Int J Clin Exp Med 2016;9(3):6078-6085
www.ijcem.com /ISSN:1940-5901/IJCEM0022261

Original Article

Down-regulation of ZIP2 and ZIP8 expression in peripheral blood mononuclear cells from hepatitis B patients and hepatitis C patients

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Received December 19, 2015; Accepted March 5, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: ZIP2 and ZIP8 belong to the ZIP family of metal-ion transporters. It can transport zinc. ZIP8 is closely related with inflammation and immunity. ZIP8 caused T cells to exhibit enhanced activation. Our lab found that ZIP2 was over-expressed in leukocytes of asthmatic infants and pulmonary tuberculosis patients with lower serum zinc level. The persistence of virus that resulted from the low antiviral immune response had been thought to contribute to the pathogenesis of Hepatitis B virus (HBV)-induced diseases. So we wondered whether ZIP2 and ZIP8 were changed in the patients with chronic hepatitis B patients (CHB) and chronic hepatitis C patients (CHC). We examined the mRNA and protein expression levels of ZIP2 and ZIP8 zinc transporters in peripheral blood mononuclear cells (PBMCs) from patients with CHB (n=40), CHC (n=23) and healthy controls (n=39). Both ZIP2 and ZIP8 mRNA levels as well as protein expression levels were significantly decreased in CHB and CHC patients compared with healthy controls. While ZIP2 and ZIP8 mRNA levels had no significant difference among CHB patients with different HBV-DNA copy numbers. ZIP2 and ZIP8 mRNA levels had no significant difference among CHC patients with different HCV-RNA copy numbers. The results indicated that decreased expression of ZIP2 and ZIP8 genes are closely associated with immunity of CHB and CHC patients and suggest a role for ZIP2 and ZIP8 genes in the initial control infection and mediate the resistance and immunity of CHB and CHC patients through the promotion and maintenance immune response of adaptive T cell.

Keywords: ZIP2, ZIP8, hepatitis B virus, hepatitis C virus

Introduction

More than 350 million people worldwide suffer from chronic Hepatitis B virus (HBV) infection, and approximately 1 million of them die annually from HBV-induced liver diseases [1, 2]. About 130-170 million people worldwide are chronically induced with hepatitis C virus (HCV) [3]. The persistence of virus that resulted from the low antiviral immune response had been thought to contribute to the pathogenesis of HBV-induced diseases [1, 4]. Scientists have proposed that CHB could be one of the main reasons for pathogenesis of hepatocarcinoma and cirrhosis [5, 6]. However, the precise mechanisms underlying the HBV-mediated immune suppression in chronic infection are not completely understood.

ZIP8 (SLC39A8) and ZIP2 (SLC39A2) belong to the ZIP family of metal-ion transporters. They can transport zinc into cells [7-9, 13]. ZIP8 is closely related with inflammation and immunity. ZIP8 is highly expressed in T cells derived from human subjects. T cell ZIP8 expression was markedly up-regulated upon in vitro activation. Overexpression of ZIP8 caused T cells to exhibit enhanced activation. Knockdown of ZIP8 in T cells in non-activated and activated cells and concomitantly reduced secretion of IFN-gamma and perforin, both signatures of activation [10]. ZIP8 is a transcriptional target of NF-κB and functions to negatively regulate pro-inflammatory responses through zinc-mediated down-modulation of IKK activity in vitro [11, 24]. Ectopic expression of ZIP8 in mouse cartilage tissue caused Osteoarthritis cartilage destruction, whereas ZIP8 knockout suppressed surgically induced Osteoarthritis pathogenesis, with concomitant modulation of Zn^{2+} influx and matrix-degrading enzymes [12].

