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Medicine in focus

Competing endogenous RNAs and cancer: How coding and non-coding molecules cross-talk can impinge on disease

Ugo Ala *

Department of Veterinary Sciences, University degli Studi di Torino, Largo Paolo Braccini 2, 10095 Grugliasco, TO, Italy

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ABSTRACT

Cancers are characterized by several dramatic biological changes. Among the many post-transcriptional regulatory mechanisms, microRNAs are known as fine-tune regulators for their transcript silencing ability. Competing endogenous RNAs (ceRNAs) are transcripts that share microRNA binding elements and can compete for them, thus regulating each other indirectly. ceRNA networks interconnect the regulatory control of different transcript classes of the coding and non-coding space and co-operate with other cellular and molecular regulatory mechanisms. Altered ceRNA networks are involved in tumor formation and progression as well as in chemoresistance, in invasion and in the onset of metastases. The analysis of changes in the balance between ceRNA transcripts could offer hints to identify novel pathways for diagnosis, prognosis and therapies in precision medicine interventions. Moreover, the possibility to query highly specific tumor databases, such as TCGA, and to combine clinical data, transcript expression and sequence information is allowing to develop specific predictive tools for precision medicine.

1. The ceRNA mechanism and its implications

Dysregulated transcriptional, post-transcriptional and translational programs that could alter dramatically the global gene regulation network are common to many cancer types. Key players in post-transcriptional regulation of gene expression are microRNAs (miRNAs), characterized by their ability to drive RNA silencing Bartel (2009). Intriguinly, certain transcript concentrations and molecular conditions allow a further modulation of this miRNA-based regulation, since many coding and non-coding transcripts can be bound by the same miRNAs. Specifically, when transcripts share one or more miRNA Response Elements (MREs), they can interact with and compete to bind the same particular batch of miRNA molecules and, as a consequence, they can cross-coordinate each other indirectly Salmena et al. (2011) [Fig. 1].

Suppose a situation with a single miRNA: miR-X and two transcripts: tr-A and tr-B, which host one miR-X MRE per molecule. miR-X is expressed with 2n molecules and the two transcripts with n molecules each: in the steady state a 1:1 ratio is reached and all tr-A and tr-B molecules are under the repressive action of miR-X. If the expression of tr-B has tripled, we now find 3n molecules of tr-B and globally we have 4n molecules of transcripts. The increased expression of tr-B leads to a new 1:2 ratio: one molecule of miR-X to two molecules of transcripts. In this new situation, the miR-X molecules can no longer act on all the transcripts' molecules therefore allowing a partial derepression of tr-A, without any variation in the transcription rate of tr-A and miR-X.

The involvement, in this cross-talk mechanism, of almost all RNA classes of the non-coding space — like long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) and pseudo-genes (Ψ-genes) — together with protein-coding genes offers an alternative but nonetheless complementary hypothesis for the role of the huge number of transcribed, but not translated, RNAs Poliseno et al. (2010).

The ceRNA mechanism alters the common conception on miRNA-based transcript regulation. Firstly, mRNA 3' untranslated regions (3'UTRs) can modulate in *cis* their own trascripts by allowing the miRNA fine-tuned balance, but also regulate in *trans* other transcripts by sequestering shared miRNAs. Secondly, ceRNAs offer an intriguing explanation of some of the unexpected consequences caused by aberrantly expressed transcripts. Specifically, a strong overexpression of a single miRNA-modulated transcript would be able to sequester a significant number of miRNA molecules resulting in a de-repression of other miRNA-modulated transcripts. Instead, a down-modulation of a single miRNA-tuned transcript would disengage a significant number of miRNA molecules thus free to bind to other RNA targets resulting in a

* Corresponding author.
E-mail address: ugo.ala@unito.it.

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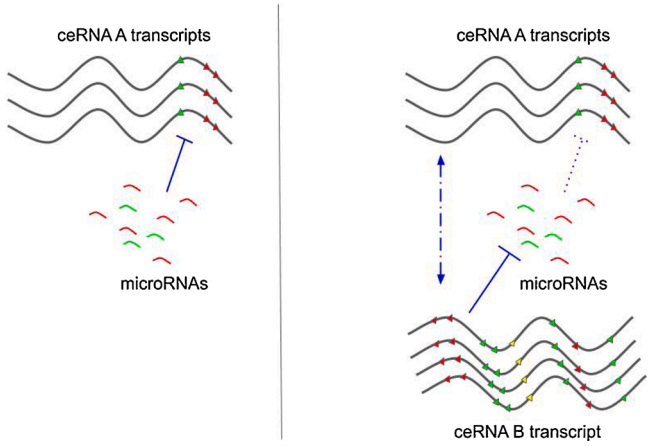

Fig. 1. *Left panel.* Transcript molecules of ceRNA A, harboring multiple miRNA Response Elements (MREs) for two different miRNAs, are under the post-transcriptional regulation of these miRNAs. *Right panel.* In the same situation, a new ceRNA B, harboring multiple MREs for the same miRNAs too, is transcribed and its molecules can sponge these miRNAs allowing a reduced post-transcriptional regulation of ceRNA A by these miRNAs.

hyper-repression of other miRNA-modulated transcripts Cesana et al. (2011) [Fig. 2].

