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Review Article

Emerging Roles of CircRNAs in Tumor Microenvironment

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Abstract

The tumor microenvironment (TME) is an integral part of cancer that serves as a harbor where tumor cells communicate with neighboring cells and non-cancerous components to determine the progression of the tumor. Researchers are increasingly turning their focus away from tumor cells alone and toward the dynamic and intricate tumor microenvironment to acquire a stronger insight into malignancies. The active crosstalk on TME and its heterogeneity make it challenging to reveal its characteristics, while details of the regulatory mechanisms remain unknown. A deep understanding of TME remodeling may provide potential biomarkers and treatment targets to enhance tumor therapy. Circular RNAs (circRNAs) are subpopulations of noncoding RNAs with unique characteristics and a wide range of biological properties involved in tumorigenesis and metastasis. Accumulating evidence has shown that circRNAs have abnormal expression and mediate signaling pathways. They play various roles in human malignancy events, such as angiogenesis, immune escape, and others. The role of circRNAs in the TME cannot be ignored, which may provide a novel path to elucidate the underlying regulatory mechanisms of TME remodeling. This review summarizes the history of TME and circRNAs and their roles and activities in the TME.

Introduction

Cancer is the most severe social and economic burden. It will overtake heart disease as the leading cause of death by 2060, with a complex mechanism that has been poorly elucidated so far.[1] Circular RNAs (circRNAs) are a distinct class of endogenous noncoding RNAs characterized by their covalently closed loop structure devoid of a 5′ cap or 3′ Poly A tail.[2] They have been implicated in various pathological and physiological processes and the occurrence and progression of malignancies. The tumor microenvironment (TME) is crucial for tumor initiation, development, metastasis, and chemotherapy resistance because it provides the "soil" for tumor cells to thrive. A multimodal communication network forms between cancer cells and the TME. This crosstalk continuously remodels the TME and promotes tumor growth via various previously identified behaviors, including angiogenesis, immune escape, and extracellular matrix remodeling (ECM). Remarkably, because of their distinctive architecture and broad effects, circRNAs are extensively involved in these events to impact tumor status profoundly.

The TME refers to the space where tumor cells can survive. The tumor cells are in touch with their adjacent cells or acellular components, making the 'space' an ecosystem. The TME encompasses immune cells, vascular endothelial cells, CAFs, and others. The "seed and soil theory" proposed by Stephen Paget described the association between cancer cells and TME for the first time.[3] Due to the general rapid growth of tumor tissue and the imperfect vascular inside, insufficient oxygen supply in the tumor tissue occurs, and the TME exhibits general hypoxia-like characteristics.[4] As the result of cell death, debris and chemokines are released, allowing inflammatory cells to infiltrate and secrete inflammatory chemicals, resulting in immunosuppression.[5] Additionally, stromal cells in the TME promote malignancy at the same time. Cancer-associated fibroblasts release growth factors and inflammatory ligands to stimulate cancer cell proliferation and angiogenesis,[6] whereas vascular endothelial cells predominantly mediate angiogenesis by secreting high levels of proangiogenic factors,[7] all of which contribute to tumor formation and metastasis. TME is essential for tumor genesis, development, invasion, metastasis, and

Keywords: Tumor microenvironment; CircRNA; CeRNA; Angiogenesis.

Abbreviations: CAF, cancer-associated fibroblasts; CeRNA, competing endogenouse RNA; circRNAs, circular RNA; COL1A1, Collagen Type I Alpha 1 Chain; CTLA-4, cytotoxic T lymphocyte-associated protein 4; ECM, extracellular matrix remodeling; MMP13, matrix metalloproteinase 13; PD-1, programmed Cell Death Protein 1; RBP, RNA binding protein; TME, tumor microenvironment.

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therapeutic response.

