Assessment of Altered Expression of CD81 by Dendritic Cells in HCV-Infected Patients Under Interferon/Ribavirin Therapy

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Abstract

Background: Hepatitis C virus (HCV) is a serious global health issue. It is estimated that 130 - 200 million people are chronically infected with HCV worldwide which accounts for 3% of the global population. Combination therapy with Pegylated Interferon and Ribavirin (PEG-IFN/RBV), has shown a low rate of sustained response. HCV genotype 4 (HCV genotype in about 90% of Egyptian patients) shows unfavorable response to combination therapy. Searching for causes of treatment failure has been the focus of many previous studies. CD81 is the most extensively characterized putative HCV receptor and the first HCV host factor to be identified by its ability to interact with a soluble form of HCV-E2 (sE2). The interaction between HCV-E2 and CD81 *in vitro* causes inhibition of the function of dendritic cells (DC), which affects the immune response to the virus.

Aim: To study the potential effect of HCV/CD81 interaction on the response to therapy in HCV patients (as a potential mechanism of treatment failure).

Methods: An analytical cross-sectional study was carried out on 20 healthy controls and 80 Egyptian chronic HCV-patients. Patients were divided into 4 groups according to their response to combination therapy: treatment naïve, EVR, NR and SVR. The results of the following lab tests were obtained from the patients' records: AST, ALT and HCV-RNA. Assessment of CD81 expression on DC by flow cytometry was done for all groups.

Results: CD81 expression on DC (CD123^{+}) cells was significantly lower in naive patients compared to control. The non-response to treatment was unrelated to the expression of CD81 on the tested cell; DC (CD11c^{+} or CD123^{+}). In the meantime, the good response to treatment was not associated with any changes in CD81 expression on DC (CD123^{+}). However, a significant rise in CD81 expression on DC (CD11c^{+}) among responders was found.

Conclusion: The failure to respond to combination therapy in HCV patients is not related to an altered expression of CD81 on both DC subsets. On the contrary, the alterations in CD81 expression on CD11c^{+} DC in those patients could be relevant for favorable control of HCV infection and favorable treatment response.

Keywords: *HCV; CD81; Dendritic Cells; PBMC*

Introduction

Hepatitis C virus (HCV), often termed the "silent epidemic", represents a significant health and social burden worldwide. It is estimated that about 500,000 deaths per year are caused by HCV [1]. In Egypt, HCV infection is a major health problem, where the prevalence is 10 folds higher than that in other countries [2]. Egypt is among the countries with the highest rate of HCV infection worldwide (> 10%) [3].

Of those with chronic HCV infection, 15 - 30% develop cirrhosis within 20 years. About 1-5% die from cirrhosis or liver cancer [4]. About 25% of liver cancer is due to HCV infection [3] and the risk of developing Hepatocellular Carcinoma (HCC) in HCV patients is about 7% [5].

Until 2011, the combination of PEG-IFN-α and RBV for 48 weeks was the approved treatment for chronic hepatitis C (CHC) [6]. However, it was not efficient and limited by drug resistance, toxicity and high cost. In January 2014, Sofosbuvir had been approved which provided a higher cure rate, fewer side effects and a two- to four-fold reduced duration of therapy [7]. However, the absence of a preventive vaccine and the high cost make the search for new treatments essential [8].

The exact mechanism(s) whereby HCV establishes and maintains its persistence and the subsequent liver damage is not well understood. One possibility is that HCV alters or inhibits selective but crucial immune functions [4]. Dendritic cells (DC) are the most potent professional antigen-presenting cells that regulate specific T-cell responses. A study showed that the cytotoxic activity of DC was upregulated to kill T cells during chronic HCV infection, which represented a mechanism of HCV immune evasion [9].

Initiation of HCV infection occurs through a complex multistep process involving a series of specific cellular entry factors. This process is likely mediated through the formation of a tightly orchestrated complex of HCV entry factors at the plasma membrane. Among HCV entry factors, the tetraspanin CD81 is one of the best characterized key player in the HCV life cycle [10].

CD81 is a membrane-associated protein that belongs to the family of tetraspanins. It is expressed widely on a variety of cell types, including hepatocytes, B lymphocytes, T lymphocytes, NK cells and dendritic cells. CD81 is the most extensively characterized putative HCV receptor and the first HCV host factor to be identified by its ability to interact with a soluble form of HCV-E2 (sE2) [11].

It contains a large extracellular loop (LEL) that is used by the virus for a productive entry into host cells (by binding with the major virus envelope protein E2) [12]. Binding of the HCV structural E2 protein to CD81 on B cells was suggested as a mechanism by which HCV may alter the activation status of lymphocytes [13]. Conclusive data documented the interaction between HCV-E2 and CD81 *in vitro*. This interaction causes a lowered activation threshold for both B and T lymphocytes and inhibition of NK cells, and DC [14].