Table 1. The clinical characteristics of the subjects used for the validation analysis

Clinical variable	HC (n=39)	CHB (n=40)	CHC (n=23)
Age, mean ± SD, y	42.5±15	47.41±14	49.7±11
Sex, male/female	27/12	25/15	12/11
HBsAg, +/-	NA	39/2	NA
HBeAg, +/-	NA	31/10	NA
Liver function tests, mean ± SD			
Alanine aminotransferase, U/L	30±10	31±16	66±19
Aspartate aminotransferase, U/L	32±8	35±12	62±17
Alkaline phosphatase, U/L	119±30	129±45	99±28
Direct bilirubin, μmol/L	5±2	9±3	6±2
Total bilirubin, μmol/L	10±4	15±5	18±11
HBV DNA, copies/mL*	NA		
		$<2\times10^4$ (n=12)	
		2×10^4~1×10^6 (n=18)	
		$>1\times10^6$ (n=10)	
			$<1\times10^6$ (n=7)
HCV RNA, copies/mL*			1×10^6~1×10^7 (n=10)
			$>1\times10^7$ (n=6)

HC, healthy control; CHB, chronic hepatitis B patients; CHC, chronic hepatitis C patients; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen. *HBV DNA <1000 was treated as 0. *HCV RNA <1000 was treated as 0. Reference range of Alanine aminotransferase: 0-40 U/L; Reference range of Aspartate aminotransferase: 0-40 U/L; Reference range of Alkaline phosphatase: 40-150 U/L; Reference range of Direct bilirubin: 0-10 μmol/L; Reference range of Total bilirubin: 4-25 μmol/L.

Table 2. The specific primer for cDNA amplification

mRNA	Primer sequence	Size
β-actin	Forward 5'-ATTGGCAATGAGCGGTTCCG-3'	158 bp
	Reverse 5'-AGGGCAGTGATCTCCTTCTG-3'	
ZIP2	Forward 5'-CTCACGATGGGCAGTGTTCTC-3'	246 bp
	Reverse 5'-ATGAAGGCAAAACCAGCGGC -3'	
ZIP8	Forward 5'-ATTGGCAATGAGCGGTTCCG-3′	177 bp
	Reverse 5'-AGGGCAGTGATCTCCTTCTG-3'	

ZIP2 functions as an importer of zinc into cells [13]. It was found in prostate, uterus, peripheral blood mononuclear cells (PBMCs) and monocytes [14, 15]. Furthermore, global cDNA array analysis of zinc-regulated human genes showed that ZIP2 was most responsive to zinc depletion [16]. Recent study demonstrated that ZIP2 plays a relevant role in intracellular zinc homeostasis during zinc deficiency and in inflammatory pulmonary diseases, characterized by its over-expression [17, 18].

In this study, we thus examined the expression levels of ZIP2 and ZIP8 in PBMCs of chronic HBV and HCV infected patients, respectively analyzed the correlations between the ZIP2 and ZIP8 expression levels and the pathology grade of CHB, the correlations between the ZIP2 and ZIP8 expression levels and the pathology grade of CHC.

Materials and methods

Patients and controls

A total of 102 subjects, including 40 patients with CHB, 23 patients with CHC and 39 healthy individuals, were enrolled in this study. The diagnosis of these CHB and CHC patients were made according to the criteria established in the National Viral Hepatitis Conference of China. All patients were hospitalized in Jinan Infectious Disease Hospital (from May 2014 to June 2014). Clinical characteristics of enrolled subjects are summarized in **Table 1**. All of the included subjects were negative for antibodies to hepatitis D virus (HDV), hepatitis G virus (HGV), and human immunodeficiency virus (HIV), and had no autoimmune liver diseases. The healthy controls were got from the campus hospital of Shandong University in a health check (May in 2014).The study was approved by the Ethics

