EBioMedicine 49 (2019) 17–18

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

A tale on rabbit ears and pan-handles, the rings that rule all

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ARTICLE INFO

Article history:
Received 16 October 2019
Accepted 16 October 2019
Available online 29 October 2019

It seems rather remarkable that an off-hand observation made decades ago on the existence of circular RNA molecules, is increasingly capturing investigators' interests [1]. In this article in *EBioMedicine*, Zhang and colleagues turned their attention to the effect of a well-known and frequently described circular RNA (circRNA) derived from the HIPK3 gene (circHIPK3) on oxaliplatin-resistance in colorectal cancer [2].

CircRNAs are formed by splicing the 3′ end of an exon to the 5′ end of its own or an upstream exon, generating a single stranded, circular molecule. Initially, circRNAs were considered to be idiosyncrasies of the splicing machinery and to comprise only a small fraction of the transcriptome, its obscurity at the time enhanced by the unknown functionality. As nicely reviewed in 2016 by Barrett & Salzman, modern RNA sequencing methods revealed that circRNAs are actually highly abundant isoforms present for thousands of human genes, they exhibit cell type-specific expression and are conserved between mouse and human [3]. The finding that circCDR1 represents a highly effective sponge for a tumor-suppressive microRNA (miRNA; miR-7) raised the interest of the cancer research field and resulted in numerous additional studies hunting for circRNAs able to bind miRNAs as well as for circRNAs with other regulatory functions [4].

In the first months of this year, three transcriptome-wide studies were published describing a large compendium of circRNAs present in large numbers of patients: 2000+ pan-cancer cases [5], 348 breast cancer cases [6] and 144 prostate cancer cases [7], with all studies reporting the presence and involvement of thousands of circRNAs. Other highlights from these studies include the observations that selected circRNAs exert functional relevance in breast and prostate cancer cell lines that is independent from the function of their linear counterpart and that circRNAs are detectable in patients' blood. circHIPK3 represents one of the relatively well studied circRNAs, which is abundantly expressed in a variety of human cell types and it is found to be important for cellular growth. In particular, this circRNA was found to sponge a number of different miRNAs [8]. Subsequent studies showed this miRNA sponging capacity to be relevant in many human malignancies, including colorectal cancer (CRC). Zeng et al. already found that high-level expression of circHIPK3 was an independent prognostic factor of poor overall survival (OS) in CRC [9] and that this was associated with miR-7 sponging *in vitro*. In the article by Zhang et al., they convincingly show that circHIPK3 is involved in oxaliplatin-resistance in CRC [2]. In summary, they found 1) increased expression of circHIPK3 in oxaliplatin-resistant CRC patients and cell lines, 2) a larger tumor size in circHIPK3 overexpressing xenograft mice models upon oxaliplatin-treatment and 3) that high circHIPK3 levels were predictive for recurrence and poor survival in oxaliplatin-platin treated CRC-patients. Mechanistically, this inhibition was found to be the result of miR-637 sponging and subsequent increase in STAT3 expression ultimately resulting in autophagy inhibition. Interestingly, a role for circHIPK3 in autophagy regulation was already described in lung cancer via sponging of miR-124–3p, further underlining its potential role as a key autophagy regulator [10].

Taken together, although there is ample evidence for the relevance of circRNAs in both healthy and diseased cells, we are only beginning to understand their biogenesis and functional roles. Next to their documented function as miRNA sponge, circRNAs have for instance been described to regulate splicing and transcription, as well as interact with RNA-binding proteins (RBPs). The fact that circRNAs lack a free 5′ or 3′ end renders them extremely stable compared to their linear counterparts, which greatly increases their potential as minimally invasively detectable biomarkers as exemplified by their recent detection in among others exosomes, saliva, plasma and urine. Above described studies already implicate the potential value of circRNAs as prognostic and/or predictive markers in oncology. On the other hand, even though thousands of circRNAs can be detected in cancer, a potential showstopper for circRNAs as biomarker for cancer detection could be the observation

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https://doi.org/10.1016/j.ebiom.2019.10.031

that, in general, circRNAS appear lower expressed in cancer cells compared to healthy cells.

With the recent availability of the large catalogues of detectable circRNAs in cancer, we have come a long way from the 'rabbit ears' and 'pan-handles' that were seen by Hsu and Coca-Prados in 1979 in their electron micrographs. It will be intriguing to see whether in future studies circRNAs will be able to redeem their clinical promise as biomarker, therapeutic target and potentially even as therapeutic vehicle.

Authors' contribution

MS and SW equally contributed to the necessary literature search and wrote this commentary together.

Declaration of Competing Interest

The authors declare no conflict of interest.

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