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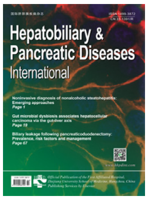

Review Article

Clinical value of circular RNAs and autophagy-related miRNAs in the diagnosis and treatment of pancreatic cancer

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ABSTRACT

Background: Circular RNAs (circRNAs) are a special group of long-chain and non-coding RNAs characterized by a closed-loop structure without 3′ and 5′ polarity. In recent years, studies have demonstrated that circRNAs act as microRNA (miRNA) sponges to regulate the function of miRNAs. Increasing evidence indicates that circRNAs and targeted miRNAs are involved in the development, progression and metastasis of various cancers and drug resistance. A number of miRNAs are known to be associated with the pathogenesis, development and treatment of pancreatic cancer by regulating the autophagic activity.
Data sources: A comprehensive literature search was executed in PubMed and EMBASE using the medical subject headings (MeSH) terms “Pancreatic Neoplasms”, “autophagy”, “RNA, circular” and “microRNA”. We also used text terms such as “diagnosis”, “prognosis” and “biomarker” to supplement the results.
Results: Autophagy-related miRNAs is closely related to pancreatic cancer. On basis of the retrieval results, we summarized the synthesis, features and functions of circRNAs and analyzed the association between autophagy-related miRNAs and pancreatic cancer.
Conclusions: circRNAs act as the miRNA sponges and there is an association between miRNAs and autophagy, which provides a new concept to broaden the knowledge about the mechanisms underlying the development, progression and metastasis of pancreatic cancer. Additionally, clinical value of circRNAs and autophagy-related miRNAs in the diagnosis and treatment of pancreatic cancer would be further verified with in-depth researches.

Introduction

Circular RNAs (circRNAs) are a special group of endogenous non-coding RNAs initially found in a virus in the 1970s [1]. With the progress of RNA sequencing technology and bioinformatics, recent studies have shown that most circRNAs in mammalian cells are a group of abundant, stable and conservative endogenous molecules [2,3]. circRNAs act as microRNA (miRNA) sponges or competitive endogenous RNAs [4,5]. circRNA–miRNA plays an important role in various tumor-related signaling pathways [6,7]. Autophagy is a self-protective mechanism for normal cells to maintain the stability of the internal environment. miRNAs exert an important regulatory effect on the activation and degree of autophagy, but diverse mechanisms of autophagy on cells in different tumor environments are important factors affecting tumor cell proliferation, migration and chemotherapy resistance. Autophagy has been demonstrated to be associated with the development, progression and metabolism of pancreatic cancer (PC) [7,8]. A variety of autophagy-related miRNAs have been proven to possess the potential of serving as biomarkers for the diagnosis, treatment or prognostic prediction of PC.

Autophagy-related miRNAs and pathogenesis of PC

The role of autophagy in tumor formation and progression is complex and linked to the cellular microenvironment and tumor types. Its effects on tumors vary greatly at different stages including tumor cell formation, epithelial-mesenchymal transition (EMT), angiogenesis and metastasis [9]. High levels of autophagy flux are associated with poor prognosis in human pancreatic tumors. A clinical trial used preoperative combined hydroxychloroquine (the only autophagy inhibitor in clinical experiments) with gemcitabine for the treatment of PC found that overall survival of patients in the combined treatment groups is better than that of patients in the monotherapy group [10]. miRNAs are endogenous non-coding small RNAs that regulate gene expression by inhibiting

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transcription or degradation of target mRNAs through pairing with complementary sites in the 3′UTR of the target mRNA [11]. A single miRNA can affect the function of signaling pathways or even biological events by controlling dozens of genes and change the threshold of reaction. In recent years, miRNAs have attracted increasing attention, knowing that they can affect the content of several key proteins in multiple steps of autophagy pathways by acting as a regulator of autophagy [12].

Ample evidence from unremittent hotspot research on miRNAs has shown that abnormalities of autophagy-related miRNAs are associated with the occurrence, diagnosis and treatment of PC.