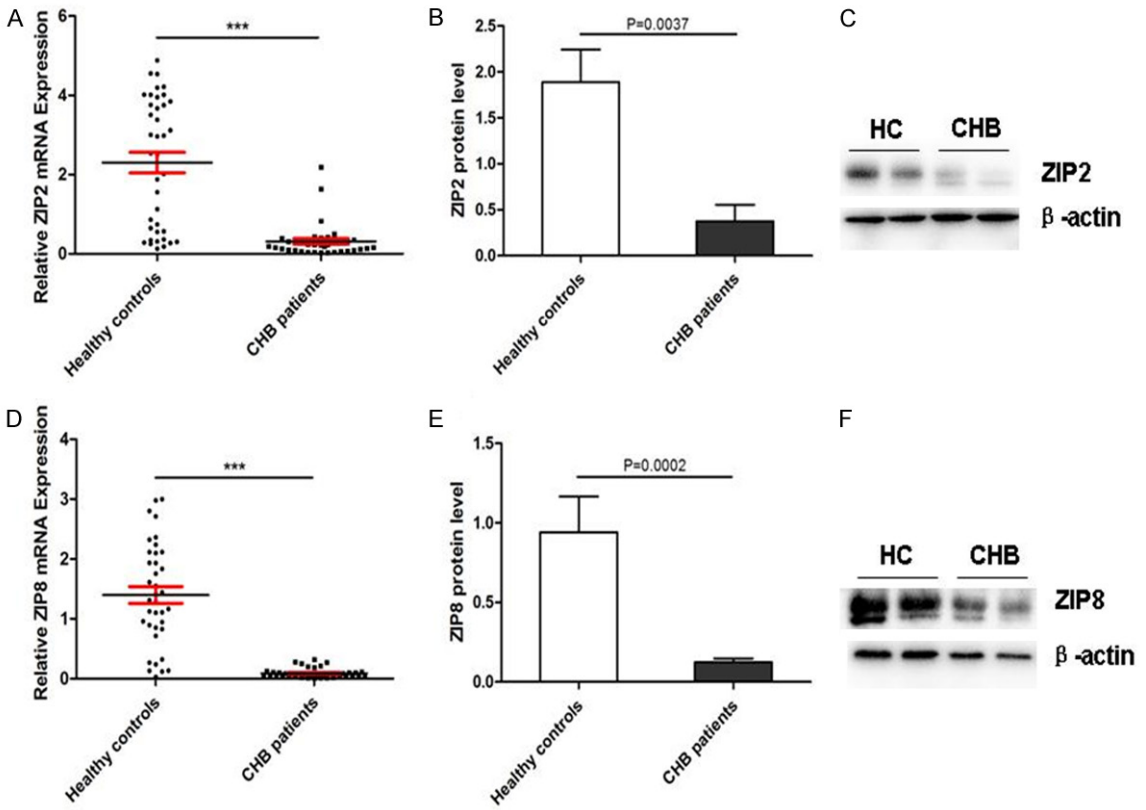

Figure 1. Real-time PCR and Western Blotting was performed to analysis the expression of ZIP2 and ZIP8 in chronic HBV infected patients. A. mRNA level of ZIP2 in PBMCs of CHB patients (n=40) and healthy controls (n=39). Results are shown as mean ± SD. The comparison between CHB and healthy controls is statistically different (P<0.0001). B. Relative ZIP2 protein expression level in healthy controls and chronic hepatitis B patients (ZIP2/β-actin, n=39, P=0.0037). Data, mean ± SD. C. Western blot analysis of ZIP2 protein level in healthy controls and chronic hepatitis B patients. Representative results were shown. β-actin was used as the control. HC and CHB: healthy controls and chronic hepatitis B patients. D. mRNA level of ZIP8 in PBMCs of CHB patients (n=40) and healthy controls (n=39). Results are shown as mean ± SD. The comparison between CHB and healthy controls is statistically different (P<0.0001). E. Relative ZIP8 protein expression level in healthy controls and chronic hepatitis B patients (ZIP8/β-actin, n=39, P=0.0002). Data, mean ± SD. F. Western blot analysis of ZIP8 protein level in healthy controls and chronic hepatitis B patients. Representative results were shown. β-actin was used as the control. HC and CHB: healthy controls and chronic hepatitis B patients.

Committee of Jinan Infectious Disease Hospital of Shandong University, and all subjects provided written informed consent prior to study participation.

PBMCs (peripheral blood mononuclear cells)

PBMCs was isolated by density gradient centrifugation as follows. Fresh anticoagulated blood from patients and healthy ones were diluted with the same volume of 0.01 M phosphate buffered saline (PBS, pH 7.2-7.4), the diluted blood was added to separation medium (TBD, China), subsequently centrifuged at 1500 rpm for 15 minutes. After centrifugation the PBMCs formed a layer between plasma and separation medium and extracted them into a tube, and at last collected the PBMCs by centrifugation.

RNA and cDNA preparation

The total RNA of PBMCs was extracted by Trizol total RNA purified kit (Sangon, China) from the leukocytes. The cDNA was synthesized from 2 ug of total RNA using the RevertAid™ First Strand cDNA Synthesis Kit (Fermentas, Canada), following the manufacturer's introduction.