CircRNA was initially observed in RNA viruses in 1976[8] and was thought to be the result of erroneously alternative splicing and ignored by researchers for almost half of a century.[9] Research on circRNAs has been gradually emerging since T.B. Hansen *et al*. discovered that they act as microRNA sponges in 2013.[10] In recent years, high-throughput technologies[11] and biometrics toolbox[12] have been utilized to explore the molecular characteristics and biofunctions of circRNAs. According to current research progress, the circRNA is mainly generated by a back-splicing event that joins the 3′ end of an exon to an upstream 5′ end to construct a circular molecular structure.[13] Via sponging miRNAs or interacting with RNA-binding proteins (RBPs), circRNAs can regulate transcription. For instance, the circRNA MBL/MBNL1 has conserved binding sites that allow them to interact with muscleblind (MBL) proteins.[14] Besides, circRNAs have been proven to be translated into the ribosome and encoded as polypeptides,[15] apparently being inconsistent with the labels of noncoding RNAs. When circRNAs react with proteins, they can also serve as their molecular scaffolds. In addition, circRNAs are significantly more stable owing to their resistance to ribonuclease (RNase) and exhibit a greater abundance than corresponding linear mRNAs.[16] Numerous studies have shown that circRNAs involve various biological functions, including tumorigenesis and metastasis.[17] This review aims to summarize the novel progression of circRNAs, notably the events implicated in TME.

CircRNAs are involved in the regulation of tumor microenvironment

The above is just the tip of the iceberg. Hanahan and Robert A summarized the hallmarks of tumors, including sustained angiogenesis, avoiding immune destruction, deregulating cellular energetics, and others.[18] These incidents serve as breakthrough points for elucidating the mechanisms of oncogenesis and uncovering anti-tumor strategies. For instance, sorafenib, approved in 2005,[19] is a targeted therapy drug that inhibits various kinases. Via suppressing tumor cell proliferation and specifically inhibiting vascular targets CRAF, VEGFR-2, *etc*., it is still the only systemic drug approved for treating hepatocellular carcinoma.[20] Moreover, since the FDA approved anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) in 2011 for advanced melanoma,[21] as well as the previously popularly adopted PD-1 inhibitors and (PD-L1), tumor immunotherapy has been revolutionized by improving T cell killing capability and avoiding immune escape.[22]

CircRNAs and the activation of fibroblast

Cancer-associated fibroblasts (CAFs) are fibroblasts that have been activated by cancer cells and exhibit the characteristics of myofibroblasts. The malignant alteration of CAFs phenotype is closely associated with tumor growth, and CAFs are the most crucial tissue components of TME.[23] A study on HCC has suggested that CXCL11 released by CAFs in HCC tissues is significantly elevated, especially in metastatic tissues, and has a cancer-promoting function. Furthermore, CXCL11 has been shown to upregulate CircUBAP2, sponging miR-4756 to increase the expression of IL-17 and IL-1, which can contribute to tumor metastasis.[24] Yanxia Zhan *et al*. utilized circRNA array analysis to identify that circHIF1A was selectively upregulated in hypoxic breast cancer exosomes specifically.[25] Additionally, circHIF1A counteracting miR-580-5p-mediated inhibition on CD44 via sponging miR-580-5p was found to be the mechanism via which CAFs modulated the stemness of cancer cells. The discovery may establish circHIF1A as a therapeutic target in breast cancer treatment. Kaihua Yang *et al*. revealed that circEIF3K/miR-214/PD-L1 signaling axis was involved in the progression of colorectal cancer.[26] Similarly, circEIF3K was confirmed to be produced by CFAs and delivered to tumor cells via exosomes, indicating a novel immunotherapy strategy. Through the LIF/STAT3 axis, circFARP1 promotes CAFs to induce gemcitabine resistance in pancreatic cancer.[27] Chen *et al*. discovered that CAFs-derived circSLC7A6 modulates CXCR5, thereby promoting colon cancer cell proliferation and invasion.[28] In addition, matrine was proved to inhibit the production of circSLC7A6 from CAFs, hence inhibiting tumorigenesis, paving a new path for targeted therapy against CAFs in the TME.

