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Original Article

Expansion of myeloid-derived suppressor cells from peripheral blood decreases after 4-week antiviral treatment in patients with chronic hepatitis C

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Abstract: Myeloid-derived suppressor cells (MDSCs) are one of the most important regulators of anti-tumor T-cell responses in cancers. This study aimed to investigate MDSCs in the peripheral blood of patients with chronic hepatitis C (CHC) before and after 4-week treatment with pegylated interferon (PEG-IFN) and ribavirin, and to evaluate their correlation with $CD4^+CD25^{high}$ regulatory T cells (Tregs) and clinical parameters. A total of 80 patients with CHC were enrolled into this study, 37 of whom were treated with PEG-IFN and ribavirin. Compared with healthy controls (0.462% [range 0.257%-0.634%]), the proportion of MDSCs in the peripheral blood of 80 CHC patients (0.601% [range 0.333%-1.027%]) increased significantly before therapy (P=0.011). For 37 HCV patients, the proportion of circulating MDSCs (0 w: 0.597% [range 0.296%-1.021%], 4 w: 0.126% [0.066%-0.239%], P<0.01) and Tregs (0 w: 2.467±0.927%, 4 w: 2.074±0.840%, P=0.047) decreased significantly after 4-week antiviral treatment. No significant correlation was found between MDSCs and Tregs. These findings suggest that MDSCs expand in the peripheral blood of CHC patients, but decrease after 4-week antiviral treatment.

Keywords: Myeloid-derived suppressor cells, hepatitis virus C, interferon, regulatory T cells, immunosuppression

Introduction

Hepatitis C virus (HCV) is a kind of ribonucleic acid (RNA) virus addicted to the liver and its infection affects about 3% of people worldwide. Acute HCV infection is prone to establish persistent infection, leading to chronic liver injury in 70-80% of hepatitis C patients, while 20% of hepatitis C patients have a risk for the development of liver cirrhosis and hepatocellular carcinoma 20-30 years later. The standard treatment until May 2011 for hepatitis C is a combination of pegylated interferon (PEG-IFN) and ribavirin [1]. This treatment has resulted in a great success in the clinical outcome with higher rate of sustained virological response and lower rate of relapse. However, there are still un-response, poor response and relapse after this treatment, which might be partially related to the immunity microenvironment.

Regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs) are two important suppressive cells. Treg cells have been reported to play a critical but not full role in the intrahepatic immunosuppression which leads to T-cell failure and viral escape [2], while little is known about MDSCs specifically in the peripheral blood of patients with chronic hepatitis C (CHC). MDSCs have been described as a heterogeneous cell population derived from hematopoietic stem cells and have been the focus of intense study mainly in the field of cancers. MDSCs mainly accumulate in the bone marrow, while a few of them exist in the peripheral blood and peripheral lymphoid tissues and at the sites of diseases of both mice and humans [3]. Infiltration of MDSCs has been reported in both rat models and humans [4, 5]. MDSCs have also been described in other pathological settings such as parasite infections [6], autoim-

mune diseases (e.g. type 1 diabetes) [7], and graft-versus-host disease after organ transplantation [8]. In the hepatic diseases such as acute fulminate hepatitis [9], hepatocellular carcinoma [10], and liver transplantation [11], the immunosuppression of MDSCs has been reported. The mechanisms involved in the immunosuppression of Treg cell have been found in HCV infection [12], while that of MDSCs was less studied. A study has found the accumulation of CD33+ MDSCs in HCV patients and the suppression of MDSCs on T cells was mediated by reactive oxygen species (ROS) [13]. Cai et al found that the MDSCs from some samples of cryopreserved peripheral blood mononucleated cells (PBMCs) were responsive to antiviral therapy [14]. In the present study, fresh PBMCs were prepared and the MDSCs were investigated in CHC patients.