Quantitative real-time PCR

The mRNA expression of zinc transporters were evaluated by quantitative real-time PCR, and

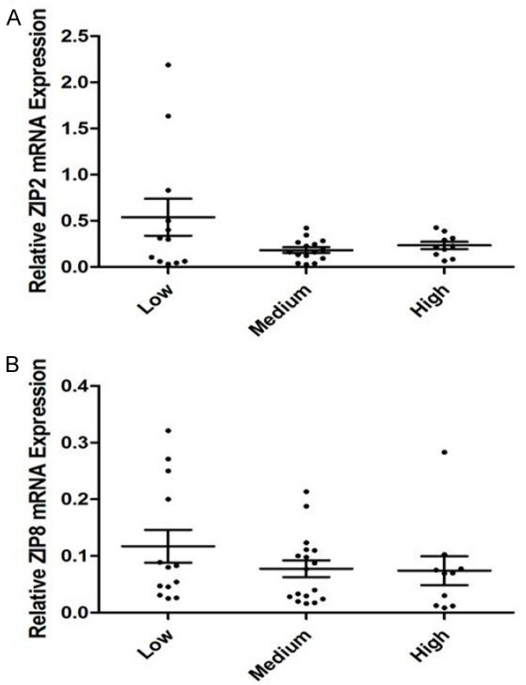

Figure 2. mRNA levels of ZIP2 and ZIP8 in PBMCs of CHB patients with different HBV-DNA copy numbers. A. Expression levels of ZIP2 were not affected by different HBV-DNA copy number. (Low: <20,000 (n=12), Medium: between 20,000-1000,000 (n=18) and High: >1,000,000 HBV-DNA copy numbers/ml (n=10)). Results are shown as mean ± SD. B. Expression levels of ZIP8 were not affected by different HBV-DNA copy number. (Low: <20,000 (n=12), Medium: between 20,000-1000,000 (n=18) and High: >1,000,000 HBV-DNA copy numbers/ml (n=10)). Results are shown as mean ± SD.

the level of β-actin mRNA was also detected as an internal control for each sample. Real-time PCR was performed in an Bio-Rad CFX96 Manager System (BIO-RAD, USA) using the SYBR Green I real-time PCR kit in accordance to the instructions of the manufacturer (TOYOBO, Japan), then melt curve from 65°C to 95°C, and each sample was run in triplicate. The PCR products were separated on a 1.5% agarose gel and were in all cases confined to a single band of the expected size. A melting-curve analysis was also performed to ensure specificity of the products. The relative mRNA expression of genes was determined using the comparative ($2^{-\Delta\Delta Ct}$) method. The specific primer sequences are shown in **Table 2**. ZIP8 mRNA level was analyzed using Taqman RT-PCR (ABI 7500 Fast Sequence Detection system, Applied Biosystems). The same mRNA expression analysis was performed on ZIP2.

Western blot analysis

Protein concentrations in the supernatant were estimated. Thirty micrograms of protein was separated by SDS-PAGE and transferred onto nitrocellulose membranes. After blocking with 5% (wt/vol) dried milk, each membrane was incubated with a primary antibody against one of the zinc transporters for 3 hours; this was followed by washing and subsequent incubation with the appropriate horseradish peroxidase conjugated IgG secondary antibody for 1 hour. Bound antibody was determined with an ECL detection system.

Statistical analysis

All statistical analyses were performed by a t test using SPSS software version 17.0. Description of quantitative variables was in the form of mean ± standard deviation. When a *P* value was less than 0.05 it was considered significant.

Results

Patients and controls

We analyzed that the demographic characteristics, clinical manifestations and laboratory measurements were shown in **Table 1**. Generally, forty chronic hepatitis B patients (n=40), twenty-three chronic hepatitis C patients (n=23) and sex- and age-matched thirty-nine healthy ones (n=39) were collected. The serum zinc level in the patients group was not significantly lower than the healthy group.