Abnormalities of autophagy-related miRNAs in PC

miR-375 can inhibit autophagy by reducing the expression of ATG7 and regulating AKT/mTOR signaling pathway [13]. It was found that miR-375 level is significantly increased in pancreas cells of PC mice as compared with that in heart, brain and liver cells [14]. According to the report by Lee et al. [15], there are 100 aberrant miRNA expressions in PC or desmoplasia, including autophagy-related miRNAs (miR-155, miR-21, miR-221 and miR-222) as observed in other human tumors. Analysis of 10 cell lines of PC and 17 pairs of PC with normal tissues using QuantiMir system showed that 95 miRNAs are differentially expressed, including autophagy-related miR-200b and miR-15b, both of which are upregulated in most PC tissues and cell lines. The expression level of these miRNAs in tissue specimens is ranging from 3 to 2018 fold high as that in normal tissues [16]. Gu et al. [17] demonstrated that miR-7 weakens autophagy by upregulating LKB1-AMPK-mTOR. Additionally, it reduces intracellular glycolysis by directly interfering with autophagy induction and vesicular elongation, thereby inhibiting PC cell metabolism and proliferation.

Although the above studies obtained the similar result that the expression of various autophagy-related miRNAs is aberrant in PC tissues and cells, whether abnormal increase in autophagy-related miRNAs plays a promoting role in the pathogenesis of PC remains to be further verified.

Autophagy-related miRNAs as potential biomarkers in the early screening and diagnosis of PC

Some miRNAs known to participate in autophagy regulation are considered potential tumor markers. A number of miRNAs provide references for tumor diagnosis [18,19]. miR-216a increases the activity of autophagy by exerting a negative regulatory effect on Beclin-1 [20]. The content of miR-216a in the feces of PC patients is significantly lower than that in the normal control group [21]. If this finding is confirmed independently in larger cohorts, miR-216a may prove to be a new marker for early screening of PC. In addition, Chen et al. observed that miR-23b-3p overexpression enhances the proliferation, migration and invasion of PC cells *in vitro*. The serum level of miR-23b-3p in exosomes of PC patients is related to CA19-9, indicating that miR-23b-3p has the potential to be a diagnostic marker of PC [22]. miR-205 is significantly upregulated in the tissue and serum of PC patients. It was discovered that the diagnostic accuracy of combined detection of serum miR-205 and CA19-9 is higher than that of CA19-9 alone, suggesting that miR-205 may be a potential diagnostic marker of PC [23].

The function of autophagy-related miRNAs may affect the malignant behavior of PC cells, though the specific mechanism remains unclear. Cellular and molecular analyses are required to confirm the diagnostic value of autophagy-related miRNAs.

Impact of autophagy-related miRNAs to the treatment and prognostic prediction of PC

The mechanism of radiation therapy for cancer cells includes the formation of free radicals that damage DNA and other cellular components, which also trigger autophagy reactions.

Some studies [24,25] have demonstrated that autophagy-related miRNAs regulate the response of tumor cells to radiation. In a study addressing the effect of radiotherapy on PC, Wang et al. [26] found that lowering the expression of miR-23b increases the expression of ATG12 and the activity of autophagy, and enhances the resistance of PC cells to radiation, while miR-216a inhibites autophagy and boostes the radiation sensitivity of PC cells [27]. AMPK-mTORC1 is the center of autophagy regulation integrating various stimulation factors and pathways into a signal of ULK complex, the initial point of autophagy. miR-148b targeting AMPKα1 was reported to inhibit the proliferation of PC cells, weaken their invasion and increase their sensitivity to chemotherapy [28]. Transfection of miR-30a, miR-30b and miR-30c into CD133+ PC cells make these cells to resist gemcitabine and ascend the capability of migration and invasion [29]. Phosphatase and tensin homolog (PTEN), a tumor suppressor, attenuates the PI3K/AKT/mTOR signaling pathway and slow down tumor growth. The axis of miR-21/PTEN/PDCD4 affected the resistance of PC cells to 5-fluorouracil [30]. In addition, clinical studies have shown that PC patients with high miR-21 expression had poor prognosis [25,31]. Serum miR-155 is decreased in PC patients, which is associated with poor prognosis [21].

In a nutshell, abnormal serum concentrations of various autophagy-related miRNAs in PC patients are correlated with the therapeutic effect. As the serum miRNA content varies in patients with different outcomes, miRNAs may also have a certain value in the evaluation of treatment and prognosis of PC.

