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Review Article

Competing endogenous RNA in cancer: a new pattern of gene expression regulation

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Abstract: The competing endogenous RNA (ceRNA) hypothesis was introduced. There is a new hypothesis about mRNA, pseudogene transcripts and long noncoding RNAs (lncRNAs) regulate each other's expression by using microRNA response elements (MREs) to compete for the binding of microMRA (miRNA). To date, numbers lines of evidence in bioinformatics, cell biology and animal models from several famous laboratories have supported the ceRNA hypothesis. We also trace the history of the concept of ceRNA and discuss the molecular mechanisms of ceRNAs in cancers and their possible applications. In this review, we try to give readers a concise and reliable illustration on the mechanism, research approaches, and perspective of ceRNA in cancer.

Keywords: CeRNA, cancer, gene expression

Introduction

miRNA is a collection of endogenous non coding RNAs comprised of about 22 nucleotides, and regulating protein expression through degeneration or inhibition translation when binding to mRNA [1]. Each miRNA targets hundreds of genes, so miRNAs act as crucial post transcription factors in the sophisticated DNA-RNA-Protein networks [2]. miRNA have its vital role identified in the field of cell development, differentiation, immune and metabolism in the organism. Based on substantial results about the function of miRNA, a hypothesis called competing endogenous RNA (ceRNA) has been brought up lately [3]. The core of the hypothesis is that mRNA, pseudogenes, long noncoding RNA (lncRNA), or other molecules, which share the same miRNA response element (MRE), combine the identical miRNA competitively, then affecting cell status [3]. This hypothesis show us a blueprint of post transcription formed with sorts of RNA, and offer a novel way to comprehend the mysterious cell function.

The ceRNA hypothesis

MiRNA and MRE are two key elements in this hypothesis. miRNA is not only capable of binding to MRE of mRNA , but also pseudogenes and lncRNA, therefore, influences the function of mRNA and lncRNA in the post transcription procedures [3]. Importantly, each miRNA has numerous RNA targets and the vast majority of RNA molecules harbors several MREs and are thus repressed by different miRNAs. This target multiplicity has led to the hypothesis that different RNAs (either pseudo-targets or legitimate targets) compete for limiting pools of miRNAs, thus acting as competitive endogenous RNAs (ceRNAs [3, 4]. Salmena [3] reported that, apart from the miRNA inhibit the function of mRNA, mRNA can also affect miRNA inversely, so the protein-coding RNA or noncoding RNA have their function by competing with miRNA, while the elemental of this mechanism is the identical MRE they share. The study of Poliseno [5] focused on PTEN and PTENP1 indicated that PTENP1 affects the expression of PTEN mRNA, because PTENP1 and PTEN share a highly homogenous sequence, that is, the identical MRE. For instance, in the case that less miRNAs are "saturated" when PTENP1 down expressed, more PTEN mRNAs are bonded with miRNA, meanwhile the post-transcription level of PTEN will be inhibited [5]. This added a solid evidence of ceRNA. ceRNA hypothesis provides

us a conception that crossing network of different transcription, but also suggests that protein-coding genes have the biology function need not be translated into protein, they are involved in post-transcription regulation at RNA level. Coding RNA and non-coding RNA form a large network ruling gene regulations [6].