Several computational biology techniques were applied in order to study the workability of the mechanism and its theoretical extent. The first mathematical models Ala et al. (2013), Figliuzzi et al. (2013), Bosia et al. (2013) put in evidence the optimal range of molecular cross-talk: a small variation in the concentration of competing transcripts would have the highest effect on the ceRNA network when all the players' concentrations were near equimolarity.

Subsequent works, combining experimental results and theoretical models, raised questions about the possibility to find physiological situations in which putative ceRNAs are in conditions of equimolarity: since the high number of putative miRNA targets, each target would be responsible only for a negligible portion of the global number of MREs and not sufficient to affect the other targets' through a competing cross-talk Denzler et al. (2014). This objection was addressed invoking the

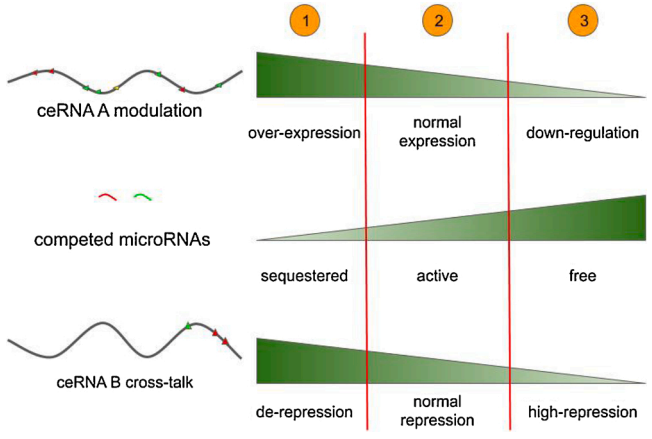

Fig. 2. A schematic representation of the ceRNA modulation mechanism. In situation 1, when ceRNA A is over-expressed, the cellular concentration of particular miRNA response elements (MREs) increases as well as the number of miRNA molecules sponged by ceRNA A, thus reducing their abundance and causing a de-repression of ceRNA B expression. In situation 2, the concentration of all transcripts allows the repressive regulation of long transcripts by miRNAs (whether translational repression or post-transcriptional degradation). In situation 3, when ceRNA A is down-regulated more miRNAs are freed from ceRNA A sponging action and thus allowed to act on and further repress ceRNA B expression.

hierarchical binding between miRNAs and targets: experimental observations have highlighted how miRNAs are likely to bind to high-affinity sites (following TargetScan Agarwal et al. (2015) classification) when miRNAs concentration is at intermediate range and the targets are more numerous than miRNAs, implying a low miRNA:target ratio Bosson et al. (2014), Denzler et al. (2016).

Alongside the mathematical models, several ceRNA databases and inferring packages have been proposed Wang et al. (2019), Zhang, Liu et al. (2019) mainly based on the correlation among putative ceRNAs themselves and the anti-correlation among ceRNAs and miRNAs, with scoring systems reflecting the assumption that a higher number of miRNAs shared between transcripts leads to a stronger mutual cross-talk.

The principles of ceRNA regulation have also been integrated in tools used to provide functional characterization for ncRNAs. PseudoFuN, for instance, is a database containing some thousands of associations between genes, Ψ-genes and miRNAs across 32 tumor types, based on differential expression and co-expression, useful to uncover novel regulatory Ψ-genes in specific tumoral contexts Johnson et al. (2019). GDCRNATools, a Bioconductor package, uses spongeScan, an improved algorithm for MRE prediction in lncRNAs, and provides several downstream analyses like functional enrichment and univariate survival analysis useful to further characterize and prioritize the key components of the regulatory mechanisms Li, Qu et al. (2018).

2. ceRNAs and cancer

From the very beginning, ceRNA networks and cancer have been linked together. The tumor suppressor PTEN and the oncogene KRAS were demonstrated to experience ceRNA influence driven by Ψ-PTEN, PTENP1, and Ψ-KRAS, KRAS1P, respectively, in specific prostate cancer cell lines Poliseno et al. (2010). Other cancer highly-expressed Ψ-genes show involvement in similar networks: OCT4-pg4 and OCT4-pg5, Ψ-genes of OCT4, a crucial gene in the regulation and maintenance of proliferation and stem cell pluripotency, are found to compete for miR-145 and lead to a ceRNA-based over-expression of OCT4 itself in hepatocellular carcinoma and endometrial cancer, respectively Wang et al. (2013), Bai et al. (2015).