Biomolecular features of circRNAs

Structures and types of circRNAs

Unlike linear RNAs, circRNAs have a closed ring structure connected by a covalent bond with neither 5′–3′ polarity nor a polyadenylated tail [32]. Based on genetic sources and sequence components, circRNAs can be divided into three types.

Exon circRNAs

This type of circRNAs is the most abundant. Exon circRNAs are generated by caudal insertion. At present, there are two major models: lariat-driven circularization and intron-pairing driven circularization [2]. The former holds the view that covalent splicing of some transcripts shortens the distance of non-adjacent exons causing skipping of the exons to form intermediate products, the introns of which are subsequently removed by intra-lariat to produce exon circRNAs. The intron-paired circularization model proposes that the exons involved in circularization are connected by complementary sequences containing introns to form circRNAs [33]. Ashwal-Fluss et al. [34] further studied and validated the intron-paired circularization model.

Intronic circRNAs

About 20% of human genetic information is introns. Most of these introns are degraded after being cut to form lassos, and some of them containing key nucleotide sequences form circRNAs. The biosynthesis of these circRNAs depends on the conserved sequences at both ends of the intron, namely, 7-nt GU-rich motif at the 5′ end and 11-nt C-rich motif at the 3′ end. These motives protect introns against debranching or degradation to keep the ring structure stable [35]. This connection mode is different from that of exon circRNAs, in that intronic circRNAs are connected by 2′–5′ phospholipid bond, while exon circRNAs are connected by 3′–5′ phospholipid bond.

Exon-intronic circRNAs

In the process of caudal splicing of exonic circRNAs, some circRNAs containing unspliced introns exist stably in the nucleus [36], which are known as exon-intronic circRNAs.

Functions of circRNAs

Acting as a ceRNA or miRNA sponge

Increasing evidence suggests that circRNAs act as a miRNA sponge or ceRNA [3,5,6]. Hansen et al. [37] found that cerebellar degeneration-related protein 1 antisense RNA (CDR1as), also known as circular RNA sponge for miR-7 has more than 70 miR-7 binding sites interacting with miRNA, thus significantly enriching miR-7 in nerve tissues and inhibiting the function of miR-7. Both circ-foxo3 and circHIPK3 have been proved to have multiple miRNA binding sites and take certain effect in physiological processes [38]. Emerging bioinformatic analyses show that thousands of circRNAs have the ability to attract miRNAs [39], though most of them need to be further confirmed by more experiments. With the efforts of researchers, studies on miRNA sponge of circRNA in the field of cancer have made progress. The roles of some circRNAs have been identified. For example, circTRIM33-12 in liver cancer [40], circPTPRA innon-small-cell lung cancer [41] and circ-SERPINE2 in gastric cancer [42].

Acting as an RNA binding protein sponge

RNA binding protein is known to participate in RNA alternative splicing, transportation and transcription in a post-transcriptional regulatory manner, thus affecting cell proliferation, oxidative stress response, senescence, apoptosis and other processes [43]. circRNAs affect the effects of RNAs by binding to a variety of RNA binding proteins stably to form RNA-protein complexes to regulate the concentration of free RNA binding proteins.

Regulating gene transcription

In the biogenesis of exonic circRNAs, the advantage of 3′and 5′ splicing sites of back splicing has a competitive relationship with the splicing of precursor mRNA [34]. The alternative splicing mechanism is the key to caudal splicing and linear splicing [2]. Knowing that synthesis of circRNAs occurs in the whole biological process, the impact of circRNAs on linear splicing is noteworthy and its critical regulatory mechanism deserves attention. Studies on EIciEIF3J and EIciPAIP2 [44] have demonstrated that they colocated with their parental gene. U1snRNP (picorbonuclear protein) binds to U1snRNA and acts as a cis-acting factor to promote the interaction between RNA pol II and the promoter. It is interesting that circRNAs not only are abundant in transcription sites but cluster in some other regions of the nucleus, suggesting that they may play a trans-regulatory role in transcription [35].