Immune suppressor activity of MDSCs has been associated with T-cell suppression involving high arginase 1 and inducible nitric oxide synthase (iNOS) activity as well as ROS production [15]. It has been reported that MDSCs may induce Treg cells [9]. This study was to detect the MDSCs in the peripheral blood of CHC patients before and after antiviral therapy with interferon and ribavirin, and to evaluate the correlation between MDSCs and Treg cells.

Materials and methods

Patients

A total of 80 CHC patients aged 15-75 years were recruited into present study from the Department of Infectious Diseases in the Third Affiliated Hospital of Sun Yat-Sen University between February 2011 and December 2012. The characteristics of these patients are shown in **Table 1**. 37 of these patients were treated with PEG-IFN (Pegasys) and ribavirin (900-1500 mg) for 1 year. The blood samples were collected before therapy and after 4-week antiviral treatment. According to the rapid virological response after antiviral treatment, patients were divided into 2 groups: (1) RVR HCV-RNA negative group; (2) NRVR HCV-RNA positive group. The remaining 43 CHC patients hadn't received antiviral treatment for many reasons and their blood samples were also collected to detect the MDSCs and evaluate their correlations with disease parameters. In addition, 50 sex- and age-matched controls were also recruited from healthy subjects who received routine physical examination in our hospital. All patients were positive for both anti-HCV and HCV RNA but negative for HBsAg and human immunodeficiency virus (HIV). Patients with concomitant metabolic or autoimmune disorders or severe dysfunction of the heart, liver and kidney were excluded from this study. Informed consent was obtained from each patient before study, and the whole study protocol was approved by the Ethics Committee of our hospital.

Collection of fresh PBMC samples

In brief, 5 ml of peripheral blood was collected from CHC patients by venipuncture before and after anti-viral treatment and from healthy controls. Blood was anti-coagulated with EDTA. After centrifugation, the plasma was removed and the PBMCs were separated by density gradient centrifugation (Ficoll-Hypaque) within 4 h.

Antibody incubation and flow cytometry

The monoclonal antibodies used in this study included PE-Cy5.5-HLA-DR, PE-CD11b, APC-CD33, FITC-Lineage cock-tail 1 (Lin 1) - CD3, CD14, CD16, CD19, CD20, CD56, PE-Cy™7-CD25, APC-Cy™7-CD4 and corresponding Isotype Control Becton Dickinson Biosciences, San Jose, CA, U.S.A. Before flow cytometry, the isolated fresh PBMCs were resuspended in PBS at 5×10^6 cells/ml. Then, 100 µl of PBMC suspension was mixed with sAb solution (2.5 µl of PE-Cy5.5-HLA-DR, 10 µl of PE-CD11b, 10 µl of APC-CD33, 10 µl of FITC-Lineage cock-tail 1 for MDSCs and 2.5 µl of PE-Cy™7-CD25, 2.5 µl of APC-Cy™7-CD4 for Treg cells). The final concentration of PE-Cy5.5-HLA-DR, PE-Cy™7-CD25 and APC-Cy™7-CD4 was 1.82%, and that of PE-CD11b, APC-CD33 and FITC-Lineage cock-tail 1 was 7.27%. Subsequently, 100 µl of PBMC suspension were mixed with corresponding Isotype sAb and incubated in dark on ice for 30 min. Cells were washed with 3 ml of PBS and resuspended. Detection and data acquisition were performed by using the FACSCalibur flow cytometer (Becton Dickinson, LSRII) and FACSDiva software (Becton Dickinson). Subsequent analysis was performed with FlowJo software (Becton Dickinson). Total PBMCs and lymphocytes were harvested firstly. PBMCs were then gated by selecting Lin-, HLA-DR negative cells. Cells expressing both CD33 and CD11b within