CD81 is down regulated frequently in response to IFN-α treatment of HCV infection [15]. Silencing of CD81 expression in hepatoma cells inhibits HCV entry while CD81 expression in HCV-resistant hepatoma cell lines confers susceptibility to HCV entry [16]. Additionally, anti-CD81 antibodies can prevent HCV infection [17].

Patients and Methods

The study included 80 HCV Patients were classified according to their response to combination therapy into: 20 Treatment-naïve HCV patients, 20 Early virological responders (EVR), 20 Sustained virological responders (SVR), 20 Non-responders (NR). Patients were recruited from the Center of treatment of Viral Hepatitis- Ismailia Fever Hospital. The study also included 20 apparently-healthy volunteers age and gender matched blood donors. Laboratory work was performed at the Clinical Pathology Department of Suez Canal University Hospital, Ismailia, Egypt.

Definitions

- Combination therapy: Pegylated-α-IFN and ribavirin in a course of 180 μg/week IFN subcutaneously and 1000-1200 mg/day Ribavirin orally for 48 weeks.
- EVR: ≥ 2 log decline in serum HCV-RNA level from baseline or undetectable HCV-RNA in serum after 12 weeks of initiation of combination therapy.
- NR: < 2 log decline in serum HCV-RNA level from baseline after 12 weeks of initiation of combination therapy.
- SVR: Undetectable HCV RNA 24 weeks after the end of full course of combination therapy.

Methodology

Patients' records' review to obtain

Demographic data (name, age, gender and residence), duration of HCV, laboratory investigations: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) *(*HITACHI 902 automatic analyzer Roche Diagnostics, Germany*)*, HCV-RNA (qualitative and quantitative) by real time PCR.

Assessment of CD81 expression on DC by flow cytometry

Blood collection (sampling): Two ml of whole blood were obtained in sterile ethylene diaminetetraacetate (EDTA) vacutainers for surface staining with monoclonal antibodies.

Surface staining by monoclonal antibodies: Two plain Falcon tubes were prepared as follow: we added whole blood (100μl), PE-conjugated anti-CD11c antibodies (Clone: HL3, BD Pharmingen, Heidelberg, Germany), Percp-conjugated anti-CD123 antibodies (Clone: 7G3, BD Pharmingen, Heidelberg, Germany), FITC-conjugated anti-CD81 antibodies (clone: JS-81, BD Pharmingen, Heidelberg, Germany). Both falcon tubes were incubated for 20 minutes at 4°C.

Lysis of red blood cells

After surface staining, lysis of red blood cells was done using 2 ml of the lysis buffer (BD pharmingen, Heidelberg, Germany), followed by incubation at room temperature for 10 minutes in the dark, then centrifugation at 1500 rpm for 5 minutes. The supernatant was discarded, and the pellets were washed twice with 2 ml phosphate buffer saline (PBS) then centrifuged at 1500 rpm for 5 minutes. Supernatant was removed and the pellet was re-suspended in 300 μl of PBS for acquisition.

Gating and interpretation of the data

The cells were acquired, and fluorescence was analyzed by the fluorescent activated cell sorter (FACS Calibur, BD, Heidelberg, Germany) using Cell Quest software. Identification of DC: Monocytes were gated depending on both side and forward scatter. From the gated monocytes, DC were identified as those cells positive for CD123 and CD11c.

Identification of Identification of CD81 on DC

Percentage of DC expressing CD81 and their mean fluorescence intensity (MFI) were measured. The histogram of CD81 expression was used to assess HCV viral receptor on DC.

Statistical analysis

Statistical analysis was performed using the software SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL). Values were expressed as median and interquartile range (p25-p75) or mean ± standard deviation (SD) as appropriate. The Kruskal-Wallis test for analysis of non-parametric data was used to compare between groups followed by post-hoc analysis using Mann-Whitney U test. Correlations were done using the Spearman's correlation coefficient. Probability levels lower than 0.05 were considered significant. Receiver operating characteristic (ROC) analysis was performed to determine sensitivity and specificity of a classifier for a discrimination threshold.

Results

DC subpopulation

CD11c^{+} and CD123^{+} DC did not differ between HCV patients and controls. However, a significant decrease in CD11c^{+} (but not CD123^{+}) subpopulation was observed among responders after 12 weeks course (EVR) compared to naïve HCV patients (23.6% vs. 70%). While, no changes in the percentage of CD11c^{+} were observed among patients who did not respond to treatment (NR). In the meantime, CD123^{+} subpopulation showed no change on the 12 weeks course therapy however, a significant increase was observed after 6 months of discontinuing therapy compared to the values at 12 weeks of therapy (2.3% vs. 0.3%) and (9 vs. 2 MFI) (Table 1).

