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T Cells In Chronic HCV Genotype 4 Infected Patients

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Abstract

The T cell responses unique to the Hepatitis C virus (HCV) are strongly related to the disease's medical history. While T cell responses are often wide and multi-specific with self-limiting infections, in the chronic stage they show many unique functional impairment characteristics. Furthermore, by acquiring mutations in exhaust inside T targeted epitopes, HCV adapts quickly to an immunological pressure. Much of our existing information about HCV specific T cell responses is assumed to pave the path for a therapeutical vaccine at long last.

Keywords: T cell, HCV, genotype 4

Introduction

Hepatitis C Virus (HCV) persists in the most of chronic HCV genotype 4 infected patients despite the presence of specific neutralizing anti- bodies and T cell responses that contributes mostly to the progression of liver disease.**(1)**

Interactions between HCV glycoproteins with high-density lipoprotein (HDL) and the scavenger receptor B1 (SCARB1) may protect from neutralizing antibodies (**2**).

They found that HCV also can escape from neutralizing antibodies by direct cell to cell transfer of the virus [**3**]. T cell failure is due to T cell exhaustion and escape mutations.

Viral escape phenomenon in HCV was reported in chronic infected patients [**4**] and experimentally infected chimpanzees [**5**], and in acute HCV infections.[**6**].

It is known that viral escape was associated with the development of chronic infection.

It is also known that absence of viral escape is associated with clearance of HCV [**7**].

Insufficient CD4+ T cell contributes to the occurrence viral escape, through dysfunctional alterations of CD8+ T cells, or by viral fitness cost [**8**].

HCV-specific CD8+ T cell dysfunction was noticed in most HCV genotype 4 infected patients and characterized by inability to secrete cytokines, such as IFN-γ, or inability to proliferate [**9**].

T cell exhaustion is characterized by an upregulation of inhibitory receptors, such as PD-1 [**10**] and a low expression of CD127 [**11**]. Intrahepatic HCV-specific CD8+ T cells with a high PD-1 expression are prone to apoptosis [**12**].

There are several inhibitory receptors expressed on top of virus-specific CD8+ T cells [**13**]. Thus T cell exhaustion is mediated by expression of several different inhibitory receptors (2B4, KLRG1, CD160 and PD-1 in chronic HCV infection) [**14**].

It is also important that the lack of CD4+ T cell help also contributes also to virus-specific CD8+ T cell exhaustion [**15**].

In chronic HCV-infected patients there is also high frequency of suppressive CD4+CD25+ T cells [**16**].

The effect of antiviral treatment on restoration of T cells is also not well known.

IFN treatment in chronic HCV infection was not associated with CD8+ T cell restoration [**17**].

However, on the other hand direct acting antiviral (DAA) treatment can restore CD8+ T cell function [**18**].

High frequency of CD4+CD25+ T cells after treatment with DAA indicates progression of liver cirrhosis and increased risk of hepatocellular carcinoma. [**18**]

References

[1] Stegmann KA, Bjorkstrom NK, Veber H, Ciesek S, Riese P, Wiegand J, et al. Interferon-alpha-induced TRAIL on natural killer cells is associated with control of hepatitis C virus infection. Gastroenterology 2010;138: 1885–1897

[2] Timpe JM, Stamataki Z, Jennings A, Hu K, Farquhar MJ, Harris HJ, et al. Hepatitis C virus cell-cell transmission in hepatoma cells in the presence of neutralizing antibodies. Hepatology 2008;47:17–24.

[3] Brimacombe CL, Grove J, Meredith LW, Hu K, Syder AJ, Flores MV, et al. Neutralizing antibody-resistant hepatitis C virus cell-to-cell transmission. J Virol 2011;85:596–605.

