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Jacobs Journal of Molecular and Translational Medicine

Review Article

# Competing Endogenous RNA: A New RNA Language of Tumors

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*Received: 05-28-2015*

*Accepted: 07-14-2015*

*Published: 07-15-2015*



Canonical genetics indicate that messenger RNA (mRNA) functions as a protein-coding template. And microRNAs (miRNAs) as a class of small non-coding RNAs have significant regulatory roles in translational repression by combining with complenmentary sequences within mRNA [1]. However, a revolutionary study has demonstrated that mRNA transcripts can crosstalk to one another by competing for common microRNAs, and this cross talk is independent from protein-coding. This novel biological role of mRNA is defined as "competing endogenous RNA" (ceRNA) activity. mRNAs, transcribed pseudogenes, and long noncoding RNAs (lncRNAs) can interact with one another using microRNA response elements (MREs). This interaction may play an important role in physiological and pathological processes, including tumor formation [2].

## PTEN ceRNA network

Pier Paolo Pandolfi et al presented a road map to predict and validate ceRNA networks. They tested this hypothesis on the key tumor suppressor PTEN. They found that SERINC1, ZNF460, and VAPA mRNAs were the ceRNAs of PTEN. Low expression of these ceRNAs in prostate and glioblastoma tumors along with reduced PTEN levels could activate the PI3K/AKT pathway and promote the tumor process. Intriguingly, PTEN downregulation by ceRNA interference was attenuated in $DICER^{Ex5}$ tumor cells. DICER is a critical enzyme involved in generating mature microRNAs. These data suggest that microRNAs are essential for PTEN regulation by these ceRNAs transcripts [3]. They also found that pseudogene PTENP1 mRNA could regulate cellular levels of PTEN mRNA and exert a growth-suppressive role, both of which rely on their ability to compete for microRNA binding [4]. In another study, Pier Paolo Pandolfi et al validated ZEB2 mRNA as a PTEN ceRNA in an oncogenic BRAF-induced mouse model of melanoma. They also showed that abnormal ZEB2 expression cooperated with $BRAF^{V600E}$and could promote melanomagenesis [5]. Additionally, Andrea Califano et al reported that siRNA silencing of miR-mediated PTEN regulators (PTEN ceRNAs) was sufficient to reduce PTEN in a 3'UTR-dependent manner and promote tumor growth in glioblastoma [6].

## ceRNA networks in multiple tumors

Oncogenes or tumor suppressor genes other than PTEN have been reported in ceRNA networks of different tumors. Recently, Pier Paolo Pandolfi et al made an intriguing observation. They showed that mice overexpressing the B-Raf pseudogene Braf-rs1 (human ortholog is BRAFP1) or its 3' UTR developed a malignancy resembling human diffuse large B cell lymphoma [7]. Abnormal expression of BRAFP1 frequently occurs in B cell lymphomas and regulates ceRNAs activity that can elevate BRAF expression and MAPK activation in vitro and in vivo [7]. Tao Xi et al proved that pseudogene CYP4Z2P facilitated breast cancer angiogenesis by acting as a ceRNA of CYP4Z1. CYP4Z2P 3'UTRs arrested interference caused by miR-211, miR-125a-3p, miR-197, miR-1226, and miR-204, which resulted in increased translation of CYP4Z1. Furthermore, ectopic expression of CYP4Z2P 3'UTRs exhibited a tumor angiogenesis role in breast cancer by inducing phosphorylation of ERK1/2 and PI3K/Akt [8]. Julian Downward et al showed that HMGA2 could promote lung cancer progression by acting as a ceRNA for the let-7 microRNA family. HMGA2 could promote a malignant transformation of lung tumor cells independent of protein-coding function but dependent on the presence of let-7 sites. During this process, let-7 expression was not changed, and TGFBR3 expression was regulated by HMGA2 ceRNA activity, which is important in HMGA2 promoting lung cancer progression

by driven TGF-β signaling. As expected, HMGA2 and TGFBR3 were coordinately up-regulated in Non-small cell lung cancer (NSCLC) patients [9]. Interestingly, ceRNA activity was also discovered among spliced isoforms of one gene. OCT4 is an important transcription factor for maintaining self-renewal of embryonic stem cells (ESCs) and tumor initiating cells[10]. Zheng XL et al found that OCT4A and OCT4B mRNA were co-expressed in several types of human tumors and demonstrated that OCT4B functioned as a ceRNA to modulate OCT4A expression in a microRNA-dependent manner. Luciferase results and protein expression detected by a western blot method suggested that OCT4A and OCT4B were regulated by miR-145, miR-335, miR-20a, miR-20b, miR-106a and miR-106b [11] . ceRNA activity has also been found in most malignant human non-small cell lung cancer tumors. Xi T et al reported that AEG-1 3'-UTR functioned as a ceRNA in human non-small cell lung cancer by regulating miR-30a activity on Snail and Vimentin. AEG-1 3'-UTRindirectly regulated the expression of Vimentin and Snail, which resulted in epithelial-mesenchymal transition of human non-small cell lung cancer [12].

## Perspective

The ceRNA hypothesis is an exciting novel RNA language of tumors and has been validated in the last few years. Related research on this topic has been published in top journals, such as Cell and Nature. The discovery of this competing endogenous RNA mechanism will enhance our understanding of miRNA and mRNA function and promote the development of novel and effective cancer treatment strategies to target key points in ceRNA networks. Although the future is promising, we still have a long way to go in ceRNA research. It will be of crucial importance to integrate the relationship of miRNA-mRNA linkage interaction with miRNA-mRNA ceRNA activity. Phillip A. Sharp et al demonstrated that endogenous miRNA and target concentrations determined susceptibility to potential ceRNA competition [13]. However, this hypothesis should be checked in more models, including mouse and human models. Because ceRNA research is still in an early stage, there are only a handful of ceRNAs, including mRNAs, lncRNAs and pseudogenes that have been validated. Future research should focus on identifying more ceRNAs and understanding if ceRNA activity represents a widespread phenomenon of RNA regulation in human tumors. Discoveries of new classes of ceRNAs in a wide range of species, such as plants, zebrafish, mice, humans and viruses, will be a thrilling challenge in the future.

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