Quantification of ZIP2 and ZIP8 expression in PBMC from chronic HBV infected patients and healthy controls by real-time RT-PCR and Western blot

The expression of ZIP2 and ZIP8 in PBMC of 40 CHB patients and 39 sex- and age-matched healthy controls were measured using quantitative real-time RT-PCR and *western Blotting*. The primers sequence was showed in **Table 2**. The real-time RT-PCR results showed that expression of ZIP2 in the PBMCs of CHB patients was reduced by 7.38 fold when compared with healthy controls. Statistical analysis of the data revealed that the difference was significant (P<0.0001) (**Figure 1A**). Expression of ZIP8 in the PBMCs of CHB patients was also

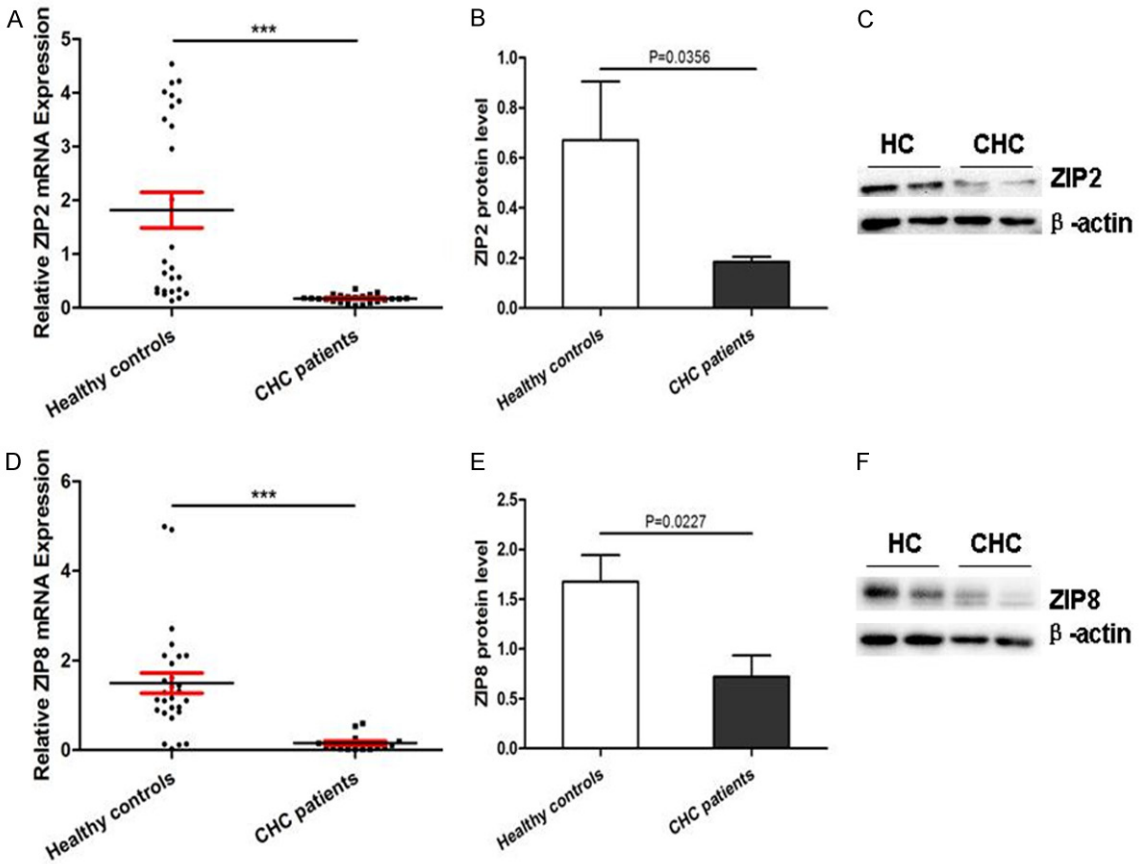

Figure 3. Real-time PCR and Western Blotting was performed to analysis the expression of ZIP2 and ZIP8 in chronic HCV infected patients. A. mRNA level of ZIP2 in PBMCs of CHC patients (n=23) and healthy controls (n=23). Results are shown as mean ± SD. The comparison between CHC and healthy controls is statistically different (P<0.0001). B. Relative ZIP2 protein expression level in healthy controls and chronic hepatitis C patients (ZIP2/β-actin, n=23, P=0.0356). Data, mean ± SD. C. Western blot analysis of ZIP2 protein level in healthy controls and chronic hepatitis C patients. Representative results were shown. β-actin was used as the control. HC and CHC: healthy controls and chronic hepatitis C patients. D. mRNA level of ZIP8 in PBMCs of CHC patients (n=23) and healthy controls (n=23). Results are shown as mean ± SD. The comparison between CHC and healthy controls is statistically different (P<0.0001). E. Relative ZIP8 protein expression level in healthy controls and chronic hepatitis C patients (ZIP8/β-actin, n=23, P=0.0227). Data, mean ± SD. F. Western blot analysis of ZIP8 protein level in healthy controls and chronic hepatitis C patients. Representative results were shown. β-actin was used as the control. HC and CHC: healthy controls and chronic hepatitis C patients.