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		Control (n = 20)	Naive (n = 20)	NR (n = 20)	EVR (n = 20)	SVR (n = 20)	p-value[#]
CD11c (%)	Median	72[a]	70[a]	58.8[ab]	23.6[b]	53.1[ab]	0.02
	IQR	6 - 86	0 - 86	13 - 75	3 - 89	12 - 83	
CD11c (absolute)	Median	258[a]	184[ab]	127[ab]	93[b]	212[ab]	0.01
	IQR	25 - 704	1 - 539	56 - 1066	13 - 358	26 - 480	
CD123 (%)	Median	1.6[ab]	1.1[ac]	1.3[ab]	0.3[b]	2.3[c]	0.001
	IQR	0 - 3	0 - 11	1 - 2	0 - 3	1 - 7	
CD123 (absolute)	Median	5[ab]	4[a]	3[b]	2[b]	9[a]	0.001
	IQR	0 - 21	1 - 22	1 - 5	0 - 11	1 - 27	

Table 1: *DC frequency in the studied population.*

a, b, c: Indicator of within group statistical difference (Post-hoc analysis using Mann Whitney test);

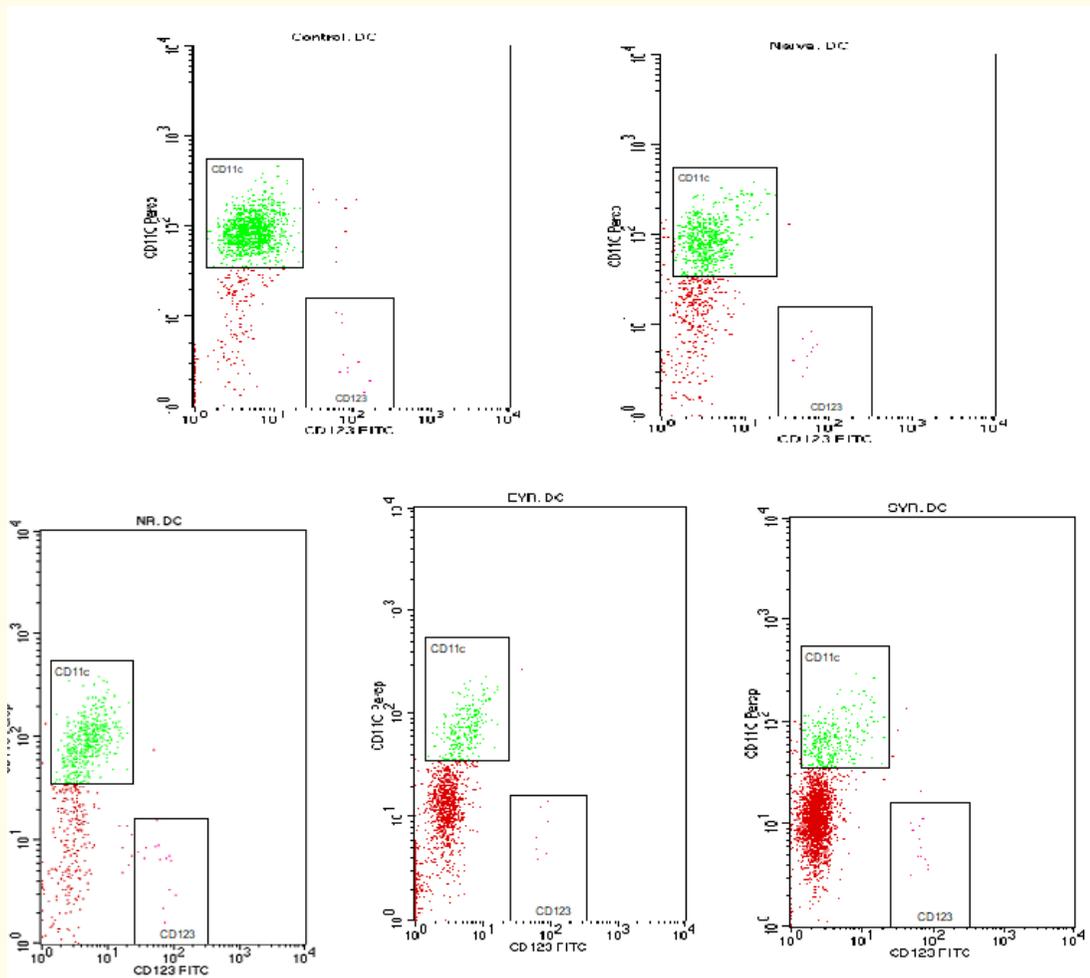*IQR: Interquartile Range; #: Kruskal Wallis; Statistical significant was considered at p ≤ 0.05.*