CircRNAs and immune escape

Tumor immune escape describes a phenomenon in which tumor progression occurs while avoiding identification and action by the immune system. In recent years, programmed Cell Death Protein 1 (PD-1) has been found to be critical for suppressing tumor immunity and increasing self-tolerance through its modulation of T-cell activity.[29] Meanwhile, Immune checkpoint inhibitors directed against PD-1 or PD-L1 have demonstrated a considerable improvement in the prognosis of patients with a range of malignancies.[30] Latest studies have noted that circRNAs are involved in this event. Cao Gao *et al*. revealed that circ-VIM binds with miR-124 competitively to promote PD-L1 expression in esophageal cancer.[31] Besides, silencing circ-VIM inhibited immune escape, providing a new strategy to suppress tumor progression. Yan-Jie Xu *et al*. discovered the hsa_circ_0136666/miR-497/PD-L1 axis in Treg-mediated immune escape in colorectal cancer.[32] Similarly, in recent research, circ 0001598 sponged miR-1184 to regulate PD-L1 expression in breast cancer, which results in CD8 T cell killing and trastuzumab resistance, exhibiting HER2-positive BC patients as a potential therapeutic target.[33] However, the mode of immunological escape mediated by circRNAs is not confined to the ceRNA mechanism.

Additionally, CTLA-4, a well-known critical immune checkpoint,[34] has been proven to be regulated by circRNAs. In Zikun Huang *et al*. research, circRNA 0003528 might function as a competing endogenous RNA to regulate the expression of CTLA-4, resulting in macrophage polarization.[35] Through analysis of several GEO databases, Rongjie Zhao *et al*. revealed that the circUBAP2-mediated ceRNA network might regulate PAAD by altering the expression of CTLA-4 and PD-1.[36] On the other hand, experiments are required to verify the initial conclusion. Taken together, circRNAs are predicted to become therapeutic targets for interfering with tumor immunity in the TME as research progresses.

CircRNAs and ECM remodeling

The extracellular matrix provides a scaffold for tumor cells to form the acellular part of the TME. It is widely accepted that ECM remodeling is a prerequisite for solid tumor metastasis.[37] In the study of the regulatory mechanism in breast cancer development, Yikun Qu *et al*. focused on the regulation of circRNAs on the extracellular matrix and observed the co-upregulated expression of circRNA-CER and matrix metalloproteinase 13 (MMP13) in breast cancer tissues.[38] MMPs are zinc-dependent endopeptidases involved in extracellular matrix remodeling. Silencing circRNACER via

siRNA inhibited the migration of MCF7 breast cancer cells. Furthermore, the miR-136/MMP13 axis was confirmed in ECM remodeling as a cancer driver. In another research, the dysregulation of hsa_circ_0000096 was linked to gastric cancer progression. The authors confirmed that hsa_circ_0000096 might lead to the overexpression of MMP-2 and MMP-9 *in vitro* and *in vivo*. However, the enhanced expression of E-cadherin after hsa_circ_0000096 knockdown demonstrates that ECM remodeling is complicated.[39] Similarly, Li *et al*. discovered that circ-ERBB2/miR-637/MMP-19 is involved in ECM remodification in gastric cancer, accelerating tumor development.[40] Therefore, the interaction between circRNAs and the ECM demands further exploration to identify the TME remodeling procession.

It is now well established that collagen is the primary structural protein in the EMC.[41] Jinghui Yang *et al*. demonstrated that hsa_circRNA_0007334 sponged to both hsa-miR-144-3p and hsa-miR-577 to evaluate MMP7 and Collagen Type I Alpha 1 Chain (COL1A1) expression, resulting in pancreatic ductal adenocarcinoma advancement.[42] Similarly, the hsa_circRNA_002178/miR-328-3p/COL1A1 axis was implicated in the development of breast cancer. Besides, hsa_circRNA_002178 silencing inhibits tumor development *in vivo*, providing us with a potential target valuable target.[43] Recently, Xiaobo Chen *et al.* confirmed that circ_0004370 works as a molecular sponge, interacting with miR-1301-3p to regulate COL1A1 expression. Silencing circ 0004370 inhibits the EMT process in esophageal cancer.[44] Therefore, the interaction between circRNAs and the ECM makes it a more suitable environment for tumor progression.