The development of ceRNA

The conception of ceRNA can be traced to 2007, Ebert [7] invented miRNA inhibitor which named miRNA sponge with a string of single MRE, through competitive combination with specific miRNA and blocking its interaction with the nature target, thus inhibiting the function of endogenous miRNA. Seitz [4] put forward the pesudotarget hypothesis in 2009 which contented the natural or artificial pseudo-target just like miRNA sponge as competitive inhibitors of miRNA suppressing the miRNA combined with the true target. Arvey [8] put forward the dilution effect hypothesis in 2010. They found the numerous of the target mRNA of miRNA in which one or several target mRNA down-regulated will lead to increase the number of miRNA and silence more other target mRNA, showing abundance of all targets have been reduced. In 2010, the conception of natural miRNA sponge was bored [9]. According to the experiment evidence [5, 10, 11], they found the natural miRNA sponge was exist in cells which can bind to the specific miRNA, suppress their functions and regulate the expression of miRNA target genes at post-transcription levels. The natural miRNA sponge can only bind to a part of miRNA when they have lower expression, meanwhile a large number of remainder miRNA bind to target mRNA and inhibit the translate function [9]. Salmena [3] perfected the ceRNA hypothesis in 2011. CeRNA was endogenous with a great variety including mRNA, pseudo-genes, long non-coding RNA (lncRNA) which different from exogenous miRNA sponge. In a ceRNA chain maybe have different MRE and bind to different miRNA. The miRNA can silence various transcript and form large scale complicated regulation network.

Participants in ceRNA interplay

miRNAs

miRNAs play an important role in ceRNA network. Precursor miRNAs (pre-miRNAs) are exported from cell nucleus to cytoplasm and form mature miRNAs. Mature miRNAs are incorporated into the Argonaute-containing miRNA-induced silencing complexes (miRISC), which then binds to MREs on the 3'-UTRs of target RNAs, leading to degradation or translation suppression of the latter [12]. Then different miRNAs can function cooperatively if an RNA transcript harbors more than one MRE

This constitutes the basis of ceRNA interaction [3]. Depending on the homology degree between MREs on RNA 3'-UTRs and miRNAs seed sequence, miRNAscan either completely degrade the target mRNAs level or blocks to translation [13-15].

mRNA

mRNAs may act as a miRNA-dependent manner provided that they share MREs that permit ceRNA cross talk. Previously, we thought mRNAs were only to be targets of non-coding RNAs regulation, but now, through ceRNA, mRNA can also regulate other mRNAs, which constitutes the regulatory network of RNA species [16]. Using a different bioinformatics approach, Califano and colleagues identified multiple mRNAs with putative ceRNA activity toward PTEN and experimental validation confirmed their 3'UTR-dependent regulation of PTEN [17].

Pseudogenes

Because the vast majority of pseudogenes do not encode for functional proteins, pseudogenes were widely considered "junk" DNA [18], but the fact that there are about 11,000 pseudogenes across the human genome. Now, researchers have found that pseudogenes play major roles in post-transcript regulation. Pseudogene transcripts are considered to act as perfect miRNA sponges because they possess many of the same MREs as their cognate genes [19].

LncRNAs

Intriguingly, other RNA species such as lncRNAs have recently begun to emerge as natural miRNA decoys. Indeed, lncRNAs are extensively targeted by miRNAs [20, 21], suggesting that they may serve as ceRNAs. Although the past two decades have witnessed the discovery of

numerous lncRNAs, only a small portion of them have been identified functionally, and very few of them have been validated to function as ceRNAs in cancers [22-24].

Functions of ceRNA regulation in cancers

ceRNA in prostate cancer

Prostate cancer is the common malignant tumor in the western countries. Its pathogenesis is not clear always. Phosphatase and tension homolog (PTEN) is a major anti-oncogene, the protein production can suppress tumor growth by inhibiting phosphatidylinositol 3-kinase/serine-threonine protein kinase (PI3K/Akt) signing pathway [25]. Phosphatase and tension homolog pseudogene 1 (PTENP1) and PTEN share with same MRE. In 2010, Laura Poliseno [5] and his team published pseudogene transcript PTENP1 can increase cellular levels of PTEN by binding to miR-19, miR-21, miR-26, and miR-214 families and exert a growth suppressive role to suppress the proliferation of cancer cells. Inversely when down-regulated the expression level of PTENP1, the more miRNA will inhibit PTEN as a result to facilitate tumor growth. The authors also extended their research to other pseudogenes such as KRAS1P, pseudogene of the famous oncogene KRAS, and found that KRAS1P overexpression elevated KRAS mRNA level and accelerated cell growth. These findings are the whole point to indicate that pseudogene functions mirror those of their cognate genes through ceRNA interplay.