Table 1. Characteristics of 80 CHC patients

		N	Proportion of MDSCs [median (25%, 75%)] (%)
Sex*	Female	25	0.452 (0.252, 0.968)
	Male	55	0.765 (0.388, 1.106)
Age*	≥15, <25	16	0.652 (0.404, 1.315)
	≥25, <35	20	0.685 (0.312, 0.999)
	≥35, <45	25	0.797 (0.414, 1.115)
	≥45, ≤75	19	0.458 (0.120, 0.989)
HCV RNA load*	<5	15	0.467 (0.308, 0.903)
	≥5, <6	14	0.557 (0.356, 1.014)
	≥6, <7	26	0.789 (0.419, 1.118)
	≥7	25	0.658 (0.313, 1.409)
HCV antibody titer*	≥5, <12	17	0.458 (0.292, 0.905)
	≥12, <14	28	0.681 (0.171, 0.979)
	≥14, <15	21	0.599 (0.275, 1.088)
	≥15	14	0.862 (0.369, 1.519)
Genotype*	Genotype 1	42	0.716 (0.396, 1.154)
	Genotype 2	11	0.324 (0.119, 0.538)
	Genotype 3	8	0.669 (0.380, 1.191)
	Genotype 6	19	0.888 (0.499, 1.236)
AST (U/L)*	≤40	32	0.891 (0.490, 1.313)
	>40, ≤80	23	0.562 (0.204, 0.964)
	>80	25	0.452 (0.150, 0.914)
ALT (U/L)*	≤35	16	0.891 (0.368, 1.106)
	>35, ≤70	26	0.560 (0.416, 1.065)
	>70	38	0.632 (0.253, 1.042)
TB (umol/l)*	≤23.9	60	0.587 (0.343, 1.006)
	>23.9	20	0.601 (0.292, 1.214)
Outcome of anti-viral treatment#,*	RVR	31	0.597 (0.284, 1.046)
	NRVR	6	0.609 (0.379, 0.976)

#Patients with antiviral treatment; *Both nonparametric and spearman test showed no significant correlations between MDSCs and other disease parameters.

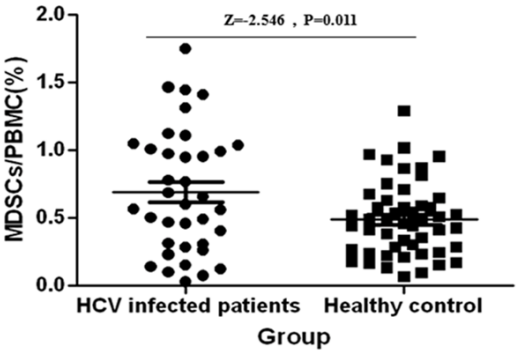

Figure 1. Circulating MDSCs in healthy controls and 80 CHC patients before treatment. When compared with healthy controls (0.462% [0.257%-0.634%]), the proportion of MDSCs were significantly increased in CHC patients (0 w: 0.601%, [0.333%-1.027%]; Z=-2.546, P=0.011).

this population were defined as MDSCs. Then, the proportion of MDSCs in PBMCs was calculated. As for lymphocytes, those positive for CD4 and highly expressing CD25 were defined as $CD4^{+}CD25^{high}$ regulatory T cells and its proportion to lymphocytes was calculated.

Serum test

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (TB) were detected in the laboratory center of our hospital with a Hitachi7170 automatic biochemistry analyzer. Hepatitis B surface antigen (HBsAg) and antibody IgM/IgG to HCV (anti-HCV) were detected by enzyme-linked immunosorbent assay (ELISA) (Kehua, Shanghai, China). HCV RNA was tested by reverse transcriptase poly-

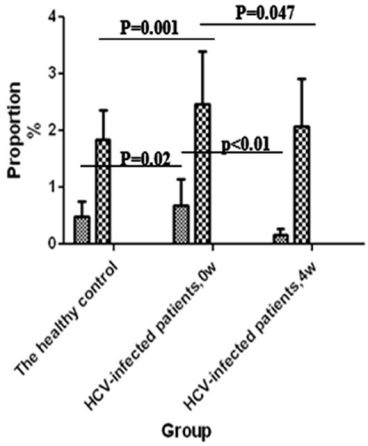

Figure 2. Proportion of MDSCs and $CD4^+CD25^{high}$ Treg cells in 37 CHC patients and healthy controls. When compared with healthy controls, both MDSCs and Treg cells in CHC patients before antiviral treatment significantly increased. Both MDSCs and Treg cells decreased after 4-week antiviral therapy.

merase chain reaction assay (DAAN Gene, Sun Yat-Sen University, China).