CircRNAs and angiogenesis

Angiogenesis, a biological process that is strictly controlled, is critical in tumor progression because blood vessels are nearly the only way energy enters the tumor microenvironment.[44] We recently discovered that circ-CCAC1 was differently expressed in cholangiocarcinoma bile exosomes and investigated its involvement in the tumor microenvironment. Circ-CCAC1 was delivered to endothelial cells through exosomes, weakening the endothelial barrier as evaluated by rhodamine leakage assays and promoting angiogenesis as indicated by tubes and vascular sprout formation compared to the control group.[45] In research by Guo Y *et al*., circ3823 was shown to increase the expression of MYC and CCND1 via the miR-30c-5p/TCF7 pathway, which stimulated colorectal cancer angiogenesis. Additionally, the expression of circ3823 in serum has high sensitivity and specificity (AUC was 0.8074) for the detection of CRC, according to receiver operating characteristic curves, indicating the possibility of circ3823 being a diagnosis biomarker.[46] Similarly, a recent study found that the Circ 0030998/miR-567/VEGFA axis is involved in the proliferation of colorectal cancer cells and angiogenesis. The authors utilized rescue assays to demonstrate that Circ 0030998 has these effects via VEGFA.[47] Yang Jiang *et al*. discovered that the U2AF2/circRNA ARF1/miR-342-3p/ISL2 feedback loop is essential to promote glioma angiogenesis through RNA pull-down and dual-luciferase reporter.[48]

In addition to the above-mentioned angiogenesis functions, circRNAs play a crucial antiangiogenic role. For instance, Yawei Li utilized RNA-seq to identify and name it bladder cancer-related circular RNA-2 (BCRC-2), which is down-regulated considerably in bladder cancer tissues and cell lines.[49] Mechanistically, circHIPK3 includes two key miR-558 binding sites and may effectively decrease heparanase production to suppress angiogenesis, inhibiting its therapeutic potential. This indicates that much remains unknown about the role of circRNAs in angiogenesis.

CircRNAs and hypoxia

Hypoxia is a common microenvironmental feature of solid tumors due to uncontrolled proliferation.[50] Numerous recent studies have established a link between circRNAs and tumor microenvironment hypoxia. Rui Yang *et al*. revealed that circWSB1 was elevated in hypoxic circumstances by HIF1α and could compete with deubiquitinase USP10 in breast cancer cells, which is essential for maintaining the stability of P53, resulting in p53 degradation and tumorigenesis.[51] However, Jun Liu *et al*. confirmed the high expression of circ 0004543 in cervical cancer tissues and cell lines and its upstream regulation mechanism of HIF1α, *i.e.*, circ 0004543 binds to hsa-miR-217 to increase the expression of HIF-1a, triggering tumorgenesis, providing us with a novel possible therapeutic target.[52] Xiwu Ouyang *et al*. focused on the phenomenon of androgen receptor (AR) restraining HCC progression in hypoxia and demonstrated that AR/circ-LNPEP/miR-532-3p/RAB9A axis is involved; the following rescue assay also demonstrated the function and the core role in the regulation.[53] Metabolic reprogramming is a hallmark of malignancy with the deepening understanding of tumor biology and the complexity of tumor metabolism.[54] In TME, hypoxia of tumor cells also results in metabolic reprogramming, leading to angiogenesis and metastasis.[55] The role of circRNAs in this process has also been gradually revealed. Yiming Jiang *et al*. investigated the regulation of HIF-1α by circRBM33 in breast cancer and evaluated glycolysis by glucose consumption and lactic acid production.[56] The authors also discovered that silencing circRBM33 inhibits the production of HIF-1α, targeted by miR-542-3p, which results in glycolysis inhibition and tumor cell death. CircRNAs are found in exosomes and act as critical regulators. Recent years have seen an increase in relevant reports, but hypoxia is rare. Li Xu *et al*. discovered that exosomes released by hypoxic lung adenocarcinoma cells could induce malignant phenotypes in normoxic ones.[57] Following that, exosomes were isolated from hypoxic and normal cells and analyzed using microarrays; circSETDB1 was initially identified and named. Additionally, they established that circSETDB1 interacts with miR-7, as a competing endogenous RNA, to regulate the expression of specificity protein1, thereby promoting tumor invasion and metastasis.

