peritoneal implantation of ovarian cancer.

Therefore, we speculate that through the in-depth study of circWHSC1 (circNSD2)/miR-1182/hTERT axis and circWHSC1 (circNSD2)/miR-145/MUC1 axis, it is expected to provide a potential effective therapeutic target for the treatment of ovarian cancer.

Cervical cancer

Cervical cancer ranks as the fourth most prevalent cancer affecting women globally. In 2018 alone, approximately 311 000 lives were claimed by this disease.[118] The primary culprit behind cervical cancer is the infection caused by the human papillomavirus (HPV) strains 16 and 18.[119] The study conducted by Li et al[120] revealed that circWHSC1 (circNSD2) exhibited high expression levels in both cervical cancer tissues and cell lines when compared to the normal control group. Furthermore, the study found a negative correlation between the expression level of circWHSC1 (circNSD2) and the overall survival rate of patients with cervical cancer. Knockdown of circWHSC1 (circNSD2) resulted in a significant inhibition of cervical cancer cell proliferation, invasion, and migration, while promoting cancer cell apoptosis. Moreover, the study also investigated the effects of circWHSC1 (circNSD2) in mouse tumor xenograft and lung metastasis models. The results demonstrated that mice with high expression levels of circWHSC1 (circNSD2) exhibited larger subcutaneous tumor volumes and weights compared with those with low expression levels. In addition, the high expression group also displayed a higher number of lung metastasis nodules, further confirming the role of circWHSC1 (circNSD2) in the malignant biological processes of cervical cancer. The main mechanism underlying these effects involves circWHSC1 (circNSD2) acting as a "molecular sponge" that competitively binds to miR-532-3p, thereby upregulating the expression of its downstream target gene, latent transforming growth factor-β binding protein 2 (LTBP2). Previous studies have reported an upregulation of LTBP2 expression in various malignant tumors, including NPC[121] and esophageal cancer.[122] In addition, the expression level of LTBP2 has been identified as an independent predictor of tumor prognosis in some studies.[123,124]

Hence, it is imperative to conduct additional investigations into the role and mechanism of the circWHSC1 (circNSD2)/miR-532-3p/LTBP2 axis and its downstream pathways in the development of cervical cancer. Such research endeavors hold the potential to not only establish a dependable prognostic marker for the diagnosis and treatment of cervical cancer but also pave the way for precise therapeutic interventions in the field.

Endometrial cancer

Endometrial cancer, a prevalent malignancy in women, necessitates a comprehensive understanding of its pathogenesis and identification of potential therapeutic targets to enhance patient prognosis and overall survival rates.[125] In a study by Liu et al,[126] it was observed that circWHSC1 (circNSD2) expression was significantly up-regulated in endometrial cancer tissues and cell lines compared with normal endometrial tissues. Further investigations revealed that circWHSC1 (circNSD2) promotes the malignant biological processes of endometrial cancer cells by upregulating the expression of nucleophosmin 1 (NPM1) through its interaction with miR-646. Nucleophosmin 1, a gene that can be translated into a nucleolar protein, exhibits its dual attributes as both a tumor suppressor gene and a proto-oncogene, playing a crucial role in the progression of various malignant tumors such as leukemia, gastric cancer, and colorectal cancer.[127,128] The oncogenic effects of the *NPM1* gene are primarily mediated through mechanisms such as gene mutation, rearrangement, deletion, and overexpression.[129] Therefore, elucidating the underlying mechanisms of the circWHSC1/miR-646/NPM1 axis in endometrial cancer holds promise for the development of targeted therapeutic interventions.

Therefore, further study of the upstream and downstream molecular pathways of circWHSC1 (circNSD2) is expected to

make an important contribution to improving the overall survival rate and prognosis of patients with endometrial cancer. Therefore, further study of the upstream and downstream molecular pathways of circWHSC1 (circNSD2) is expected to make an important contribution to improving the overall survival rate and prognosis of patients with endometrial cancer.

