Editorial Commentary

Impact of circRNA on the complex regulatory network of the cell

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MicroRNAs (miRNAs) are small nucleotides that can bind to messenger RNA (mRNA) preventing its translation. Different mRNA targets can have the same miRNA binding site leading to a miRNA-mediated cross-talk between competitive endogenous RNA (ceRNA) species (1-3). Circular RNAs (circRNAs) are yet another example of ceRNAs (4), first discovered by electron microscopy in an RNA virus in 1976 (5). These are single stranded non-coding RNAs that have their 3' and 5' ends covalently linked due to back-splicing, thus acquiring a circular form. Due to their low transcript abundance, circRNAs were originally thought to be a byproduct of aberrant splicing of mRNA (6). In recent years, however, progress in high-throughput technologies and bioinformatics lead to the identification of many new circRNAs. Owing to their circular structure, circRNAs are very stable and are typically expressed in tissue-dependent and developmental-specific ways (7,8). Most circRNAs originate from coding regions of the genome, mainly including exons (9), although they could in principle be generated from any genome regions. Recent results show that circRNAs can act as splicing or transcriptional regulators (10-13) and as miRNA sponges (9,14).

The key open issue for the years to come is to elucidate the physiological and pathological role of circRNAs in the complex network of the cell metabolism. Working along this direction, the paper by Sekar *et al.* describes the unique expression of 4,438 circRNAs in human astrocytes comparing healthy elderly subjects and 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). These results are consistent with the important 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 modulated by circRNAs.

Another interesting result of the paper by Sekar *et al.* is related to the impact of circRNAs in tumors. In the last year, a large number of papers suggest a possible use of circRNAs as biomarkers for aggressive phenotypes of tumor cells (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 also shows that this particular circRNA acts as a sponge, targeting miR-124 (16). In another recent 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 not only of tumors but also of other pathologies (20,21). In spite of the increasing evidence supporting an important regulatory role of circRNAs in the complex metabolic network of the cell, the relevance of these factors are mainly related to their stability and abundance. In fact, thanks to these characteristics they could be detected in the blood (22)

that represents an important and easy way to follow patients with diseases.

To achieve the goal of using circRNAs as targets for diagnosis or prognosis, a crucial aspect is to construct the list of the most important circRNAs playing a critical role for specific pathologies and thus to understand their role inside the metabolic network of the cells (9). In this direction, an interdisciplinary approach combining theory and experiments would be necessary to provide a general interpretative framework. Our group has recently developed a theoretical model for the miRNA-mediated cross-talk of circRNAs and mRNAs (23). Thanks to this model, we investigated if circRNA and mRNA compete for binding the miRNA or there is a co-generation of the circRNA/mRNA pair which introduces an additional feedback loop to the network (23). A comparison between the theory and experimental data confirms that the cells can exploit both theoretical scenarios (23). Our approach describes a general method to study the relevance of circRNAs under different conditions (23).

In another recent theoretical study, the authors investigated the possible role of circRNAs in relation to biological oscillations (24). The latter seems to be crucial to the normal function of living organisms regulating a wide variety of biological processes. Biological oscillations, actually, appear as a collective dynamic behavior of an ensemble of interacting components in the cell. In eukaryotes, oscillatory processes are due to interactions at the protein and RNA levels. Dhawan *et al.* showed that non-coding RNA acts 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 all this evidence is starting to clarify important functional differences between distinct RNA species including circRNA. In the near future, it will be important to explore in a deeper way the intricate network modulated by circRNAs and the role of circRNAs during physiological or pathological conditions such as development and phenotypic switching. In this connection, recent emerging evidence revealed that circRNAs are spatiotemporally regulated and dynamically expressed during brain development (25). This could have a relevant influence for development and in diseases related to the CSC. The latter aspect appears particularly intriguing due to the complexity of the brain and the connection with the environment and specific diseases, genetic or acquired. Related to phenotypic switching processes, the plasticity of the cells appears particular relevant during the development but also in pathological conditions such as tumors.

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