reduced by 15.71 fold when compared with healthy controls. Statistical analysis of the data revealed that the difference was significant (P<0.0001) (**Figure 1D**). Western blotting to determine the protein level of ZIP2 and ZIP8 in PBMCs of CHB patients and healthy controls (**Figure 1B**, **1C**, **1E** and **1F**). A highly significant decrease in ZIP2 and ZIP8 expression was found in the PBMCs of CHB patients compared with healthy controls (P=0.0037, P= 0.0002), which is consistent with the qRT-PCR results. The association of ZIP2 and ZIP8 mRNA expression with HBV copy numbers/ml was analyzed respectively. The results revealed that the mRNA levels of ZIP2 and ZIP8 were not different among CHB patients with less than 20,000 HBV copy numbers/ml (n=12), between 20,000 to 400,000 HBV copy numbers/ml (n=18) and greater than 1000,000 HBV copy numbers/ml (n=10) (P>0.05) (**Figure 2A** and **2B**).

Quantification of ZIP2 and ZIP8 expression in PBMC from chronic HCV infected patients and healthy controls by real-time RT-PCR and Western blot

The expression of ZIP2 and ZIP8 in PBMCs of 23 CHC patients and 39 sex- and age-matched healthy controls were measured using quanti-

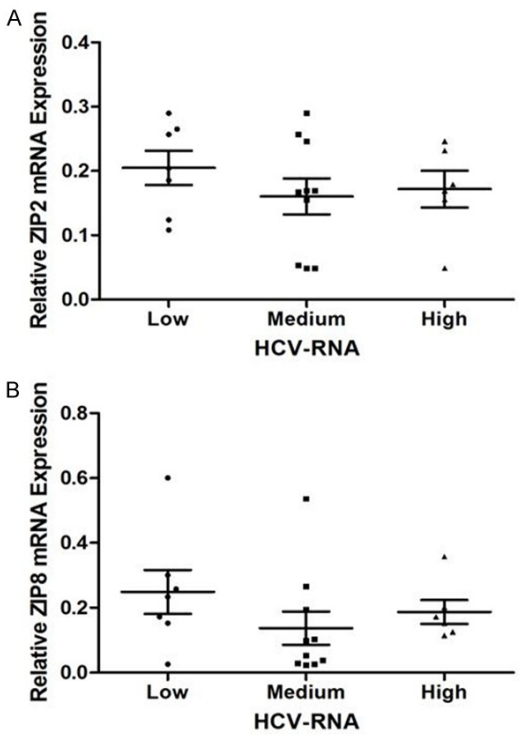

Figure 4. mRNA levels of ZIP2 and ZIP8 in PBMCs of CHC patients with different HCV-RNA copy numbers. A. Expression levels of ZIP2 were not affected by different HCV-RNA copy number (Low: $<1\times10^6$ (n=7), Medium: between 1×10^6 and =10) and High: $>1\times10^7$ HCV-RNA copy numbers/ml (n=6)) (P>0.05). Results are shown as mean ± SD. B. Expression levels of ZIP8 were not affected by different HCV-RNA copy number (Low: $<1\times10^6$ (n=7), Medium: between 1×10^6 and 1×10^7 (n=10) and High: $>1\times10^7$ HCV-RNA copy numbers/ml (n=6)) (P>0.05). Results are shown as mean ± SD.