Figure 1: *DC Frequency in the studied population.*

CD81 surface expression on DC in HCV patients versus normal control:

a) CD81 surface expression on CD11c DC: The absolute count of CD11c DC expressing CD81 as well as its CD81 MFI in naïve HCV patients was significantly lower compared to control.

b) CD81 surface expression on CD123 DC: Percentage of CD81 expression plus its MFI by CD123 cells of naive HCV patients was significantly lower as compared to control.

CD81 surface expression on DC in relation to HCV combination therapy

To assess the effect of HCV combination therapy on CD81 expression on DC, naïve HCV patients were compared to those with different responses to combination therapy namely NR, EVR and SVR (Table 2).

		Control (n = 20)	Naive (n = 20)	NR (n = 20)	EVR (n = 20)	SVR (n = 20)	p-value[#]
CD81 expression by CD11c Myeloid dendritic cells							
CD81 (%)	Median	7.9[a]	5.9[a]	6.7[a]	27.8[b]	4.4[a]	0.001
	IQR	2 - 29	0 - 53	2 - 50	6 - 52	2 - 19	
CD81 (absolute)	Median	18[a]	8[b]	7[b]	18[a]	9[b]	0.02
	IQR	1 - 148	0 - 36	2 - 437	5 - 68	2 - 80	
CD81 (MFI)	Median	60.2[a]	15.4[bc]	19.4[bc]	49.7[a]	17.5[c]	0.0001
	IQR	26 - 116	0 - 68	3 - 106	15 - 96	8 - 95	
CD81 expression by CD123 Plasmacytoid dendritic cells							
CD81 (%)	Median	11.3[a]	2.9[b]	1[b]	3.8[b]	1.9[b]	0.001
	IQR	0 - 43	0 - 5	0 - 7	0 - 30	0 - 190	
CD81 (absolute)	Median	1	1	1	1	1	0.2
	IQR	0 - 6	0 - 2	0 - 1	0 - 1	0 - 1	
CD81 (MFI)	Median	26[a]	6.1[b]	12.2[b]	14.8[ab]	10[b]	0.0001
	IQR	0 - 415	0 - 53	6 - 22	7 - 55	6 - 25	

Table 2: CD81 surface expression on DC derived from PBMC.

a, b, c: Indicator of within group statistical difference (Post-hoc analysis using Mann Whitney test);

IQR: Interquartile Range; #: Kruskal Wallis. Statistical significant was considered at p ≤ 0.05.

HCV Non-responders

Patients who did not respond to treatment (NR) did not show any difference in the expression of CD81 on any of the tested cells (DC); comparable findings were observed between naïve patients and NR as regards the percentages, absolute count or MFI of CD81 expressing DC (CD11c^{+} or CD123^{+}).

HCV responders

Response to treatment after 12 weeks of therapy (EVR) was not associated with any changes in CD81 expression on DC (CD123^{+}). However, a significant rise in the percentage and MFI of CD81 expression on CD11c^{+} DC was observed in EVR group compared to either naïve HCV patients or NR.

Correlation between ALT, AST, viral load and HCV duration and CD81 percentage expression

Serum ALT, AST, viral load as well as HCV disease duration were tested as prognostic factors for response to treatment in HCV patients. A negative correlation between the percentage of CD81 expression by CD11c DC and liver transaminases (ALT and AST) was found (Table 3).

	ALT		AST		Viral load		HCV duration	
	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
CD81% by CD11c cells	-0.4	0.004	-0.4	0.001	-0.03	0.8	0.07	0.5
CD81% by CD123 cells	-0.03	0.8	-0.02	0.8	0.2	0.06	-0.01	0.9

Table 3: *Correlation between CD81 expression and prognostic factors of treatment response.*

ρ: Spearman Rank Correlation; Control cases are excluded. Statistical significant was considered at p ≤ 0.05.