Protein translation

Like linear mRNAs, circRNAs can also be translated into proteins. circRNAs with internal ribosomal entry sites and initiating codon ATG, which were initially found in 1995, act as a translation template just like mRNAs [19]. In recent years, more studies have found that circRNAs act as templates of protein synthesis, such as circMbl [45], circ-ZNF609 [46], circ-FBXW7 [47], and circ-SHPRH [48]. In addition, circRNAs regulate protein expression by blocking the transcription initiation sites [49]. These functions of circRNAs in protein translation may be involved in tumor development and progression [33]. Nevertheless, the specific roles of circRNAs are worthy of further study.

circRNAs and pathogeneses of PC

Clinical studies have demonstrated that the concentrations of certain circRNAs in tumor tissues are significantly different from those in normal tissues. circRNAs are related to the clinical characteristics of tumors such as tumorigenesis, metastasis and staging, thus providing a new point for the study of tumor pathological mechanisms. A ci-SIRT7 knockout experiment [50] showed that the expression of SIRT7 mRNA is reduced, demonstrating that ci-SIRT7 regulates the expression of parental genes as cis-acting factors. This experiment also revealed that SIRT7 (one of the histone deacetylase III) in PC inhibits tumor cell proliferation and is positively correlated with prognosis. There are abundant circRNAs in exosomes [51], suggesting that serum circRNAs may serve as a new biomarker for tumor diagnosis in the future. Compared with traditional linear miRNA sponges with only a single miRNA bounding site, circRNAs containing multiple miRNA bounding sites present with a highly efficient anti-cancer effect in mammal melanoma cell lines [52]. The clinical study by Li et al. [53] found that the expression of circRNA-IARS in PC tissues is obviously higher than that in adjacent tissues; the postoperative survival time of patients with high expression of circRNA-IARS is significantly shorter than that in patients with low expression; and the level of circRNA-IARS is associated with lymphatic invasion, liver metastasis and TNM stage of tumors. Recently, investigators found that circ-PDE8A had similar clinical significance [54]. The sponge functions of circRHOT1 on several miRNAs, and circ_0007534 on miR-625 and miR-892b are found to be associated with the progression and prognosis of PC [55,56]. Combinations of multiple circRNAs and miR-15a through the complementary sequence affected the proliferation and EMT of PC cells. circRNA interaction with miR-506 had impact on the progression of PC and chemotherapy resistance [57]. In the study of gemcitabine resistance, it was demonstrated that silencing circRNAs eliminates the resistance of PACN-1 cells to gemcitabine [52], suggesting that circRNAs may be an important factor to improve the chemosensetivity of PC.

Interaction between circRNAs and autophagy-related miRNAs has become a new concept for the diagnosis and treatment of PC

Knowing that miRNA sponge is one of the main functions of circRNAs, the relationship between circRNAs and autophagy-related miRNAs has aroused increasing attention. In recent years, the development of bioinformatics has provided favorable conditions for the research on their relationship.

Some target miRNAs of circRNAs have been confirmed, and the details are shown in Table 1. Starbase database showed that hsa-circ-002008 is correlated with miR-200 [61]. Using GO analysis, Shang et al. [62] found that hsa-circ-0001358 is closely related to the adhesion of hepatocellular carcinoma cells and the hsa-circ-0001358 level is positively correlated with the tumor volume of hepatocellular carcinoma, suggesting that it may play a role in regulating tumor metastasis and proliferation. Sequence analysis by Arraystar revealed that hsa_circ_0005075 had miR-23b binding sites. Experiments *in vivo* and *in vitro* have proved that hsa_circ_101280 promotes hepatocellular carcinoma proliferation and blocks apoptosis by acting as a miR-375 sponge [63].

The analysis of biological information [64] showed that DUSP1 and MRPS35_hsa_circ_001042 interacted with miR-148b in the MAPK signaling pathway. The expression of circ_0026344 in colorectal cancer tissue is decreased, and patients with low circ_0026344 expression had poor prognosis. After that, circ_0026344 has been verified to play a sponge function of miR-21 in colorectal cancer [65]. Recently, a down-regulated expression

Table 1
circRNAs and corresponding autophagy-related miRNAs.

