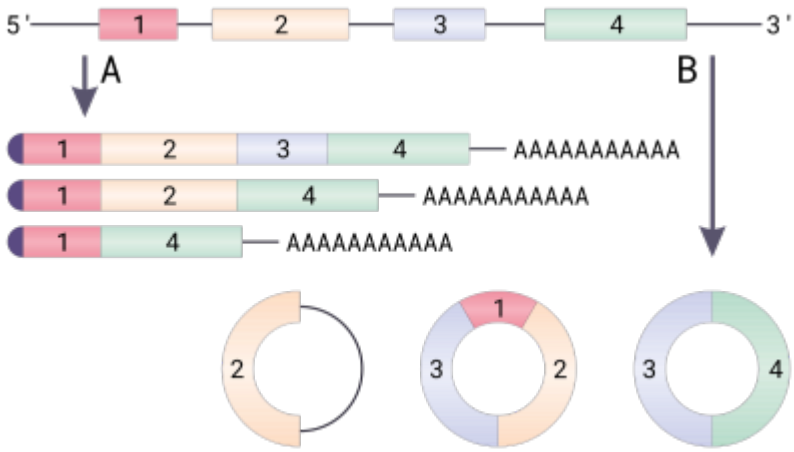
Circular RNA

- Circular RNAs and doxorubicin resistance in cancer: molecular mechanisms and potential treatment targets
- CircTBCD/IGF2BP2 complex stabilizes IGF-1R mRNA in an m6A-dependent manner to promote bone metastasis in nasopharyngeal carcinoma
- Perspectives on NcRNAs in HBV/cccDNA-driven HCC progression
- RNA sequencing reveals circular RNA expression patterns in chronic intermittent hypoxia
- Circular RNA as a potential biomarker for obstructive sleep apnea
- CircRNA: the potential biomarkers and therapeutic targets in oral squamous cell carcinoma (OSCC)
- Identification of the microglia-associated signature in experimental autoimmune encephalomyelitis
- circRNA hsa_circ_0072107 aggravates myocardial hypertrophy via its function as a competitive endogenous RNA of miR-516b-5p

---



Circular RNA (or circRNA) is a type of single-stranded RNA which, unlike the better known linear RNA, forms a covalently closed continuous loop, i.e., in circular RNA the 3' and 5' ends normally present in an RNA molecule have been joined together. This feature confers numerous properties to circular RNAs, many of which have only recently been identified.

Circular RNAs (circRNAs) are widespread throughout the eukaryotic genome. The expression of circRNAs is regulated by both cis-elements and trans-factors, and the expression pattern of circRNAs is cell type- and disease-specific.

Most often, aneurysms occur in large blood vessels - the aorta (Thoracic Aortic Aneurysm (TAA) and Abdominal Aortic Aneurysm (AAA) and brain vessels (Intracranial Aneurysm (IA)). Despite the presence of significant differences in the pathogenesis of the development and progression of IA and TAA/AAA, there are also similarities. For instance, both have been shown to be strongly influenced by shear stress, inflammatory processes, and enzymatic destruction of the elastic lamellae and

extracellular matrix (ECM) proteins of the vascular wall. Moreover, although IA and TAA are predominantly considered an arteriopaty with different pathological mechanisms, they share risk factors with AAA, such as hypertension and smoking. However, there is a need for a more in- -depth study of the key elements that may influence the formation and progression of a particular aneurysm to find ways of therapeutic intervention or search for a diagnostic tool. Today, it is known that the disruption of gene expression is one of the main mechanisms that contribute to the development of aneurysms. At the same time, growing evidence suggests that aberrant epigenetic regulation of gene function is strongly related to the genesis of aneurysms. Although much has been studied of the known protein-coding genes, circular RNAs (circRNAs), a relatively new and rapidly evolving large family of transcripts, have recently received much scientific attention. CircRNAs regulate gene expression through the sponging of microRNAs (miRNAs) and can also be used as therapeutic targets and biomarkers. Increasing evidence has implicated circRNAs in the pathogenesis of multiple cardiovascular diseases, including the development of aneurysms. However, the mechanism of dysregulation of certain circRNAs in a particular aneurysm remains to be studied. The discovery of circRNAs has recently advanced our understanding of the latest mode of miRNAs/target genes regulation in the development and progression of IA and TAA/AAA. The aim of this study is to compare the expression profiles of circRNAs to search for similar or different effects of certain circRNAs on the formation and progression of IA and TAA/AAA [1)].