CD81 expression as a predictor of response to combination therapy in HCV patients

CD81 expression in naïve vs EVR

We have assessed whether CD81% expression among naive patients could predict the virologic response after 12 weeks of therapy (EVR). Using ROC curve, CD81% expression by CD11c DC among naïve patients was able to predict the virologic response to combination therapy among responders at a cutoff value of > 0.082 with 90% sensitivity and 80% specificity (p = 0.001) (Figure 2a). However, CD81% expression by CD123 DC could not predict early virologic response to combination therapy (p = 0.9) (Figures 2b).
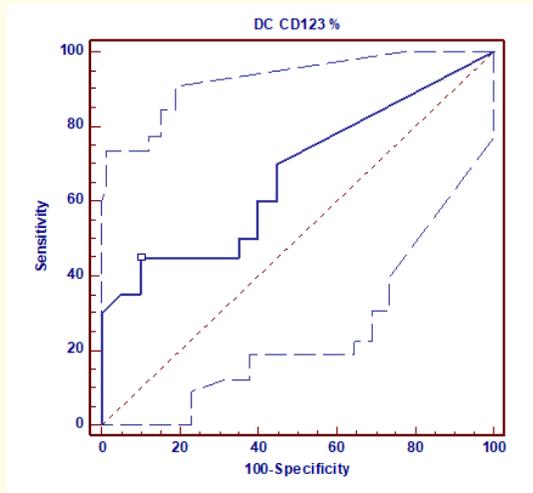
CD81 expression in naïve vs NR

We have assessed whether CD81% expression among naïve patients was able to predict the failure to respond to combination therapy after 12 weeks of therapy. Using ROC curve, CD81% expression by CD11c and CD123 DC could not predict the failure to respond to combination therapy among responders (p = 0.4, p = 0.06 respectively) (Figures 3a and 3b).
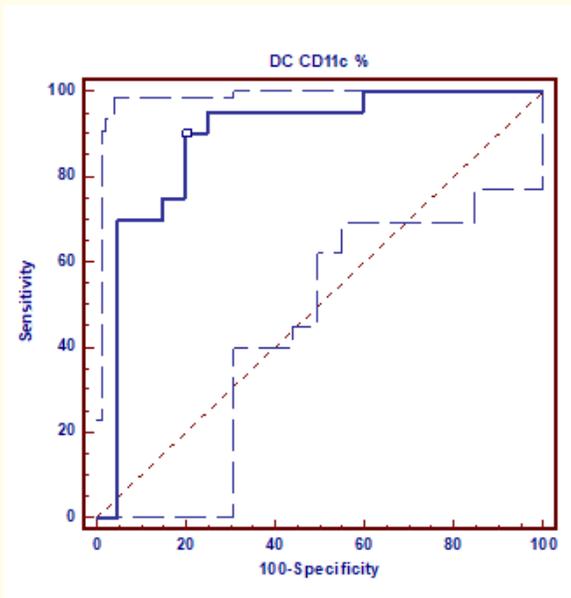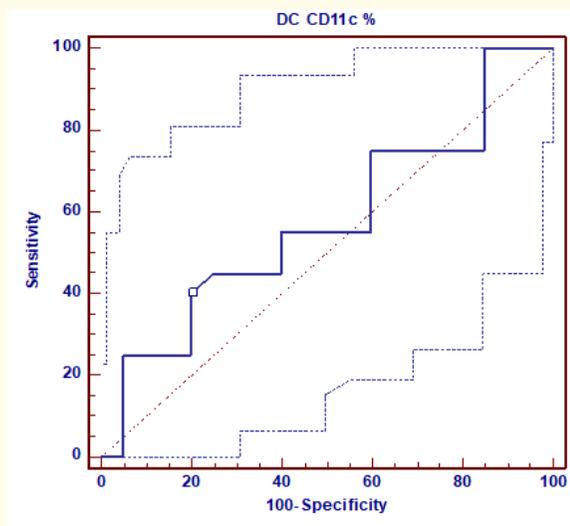

Area under the curve	89%
Standard error	0.06
95% confidence interval	0.744 - 0.963
p-value	0.001
Best cut off value	> 0.082
Sensitivity	90%
Specificity	80%
Positive predictive value	82%
Negative predictive value	89%
Positive likelihood ratio	4.5
Negative likelihood ratio	0.12

Figure 2a: *ROC curve analysis for value of CD81% expression by CD11c DC to predict early virological response among naïve patients.*
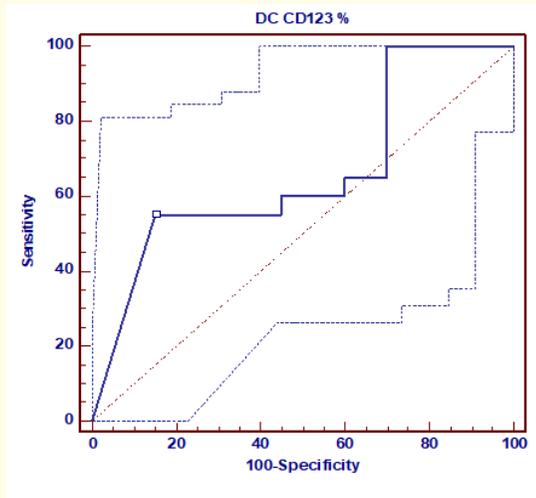
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Area under the curve	50%
Standard error	0.09
95% confidence interval	0.34 - 0.664
p-value	0.9
Best cut off value	≤ 0.001
Sensitivity	30%
Specificity	80%
Positive predictive value	55%
Negative predictive value	52%
Positive likelihood ratio	1.5
Negative likelihood ratio	0.88