After evidence deriving mostly from in-silico and in-vitro analysis and from solid tumors, an important contribution derived from a diffuse large B cell lymphoma in-vivo experiment. Clues for a ceRNA mechanism involving BRAF and Ψ-BRAF brought to the generation of specific Dox-inducible engineered mice with the possibility to overexpress the full-length murine Ψ-B-Raf, Braf-rs1, its Ψ-CDS or its Ψ-3'UTR. Interestingly, even if with different severity, induced high-expression of the Ψ-gene (or its single components) was able to increase levels of BRAF and to promote B cell lymphoma, by sequestering specific miRNAs shared by both the Ψ-gene and its cognate gene, like miR-134, miR-543 and miR-653 Karreth et al. (2015).

The ability of cancer cells to bypass or manage the presence of therapies is the result of several cellular and molecular mechanisms used to promote their survival and avoid apoptosis Zheng. (2017). For instance, in the subset of 786-O-R and ACHN-R renal cancer cells characterized by chemoresistance, lncRNA HOX-antisense intergenic RNA (HOTAIR), known to regulate chromatin state, is involved in sunitinib resistance. More in detail, highly expressed HOTAIR transcript sequesters miR-17-5p molecules and thus indirectly de-represses Beclin1, an important player in the formation of autophagosomes. In this scenario, autophagy of renal cancer cells is enhanced by HOTAIR-driven Beclin1 up-regulation and increases chemoresistance Li et al. (2020). On the other hand, gemcitabine resistance of pancreatic cancer can be reverted by over-expression of the lncRNA growth arrest-specific 5 (GAS5). Specifically, in this tumoral context, the chemotherapy resistance is promoted by the expression of miR-221. Amongst the targets of miR-221, GAS5, when over-expressed, is capable of buffering miR-221 molecules. This sponge effect is able to

reverse miR-221 induced proliferation, migration, epithelial-mesenchymal transition (EMT) and chemotherapy resistance Liu et al. (2018).

In leukemias, lncRNAs play a significant role, too. For instance, in Acute Myeloid Leukemia (AML), the lncRNA HOXA-AS2 is found highly expressed in AML patients after adriamycin treatment and in U/A and T/A ADR (Adverse Drug Reaction) cell lines, implying a possible involvement in the resistance to adriamycin-based chemotherapy. Moreover, HOXA-AS2 inhibition suppresses cell proliferation and promotes apoptosis. Specifically, high levels of HOXA-AS2 sequester miR-520c-3p molecules thus de-repressing S100A4 protein, already known for its capacity to promote invasion and metastasis formation in several tumors, including AML. Interestingly, experimental results suggest that HOXA-AS2 silencing could affect S100A4 expression, thus reverting adriamycin-induced chemoresistance. Therefore, HOXA-AS2-targeted therapy could be a promising program in association with adriamycin-based chemotherapy Dong et al. (2018).

Beyond involvement in chemoresistance, several ncRNAs acting as ceRNAs have direct associations with metastasis formation and invasion too. In Osteosarcoma, metastasis-associated lung adenocarcinoma transcript 1 lncRNA (MALAT1) highlights even more the numerous biological mechanisms that cancer is able to follow. It is found to act as ceRNA impinging on different pathways by competing for several independent miRNAs: miR-144-3p, miR-34a, miR-34c-5p, miR-449a and miR-449b. In particular, osteosarcoma cell lines and osteosarcoma tissues are characterized by a high-expression of MALAT1 and, at the same time, a down-modulation of the two miRNA clusters, miR-34a/c-5p and miR-449a/b Wang et al. (2017). MALAT1 knockdown is able to suppress cell proliferation and metastasis, and among the miRNA targets that show a ceRNA cross-talk modulation are the proto-oncogenes c-Met and SOX4, both already studied for their involvement in cell migration, invasion, epithelial-mesenchymal transition (EMT) and cancer metastasis. In a similar cellular setting, MNNG/HOS osteosarcoma cells, MALAT1 was proven to sponge miR-144-3p and to promote proliferation and metastasis by ceRNA cross-talking with ROCK1/ROCK2. To further study the ability of highly expressed MALAT1 to spread metastasis, MALAT1-overexpressing MNNG/HOS cells were subcutaneously inoculated into nude mice and, after 6 weeks, lungs presented a high number of tumor nodules demonstrating the role of up-regulation of MALAT1 in promoting pulmonary metastasis of osteosarcoma Sun et al. (2019).

