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Letter to the Editor

MicroRNA-552 in colorectal cancer with poor prognosis. Its role as a novel molecular biomarker

Dear Editor,

Amongst the biomolecules currently used for laboratory diagnosis in colorectal cancer (CRC),[1,2] many have been shown to be insufficient for predicting prognosis in the critical stages of the disease. This is still the case today, even though significant advances have been made in early diagnosis and therapeutic strategies, e.g. with extensive SNP analysis in oncogenes. CRC still draws great attention worldwide because of its high incidence rate and mortality. At the moment, specific and selective diagnosis by optimal molecular biomarkers is of utmost necessity in patients with poor prognosis, because of the extremely low therapeutic potential and the need for a fast response for a possible individualized target therapy[2].

Over the last decade, micro-RNA functions study have changed our understanding of cells and diseases with a particular emphasis on cancer biology. For this reason, several miRNAs are currently being intensively studied and proposed as promising candidates in cancer therapy and/or as biomarkers to reveal disease progression and prognosis[1]. The use of miRNAs in cancer diagnosis could offer several advantages[1]. First of all, the non-invasive nature of miRNA-based assays, together with their sensitivity, selectivity, and specificity in detecting cancers. Furthermore, another positive point for proposing these biomolecules as interesting molecular targets is due to the fact that they use easy and less expensive tools, such as the Real-time quantitative PCR, to detect genic expression levels[3-9].

In this context, the paper by Wang et al[10], describing miRNA-552 on CRC, is particularly interesting. The authors noted the possibility of using miR-552 as biomarker in CRC with poor prognosis. In fact, as already showed by Cao et al[11], miR-552 promotes tumor cell proliferation and migration. Furthermore, it was detected in high levels in advanced forms of CRC.

Genomic Organization and Biological Function of miR-552

The miR-552 gene is located in chromosome 1 and is 96 bp long (gene-card report). The final mature RNA is represented by a short oligonucleotide of 21 bp, Figure 1. If we consider its interaction with the biochemical pathway of cytochrome P450, the function of this miRNA acts at two points inside the cell, i.e. as an inhibitor at the transcriptional and post-transcriptional level, in the nucleus, and cytosol, respectively. Although the function of nuclear miRNAs has yet to be fully discovered, emerging findings have supported the possibility of gene silencing molecules in mammalian cells. The failure of protein transcription, such as an enzyme, can often lead to undesirable biological results. For example, the inhibition of P450 by miR-552 can induce the generation of reactive oxygen species (ROS) in hepatic cells, due to the failure in the oxidation rate of crucial metabolites, for example ethanol. This could be responsible for different adverse biological events such as: (i) hepatic insulin resistance and (ii) oncogenes activation.

In CRC the function of miR-552 in cancer promotion and dissemination is activated via the Wnt/β-catenin pathway and its expression level is significantly upregulated[10,11]. In particular, Cao et al[11] explain the effective role that this miRNA plays in CRC. The authors showed how the transcriptional level of miR-552 in both cancer tissues recruited from patients and in cell lines, was strictly associated with the Dachshund family transcription factor 1 level, (DACH1). This is a