circRNA	Target miRNA	Autophagy	Related molecules or pathways	Effects on pancreatic cancer	References
hsa_circ_101280	miR-375	Inhibition	ATG7/AKT/mTOR	Potential diagnostic marker	[13,14,63]
CDR1as/ciRS-7	miR-7	Inhibition	LKB1-AMPK-mTOR	Inhibit glycolysis, cell proliferation	[17,37]
hsa_circ_Foxo3	miR155	Inhibition	PI3K/AKT/mTOR	Poor prognosis	[21,37]
hsa_circ_0005075	miR-23b	Enhancement	ATG12	Promote progress, increase radiotherapy resistance, potential diagnostic markers	[22,25,62]
hsa_circ_001042	miR-148b	Inhibition	MAPK	Inhibit cell proliferation, weakens invasion	[28,64]
hsa_circ_0026344	miR-21	Inhibition	PTEN/PDCD4	Increased resistance to5-FU, poor prognosis	[30,31,65]
circ-PDE8A	miR-338	Inhibition	MACC1/MET/ERK or AKT/mTOR	Promotes metastasis, poor prognosis, potential diagnostic marker	[54]
hsa_circ_103076/100435	miR-15a	Induction	Rictor/mTOR1	Inhibit cell proliferation, EMT	[57,58]
hsa_circ_101717/10408	miR506	Inhibition	BECN1	Promote progress, enhance the resistance to chemotherapy	[57,59]
hsa_circ_0001358	miR-200b	Inhibition	ATG12	Potential diagnostic marker	[60,62][a]
hsa_circ_0071922	miR-663a-5p	Inhibition	PI3K/AKT/mTOR	Reduce proliferation and invasion	[66][a]
hsa_circ_0000156	miR-154-3p	Inhibition	Insulin signaling or p53 pathways	–	[66][a]

[a] Need to be confirmed by biological experiments. ATG7: autophagy-related gene 7; AKT: protein kinase B; mTOR: mammalian target of rapamycin; LKB1: liver kinase B1; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositol-3-kinase; ATG12: autophagy-related gene 12; PTEN: phosphate and tension homology deleted on chromosome; PDCD4: recombinant human progrmammed cell death 4; MACC1: metastasis associated in colon cancer 1; MET: mesenchymal to epithelial transition factor; ERK: extracellular regulatory protein kinase; Rictor: rapamycin-insensitive companion of mTOR.

of miR-663a-5p and miR-154-3p in PC is observed. After that, others studied the mechanism and found that these miRNAs are involved in autophagy through several signaling pathways. In addition, they detected circRNAs that had binding sites for these two miRNAs [66].

The relationship between circRNAs and autophagy-related miRNAs has gradually become clear in recent years, which provides a foundation for the study of the action mechanism underlying the effect of circRNAs on autophagy and the further effect on PC.

Summary and outlook

Autophagy is closely related to PC. Autophagy inhibits apoptosis and reduces ROS production which is beneficial for maintaining the balance of energy metabolism to affect the development of PC [7]. Anti-pancreatic cancer drugs significantly regulate autophagy, and the level of autophagy has an impact on the efficacy of chemotherapy drugs [67,68].

More properties and functions of circRNAs have been revealed, especially with respect to the function of miRNA sponge. circRNAs are involved in the development and progression of a variety of tumors, including PC. As previously mentioned, some circRNAs acting as RNA sponges interact with autophagy-related miRNAs in a variety of tumors, such as hepatocellular carcinoma, non-small-cell lung cancer and colorectal cancer. The relationship between circRNA, miRNA and autophagy has also been directly verified in the study of PC. Wei et al. [66] worked on studying potential ceRNA networks involved in autophagy of PC. In their research, various databases were applied to predict the ceRNAs of miR-663a-5p and miR-154-3p. Furthermore, they uncovered the putative autophagy pathways the circRNAs participated in PC through the bioinformatics analysis. More studies have confirmed the clinical value of circRNA in PC lately [58,69].

The role of miRNAs in autophagy is worthy of attention. Abnormal expression of autophagy-related miRNAs in PC may make them potential biomarkers for the diagnosis and treatment of PC. The use of circRNAs may provide a new method for early screening and treatment of PC. The key topic is studying the specific mechanism of circRNAs' miRNA sponge function on autophagy to verify and understand the correlation between circRNAs, corresponding miRNAs and the occurrence, treatment and prognosis of PC.

Contributors

BSR proposed the study. JPC searched databases and wrote the first draft. BSR revised the manuscript. Both authors contributed to the design and interpretation of the study and approved the final version to be published. BSR is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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