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Editorial – 'Sponging' a carcinoma as a Circular RNA

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CircRNA Biogenesis and miRNA Sponging

CircularRNAs (circRNAs) are endogenous non-coding RNAs, stable, abundant, and conserved through evolution, regulating several physiological and pathological mechanisms, assuming an emerging pivotal role in biomedical sciences. CircRNAs have been reported in all eukaryotes known, including plants, yeast, fishes, worms and they are from 5-30% conserved in human and mice transcriptome. CircRNAs are covalently closed circular RNA molecules forming between a downstream 3′ splice site and an upstream 5′ splice site in a linear precursor mRNA and are transcribed by RNA polymerase II and originate from exons, introns, antisense, 5′ or 3′ untranslated and intergenic genomic regions[1]. The most important mechanism unfolding the biological function of circRNAs is the capacity to sponge microRNAs[2]. Sponging miRNAs, the circRNAs modulate the post-transcriptional regulation of mRNA gene target, inhibiting miRNA-mediated repression of translation. In addition, circRNAs compete with endogenous RNA molecules, associate and bind RNA-binding proteins, and tune splicing.

CircRNAs are abundantly expressed in the brain and up to 50% they are expressed in a tissue-dependent manner, assuming a clinical importance in cancer pathogenesis and neurodegenerative diseases as valuable diagnostic biomarkers[3].

The circular RNA-miRNAs connection represents one of the most investigated research field in cancer translational medicine, opening a new therapeutic perspective.

CircRNA in Squamous Cell Carcinoma

In recent years, circRNAs discovery and analysis in head and neck squamous cell carcinoma and, in particular, on oral cavity, increased by use of high-throughput sequencing and RT-qPCR linked to bionformatics tools as circBase. In this regard, it is very important to highlight the need to define a standard unifying nomenclature of circRNA, such as circBank, aimed at standardizing the surveys after the construction of the expression database. The circRNA landscape expression profile in oral squamous cell carcinoma evidenced both overexpression that downregulation, exploring these molecules mainly as oncogenes with respect to tumor suppressor genes.

Use of circRNA in Clinical Environment

CircRNA evaluation and expression has been investigated to monitor progression, invasion and recurrence of several head and neck cancers[4,5]. Recently, their monitoring has been proposed to support the diagnosis of oral squamous cells carcinoma (OSCC)[6]. There are a series of different circRNAs that can be studied[6] for analyzing different tumor findings. Zao et al[7] showed that circUHRF1 was markedly upregulated in the OSCC cells and tissue; its overexpression was closely correlated with the poor prognosis of OSCC. The authors suggested that circUHRF1 promoted proliferation, migration, invasion, and epithelial mesenchymal transformation (EMT) *in vitro*, and tumor growth *in vivo*[7]. Moreover, Zhang et al[8] studied the effects of circular RNA hsa_circ_009755 on proliferation, migration, invasion, and apoptosis in OSCC cells *in vitro*; the authors found a low expression of hsa_circ_009755 both in OSCC tissues and in the studied OSCC cell lines. By silencing hsa_circ_009755, the researchers noted a significant enhanced proliferation, migration, and invasion and suppression of OSCC cells apoptosis; their results underlined the importance of hsa_circ_009755 in the tumor genesis of OSCC[8]. A series of others circRNAs presented oncogenic potential in OSCC[9,10]. Circular RNA hsa_circ_0007059 was also indicat-

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ed as potential marker to indicate the prognosis of OSCC[10]; the authors performed a case-control study that validated their theory showing how was relevant the upregulation of 007059 as predictor of poor prognosis. Li et al[11] studied the expression of Hsa_circ_0004491 in 40 paired OSCC patients comparing with normal tissue samples; the researchers found that the expression of this circRNA was related with the presence of distant metastasis. These results add another potential role to the measure of circRNA, as they can be useful to monitor aggressiveness, diffusion and prognosis of OSCC[8-11]. However, since circRNAs are numerous and only a portion of them has been studied, their role in clinical practice has to be validated on larger samples.

Perspectives on CircRNA

Molecular investigations are the starting point for unraveling the role of circRNA in personalized approaches to OSCC, as they become a potential target of tumor progression, biomarkers and "Trojan horse" of resistance to chemotherapy. CircRNA research opens several questions as the circRNA biogenesis regulation, the functional mechanism of tuning of molecular pathways in selected tissues and organs, both in physiological and pathological conditions and their employment as biotechnological weapons to fight cancer. In particular, a very interesting issue is represented by the relationship between circRNA and exosomes, with a double point of view as biomarkers and delivery therapy tool. In the future, it might be possible to develop a specific expertise dedicated to managing RNA molecules, including circRNAs, miRNAs and long non-coding RNAs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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