Statistical analysis

The proportion of MDSCs and Treg [16] were expressed as medians and ranges or mean ± standard deviations (SD). The proportion of MDSC and Treg was compared between CHC patients before treatment and healthy controls with nonparametric Mann-Whitney U test. The comparisons of the proportion of Treg cells were done with a 2-tailed Student t test. The proportion of MDSCs and Treg before and after treatment was compared with non-parameters Wilcoxon symbols test and paired t test, respectively. The correlation of MDSCs with Treg, gender, age, HCV RNA load, HCV antibody titer, HCV genotype, AST, ALT, TB and clinic outcome of anti-viral treatment was evaluated with the Spearman and nonparametric test. Statistical analysis was performed with SPSS version 16.0. A value of $P<0.05$ was considered statistically significant.

Results

MDSCs in CHC patients

Cells negative for Lineage cock-tail 1 and HLA-DR, but positive for both CD11b and CD33 were defined as MDSCs, while those positive for CD4 and highly expressing CD25 as Treg cells. MDSCs significantly elevated in CHC patients as compared to healthy controls ($Z=-2.546$, $P=0.011$). In addition, the proportion of MDSCs was higher in males than in females and they decreased with the level of ALT, both of which did not reach statistical significance. Age, HCV RNA load, HCV antibody titer, HCV genotype, AST, ALT, TB and early clinic outcome of anti-viral treatment did not correlate with the proportion of MDSCs. Though MDSCs have been reported to mediate the development of Treg cells [9], flow cytometry in the present study didn't show the same trend and the correlation analysis showed the *P* value was 0.949. The proportion of circulating MDSCs is shown in **Figure 1** and the correlation of MDSCs with gender, age and other parameters is summarized in **Table 1**.

MDSCs decrease after 4-week antiviral treatment

Of 37 patients receiving anti-viral therapy, 31 showed a rapid virological response (RVR), and 6 had no rapid virological response (NRVR). Both of them had a significant increase in the proportion of MDSCs to PBMC (RNR: median 0.597%, range 0.284%-1.046%, NRVR: median 0.609%, range 0.379%-0.976%) and the proportion of $CD4^+CD25^{high}$ to lymphocytes. However, the proportion of MDSCs and $CD4^+CD25^{high}$ of patients in both RVR group and NRVR group increased significantly, but no marked differences were noted between groups. After 4 weeks of antiviral treatment, both MDSCs and $CD4^+CD25^{high}$ regulatory T cells decreased (**Figure 2** and **Table 2**).

Discussion

MDSCs lack the mature myeloid marker on the cell surface. In mice, both the myeloid lineage differentiation antigen Gr-1 and integral protein alpha (CD11b, or macrophage-1) are described as markers of MDSCs. While in humans, MDSCs are defined as cells lacking markers of mature myeloid and lymphoid cells (such as CD3, CD19, CD57 and MHC class II molecule HLA-DR), but express both CD11b and CD33 [17]. Inhibitory activity of MDSCs has been mainly attributed to the production of arginase 1, iNOS, ROS and induction of Treg cells in many diseases [18]. MDSCs can suppress T-cell and B-cell function by direct cell-cell contact. Different antigens are as the markers of MDSCs in different studies. HLA-DR-CD33+ was used as a marker in renal cancer [4], and CD14+HLA-DR-/low as a marker in liver cancer [9]. In the present study, lin-HLA-DR-CD33+CD11+ was used as the marker of MDSCs as in gastric cancer [16].