Figure 2b: *ROC curve analysis for value of CD81% expression by CD123 DC to predict early virological response among naïve patients.*

Area under the curve	57%
Standard error	0.09
95% confidence interval	0.408 - 0.728
p-value	0.4
Best cut off value	> 0.082
Sensitivity	40%
Specificity	80%
Positive predictive value	67%
Negative predictive value	57%
Positive likelihood ratio	2
Negative likelihood ratio	0.75

Figure 3a: *ROC curve analysis for value of CD81% expression by CD11c DC to predict non-response to combination therapy among naïve patients.*

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Area under the curve	66%
Standard error	0.09
95% confidence interval	0.495 - 0.803
p-value	0.06
Best cut off value	≤ 0.001
Sensitivity	55%
Specificity	80%
Positive predictive value	73%
Negative predictive value	64%
Positive likelihood ratio	2.75
Negative likelihood ratio	0.56

Figure 3b: *ROC curve analysis for value of CD81% expression by CD123 DC to predict non-response to combination therapy among naïve patients.*
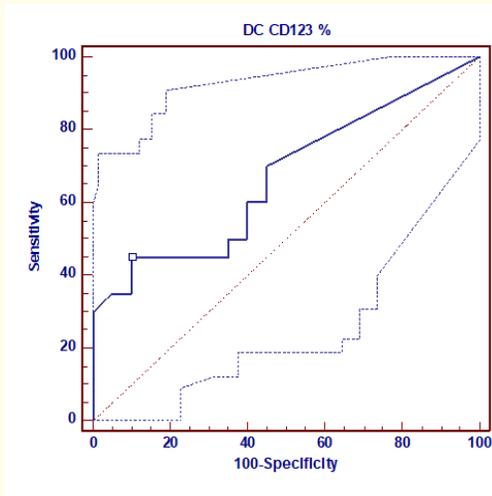
CD81 expression in EVR vs NR

We have assessed whether CD81% expression on DC could discriminate between responders and NR after 12 weeks of combination therapy using ROC curve. CD81% expression on CD11c and CD123 DC was able to discriminate between responders and NR at a cutoff value of >0.069 with 95% sensitivity and 55% specificity (p = 0.002) (Figure 4a), and a cutoff value of >0.056 with 45% sensitivity and 90% specificity (p = 0.004) (Figures 4b).
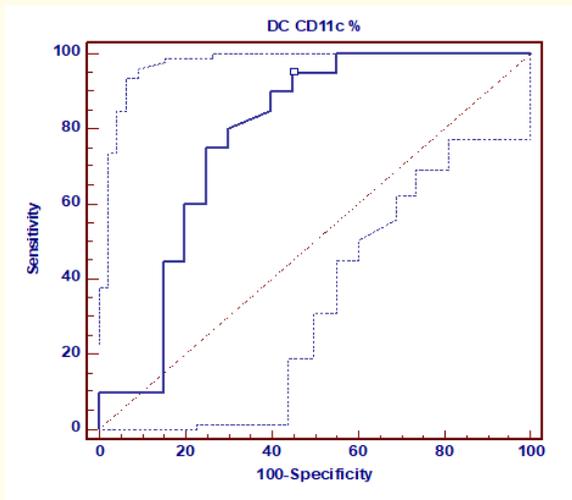
Area under the curve	78%
Standard error	0.07
95% confidence interval	0.618 - 0.893
p-value	0.002
Best cut off value	> 0.069
Sensitivity	95%
Specificity	55%
Positive predictive value	68%
Negative predictive value	92%
Positive likelihood ratio	2.11
Negative likelihood ratio	0.09

***Figure 4a:*** *ROC curve analysis for value of CD81% expression by CD11c DC to predict early virological response among NR.*

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09

Area under the curve	67%
Standard error	0.09
95% confidence interval	0.502 - 0.809
p-value	0.04
Best cut off value	> 0.056
Sensitivity	45%
Specificity	90%
Positive predictive value	82%
Negative predictive value	62%
Positive likelihood ratio	4.5
Negative likelihood ratio	0.6