tative real-time RT-PCR and *western Blotting*. The real-time RT-PCR results showed that expression of ZIP2 in the PBMCs of CHC patients was reduced when compared with healthy controls. Statistical analysis of the data revealed that the difference was significant (P<0.0001) (**Figure 3A**). Expression of ZIP8 in the PBMCs of CHC patients was also reduced when compared with healthy controls. Statistical analysis of the data revealed that the difference was significant (P<0.0001) (**Figure 3D**). Western blotting was used to determine the protein level of ZIP2 and ZIP8 in PBMCs of CHC patients and healthy controls (**Figure 3B**, **3C**, **3E** and **3F**). A highly significant decrease in ZIP2 and ZIP8 expression was found in the PBMCs of CHC patients compared with healthy controls (P=0.0356, P=0.0227), which is consistent with the qRT-PCR results. The association of ZIP2 and ZIP8 mRNA expression with HCV copy numbers/ml was analyzed respectively. The association of ZIP2 and ZIP8 mRNA expression with HBV copy numbers/ml was analyzed respectively. The results revealed that the mRNA levels of ZIP2 and ZIP8 were not different among CHC patients with less than 1×10^6 HCV-RNA copies/ml (n=7), between 1×10^6 and 1×10^7 HCV-RNA copies/ml (n=10), and greater than 1×10^7 HCV-RNA copies/ml (n=6) (P>0.05) (**Figure 4A** and **4B**).

Discussion

Hepatitis B virus affects a large population in the world, the situation is worse in developing countries. In this study, the expression of ZIP2 and ZIP8 were researched in the CHB and CHC patients, the results showed that the expression of ZIP2 and ZIP8 mRNA and protein in the CHB and CHC patients were significantly lower than in the control group respectively. Our lab found that ZIP2 over-expressed in asthmatic infants leukocytes and PTB patients PBMC with lower serum zinc level [18, 19]. Cousins R. J, et al. studies showed human monocytic/macrophage THP-1 cells depleted of zinc with TPEN(a membrane permeate metal chelator) caused up regulation of ZIP2 at least 27-fold [16]. The ZIP2 knock-out mice showed expression of ZIP2 exhibited highly cell-specificity; ZIP2 expressed obviously in a subpopulation of immature dendritic cells [20]. All these indicate that ZIP2 may play a role in the immune system especially when the body is zinc deficiency. But in this study, CHB and CHC patients didn't have lower serum zinc level compared with healthy group. CHC patients can be cured with INF. Knockdown of ZIP2 by siRNA decreased ZIP2 levels in PBMC from PTB patients and concomitantly reduced expression of INF-γ and increased expression ofIL-6 [19]. The results indicated that ZIP2 protein may be closely associated with immunity of CHB and CHC patients.

In this study, the expression of ZIP8 mRNA and protein in the CHB and CHC patients were significantly lower than in the control group respectively. Aydemir TB found that ZIP8 was markedly up-regulated in activated human T cells, overexpression of ZIP8 increased of IFN-γ level in vitro. And knockdown of ZIP8 in T cells by siRNA

could decrease ZIP8 levels and concomitantly reduce secretion of IFN-γ and perforin [10]. The study also found that ZIP8 expression was significantly induced at the onset of infection and ZIP8 was intricately involved in maintaining innate immune defense [21]. ZIP8 is directly regulated by NF-κB at the transcriptional level, making it unique and highly specialized to allow the rapid sequestration of zinc in response to infection. Inflammatory mediators such as LPS and TNF-α induce ZIP8 expression in the lung, and expression of glycosylated ZIP8, which localizes to plasma membrane and mitochondria [22]. Knockdown of ZIP8 reduced cellular zinc content, impaired mitochondrial function in response to TNF-α and increased cell death [23]. In this article there was a decrease of ZIP8 expression in the HBV and HCV patients. But serum zinc level of the CHB and CHC patients was in normal range. The results indicated that ZIP8 protein may be closely associated with immunity of CHB and CHC patients.

We analyzed the correlation between ZIP2 level and HBV DNA copies/ml, between ZIP2 level and HCV RNA copies/ml, between ZIP8 level and HBV DNA copies/ml, between ZIP8 and level and HCV RNA copies/ml, the results showed that there were no correlations with them. On the one hand, It may be that the cases samples which we collected were not big enough, so we can not directly say that there were no correlation with them in the ZIP2 or ZIP8 expression levels and the pathology grade of CHB and CHC. This result may also need to increase the sample size in order to prove once again. On the other hand, decreased levels of ZIP2 and ZIP8 expression might be related to virus infection but has nothing to do with the HBV DNA copies and HCV RNA copies.

Acknowledgements

This work was supported by grants from the Shandong Provincial Nature Science Foundation of China (No. ZR2011HM049).

Disclosure of conflict of interest

None.

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