Circular RNAs (circRNAs) have emerged as critical regulators of tumor immunity, particularly in the PD-1/PD-L1 pathway, and have shown potential in predicting immunotherapy efficacy. Yet, the detailed roles of circRNAs in cancer immunotherapy are not fully understood. While existing databases focus on either circRNA profiles or immunotherapy cohorts, there is currently no platform that enables the exploration of the intricate interplay between circRNAs and anti-tumor immunotherapy. A comprehensive resource combining circRNA profiles, immunotherapy responses, and clinical outcomes is essential to advance our understanding of circRNA-mediated tumor-immune interactions and to develop effective biomarkers.

Methods: To address these gaps, we constructed The Cancer CircRNA Immunome Atlas (TCCIA), the first database that combines circRNA profiles, immunotherapy response data, and clinical outcomes across multicancer types. The construction of TCCIA involved applying standardized preprocessing to the raw sequencing FASTQ files, characterizing circRNA profiles using an ensemble approach based on four established circRNA detection tools, analyzing tumor immunophenotypes, and compiling immunotherapy response data from diverse cohorts treated with immune checkpoint blockades (ICBs).

Results: TCCIA encompasses over 4,000 clinical samples obtained from 25 cohorts treated with ICBs along with other treatment modalities. The database provides researchers and clinicians with a cloud-based platform that enables interactive exploration of circRNA data in the context of ICB. The platform offers a range of analytical tools, including browse of identified circRNAs, visualization of circRNA abundance and correlation, association analysis between circRNAs and clinical variables, assessment of the tumor immune microenvironment, exploration of tumor molecular signatures, evaluation of treatment response or prognosis, and identification of altered circRNAs in immunotherapy-sensitive and resistant tumors. To illustrate the utility of TCCIA, we showcase two examples, including circTMTC3 and circMGA, by employing analysis of large-scale melanoma and bladder cancer cohorts, which unveil distinct impacts and clinical implications of different circRNA expression in cancer immunotherapy.

Conclusions: TCCIA represents a significant advancement over existing resources, providing a

comprehensive platform to investigate the role of circRNAs in immuno-oncology [2].

Functions

Similar to other types of non-coding RNAs, functions of circRNAs are also versatile. CircRNAs have been reported previously to function as microRNA (MicroRNA) sponges, protein sponges, coding RNAs, or scaffolds for protein complexes.

Increasing evidence has confirmed that circRNAs are involved in regulating the development and progression of various tumors.

Circular RNA in glioma

Several circRNAs have been reported to play important roles in human malignancies, including glioma.

Liu et al. reviewed several reports related to circRNAs and glioma, as well as the potential diagnostic and therapeutic applications of circRNAs in brain cancer. In general, some circRNAs, such as circSMARCA5 and circCFH, are found to be expressed in a glioma-specific pattern, these circRNAs may be used as tumor biomarkers. In addition, some circRNAs have been found to play oncogenic roles in glioma (e.g., circNFIX and circNT5E), whereas others have been reported to function as tumor suppressors (e.g., circFBXW7 and circSHPRH). Furthermore, circRNA is a good tool for protein expression because of its higher stability compared to linear RNAs. Thus, circRNAs may also be an ideal choice for gene/protein delivery in future brain cancer therapies. There are some challenges in circRNA research in glioma and other diseases. Research related to circRNAs in glioma is comparatively new and many mysteries remain to be solved [3].

Circular RNA 0001438

Gastric cancer has become a great challenge to human health in the world. We studied the expression and role of the circular RNA 0001438 (circ_0001438) to find a biomarker to assess the prognosis of gastric cancer. Through a polymerase chain reaction, circ_0001438 expression in gastric cancer was detected. Chi-square test, multi-factor Cox regression, and Kaplan-Meier analyses were used to determine the association between circ_0001438 and the patient's clinical condition and prognosis. Using the luciferase reporter gene system, the interaction between circ_0001438 and miR-1290 was analyzed, and the regulatory impact of circ_0001438/miR-1290 on the activity of gastric cancer cells was examined flowing the Transwell assay and CCK8 assay. In gastric cancer tissues and cells, circ_0001438 expression was downregulated, and miR-1290 expression was upregulated and the two were negatively correlated. miR-1290 inhibitors were transfected and significantly increased the activity of circ_0001438 luciferase, while miR-1290 mimics decreased the activity. Overexpression of circ_0001438 decreased miR-1290 expression and inhibited the proliferation and metastasis of gastric cancer cells, which was reversed when miR-1290 mimics were transfected. Additionally, there was a correlation between circ_0001438 expression and lymph node

metastases, tumor size, and TNM stage of gastric cancer. Low circ_0001438 expression predicts poor prognosis of gastric cancer patients. circ_0001438 is a biomarker for tumor development and clinical prognosis in gastric cancer. It works by downregulating miR-1290 to control the activity of gastric cancer cells [4].