Figure 4b: *ROC curve analysis for value of CD81% expression by CD123 DC to predict early virological response among NR.*
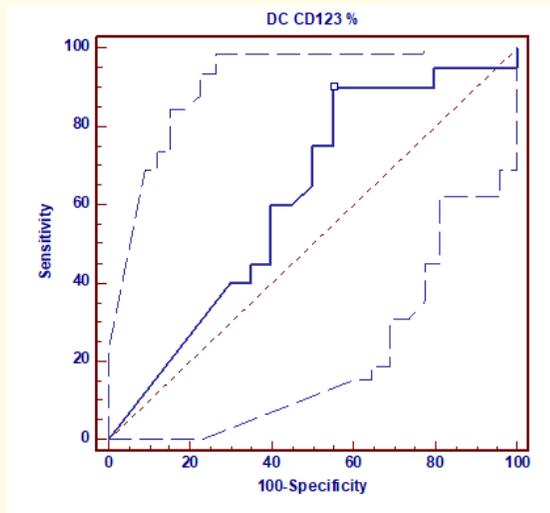
CD81 expression in EVR vs SVR

We have assessed whether CD81% expression among responders to treatment after 12 weeks of therapy (EVR) could predict the sustained virologic response after 6 month of drug discontinuation (SVR). Using ROC curve, CD81% expression by CD11c DC was able to predict the sustained virologic response to combination therapy among responders at a cutoff value of ≤ 0.103 with 85% sensitivity and 80% specificity (p = 0.001). However, CD81% expression by CD123 DC could not predict sustained virologic response to combination therapy among responders (p = 0.2) respectively (Figure 5a and 5b).
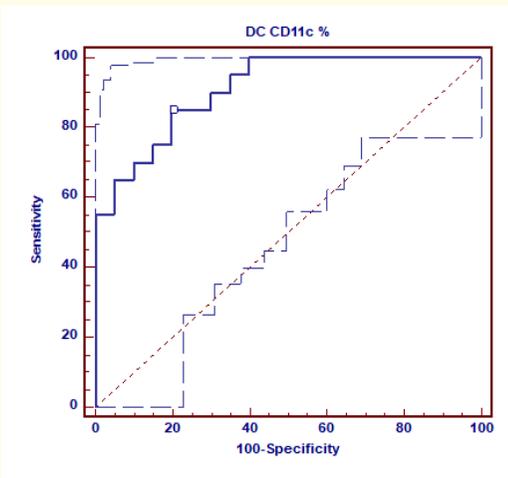
Area under the curve	91%
Standard error	0.04
95% confidence interval	0.776 - 0.976
p-value	0.001
Best cut off value	≤ 0.103
Sensitivity	85%
Specificity	80%
Positive predictive value	81%
Negative predictive value	84%
Positive likelihood ratio	4.25
Negative likelihood ratio	0.19

Figure 5a: *ROC curve analysis for value of CD81% expression by CD11c DC to predict sustained virological response among EVR.*

Figure 5b: *ROC curve analysis for value of CD81% expression by CD123 DC to predict sustained virologic response among EVR.*

Discussion

HCV combination therapy has shown a low rate of favorable response in HCV genotype 4 (HCV genotype in about 90% of Egyptian patients) [18]. Searching for causes of treatment failure has been the focus of many previous studies.

CD81 is the most widely characterized putative HCV receptor and the first HCV host factor to be identified by its ability to interact with a soluble form of HCV-E2. Investigating the potential outcome of the interaction between HCV and CD81 on the response to therapy may help understanding the mechanism of treatment failure and searching for more effective therapeutic approaches for HCV infection with genotype 4. The aim of this present study was to study the possible alteration in CD81 expression on DC that could predispose to treatment failure in HCV patients.

Dendritic cells are well known central regulators in both innate and adaptive immune responses against viruses. DC defects may contribute to chronicity in HCV infection and determine response to PEG-IFN and RBV therapy via poor T cell stimulation [19].

CD11c+ and CD123+ DC did not differ between naïve HCV patients and normal control. While, a significant decrease in CD11c+ was observed among responders (compared to naïve HCV patients). As regards, CD123+ subpopulation, no change on the 12 weeks course therapy, however, a significant increase was observed after 6 months of discontinuing therapy compared to the values at 12 weeks of therapy. These findings may suggest that IFN-α plus ribavirin therapy could have a direct incidence on the pool of circulating DC. Our finding agreed with previous reports who reported a reduction in circulating MDC and PDC in HCV patients receiving combined IFN-α/RBV antiviral therapy [20]. Also, Itose., *et al.* [21] showed that reduction of PDC after the introduction of combination therapy was much greater in the responders compared to SVR.