lncRNA PVT1 allows to further highlight the complexity of RNA molecules involved in ceRNA networks. In normal breast tissues, lncRNA PVT1 is part of a specific ceRNA network whereas, in breast invasive carcinoma, it ceases to act as ceRNA although significantly up-regulated. An intriguing hypothesis for this radical ceRNA rewiring relies on the differential expression of alternative isoforms. Specifically, in invasive breast cancer, the PVT1 isoform that hosts the miRNA binding sites is subject to a drastic reduction in concentration in favor of other isoforms without MREs, thus obtaining the upregulation of the isoform which is unable to act as a ceRNA Conte et al. (2017). Moreover, a specific circRNA, circ-PVT1, arises from one exon of the lncRNA PVT1. The circ-PVT1 harbors MREs for different miRNAs and its activity as a ceRNA has been observed in two different contexts: in paclitaxel resistance of gastric cancer cells through the axis ZEB1/miR-124-3p and in proliferation and invasion in Non-Small Cell Lung Cancer through the E2F2/miR-125b network Liu et al. (2019), Li, Zhang et al. (2018).

2.1. ceRNAs and clinical perspectives

These important evidences in several cancer development and drug-response steps led to consider the ceRNA mechanism also for diagnosis and prognosis: ceRNA networks can thus be used to reveal novel clinically relevant ncRNAs and mRNAs as biomarkers or as possible therapeutic targets.

Moreover, the large amount of clinical and expression data organized into TCGA (http://cancergenome.nih.gov/) database, GEO (https://www.ncbi.nlm.nih.gov/geo/) and ArrayExpress (https://www.ebi.ac.uk/arrayexpress/) datasets and the NCI's Genomic Data Commons (GDC, https://gdc.cancer.gov/) allowed to increase the scope and accuracy of these predictions Paul et al. (2018). A lung squamous cell carcinoma (LUSC) study highlighted the differentially expressed transcripts from several GEO microarray LUSC projects and those from TCGA LUSC patients. The good consensus overlap of 129 up- and down-modulated transcripts between the array-based and sequences-based analyses served as a starting point for the functional characterization of both transcripts and associated-proteins. Specifically, a ceRNA network was built up integrating differentially expressed coding RNAs, lncRNAs and miRNAs with the GDCRNATools software: EZH2, ABCC5, and KIF23 mRNAs were found to be under the putative regulation of ceRNA networks and their low expression was associated with shorter survival times Li, Gu et al. (2018).

The same availability of clinical and expression data has also facilitated the transition from preclinical association clues toward personalized medicine studies with promising clinical evidence, aiming to provide the most accurate individual prognostic knowledge before surgery and enhance the effectiveness of individual treatments.

In particular, the possibility to build a ceRNA network specific for each pathological state — merging information of differentially expressed miRNAs, protein-coding genes and ncRNAs according to the similarity of their MRE profiles — allowed the development of predictive tools for precision medicine. In colorectal cancer (CRC), a specific ceRNA network consisting of 14 lncRNAs, 29 miRNAs, and 79 mRNAs was identified. From the same network, a predictive multivariate Cox regression model highlighted a signature based on 15 mRNAs as independent risk factors for tumor prognosis. Further Kaplan Meier analysis confirmed that patients characterized by high expression for this signature had significantly poorer overall survival than those with low expression. Moreover, two predictive tools for precision medicine were proposed: the Smart Cancer Survival Predictive System for on-line Overall Survival prediction and the Gene Survival Analysis Screen System to further explore survival curves for specific gender and pathological stage subgroups Zhang, He et al. (2019).

3. Conclusions

The ceRNA-based post-transcriptional mechanism has received extensive experimental confirmation and its effects have been verified in many normal and pathological conditions, from neurodegenerative diseases to immune and autoimmune responses, from heart diseases to cancers. In principle, basically all cancer types can be subjected to and partially driven by the ceRNA mechanism: from solid tumors to leukemias and lymphomas, ceRNA networks show how long and short RNA molecules are deeply interconnected and can influence each other. Protein-coding transcripts, lncRNAs, pseudo-genes, circRNAs and miRNAs are gathered in complex regulatory networks that join other levels of transcriptional and post-transcriptional organization, forming multilevel networks of interaction and regulation.

The growing amount of expression and sequence data, interaction effects, clinical stratification, available from reference cancer consortia such as TCGA, has allowed to investigate the effects of de-regulation and reprogramming in specific subsets of patients.

However, the identification of the ceRNA networks and the exploration of their role are based on two strategies that both suffer from limitations. Bioinformatics predictions derive from statistical methods and indirect evidence, and in vitro verifications are based on induced knockdown and/or overexpression experiments that have a profound impact on biological contexts. A great deal of effort is needed to verify that the proposed ceRNA networks play an essential role in pathologies. Nevertheless, they can provide an alternative starting point to dissect the intertwined gene regulatory networks and to discover new molecules that can be used as diagnostic, prognostic and therapeutic targets in precision medicine interventions.

4. Disclaimer

Author Contributions

UA conceived the review, collected and analyzed information, prepared the figures and wrote the manuscript.

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Conflicts of interest

The author declares no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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