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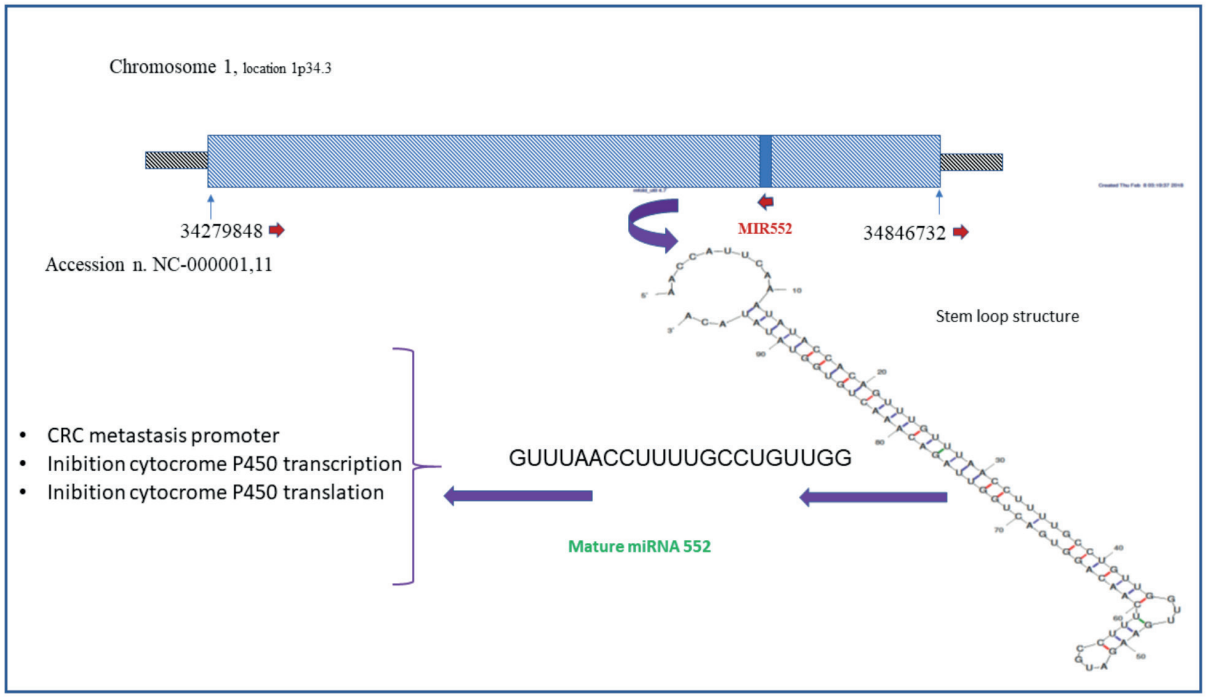

Figure 1. Genetic organization of the miR-552 gene, the stem loop structure of its primary transcript and main functions recently described[1].

chromatin-associated protein, which is able to bind some transcription factors to regulate gene expression. It represents an important protein for allowing cell fate determination during development, but the expression of the DACH1 gene results as being very low, or even lost, in CRC forms with poor prognosis[11]. However, the exact molecular mechanisms for the anti-tumor roles of DACH1 in CRC still lack of extensive understanding[10]. Different *in vitro* and *in vivo* studies have described how the transcriptional levels of miR-552 and DACH1 are negatively correlated, in which an increase in miR-552 determine a decrease in DACH1 and, consequently, an increased risk for highly aggressive metastatic CRC cancer. Wang et al10 has expressed the biological results of Cao et al[11] through clinical-biochemical features in a cohort of CRC patients. Out of 183 pairs of primary CRC, miR-552 was evaluated by quantitative Real-time PCR with a genic expression protocol, analyzing the association between the miR-552 expression level and the patient's clinical parameters. miRNA expression was significantly higher in CRC tissues than in the corresponding non-cancerous tissues; interestingly, the survival curve suggested a strong correlation between miR-552 expression and fate prognosis[10]. Figure 2 shows the % differences in CRC tissues with low and high miR-552 levels for the significant clinicopathological features of patients ($p<0.05$). As can be seen, high levels of transcription are significantly associated with: (i) histological grade of CRC, (ii) lymph node metastasis and with (iii) classification of malignant tumors (TMN).

The standard of care for patients with CRC is represented by adjuvant chemotherapy with, in some cases, surgical tumor resection[12-15]. Current clinical guidelines for CRC provide clear instructions for chemotherapy for TMN high-risk patients, but are insufficient to individualize a precise therapy. As regards this, a high specific pathological marker could predict response to individualized therapy in a convenient, fast, and inexpensive way, which would also be able to condition humor and comfort levels in patients with cancer[15-17]. Molecular pathology based on miRNA (miRNAome) is an emerging and crossover discipline that has focused its study on the miRNA population involved in CRC biology for advanced uses in diagnosis as well as in

