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Original article

MiR-670-5p induces cell proliferation in hepatocellular carcinoma by targeting PROX1

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ABSTRACT

MiRNAs, as oncogenes or as anti-oncogenes, play critically regulated roles in human cancers at posttranscriptional level. A number of dysregulated miRNAs has been observed in HCC. However, the expression and function of miR-670-5p have not been evaluated in HCC to date. In this study, we examined and confirmed the over-expression of miR-670-5p in HCC and in hepatoma-derived cells Hep3B. At least 60% of HCC tissues showed a greater than three-fold enhance in the expression of miR-670-5p compared with paired adjacent non-cancerous tissues. Knockdown studies for miR-670-5p showed that the expression of miR-670-5p promoted cellular proliferation. In tissues and cells with high expression of miR-670-5p, decreased expression of PROX1, a miR-670-5p predicated target, was detected. It confirmed that PROX1 expression was obviously affected by the expression of miR-670-5p. Furthermore, overexpression of PROX1 greatly inhibitted cellular proliferation. Therefore, it was inferred that miR-670-5p may play important roles in enhancing proliferation activity that is associated with HCC by modulating PROX1 expression at posttranscriptional level.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide with highest incidence, especially in Asia [1]. The high mortality is mainly attributed to a result of rapid progression and a lack of effective therapies. Although the surgical removal of the tumor is considered as the better means for treating HCC, it also bring out negative effects after operation. Therefore, study of the molecular mechanisms that control progression of HCC is important for the development of new therapeutic strategies.

MicroRNAs (miRNAs) are endogenous and small RNA molecules that play critical roles in post-transcriptional regulation by directly targetting mRNAs [2]. A number of miRNAs has been demonstrated to altered express in the occurrence and development of various human cancers, including HCC. miR-199a-5p was observed to be significantly down-regulated in HCC tissues and cell lines [3]. miR-122, as a liver-specific miRNA, is proved to impacts cell differentiation, proliferation, metabolism, stress and other liver processes by regulating the expression of a large number of target genes [4–6]. miRNA-433 was down-regulated in HCC tissues and cells and overexpression of miRNA-433 significantly suppressed the proliferation through restoring PI3K/AKT signaling in HepG2 cells [7]. miR-744 was also down-regulated in tissues and cells related to HCC and restoration of miR-744 decreased cell growth and restored G1 accumulation [8]. However, little has been carried out to identify the potential roles of miR-670-5p in HCC. Thus in present study, we detected miR-670-5p in HCC specimens and in hepatoma-derived cells. Apart from the expression in HCC, the functional effect of miR-670-5p was also detected in vitro. Our results showed that miR-670-5p was elevated in HCC and could modulate cell proliferation. A transcription factor PROX1 was identified as a target of miR-670-5p in HCC. Furthermore, the PROX1 expression was repressed by miR-670-5p and this posttranscriptional regulation may be important in enhancing proliferation activity that is associated with HCC.

2. Materials and methods

2.1. Patient samples

28 patients had been diagnosed with HCC and underwent resection at Shandong Jining NO.1 People's Hospital from 2012 to 2014. The paired adjacent non-cancerous tissues (NT) were obtained as control. All patients were informed consent by the

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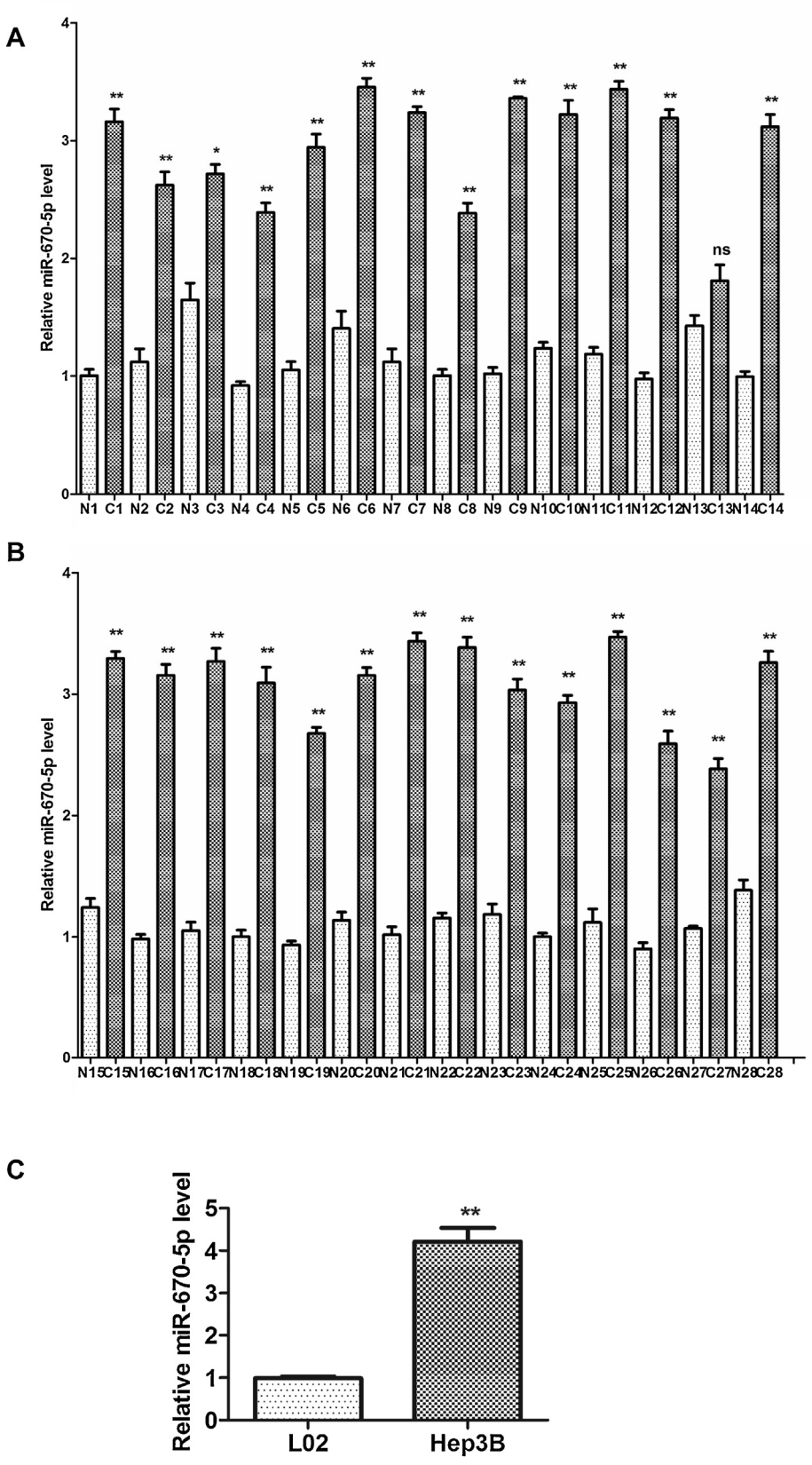

Fig. 1. miRNA-670-5p expression was detected in HCC tissues and cells using Real-time qPCR analyses.
(A and B) miRNA-670-5p was significantly increased in 27HCC tissues compared with NT except for one pair of specimens. Furthermore, at least 60% of HCC tissues showed a greater than three-fold enhance in the expression of miR-670-5p compared with NT. (C) The expression of miR-670-5p was also evaluated in HCC cell lines Hep3B. miR-670-5p expression was increased with four-fold in Hep3B compared with normal liver cell lines L02. U6 RNA was assessed as an endogenous control. $^{**}p < 0.01$, $^{*}p < 0.05$.