Editorial

ciRS-7 acts as a master player in colorectal cancer

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Colorectal cancer (CRC) represents a critical health burden worldwide (1,2). Although patients with localized CRC have a 5-year survival rate of about 90%, this ratio dramatically drops in patients with metastatic tumors (2). Standard and liquid biopsy are extremely effective for the identification of critical genetic lesions and to study clonal evolution in CRC (3,4). However, only a minor fraction of oncogenic mutations are clinically actionable, indicating that other novel therapeutic strategies are urgently needed.

The recent discovery that our genome is pervasively transcribed (5) opens a novel scenario in which non-coding RNA (ncRNA) molecules can potentially play a pivotal role in the control of cellular homeostasis and transformation. Circular RNAs (circRNAs) represent a new class of ncRNA whose production is finely regulated during development and differentiation (6). CircRNAs originate from the non-canonical splicing of both coding and ncRNAs in which an upstream splice acceptor is covalently bound to a downstream splice donor in a process called back-splicing (7). While in the last decade, the role of microRNAs (miRNAs) in tumorigenesis has been extensively investigated (8), the impact of other ncRNA species such as circRNAs remains largely unexplored (9,10).

Interestingly, coding and ncRNAs intertwine complex relationships built on base pair complementarity (11). The theory of competing endogenous RNAs (ceRNAs) predicts that any RNA molecule can potentially regulate the level of multiple transcripts by subtracting (or 'sponging') miRNAs from other RNAs sharing, throughout their sequence, the same miRNA responsive elements (MREs) (12). CircRNAs, and in particular the circRNA sponge for miR-7 (ciRS-7), epitomize the ceRNA activity (13-15). CiRS-7 originates from the antisense strand of the *CDR1* gene and, as any other circRNA, it is particularly stable and resistant to RNA degradation (13,14). However, ciRS-7 acts as a very powerful RNA sponge for miR-7, since its sequence contains more than 70 different MREs for this miRNA (13,14) CiRS-7 is highly abundant in the mammalian brain (13,14). Accordingly, the knock out mouse model develops dysfunction of excitatory synaptic transmission and neuropsychiatric-like alterations (16).

Intriguingly, Weng *et al.* have recently identified ciRS-7 as a critical circRNA in CRC pathogenesis (17). The analysis of ciRS-7 expression in 153 CRC and 44 matched normal mucosae revealed the over-expression of this circRNA in tumor specimens. The authors further validated this analysis in a cohort of 165 cases. Notably, ciRS-7 was overexpressed in advanced CRC, especially in patients with T4 disease and more advanced stages. Moreover, high ciRS-7 expression correlated with poor overall survival in patients. Since miR-7 is frequently dysregulated in cancer (18) and ciRS-7 acts as a potent miR-7 sponge (*Figure 1A*), the authors investigated the biological relationship between these two ncRNAs in CRC. In accordance with the ceRNA hypothesis, ectopic expression of miR-7 in CRC cells strongly impaired cell proliferation, migration, invasion and protection from apoptosis. On the other hand, the co-expression of ciRS-7 dramatically reduced the oncosuppressor potential of miR-7 both *in vitro* and *in vivo* (xenografts) (*Figure 1B*). Mechanistically, Weng *et al.* analyzed two well-established miR-7 target genes, *EGFR* and *RAF1*. Both genes were found downregulated at the mRNA and protein level in CRC cells over-expressing miR-7. Conversely, EGFR and RAF1 were not modulated when CRC cells were transfected with miR-7 and ciRS-7 constructs, suggesting that

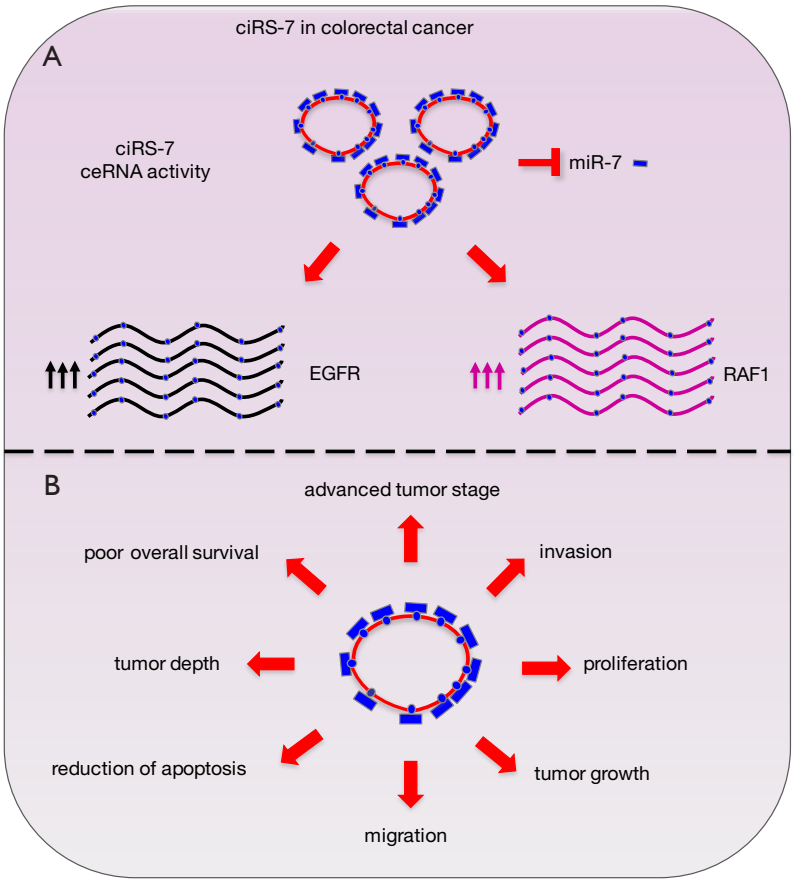

Figure 1 ciRS-7 impacts on colorectal cancer. (A) circRNA CDR1 as/ciRS-7 is overexpressed in colorectal cancer specimens. ciRS-7 acts as potent ceRNA in CRC by increasing the level of EGFR and RAF1, two critical miR-7 target genes. (B) The oncogenic properties of ciRS-7 identified by Weng *et al.* in CRC. MicroRNA Responsive Elements and microRNAs are indicated as circles and rectangles, respectively, on the RNA molecules. CRC, colorectal cancer.

ciRS-7 was acting as a potent sponge for miR-7 (*Figure 1A*). Finally, the authors analyzed the level of miR-7, ciRS-7, EGFR and RAF1 in CRC specimens. Notably, the levels of expression of ciRS-7 and miR-7 as well as of EGFR/RAF1 and miR-7 were found inversely correlated in CRC specimens, while ciRS-7 expression was found positively associated with EGFR and RAF1 in the same patients.

In the last decade the improvement in deep sequencing technologies and bioinformatic analysis has shed light on the biological relevance of the so called "dark matter" of our genome. The work by Weng *et al.* highlights the impact of circRNAs in cancer pathogenesis. In this specific case ciRS-7 represents either a powerful prognostic biomarker or a future possible therapeutic target for advanced CRC.

The recent discovery that circRNAs can also be efficiently translated (19-21) adds a novel level of complexity, since these peptides can potentially influence gene function at the post-translational level. It is now evident that revealing the complex relationships between coding and ncRNAs in normal and transformed cells represents the crucial step to develop novel therapeutic strategies and diagnostic tools for cancer treatment.

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