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Letter to the Editor

miR-494 inhibits invasion and proliferation of gastric cancer by targeting IGF-1R

Dear Editor,

We think that this paper by Dr. Zhao et al[1], published on Eur Rev Med Pharmacol Sci and titled "miR-494 inhibits invasion and proliferation of gastric cancer by targeting IGF-1R" is another important piece of the complicated landscape of oncogenesis, in fact only recently, microRNAs (miRNAs) have been suggested to be closely associated with tumorigenesis[1].

In particular, this article focuses attention on Gastric cancer (GC) and on this exact microRNA-4941.

GC is the fifth most frequent cancer and the third leading cause of cancer-related death worldwide[2]. In spite of surgery and multimodal therapy, the outcome of gastric cancer in advanced stages is still poor. Therefore, it is urgent to elucidate the mechanisms that underlie the tumor genesis and aggressiveness of this type of tumor. Targeted therapies became a topic goal in GC treatment. The description of trastuzumab, (anti-HER2 antibody) efficacy plus chemotherapy in patients with HER2-neu-positive, in ToGA trial and of Ramucirumab (VEGFR-2 antibody) has revealed promising results in the treatment of patients with advanced or metastatic GC. However, other trials are assessing the safety and efficacy of targeted therapies such as VEGFR inhibitors (Sorafenib and bevacizumab) and EGFR inhibitors (cetuximab and erlotinib) combined with chemotherapy in patients with advanced gastric adenocarcinoma who have not achieved ideally a clinical benefit[3]. To improve the poor prognosis of gastric cancer patients, it is important to understand the molecular mechanisms underlying and supporting tumor-cell survival and invasion. Epigenetic alterations, mainly aberrant DNA methylation, histone modifications and microRNA (miRNA) expression play a central role in many diseases, including GC[4]. Many studies[5] have identified a large number of up-regulated oncogenic miRNAs and down-regulated tumor-suppressor miRNAs in this type of cancer. Epigenetic events refer to alterations that promote gene expression variation without changing the DNA sequence yet leading to transcriptional activation or silencing of the gene.

MicroRNAs (miRNAs) are evolutionally conserved, endogenous, non-coding, small (20~23 nucleotides) RNAs, which regulate gene expression at the post-transcriptional level. In general, miRNA genes are located in intergenic regions, suggesting that most miRNA genes are transcribed as autonomous transcription units. Moreover, these molecules are usually transcribed by RNA polymerase II, generating long primary transcripts (pri-miRNAs). Then, these premiRNAs are processed to generate a double stranded RNA, which includes the mature miRNA. The mature miRNAs repress protein translation through binding to the target protein-coding mRNAs by base pairing to partially complementary regions frequently located at the 3'-untranslated regions (3'-UTR) of the target transcript[6,7].

Moreira et al[8] suggested the existence of gastric tissue and organ miRNA expression signatures. Accordingly, Gomes et al[9] observed a specific expression signature of let-7b, miR-21, miR-29c, miR-31, miR-192, miR-141, miR-148c and miR-451 in GC.

In cancer, miRNAs can function as oncogenes and/or tumor suppressor genes depending on the outcome of the target mRNA (oncomiRNA or tsmiRNA, respectively). Increased activity of an oncomiRNA leads to inhibition of apoptosis and cell proliferation.

In contrast, decreased activity of a tsmiRNA leads to increased tumor formation, because *in vitro* and *in vivo* introduction of tsmiRNAs promotes antitumoural activity by restoring lost tumor suppressor activity and the use of antagomirs inhibits the pro-tumorigenic activity of oncomiRNAs.

miR-494 as a commonly down-regulated miRNA in tumor tissues of patients; the upregulation of miR-494 could inhibit proliferation and invasion of cells *in vitro* and *in vivo*.

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Each miRNA seems to modulate tens to hundreds of target genes to coordinate cellular signaling pathways.

In the current study, the authors examine the role of miRNA-494 in the carcinogenesis and progression of GC and to investigate its target gene. Here, using quantitative real-time polymerase chain reaction (qRT-PCR) and luciferase reporter assay in gastric cancer tissues and cell lines, they demonstrated the significantly lower level miR-494 in patients with GC than healthy controls, and that the insulin-like growth factor 1 receptor (IGF1R) is a target gene of miR-494. miR-494 binds to the 3-untranslated region (UTR) of IGF1R and inhibits the expression of the IGF1R protein[1].

The data, therefore, suggest that miR-494 plays an important role in the development and progression of gastric cancer, implicating possible applications in the clinic as a new common therapeutic target and prognosis biomarker. We suggest that will be interesting to note if a low expression of miR-494 correlated significantly with poor overall survival and prognosis of GC patients. Moreover, miRNA-based anticancer therapies have recently been explored, either alone or in combination with current targeted therapies. However, the strategy to use currently miRNAs for targeted therapy in the near future is probably over-optimistic, considering that therapeutics studies are still immature because of the big number of genes that a single miRNA can target, leading to a pleiotropic effect that limits their manipulation at the systemic level. Nevertheless, the increasing capability of producing synthetic interfering miRNAs with higher affinity to the desired target is minimizing this barrier[10,11].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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