Circular RNA VPS18

The aim of this study is to explore the biological roles and underlying mechanisms of circRNA vacuolar protein sorting 18 homolog (circVPS18) in glioblastoma. A quantitative real-time polymerase chain reaction (qRT-PCR) was performed to measure the expression of circVPS18, microRNA (miR)-1299-3p, and branched-chain amino acid transaminase 1 (BCAT1). In vitro experiments were conducted using 5-ethynyl-2'-deoxyuridine (EdU), flow cytometry, transwell, and tube formation assays, respectively. Western blot was conducted to examine all protein levels. Dual-luciferase reporter assay and RNA immunoprecipitation (RIP) assay were employed to confirm the interaction between miR-1229-3p and circVPS18 or BCAT1. The murine xenograft model was established to conduct in vivo assay. CircVPS18 and BCAT1 were highly expressed while miR-1229-3p was lowly expressed in glioblastoma tissues and cells. CircVPS18 knockdown inhibited glioblastoma progression by inhibiting cell proliferation, migration, invasion, and angiogenesis, and promoting cell apoptosis. Moreover, miR-1229-3p could be targeted by circVPS18; inhibition of miR-1229-3p could invert the suppressive effect of circVPS18 knockdown on glioblastoma tumorigenesis. Furthermore, BCAT1 was a target of miR-1229-3p; functionally, BCAT1 overexpression could reverse the inhibitory effects of miR-1229-3p upregulation on glioblastoma cell malignant phenotypes. Moreover, we also verified that circVPS18A could regulate BCAT1 expression by sponging miR-1229-3p. Additionally, circVPS18 silencing also restrained tumor growth and metastasis in vivo. CircVPS18 accelerated glioblastoma progression by miR-1229-3p/BCAT1 axis, providing a potential therapeutic target for glioblastoma [5].

circFBXW7

The aim of a study of Gao et al. from the Department of Neurosurgery, People's Hospital of Lanling County, Linyi, Shandong, China was to examine the effect of circFBXW7 on glioma progression and to determine its underlying mechanism.

qRT-PCR was performed to measure the expression of circFBXW7, miR 23a-3p, and PTEN in tissues and cell lines of glioma. The proliferation ability of glioma cells was examined using the CCK-8 assay. Glioma cell migration and invasion capacity were detected using Transwell assays. The dual-luciferase reporter gene assay was employed to examine the correlation between miR-23a-3p and circFBXW7 or PTEN. The expression levels of the related genes were determined using western blotting analysis. A glioma xenograft tumor model was employed to evaluate the functional roles of circFBXW7 in vivo.

CircFBXW7 was found to be aberrantly downregulated in glioma tumor tissues and cell lines. Overexpression of circFBXW7 was found to significantly inhibit the proliferation, migration, and invasion ability of the glioma cells. Moreover, bioinformatic analysis and dual-luciferase reporter assays confirmed that circFBXW7 can directly target miR-23a-3p, which then blocks the binding of miR-23a-3p to the 3' untranslated region (UTR) of PTEN. Mechanically, circFBXW7 suppresses cell proliferation and metastases in glioma by sponging miR-23a-3p, resulting in elevated PTEN expression. In addition, in vivo experiments also confirmed that circFBXW7 overexpression effectively halts tumor growth and metastases. Consistent with the in vitro observations, circFBXW7 overexpression significantly decreased miR-23a-3p, Ki-67, and N-cadherin, as well as increased PTEN

and E-cadherin levels.

The results revealed that circFBXW7 exhibits anti-proliferative and anti-metastases activities via sponging miR-23a-3p to elevate PTEN expression in glioma, which may offer a novel target for clinical therapy and diagnosis of glioma [6].

circCCDC9

circCCDC9

circ_0004872

circ_0004872

circ_0079593

The article “Circular RNA circ_0079593 promotes glioma development through regulating KPNA2 expression by sponging miR-499a-5p, by Z. Yang, C. Li, X.-Y. Fan, L.-J. Liu, published in Eur Rev Med Pharmacol Sci 2020; 24 (3): 1288-1301-DOI: 10.26355/eurrev_202001_20186-PMID: 32096160” has been retracted by the authors as they cannot ensure the reliability of the results (Figure 6C could not be repeatedly verified). The Publisher apologizes for any inconvenience this may cause. https://www.europeanreview.org/article/20186 [7].