Moreover, Kanto., *et al.* (2004) also observed that in patients who cleared HCV after receiving IFN-alpha-based therapy, DC counts were comparable to those of healthy volunteers. Goutagny., *et al.* [22] observed that responders and non-responders patients had a significant decrease in the percentage of PDC in PBMC, compared with healthy individuals and untreated HCV patients. On other words, PBMC from HCV-infected patients receiving therapy display a lower percentage of circulating PDC. Mengshol., *et al.* [23] observed the percent of PDC increased significantly towards normal controls after therapy. Nattermann., *et al.* [24] found that patients who became HCV-RNA(-) under combined antiviral therapy with interferon-alpha and ribavirin displayed BDCA-1 (MDC) and BDCA-2 expression (PDC), which was

identical to that found in healthy individuals. Wertheimer., *et al.* [25] revealed no significant difference in either circulating MDC or PDC in subjects with spontaneously resolved HCV infection.

In contrast to our results, Cicinnati., *et al.* [20] showed that proportions of MDC and PDC were significantly lower in patients with chronic HCV infection compared with healthy volunteers. In addition, Della Bella., *et al.* [26] observed a significant reduction of both MDC and PDC in chronic HCV patients. Kanto., *et al.* [27] also observed that the absolute number of MDC and PDC were significantly lower in patients with chronic HCV than in healthy volunteers. Kunitani., *et al.* [28] showed that the numbers of circulating DC subsets in patients with liver diseases are decreased as compared with those of normal controls. Murakami., *et al.* [29] observed that the frequencies of PDC and MDC were significantly lower in patients with CHC compared to those of normal controls. Nattermann., *et al.* [24] found that a significantly lower proportion of circulating BDCA-1 expressing DC (MDC) and BDCA-2 expressing DC (PDC) in HCV-infected patients as compared with healthy individuals. Wertheimer., *et al.* [25] revealed significant reduction in both circulating MDC and PDC in patients with liver disease (with and without HCV infection).

The heterogeneity of the patients enrolled in the above mentioned studies in terms of mode of transmission, age and duration of HCV infection, virological characteristics (HCV genotypes, subtypes and viral loads) and the presence of coinfections or of advanced liver disease could account for the diversity of the results.

CD81 is an essential co-receptor for HCV which has an important function in the process of lymphocytes activation [30]. CD81 expression may be changed directly by the antiviral therapy or indirectly by reduction of the HCV serum level. The regulation of CD81 expression on lymphocyte and monocyte subtypes may be relevant for the control of viral infection and treatment response.

The percentage and/or the absolute count and/or MFI of CD81 surface expression by DC (CD11c and CD123) was significantly lower in naïve HCV patients compared to control. This could be a drawback of the small sample size of the studied population; further study on larger number would support of overlook this finding.

Studying the CD81 surface expression on DC in relation to HCV combination therapy revealed that HCV NR did not show any difference in the expression of CD81 on any of the tested cell type (DC); comparable findings were observed between naïve patients and NR as regards the percentages, absolute count or MFI of CD81 expressing DC (CD11c^{+} or CD123^{+}). Moreover, response to HCV treatment after 12 weeks of therapy (EVR) was not associated with any changes in CD81 expression on DC (CD123^{+}). However, a significant rise in the percentage and MFI of CD81 expression of CD11c^{+} DC was observed among responders compared to either naïve patients or NR.

The correlation between CD81 expression and some host and viral factors revealed a negative correlation between the percentage of CD81 expression by CD11c DC and liver transaminases (ALT and AST). While, no correlations were found between CD81 expression and, either HCV viremia or disease duration. This indicates that the changes in CD81 expression during treatment seem to be caused mainly by a direct effect of IFN-α on CD81 expression and not due to HCV concentration.

Prediction of virologic response in patients with chronic hepatitis C is highly important for both the patients and the community. In the current study we tested the ability of CD81 expression by DC to predict i) response, ii) non-response, and iii) sustained response to combination therapy in a cohort of HCV infected patients.

According to our findings, i) CD81% expression by DC (CD11c^{+}) among naïve patients was able to predict the early virologic response. ii) CD81% expression by DC (CD11c^{+}) was able to predict the sustained virologic response to therapy among responders iii) CD81% expression by DC (CD123 and CD11c) could predict the failure to respond to therapy. iiii) CD81% expression on DC (CD11c^{+} and CD123^{+}) could discriminate between responders and non-responders.

Conclusion

The failure to respond to combination therapy in HCV patients is not related to an altered expression of CD81 on either CD11c^{+} or CD123^{+} DC. On the contrary, the alterations in CD81 expression on CD11c^{+} DC in those patients could be relevant for favorable control of HCV infection and favorable treatment response.

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