Clinical application of circRNAs

The diverse functions and characteristics of circRNAs in TME provide us with novel methods to monitor the presence of cancers or their progression. For instance, circRNA_0000392 was found to be abundant in colorectal cancer tissues, associated with the distant metastasis and lymph node metastasis of CRC positively,[58] and may serve as a biomarker. Stella M *et al*. considered that serum exosomes make circRNA an ideal marker for improving stability and enrichment.[59] They discovered that the expression of circSMARCA5 and circHIPK3 were increased in exosomes isolated from glioblastoma multiforme patients' serum. Both circRNAs can differentiate between GBM and a healthy group. A diagnostic model which involves the two circRNAs and some known GBM markers, including NLR, PLR, and LMR, was established to achieve a more precise prediction (AUC 0.901 (0.7912 to 1.000), 95% CI). In addition to the function of biomarkers, circRNAs are also performing as potential therapeutic targets due to their diverse roles in TME.

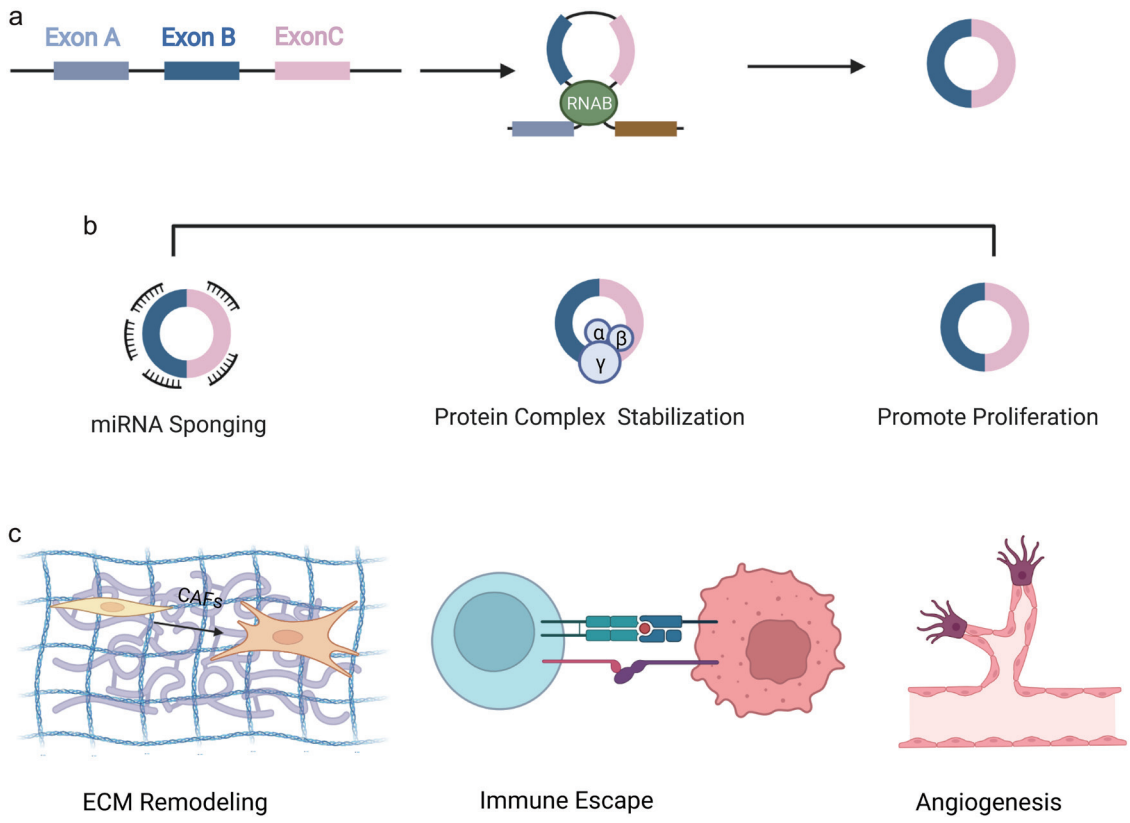

Fig. 1. Overview of circRNA in tumor microenvironment. (a) The primary Biogenesis model of circRNAs is alternative splicing; (b) CircRNAs perform biological functions via MicroRNA sponging, protein complex stabilization, and promoting proliferation; (c) In TME, circRNAs are involved in many core processes, including ECM remodeling, CAFs formation, immune escape, and angiogenesis. CAF, cancer-associated fibroblasts; ECM, extracellular matrix remodeling; Exon, expressed region; TME, tumor microenvironment.

For example, Ke Hu *et al*. confirmed that CircUBE2D2 capsuled by exosomes enhances the level of ER alpha by binding to miR-200a-3p to increase tamoxifen resistance, offering novel insights on the enhancement of tamoxifen's performance in breast cancer patients.[60] This shows that the application of the exosome makes it a more effective therapy method.

Future direction

Complex interactions in the TME provide more realistic cancer incidences and allow for more in-depth research into cancer progression mechanisms. The stable characteristics and regulator roles of circRNAs become active molecules in the TME, as we know from considerable progress. Future research may make significant advances in the following directions: a. The analysis of circRNAs in TME is still in its early stages. Exosomes have increasingly gained interest because they are