Research Article

Detection of the level of micro RNA 224 in patients with hepatocellular carcinoma.

Nady M. Semeda, Hala I. Mohammed, Zeinab M. Saad and Wael Soliman.
Department of Tropical Medicine, Faculty of Medicine, Minia University.

Abstract

Background: Liver cancer, predominantly hepatocellular carcinoma (HCC), is the second most deadly cancer worldwide. HCC is the most rapidly increasing cause of cancer-related mortality in the U.S. In Canada, total health care costs associated with HCV are expected to increase by 60% until they peak in 2032. Given the extremely frequent tumour recurrence even after aggressive treatment (70% after 5 years of surgical resection) and limited treatment options available for advanced-stage liver disease, including liver transplantation, a costly proposition, prevention of HCC development in patients with advanced liver fibrosis may be the most effective strategy to substantially impact patient survival. **Aim of study:** to detect the level of miR224 in different stages of hepatocellular carcinoma. **Methods:** An observational study, in Tropical Medicine Department, El-Minia University Hospital, El-Minia,-Egypt. Patients with hepatocellular carcinoma on top of HCV induced Liver cirrhosis collected among the patients of tropical medicine department from January 2017 to January 2018. Patients were divided into 3 groups according to Barcelona classification of liver cancer (BCLC) into, group 1 with BCLC A, group 2 with BCLC B, group C with BCLC C, and control group of LC without HCC, for all groups: history, examination and routine investigations, abdominal ultrasound, Multislice CT scan and miR-224 assay were done. **Results:** there was a significant difference between the level of miR 224 in different stages of hepatocellular carcinoma with the lowest level in BCLC A and the highest level in BCLC C with P value 0.001 indicating its role in predicting aggressiveness of hepatocellular carcinoma. **Conclusion:** miR-224 could serve as a good prognostic biomarker for HCC, and can be used as a marker predicting aggressiveness of HCC.

Keywords: LC, Hepatocellular carcinoma, miR–224.

Introduction

In patients with chronic HCV infection, the risk of HCC gradually increases as liver fibrosis progresses. Once cirrhosis is established, the annual incidence of HCC is extremely high (1-7% per year), although HCC rarely develops in less fibrotic livers[(1)]. The emergence of highly effective direct-acting antivirals (DAAs) for HCV is expected to reduce HCV-related HCC[(2)]. However, HCV eradication does not eliminate the risk of HCC, especially when the patients already have advanced liver fibrosis[(3)].

Although molecular mechanisms of HCV-induced HCC development have not been fully elucidated, these epidemiological observations suggest that the major role of HCV in carcinogenesis is to create a cirrhotic tissue microenvironment that serves as a carcinogenic milieu. In addition, direct carcinogenic effects of HCV proteins have been suggested in a variety of experimental models as additional drivers of HCV-induced HCC development[(4)].

MiR-224 is a potential oncogenic MiRNA that impacts multiple crucial cellular processes[(5)].

Transfection of miR-224 induced neuronal phenotypic changes by affecting the expression of neuronal-specific markers in stem cells derived from both mouse neural/brain tumor and human glioblastoma multiforme[(6)].

MiR-224 is greatly up-regulated in human HCC when compared to both paired peri-tumoral cirrhotic tissues and cirrhotic livers without HCC, and plays a role in cell proliferation, migration, invasion and anti-apoptosis[7].

Aim of study

To estimate the role of miR-224 in predicting aggressiveness of HCC by comparing its level in different stages of HCC patients.

Patients and Methods

Subjects

This study included thirty five patients with hepatocellular carcinoma (HCC) on top of hepatitis C virus (HCV) related liver cirrhosis and twenty patients with liver cirrhosis without hepatocellular carcinoma, matched for age and sex to studied group, as control group, all the patients were selected from the visitor to Tropical Medicine Department El-Minia university hospital.

Results

Table 1: shows the demographic data of studied groups of patients with HCC and control group of patients with LC

		HCC(n=35)	LC (n=20)	P value
Age in years (mean ± SD)		52±4	48± 10	0.544
Sex	Male	17(48.6%)	8(35%)	0.889
	Female	18(51.4%)	12(65%)	0.887

Table 2: shows the demographic data of the different three groups of patients with

Patients groups		Patients with HCC (n=35)			Patients with LC (n=20)	P value
Age in years (mean ± SD)		Group A ($n_=$ 15)	Group B (n= 10)	Group C (n=10)		
		45±11	55±8	57± 9	48± 10	0.776
Sex	Male	8(55%)	4(40%)	5(50%)	8(35%)	0.545
	Female	7(45%)	6 (60%)	5(50%)	12(65%)	0.667

HCC and the group of patients with LC:

Table 3: The mean levels of laboratory data in different HCC groups

Lab parameters mean±SD	HCC patients (n=35)			P value	
	Group A	Group B	Group C		
HB(gm%) Mean±SD	11.3±1.3	10.3± 1.4	9.7±.95	**P1 = 0.001 P2 = 0.001 P3 = 0.001**	**0.001**
Platelets Mean±SD	165.801±6515	110.803±8159	90.456±8657	P1=0.001 P2=0.001 P3=0.001	0.001
ALT(IU/ml) Mean±SD	28.8±7.8	63.8±6.3	114.6±1.4	P1=0.001 P2=0.001 P3=0.001	0.001
Bilirubin(mg/dl) Mean±SD	1.1±0.29	2.9±.003	5.6±0.1	P1=0.001 P2=0.001 P3=0.001	0.001

Table 4: The mean of level of miR 224 in studied patients of HCC and control groups

Variant	HCC patients			Control group	P value	
	Group A	Group B	Group C			
MiR 224 (CT value) (Mean±SD)	8.9±0.4	11.7± 0.5	14.4±.0.6	6.1±1.3	P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001	0.001

Discussion

Hepatocellular carcinoma (HCC) constitute the fifth common cancer and the second most frequent cause of cancer-related death around the world, with 854,000 new cases and 810,000 deaths per year, constituting for 7% of all cancers. Hepatocellular carcinoma (HCC) make about 90% of primary liver cancers and constitutes a major health problem all around[(8)].

miR-224 is one of the commonly over-expressed miRNAs in hepatocellular carcinoma (HCC)[(9)]. The upregulation of miR-224 starts form the precancerous stage and completed throughout HCC development[(10)]

When evaluating the ability of MiR- 224 in predicting progression and prognosis of HCC, we found that the serum level of miRNA 224 was increased as the tumor grade increase with its lowest level in BCLC A and its highest level in BCLC C, and these results was significant (P value 0.001), denoting the ability of MiR- 224 to predict the disease progression of HCC.

These results were consistent with results of Samah Mamdouh, et al., (2017), who found the same results in their study of 50 HCC patients and 20 healthy volunteers, and they found statistically significant difference between levels of MiR-224 in different grades of HCC (P value 0.02).[(11)]

This also was consistent with the results of Li-Ping Zhnang, et al., (2016) who studied. One hundred and eighty-two patients. The majority of patients were men and long-term hepatitis B virus (HBV) related cirrhosis. Of the 182 patients with HCC, the serum miR-224 levels were significantly higher in the stage C patients compared with the stage A and B patients (P= 0.005).[(12)].

Conclusion

In conclusion, miR 224 can play an important role in predicting grade and prognosis of HCC.

References

1- International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012 [Internet]. Lyon: International Agency for Research on Cancer; c2014.
2- American Cancer Society. Cancer facts & figures 2014 [Internet]. Atlanta: American Cancer Society; 2014 [cited 2014 Dec 4].
3- Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.
4- European Association for the Study of the Liver; European Organisation tor Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943
5- M. Mitsunobu, A., et al., "Intrahepatic metastases in hepatocellular carcinoma: the role of the portal vein as an efferent vessel," Clinical & Experi-

mental Metastasis, vol. 14, no. 6, pp. 520–529, 2015.

6- D. P. Bartel, "MicrRNAs: genomics, biogensis, mechanism and function," Cell, vol. 116, pp. 281–297, 2004.

7- G. A. Calin, et al., "Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers," Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 9, pp. 2999–3004, 2017.

8- Y. Zhang, et al., "Involvement of micro RNA-224 in cell proliferation, migration, invasion, and anti-apoptosis in hepatocellular carcinoma, Journal of Gastroenterology and Hepatology, vol. 28, no. 3, pp. 565–575, 2016.

9- Y. Wang, et al., "MicroRNA-224 is up-regulated in hepatocellular carcinoma through epigenetic mechanisms," The FASEB Journal, vol. 26, no. 7, pp. 3032–3041, 2017.

10- P. Gao, et al., "Deregulation of micro RNA expression occurs early and accumulates in early stages of HBV-associated multistep hepatocarcinogenesis," Journal of Hepatology, vol. 54, no. 6, pp. 1177–1184, 2016.

11- Samah Mamdouh, et al., "Evaluation of Mir–224, Mir–215, Mir–143 as serum biomarkers for HCV associated hepatocellular carcinoma", Asian Pac J cancer pev, 18(11), 3167-3171, 2017.

12- Li-ping Zhuang, et al., serum mIR 224 reflect stage of hepatocellular carcinoma and predict survival, Biomed research international, volume 2015, article ID 731781, 2016.