Table 2. Proportion of MDSCs and $CD4^+CD25^{high}$ Treg cells

	Healthy controls (N=50)	CHC Patients (N=37)	
		Week 0	Week 4
MDSCs (%) [Median (25%, 75%)]	0.462 (0.257, 0.634)	0.597 (0.296, 1.021)	0.126 (0.066, 0.239)
Treg (%) [Median (25%, 75%)]	1.820 (1.405, 2.275)	2.570 (1.750, 2.940)	2.090 (1.435, 2.730)

Mainly transmitted by blood transfusion and drug abuse, HCV has been one of international health problems. Immune microenvironment is a critical determinant of the outcome of HCV infection. The immunity in 20-30% of acute HCV infection patients is strong enough to get rid of viruses, while that in the resting 70-80% is not so strong or impaired, and thus patients fail to eradicate viruses, leading to long term viral replication and immunopathological damage to the liver, which increases the susceptibility to the liver cirrhosis and hepatic cancer. HCV has been reported to cause the accumulation of MDSCs in a ROS-dependent feature [13]. In our study, when compared with healthy controls, CHC patients had a significantly increase in the proportion of MDSCs and Treg cells. Both of them act as a counterbalance to immune response and prevent severe damage to the liver. However, they suppress the antiviral response and facilitate the viral replication and chronic diseases at the same time.

MDSCs cooperate with Treg cells to suppress the antiviral response of T cells, B cells and NK cells during HCV infection. Some studies have shown the correlation between MDSCs and Treg cells: Treg cells increased with the decrease in MDSCs [9, 19] and a compensatory expansion of MDSCs was due to a lack of Treg cells [20]. However, in our study, no correlation was been found between them. It's reported that the increased activated Treg cells could protect HCV-infected liver from excessive antiviral immune response and delay the progression into liver fibrosis [2]. As another type of suppressor cells, MDSCs were also reported to slow the process of fibrosis by producing Arg1 [21]. Both MDSCs and Treg cells can not only suppress the immune function but attenuate inflammation and liver damage at the meantime. However, mechanism of these interactions between them is so complex that further investigations are needed.

To evaluate the effect of antiviral administration on MDSCs, the MDSCs from peripheral blood of 37 HCV-infected patients were compared before and after 4-week antiviral treatment. A significant reduction in MDSCs was found after 4-week antiviral treatment, which was consistent with the findings from the study of Cai et al [14]. The reduction in MDSCs after antiviral treatment may contribute to the disinhibition of immune system and promote the antiviral response of T cells. This provided another mechanism for the antiviral effect of interferon in HCV infection. IFN-α has been reported to improve the immunity microenvironment by inducing the maturation of MDSCs *in vitro* [22]. The decrease in MDSCs might be related to IFN-α which helped to improve the immunity in HCV infection and remove viruses. In both mice and humans, MDSCs have been reported to decrease the IFN response [23, 24]. However, there was no marked difference in the proportion of MDSCs between RVR patients and NRVR patients. IFN response may not be affected by MDSCs in the early phase of antiviral treatment and the MDSCs before treatment was not predictive for the short term outcome of anti-viral therapy. In addition, there was no correlation between MDSCs and Tregs after 4-week treatment. The interaction between IFN-α and immune microenvironment of host is very complicated and the role of MDSCs in this interaction may provide a new direction. To better understand the response of MDSCs to the combined therapy with PEG-IFN and Ribavirin, we will continue our study on the role of MDSCs in the antiviral treatment of CHC.

Conclusion

MDSCs expand in the peripheral blood of CHC patients, which may be associated with the immunosuppression and viral replication. MDSCs reduce after anti-viral treatment, which may help to strengthen the immunity to clear viruses. Some new treatments such as ATRA have been reported to differentiate MDSCs into relatively mature DC and improve the immunity [25]. Our findings provide a new immunotherapy aiming at the role of MDSCs in hepatitis C,

especially for those with worse outcome or relapse.

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Disclosure of conflict of interest

No conflicts of interest, financial or otherwise, are declared by the author(s).

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