CircRNA_0050486

circ_0050486 knockdown inhibited inflammation and apoptosis by targeting miR-1270 in oxLDL-induced THP-1 macrophages. This finding may provide a potential therapeutic target for atherosclerosis [8].

Hsa_circ_0072309

Hsa_circ_0072309

hsa_circ_0001445

hsa_circ_0001445

hsa circ 0000690

The expression of hsa_circ_0000690 can act as a diagnostic marker for IA and predict the prognosis of 3 months after operation and is closely related to the volume of hemorrhage [9)]

circRNA/Wnt axis

Accumulating evidence indicates that the circRNA/Wnt axis modulates the expression of cancer genes and then regulates cancer progression. Wnt pathway-related circRNA expression is obviously associated with many clinical characteristics. CircRNAs could regulate cell biological functions by interacting with the Wnt pathway. Moreover, Wnt pathway-related circRNAs are promising potential biomarkers for cancer diagnosis, prognosis evaluation, and cancer treatment [10)].

References

1)
Gareev I, Beylerli O, Ahmad A, Ilyasova T, Shi H, Chekhonin V. Comparative Analysis of Circular RNAs Expression and Function between Aortic and Intracranial Aneurysms. Curr Drug Targets. 2024 Aug 30. doi: 10.2174/0113894501319306240819052840. Epub ahead of print. PMID: 39219419.
2)
Wang S, Xiong Y, Zhang Y, Wang H, Chen M, Li J, Luo P, Luo YH, Hecht M, Frey B, Gaipl U, Li X, Zhao Q, Ma H, Zhou JG. TCCIA: a comprehensive resource for exploring CircRNA in cancer immunotherapy. J Immunother Cancer. 2024 Jan 11;12(1):e008040. doi: 10.1136/jitc-2023-008040. PMID: 38212124.
3)
Liu J, Zhao K, Huang N, Zhang N. Circular RNAs and human glioma. Cancer Biol Med. 2019 Feb;16(1):11-23. doi: 10.20892/j.issn.2095-3941.2018.0425. PubMed PMID: 31119043; PubMed Central PMCID: PMC6528446.
4)
Ren B, Hua J, Zhang C, Zhang Y, Wang Y, Liu L. Expression and Significance of the Circular RNA circ_0001438 in the Development of Gastric Cancer. J Environ Pathol Toxicol Oncol. 2025;44(1):21-29. doi: 10.1615/JEnvironPatholToxicolOncol.2024053645. PMID: 39462446.
5)
Huang Q, Li W, Huang Y, Chen Q, Wei W. Circular RNA VPS18 Promotes Glioblastoma Progression by Regulating miR-1229-3p/BCAT1 Axis. Neurotox Res. 2022 Jul 1. doi: 10.1007/s12640-022-00530-6. Epub ahead of print. PMID: 35776379.
6)
Gao ZG, Yang P, Huang J, Ding YQ. CircFBXW7 Alleviates Glioma Progression through Regulating MiR-23a-3p/PTEN Axis. Anat Rec (Hoboken). 2020 May 4. doi: 10.1002/ar.24410. [Epub ahead of print] PubMed PMID: 32365279.
7)
Yang Z, Li C, Fan XY, Liu LJ. Retraction Note: Circular RNA circ_0079593 promotes glioma development through regulating KPNA2 expression by sponging miR-499a-5p. Eur Rev Med Pharmacol Sci. 2022 Oct;26(20):7317. doi: 10.26355/eurrev_202210_29998. PMID: 36314300.
8)
Wang K, Bai X, Mei L, Miao Y, Jin F. CircRNA_0050486 promotes cell apoptosis and inflammation by targeting miR-1270 in atherosclerosis. Ann Transl Med. 2022 Aug;10(16):905. doi: 10.21037/atm-22-3745. PMID: 36111016; PMCID: PMC9469134.
9)
Huang Y, Cao H, Qi X, Guan C, Que S. Circular RNA hsa_circ_0000690 as a potential biomarker for

diagnosis and prognosis of intracranial aneurysm: Closely relating to the volume of hemorrhage. Brain Behav. 2023 Mar 6:e2929. doi: 10.1002/brb3.2929. Epub ahead of print. PMID: 36879365.
10)
Xue C, Li G, Zheng Q, Gu X, Bao Z, Lu J, Li L. The functional roles of the circRNA/Wnt axis in cancer. Mol Cancer. 2022 May 5;21(1):108. doi: 10.1186/s12943-022-01582-0. PMID: 35513849.