CircWHSC1 (circNSD2) Expression in Human Non-Tumor Disease and Its Regulatory Mechanism

Post-myocardial infarction repairs

Recently, Wei et al[130] conducted a study that further supports the role of circWHSC1 (circNSD2) in promoting angiogenesis and proliferation in cardiomyocytes (CMs). They found that the expression of circWHSC1 (circNSD2) in EVs derived from endothelial cells (ECs) was significantly increased under hypoxic conditions. These EVs were capable of targeting CM cells. Moreover, the high expression of circWHSC1 (circNSD2) in CMs was found to promote the proliferation and angiogenesis of adult CM. The underlying mechanism behind this phenomenon was speculated to involve circWHSC1 ability to promote the phosphorylation of TRIM59. Phosphorylated TRIM59, in turn, could activate and maintain high levels of phosphorylated pSTAT3. This activation of pSTAT3 was found to up-regulate the expression of cyclin B2, thereby promoting CM regeneration and facilitating myocardial function recovery following myocardial infarction. This finding holds promise for the potential recovery of cardiac function in patients who have experienced myocardial infarction.

However, it is important to note that the study did not provide a definitive answer regarding the mechanism by which circWHSC1 (circNSD2) induces angiogenesis in the myocardium. Further research is needed to elucidate this aspect of circWHSC1 role in promoting angiogenesis in the heart.

Conclusions and Future Perspectives

circRNAs play a crucial role in the intricate gene regulatory network, exerting significant influence on tumorigenesis and developmental processes. This article aims to provide an overview of the recent advancements in the study of circWHSC1 (circNSD2), shedding light on its biological functions and potential clinical implications in diverse neoplastic conditions. By delving into the mechanisms through which circWHSC1 (circNSD2) modulates tumor development, this review contributes to a deeper comprehension of its regulatory role in cancer progression. Recent studies have demonstrated a notable upregulation of circWHSC1 (circNSD2) expression in various solid tumors, including NPC, lung cancer, breast cancer, liver cancer, colorectal cancer, ovarian cancer, cervical cancer, endometrial cancer, and more. This heightened expression of circWHSC1 (circNSD2) primarily functions as a miRNA sponge, thereby promoting cancer progression. These findings highlight the significance of circWHSC1 (circNSD2) as a potential biomarker and therapeutic target in diverse neoplastic conditions. The elevated expression of circWHSC1 (circNSD2) influences the expression of its downstream target genes via the ceRNA process and the associated miRNA competitive binding. This interaction subsequently plays a pivotal role in various aspects of tumor behavior, such as proliferation, invasion, migration, TNM staging, EMT, MMT, resistance to radiotherapy, and patient prognosis. These attributes suggest that circWHSC1 (circNSD2) could potentially serve as an effective diagnostic or prognostic biomarker for tumors in future clinical practice. Further investigation suggests that the oncogenic influence of circWHSC1 (circNSD2) might be linked to the abnormal activation of several signaling pathways, including NF-κB, PI3K/AKT, AMPK/MTOR, and Wnt/β-catenin. Notably, compared with linear RNA molecules, circRNAs possess distinctive attributes, such as increased stability and resistance to degradation. This feature allows circWHSC1 (circNSD2) to persist and accumulate within cells, maintaining its functionality over a long period. These properties make it highly suitable as a clinical biomarker. Recent research highlights that circRNA can be enriched in exosomes, playing a vital role in intercellular communication. Studies report that circWHSC1 (circNSD2) can be secreted as exosomes, promoting peritoneal metastasis in ovarian cancer. Moreover, circWHSC1 (circNSD2) has demonstrated significant regulatory activity in CM regeneration and myocardial function recovery postmyocardial infarction, which further underscores the heterogeneity and functional diversity of circRNA expression.

Despite these strides, current research on circWHSC1 (circNSD2) is mostly restricted to its role as a miRNA sponge, which does not fully represent its functionality and modes of action in tumorous diseases. Moving forward, we aim to enhance research on other roles and mechanisms of circWHSC1 (circNSD2) in tumors and design targeted therapeutic strategies based on the corresponding molecular action pathways. These initiatives may offer tangible and effective targets for precision treatment in oncology. In addition, they hold the potential to offer novel therapeutic avenues for patients with myocardial ischemia-related diseases.

Author Contributions

XZ and YY drafted and revised the article. XW and HW collected relevant articles and helped to revise the article. LZ and JH reviewed the article. XZ designed tables and charts. All authors contributed to the article and approved the submitted version.

Availability of Data and Materials

Main data are shown in this article, and additional data about this study could be obtained from the corresponding author on reasonable request.

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