carriers in the tumor microenvironment. CircRNAs are encapsulated in exosomes, which provide them more stability and specificity, taking this as an opportunity to make breakthrough progress; b. The tumor microenvironment is heterogeneous, and the function of circRNAs in specific conditions, such as acidic environments or changes in interstitial pressure, has yet to be determined. These works will give a more accurate and comprehensive view of tumor progression. c. There have been numerous advances in tumor immunotherapy. The expression level or functions of several essential receptor molecules regulated by circRNAs may disclose their fundamental roles in tumor immunity. With the accumulation of basic research, circRNAs are continuously transformed into clinical applications to improve the treatment of cancers. How to improve the safety of a treatment or precise drug delivery determines the application prospects of these star circRNAs.

Summary and outlook

CircRNAs, a novel family of noncoding RNAs, perform critical roles in the TME (Fig. 1). In this review, we summarized recent advances in the regulatory functions of circRNAs in many events, including angiogenesis, ECM remodeling, and immune escape. However, the physiological and pathological activities of circRNAs in the TME remain largely unclear. In general, circRNAs work primarily via the ceRNA mechanism; nevertheless, most circRNAs cannot do so because they lack miRNA binding sites. Therefore, research on circRNAs translation or interaction with RNA-binding proteins is expected. As summarized in our study, exosomes, as stable carriers of cellular communication in TME, may amplify the structural and functional benefits of circRNAs and deserve concern. Last but not least, more clinical trials are to be conducted to ensure the safety of circRNAs research results to clinical translation. We are convinced that the roles of circRNAs in critical events in the TME will be gradually uncovered to serve as tumor markers or therapeutic targets.

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Conflict of interest

YX has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since March 2022. The authors have no other conflict of interest related to this publication.

Author contributions

Contributed to study concept and design (YX), drafting of the manuscript (LY), critical revision of the manuscript (YX), and supervision (YX).

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