Editorial
Title: Impact of circRNA on the complex regulatory network of the cell
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microRNAs (miRNAs) are small molecules nucleotides interacting with messenger RNA (mRNA) targets and therefore serving as regulators of gene expression. The presence of different targets that have the same miRNA binding site leads to a miRNA-mediated cross-talk between competitive endogenous RNAs species (1-3). Circular RNAs belongs to ceRNAs and are single stranded non-coding RNAs that have their 3' and 5' ends covalently linked due to back-splicing. The latter (4) was first identified in an RNA virus in 1976 by electron microscopy (5) and at the beginning circRNAs were considered as a byproduct of aberrant splicing of mRNA processes because of their low transcript abundance (6). However, thanks to high-throughput technologies and bioinformatics analysis many circRNAs were identified. This analysis revealed that they are stable and often expressed in a tissue or developmental-specific way (7, 8). While circRNAs can be generated from any region of the genome, the majority of them are generated by coding regions, mainly including exons (9). Recent evidence shows that circRNAs work as splicing or transcriptional regulators (10-13) and as miRNA sponges (9, 14).

The most important aspect that should be elucidated in the next years is the physiological and pathological role of circRNAs in the complex network of the cell. Working along this direction, the paper by Sekar et al. describes a unique expression of 4438 circRNAs in human astrocytes obtained from healthy elderly subjects and in Alzheimer's disease (AD) patients (15). *In silico* analysis of circRNA-miRNA networks allows the authors to identify an enrichment in the immune response (15), in agreement with the critical role played by astrocytes as immune sensors in the brain. Indeed, astrocytes play a pivotal role in many critical functions of the central nervous system (CSC) such as energy storage, metabolism and homeostasis, in addition to the immune system. It would be interesting in the near future to compare elderly and young subjects to investigate if during aging there are some important changes reveailed by circRNAs.

Another interesting result in the paper comes from studies on tumors. In the last year, a high number of papers show the possible use of circRNAs as biomarker of an aggressive phenotype (16-23). In particular, in glioblastoma multiforme (GBM), it has been found that circMMP9 acts as an oncogene promoting the proliferation, migration and invasion abilities of GBM cells (16). Moreover, the same study shows that this particular circRNA serves as a sponge that directly targets miR-124 (16). In another study, the role and underlying regulatory mechanisms of circFNDC3B was investigated in bladder cancer (BC) (17). In particular,

circFNDC3B was shown to act as a miR-1178-3p sponge to suppress G3BP2, thereby inhibiting the downstream SRC/FAK signaling pathway (17). The role of circRNAs has also been investigated in hepatocellular carcinoma (18) and in breast cancer (19). Recent reviews also highlight the important role of circRNAs as biomarkers in tumors and other pathologies (20-21). In spite of the increasing evidences of the important regulatory role of circRNAs in the complex network of the cell, the relevance of these factors stems from their stability and abundance. In fact, thanks to these characteristics they could be detected in the blood (22).

To achieve the goal of using circRNAs as target for diagnosis or prognosis, a crucial aspect is to construct a list of circRNAs playing a critical role for specific pathologies and to understand in a deep way their role inside the network of the cell (9). In this direction, an interdisciplinary approach combining theory and experiments can be very useful to prove a general framework. Our group recently has developed a theoretical model for the miRNA-mediated cross-talk of circRNAs and mRNAs (23). Thanks to this model, we investigate two important different scenarios: in the first case circRNA and mRNA compete for binding the miRNA but there is no other relation between the two RNAs; in the second case we study the scenario where there is a co-generation of the circRNA/mRNA pair which introduces an additional feedback loop to the network (23). Our results clearly show that in both cases we have a cross-talk between circRNA and mRNA (23). The comparison of the theory with experimental data, confirms that the cells can use both theoretical scenarios (23). Our findings, thereby, confirm the relevance of circRNAs in cell regulation and suggest that they could be used as biomarkers. Moreover, our approach describes a general approach to study the relevance of circRNAs under different conditions (23).

In another recent theoretical study, the authors investigated the possible role of circRNAs in biological oscillations (24). The latter are crucial to the normal function of living organisms regulating a wide variety of biological processes. They, actually, appear as the collective dynamic behavior of an ensemble of interacting components in the cell. In eukaryotes, in fact, oscillatory process are due to interactions at the protein and RNA levels. Dawan et al showed that non-coding RNA act as microRNA (miRNA) sponges giving rise to oscillatory behavior (24). They also tested this behavior experimentally, demonstrating that the control of these non-coding RNA dynamically creates oscillations or stability (24).