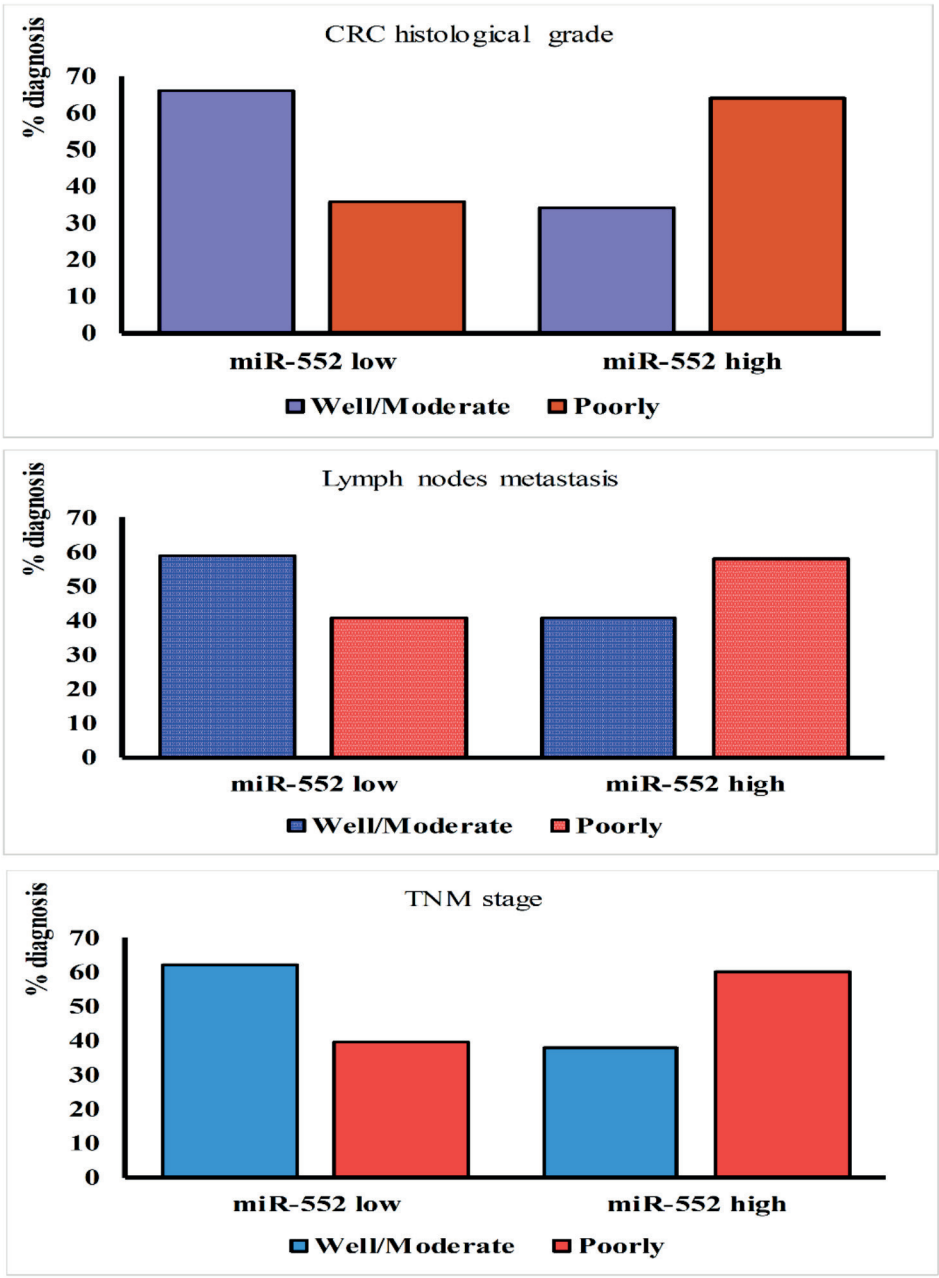

Figure 2. Correlation % between some significant clinicopathological features and miR-552 expression in CRC ($p<0.05$)[10].

cancer therapy. Amongst the different miRNAs recently described in CRC, the miR-552 studied by Wang et al[10] may be a very strong target in CRC with poor prognosis. In particular, it could speed up clinical assessment as regards fate prognosis, for a possible targeted therapy.

Conflict of interest

The authors declare no conflicts of interest.

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