CeRNA in colorectal cancer

The ceRAN is not only between pseudogenes transcription and homologous gene transcription, but also between mRNA and mRNA. Tay [26] showed that vesicle-associated membrane protein A (VAPA) gene and CCR4-NOT transcription complex, sumnit 6-like (CNOT6L) gene were the ceRNA of PTEN mRNA. VAPA mRNA can competitive bind miR-17, miR-19a, miR-20a, miR-20b, miR-26b, miR-106a, miR-106b to regulate the level of PTEN, while CNOT6L mRNA can competitive bind miR-17, miR-19a, miR-19b, miR-20a, miR-20b, miR-106b to regulate the level of PTEN and influence PI3K/Akt pathway [26]. When the VAPA and CNOT6L mRNA both have overexpressed and boundd miRNA which shared with PTENed to lead PTEN protein improved and enhance the anti-tumor ability. On the other hand when VAPA and CNOT6L mRNA down-regulate to release abound of miRNA which target to PTEN, leading to decrease PTEN protein, and reduce the anti-tumor capacity [26].

CeRNA in melanoma

PTEN inactivation or imbibition is a common phenomenon in various tumors. So it is a classic representative to research ceRNA. Karreth [27] reported that zinc finger E-box binding homeobox 2 (ZEB2) gene transcript is ceRNA of PTEN mRNA, both of them share with the same binding site of miR-25, miR-92a, miR-181, miR-200b. PTEN protein will be elevated and inhibit melanoma growth when over-expression of ZEB2. In the opposite, when silencing ZEB2, the expression level of PTEN will be decreased and promote melanoma development.

CeRNA in glioblastoma

Sumazin [17] analyzed the malignancy glioblastoma gene expression data which come from the cancer genome atlas(TCGA). They regarded there were more than 248,000 miRNA mediate interrelation, including 7,000 gene transcript interaction by ceRNA. They found several signing pathway interaction by ceRNA, including PTEN, platelet-derived growth factor receptor, a polypeptide (PDGFRA), retinoblastoma 1 (RB1), vascular endothelial growth factor A (VEGF-A), signal transducer and activator of transcription 3, STAT3) and Runt-related transcription factor 1, RUNX1) [17]. It is indicated universality and extensive of ceRNA phenomenon.

CeRNA in liver cancer

Recent works had revealed that a kind of lncRNA called highly up-regulated in liver cancer (HULC) play important roles in many oncogenic processes including liver cancer. Wang [22] and his colleagues found that HULC, as natural miRNA sponge, inhibits miR-372, then sets free the restraint effect which miR-372 imposes on camp dependent protein kinase catalytic β (PRKACB), therefore, promotes protein kinase A (PKA) signal pathway. The study mentioned explicates that lncRNA can also work as ceRNA, apart from pseudogene transcript or mRNA, and it revealed the complicate relationship between uncoding RNAs.

Generally, miRNA works through binding the 3'-UTR of some specific mRNAs, besides 3'-UTR is found to be the center of ceRNA network. Study by Fang [28] et al concerning about the hyaluronic acid binding protein versican in the hepatocyte carcinoma oncogenesis, finding that the 3'-UTR of versican mRNA is capable of competitive combination of miR-133a, miR-144, miR-199a-3p and miR-431 and regulates expressions of these targets, thus supporting the development, metastasis and invasion of hepatocyte carcinoma cells, and inhibiting the apoptosis.