Taken together this evidence starts to detangle the understanding of important functional differences between distinct RNA species including circRNA. In the near future, it will be important to explore this intricate network and the role of circRNAs during the development. Recent emerging evidence revealed that circRNAs are spatiotemporally regulated and dynamically expressed during brain development (25). This could have a relevant influence on the development and diseases of the central nervous system. This aspect appears particular intriguing due to the complexity of the brain and the connection with the environment and specific diseases, genetic or acquired.

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References

1. Figliuzzi M, De Martino A, Marinari E. RNA-based regulation: Dynamics and response to perturbations of competing RNAs. Biophysical Journal 2014; 4: 1011-22.
2. Bosia C, Pagnani A, Zecchina R. Modelling Competing Endogenous RNA Networks Plos One 2013; 8: e66609.
3. Eriksson J, Le Joncour V, Nummela P, Jahkola T, Virolainen S, Laakkonen P, Saksela O, Hölttä E. Gene expression analyses of primary melanomas reveal CTHRC1 as an important player in melanoma progression Oncotarget 2016; 7: 15065-92.
4. Qu S, Yang X, Li X et al. Circular RNA: A new star of noncoding RNAsb. Cancer Lett 2015; 365: 141-8.
5. Sanger H L, Klotz G, Riesner D et al. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. PNAS USA 1976; 73: 3852-6.
6. Cocquerelle C, Mascrez B, Hétuin D, Bailleul B. Mis-splicing yields circular RNA molecules. FASEB J 1993; 7: 155-60.
7. William J, Sorrentino J A, Kai W et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 2013; 19: 141-157.
8. Conn SJ, Pillma KA, Toubia J et al. The RNA binding protein quaking regulates formation of circRNAs. Cell 2015; 160: 1125-34.
9. Memczak S, Marvin J, Antigoni E et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 2013; 495: 333-8.
10. Zhang Y, Zhang X Chen T et al. Circular intronic long noncoding RNAs. Mol Cell 2013; 51: 792-806.
11. Ashwal-Fluss Rand, Meyer M Pamudurti N, et circRNA biogenesis competes with pre-mRNA splicing. Mol Cell 2014; 56: 55-66.
12. Jeck WR, Sharpless N E Detecting and characterizing circular. RNAs Nature Biotech 2014; 32: 453-61.
13. Li Z. Huang C., Bao C, Chen L et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 2015; 22: 256-64.

14. Ebbesen K K, Kjems J, Hansen T B. Circular RNAs: Identification, biogenesis and function. BBA 2016; 1859, 163-8.
15. Sekar S, Cuyugan L, Adkins J, et al. Circular RNA expression and regulatory network prediction in posterior cingulate astrocytes in elderly subjects. BMC Genomics 2018; 19: 340.
16. Wang R, Zhang S, Chen X et al. EIF4A3-induced circular RNA MMP9 (circMMP9) acts as a sponge of miR-124 and promotes glioblastoma multiforme cell tumorigenesis. Mol Cancer 2018; 17, 166.
17. Liu H, Bi J, Dong W, Yang M, et al. Invasion-related circular RNA circFNDC3B inhibits bladder cancer progression through the miR-1178-3p/G3BP2/SRC/FAK axis. Mol Cancer 2018; 17: 161.
18. Matboli M, Shafei A E, Ali M A et al. circRNAs (hsa_circ_00156, hsa_circ _000224, and hsa_circ _000520) are novel potential biomarkers in hepatocellular carcinoma. J Cell Biochem 2018; doi 10.1002/jcb.28045
19. Zeng K, He B, Yang B B et al The pro-metastasis effect of circANKS1B in breast cancer Mol Cancer 2018; 17, 160.
20. Yao R, Zou H, Liao W. Prospect of Circular RNA in Hepatocellular Carcinoma: A Novel Potential Biomarker and Therapeutic Target**.** Front Oncol 2018; 8: 332.
21. Zhang Z, Yang T, Xiao J. Circular RNAs: Promising Biomarkers for Human Diseases. EBioMedicine 2018; 34: 267-274.
22. Qu S, Zhong Y, Shang R, et al. The emerging landscape of circular RNA in life processes. RNA Biol 2017; 14: 992-99.
23. Fumagalli MR, Zapperi S, La Porta CAM. Impact of the cross-talk between circular and messenger RNAs on cell regulation. J Thor Biol 2018; 454: 386-395.
24. Dhawan A., Harris AL, Buffa FM, Scott JG. Endogenous mirna sponges mediate the generation of oscillatory dynamics for a non-coding RNA network. J Theor Biol doi: 10.1016/j.jtbi.2018.10.055
25. Chen BJ, Huang S, Janitz M. Circular RNAs: Changes in circular RNA expression patterns during human foetal brain development. Genomics 2018; doi: 10.1016/j.ygeno.2018.04.015