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Original Article

IFN-γ, IL-17, IL-22$^+$ CD4$^+$ subset in patients with hepatitis C virus and correlation with clinical factor

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Abstract: Background: CD4$^+$ T cell responses in HCV infection have a crucial role in the immunopathology of hepatitis C virus (HCV) infection. Our aim was to investigate the frequency of Th1, Th17, and Th22 cells in HCV-infected patients and elucidate their role in the progression of the disease. Methods: Twenty-six HCV-infected patients and 26 healthy individuals were recruited. Peripheral blood mononuclear cells (PBMCs) were stained to separate CD4, IFN-γ, IL-17, and IL-22 producing cells using flow cytometry. Results: Results showed that the mean expression of IL-22 in CD4$^+$ T cells was significantly lower in HCV-infected patients compared to healthy controls. About correlation with clinical factor and T subsets, a negative correlation between the frequency of CD4$^+$ IFN-γ$^+$ cells and Thyroxine level (T4) was observed in the patients. The data showed a positive link between thyroid-stimulating hormone (TSH), cholesterol levels, and the frequency of Th17 cells. In addition, a positive correlation was seen between serum creatinine level with both Th1 and Th17. Ultimately, it was found that there was a positive link between viral burden and IL-17$^+$ IL-22$^+$ cells and a negative correlation between viral load and pure Th22. Conclusions: Our findings indicate that Th22 cells may play a part in the immunopathology of HCV and show the associations between Thelper subsets and the clinical signs of the disease.

Keywords: Hepatitis C, Th1, Th17, Th22, inflammation

Introduction

Hepatitis C is a liver infection that arises from the hepatitis C virus (HCV) categorized as a hepatotropic and non-cytopathic virus that is transmitted through contaminated blood products, sexual activity, and intravenous drug use [1, 2]. HCV infection remains a major global health problem, with around 58 million people of the world population being infected with it, while there is no vaccine for clinical use yet [3]. HCV infection is the prime cause of acute hepatitis, consequently resulting in chronic liver disease, which is characterized by fibrosis and cirrhosis and may ultimately lead to hepatocellular carcinoma (HCC) [4, 5]. In the chronic course of HCV infection, persistent virus replication in the hepatocytes may promote the stimulation of inflammatory responses leading to progressive fibrosis and damage to the liver [6].

It has been established that during HCV infection, a wide variety of cytokines contribute to viral clearance but also tissue injury [7]. The pro-inflammatory cytokines are fundamental prerequisites for initiating the inflammatory cascades and sustaining the chronic infection, which eventually results in hepatocellular liver injury [8]. Besides, chronic and inflammatory courses of HCV infection might cause an imbalance between the expression of pro-inflammatory and anti-inflammatory cytokines and che-

the viral load, genotypes, the extent of liver fibrosis and damage, and duration of inflammatory responses. Notwithstanding these limitations, our results provide new insights into the role of different helper subsets and their cytokine profiles in the pathology of HCV infection, which would be a fruitful area for further research.

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Disclosure of conflict of interest

None.

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References

[1] Schillie S, Wester C, Osborne M, Wesolowski L and Ryerson AB. CDC recommendations for hepatitis C screening among adults - United States, 2020. MMWR Recomm Rep 2020; 69: 1-17.

[2] Michalak TI. HCV lymphotropism and its pathogenic significance. Hepatitis C-From Infection to Cure 2018; 45-65.

[3] Taha G, Ezra L and Abu-Freha N. Hepatitis C elimination: opportunities and challenges in 2023. Viruses 2023; 15: 1413.

[4] Gülcicegi DE, Goeser T and Kasper P. Prognostic assessment of liver cirrhosis and its complications: current concepts and future perspectives. Front Med (Lausanne) 2023; 10: 1268102.

[5] Khatun M and Ray RB. Mechanisms underlying hepatitis C virus-associated hepatic fibrosis. Cells 2019; 8: 1249.

[6] Mondelli MU, Ottolini S, Oliviero B, Mantovani S, Cerino A, Mele D and Varchetta S. Hepatitis C virus and the host: a mutual endurance leaving indelible scars in the host's immunity. Int J Mol Sci 2023; 25: 268.

[7] Abouelasrar Salama S, Lavie M, De Buck M, Van Damme J and Struyf S. Cytokines and serum amyloid A in the pathogenesis of hepatitis C virus infection. Cytokine Growth Factor Rev 2019; 50: 29-42.

[8] Neuman MG and Cohen LB. Inflammation and liver cell death in patients with hepatitis C viral infection. Curr Issues Mol Biol 2021; 43: 2022-2035.

[9] Pocino K, Stefanile A, Basile V, Napodano C, D'Ambrosio F, Di Santo R, Callà CAM, Gulli F, Saporito R, Ciasca G, Equitani F, Basile U and Marino M. Cytokines and hepatocellular carcinoma: biomarkers of a deadly embrace. J Pers Med 2022; 13: 5.

[10] Ryscavage P, Hussien S, Seung H and Hynicka L. CD4+ T-cell recovery in HIV/hepatitis C co-infected patients following successful hepatitis C treatment. HIV Med 2024; [Epub ahead of print].

[11] Borhani K, Bamdad T, Hashempour A, Salek Farrokhi A and Moayedi J. Comparison of the inhibitory and stimulatory effects of Core and NS3 candidate HCV vaccines on the cellular immune response. Am J Clin Exp Immunol 2023; 12: 153-163.

[12] Kunkl M, Frascolla S, Amormino C, Volpe E and Tuosto L. T helper cells: the modulators of inflammation in multiple sclerosis. Cells 2020; 9: 482.

[13] Rožman P and Švajger U. The tolerogenic role of IFN-γ. Cytokine Growth Factor Rev 2018; 41: 40-53.

[14] Castro F, Cardoso AP, Gonçalves RM, Serre K and Oliveira MJ. Interferon-gamma at the crossroads of tumor immune surveillance or evasion. Front Immunol 2018; 9: 847.

[15] Ng CT, Fong LY and Abdullah MNH. Interferon-gamma (IFN-γ): Reviewing its mechanisms and signaling pathways on the regulation of endothelial barrier function. Cytokine 2023; 166: 156208.

[16] Pratim Das P and Medhi S. Role of inflammasomes and cytokines in immune dysfunction of liver cirrhosis. Cytokine 2023; 170: 156347.

[17] Cachem FCOF, Dias AS, Monteiro C, Fernandes G, Delphim L, Tavares F, Maciel AMA, Amendola-Pires MM, Brandão-Mello CE, Andrade RM and Bento CAM. Different core-specific T cell subsets are expanded in chronic hepatitis C with advanced liver disease. Cytokine 2019; 124: 154456.

[18] Matsuzaki G and Umemura M. Interleukin-17 family cytokines in protective immunity against infections: role of hematopoietic cell-derived and non-hematopoietic cell-derived interleukin-17s. Microbiol Immunol 2018; 62: 1-13.