OCT-4 is a regulator of pluripotential embryo stem cells, while is expressed aberrantly in many sets of tumors. Wang [29] found that in HCC, OCT4-PG4, pseudo gene of OCT4, uncages the inhibition of miR-145 to OCT4 by combining miR-145 competitively, which may provide a substantial example that pseudo gene poses as a ceRNA, through a competitive relationship with homogenous transcript.

ceRNA in breast cancer

Breast cancer is women' first killer of tumor. Enormous time and efforts have been spent on the mechanism of breast cancer, while recently, some encouraging progresses in ceRNA in breast cancer have been made. Like Versican mRNA works as a ceRNA in liver cancer, it was also been proven as a competitive combination of miR-136, miR-144 and miR-199a-3p, controls the level of PTEN and RB1, and influences the developments of breast cancer cell [30]. Another example of ceRNA in breast cancer is that miR-216a, miR-330 and miR-608, whose targets are the mRNA of CDC42, can combine the 3'-UTR of CD44 mRNA competitively, while over-expression of 3'-UTR of CD44 mRNA can relieve the clamp-down of CD44 itself and CDC42 by these miRNA, in consequences, breast cells are inhibited by CD44 and CDC42. These effects can be observed and proved in the mice experiments [31].

Perspectives and future direction

MiRNA sponge can inhibit specific miRNA activity [7]. Relative to miRNA sponge, the advantage of ceRNA can inhibit the activity of miRNA by changing the amount and types of MRE. So Tang [32] development a artificial ceRNA named short tandem target mimic (STTM), suppressing the function of various of miRNA. The recent researches show that circRNA can also play a role in the form of ceRNA [33, 34]. It is found that the fourth class of ceRNA formation at present. Cirs-7 had a lot of binding region of miRNA-7 and play a role of efficient inhibitors [35]. Because of miRNA-7 can regulate the expression of tumor gene, it was playing an important role of cirs-7/miR-7 in tumorigenesis. Liu [36] build the artificial circRNA to inhibit the activity of miRNA-21 and miRNA-221, resulting in perfect antitumor activity than miRNA sponge and other miRNA inhibitors.

In the future we need a further research to found ceRNA network was how to play a role in the tumor development. We focus the ceRNA research on mRNA, however the more research showed that lncRNA also can be ceRNA, for example lncRNA-Ror and lncRNA-h19 could competitive combine miRNA-145 and let-7 family respectively [37, 38]. So far miRNA, pseudogenes, lncRNA and circRNA can interact with miRNA and participate in the regulation of ceRNA network. They are playing an immeasurable role in the tumor development.

The application and deficiencies of ceRNA hypothesis

ceRNA hypothesis showed us the newly post-transcription regulation model and explained the relationship between different transcript and cell function. Xu [39] found the relationship between autophagy and apoptosis by using ceRNA hypothesis. The gene transcription will be interaction which involved in autophagy and apoptosis by competitively combing the same miRNA. When the autophagy genes were down-regulated, the more miRNA will be combined to apoptosis gene transcription which shared the same MRE, resulting in the decrease of apoptosis protein.

Of course ceRNA hypothesis also exist some shortcomings. This hypothesis was showed that the specific level of intra-cellular was stable and without considering when the miRNA level changed which exist in intra-cellular. On the other hand, miRNA play a silent function besides needing MRE, the RNA-induced silencing complex (RISC) was also needed. However the ceRNA hypothesis was not corrected with the interaction between RISC and miRNA [34]. Khan [40] showed that when overexpress spe-

cific miRNA can bonded to RISC leading to the other miRNA can not bind to RICS and lost the function of silencing gene expression, increasing the other target gene expression.

Though ceRNA hypothesis needs more work to verify the rationality and validity, and more details are to be unveiled, ceRNA plays an important role in the regulation of gene expression undisputedly. Our future work will focus on the connection between ceRNA and other regulation methods in gene expression, and another hotspot will be the contribution it devotes in it [41]. Besides, it was conformed that disorder of ceRNA may induce the development of diseases [42]. To have a deep insight of ceRNA may help us in the pathological procedure [43].

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Disclosure of conflict of interest

None.

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