[4] Chang KM, Rehermann B, McHutchison JG, Pasquinelli C, Southwood S, Sette A, et al. Immunological significance of cytotoxic T lymphocyte epitope variants in patients chronically infected by the hepatitis C virus. J Clin Invest 1997;100:2376–2385.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

[5] Weiner A, Erickson AL, Kansopon J, Crawford K, Muchmore E, Hughes AL, et al. Persistent hepatitis C virus infection in a chimpanzee is associated with emergence of a cytotoxic T lymphocyte escape variant. Proc Natl Acad Sci USA 1995;92:2755–2759.
[6] Erickson AL, Houghton M, Choo QL, Weiner AJ, Ralston R, Muchmore E, et al. Hepatitis C virus-specific CTL responses in the liver of chimpanzees with acute and chronic hepatitis C. J Immunol 1993;151:4189–4199.
[7] Cox AL, Mosbruger T, Lauer GM, Pardoll D, Thomas DL, Ray SC. Comprehensive analyses of CD8+ T cell responses during longitudinal study of acute human hepatitis C. Hepatology 2005;42:104–112.
[8] Tester I, Smyk-Pearson S, Wang P, Wertheimer A, Yao E, Lewinsohn DM, et al. Immune evasion vs. recovery after acute hepatitis C virus infection from a shared source. J Exp Med 2005;201:1725–1731
[9] Neumann-Haefelin C, Thimme R. Adaptive immune responses in hepatitis C virus infection. Curr Top Microbiol Immunol 2013;369:243–262.
[10] Rehermann B. Hepatitis C virus vs. innate and adaptive immune responses: a tale of coevolution and coexistence. J Clin Invest 2009;119:1745–1754.
[11] Radziewicz H, Ibegbu CC, Fernandez ML, Workowski KA, Obideen K, Wehbi M, et al. Liver-infiltrating lymphocytes in chronic human hepatitis C virus infection display an exhausted phenotype with high levels of PD-1 and low levels of CD127 expression. J Virol 2007;81:2545–2553.
[12] Penna A, Pilli M, Zerbini A, Orlandini A, Mezzadri S, Sacchelli L, et al. Dysfunction and functional restoration of HCV-specific CD8 responses in chronic hepatitis C virus infection. Hepatology 2007;45:588–601.
[13] Nakamoto N, Kaplan DE, Coleclough J, Li Y, Valiga ME, Kaminski M, et al. Functional restoration of HCV-specific CD8 T cells by PD-1 blockade is defined by PD-1 expression and compartmentalization. Gastroenterology 2008;134:1927–1937, 1937 e1921–e1922.
[14] Golden-Mason L, Palmer B, Klarquist J, Mengshol JA, Castelblanco N, Rosen HR. Upregulation of PD-1 expression on circulating and intrahepatic hepatitis C virus-specific CD8+ T cells associated with reversible immune dysfunction. J Virol 2007;81:9249–9258.
[15] Radziewicz H, Ibegbu CC, Hon H, Osborn MK, Obideen K, Wehbi M, et al. Impaired hepatitis C virus (HCV)-specific effector CD8+ T cells undergo massive apoptosis in the peripheral blood during acute HCV infection and in the liver during the chronic phase of infection. J Virol 2008;82: 9808–9822
[16] Kroy DC, Ciuffreda D, Cooperrider JH, Tomlinson M, Hauck GD, Aneja J, et al. Liver environment and HCV replication affect human T-cell phenotype and expression of inhibitory receptors. Gastroenterology 2014;146:550–561.
[17] Schlaphoff V, Lunemann S, Suneetha PV, Jaroszewicz J, Grabowski J, Dietz J, et al. Dual function of the NK cell receptor 2B4 (CD244) in the regulation of HCV-specific CD8+ T cells. PLoS Pathog 2011;7:e1002045.
[16] Bengsch B, Seigel B, Ruhl M, Timm J, Kuntz M, Blum HE, et al. Coexpression of PD-1, 2B4, CD160, and KLRG1 on exhausted HCV-specific CD8+ T cells is linked to antigen recognition and T cell differentiation. PLoS Pathog 2010; 6:e1000947.
[17] Boettler T, Spangenberg HC, Neumann-Haefelin C, Panther E, Urbani S, Ferrari C, et al. T cells with a CD4+CD25+ regulatory phenotype suppress in vitro proliferation of virus-specific CD8+ T cells during chronic hepatitis C virus infection. J Virol 2005;79:7860–7867.
[18] Cabrera R, Tu Z, Xu Y, Firpi RJ, Rosen HR, Liu C, et al. An immunomodulatory role for CD4(+)CD25(+) regulatory T lymphocytes in hepatitis C virus infection. Hepatology 2004;40:1062–1071.