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The Role of Myeloid-Derived Suppressor Cells (MDSCs) in the Immune Response Regarding Hepatitis C

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Abstract

Purpose of review: Hepatitis C virus infection and the immune response in babies and adults.

Findings: The presence of MDSCs in new-borns makes Hepatitis C chronic in the first years of life in the case of exposure to virus. The expansion of MDSCs allows the immune system to maintain the chronic infection with Hepatitis C because MDSCs are responsible for the disfunction of the immune system and not the virus itself. MDSCs express CTLA-4, who is a protein receptor that functions as an immune checkpoint and down-regulates immune responses. The expression of the CTLA-4 protein in the lymph node allows the manifestation of hepatitis C and allows the inhibition of T cells against HCV RNA.

Summary: MDSCs are responsible for chronic Hepatitis C infection. The expansion of MDSC is the format in which hepatitis C manages to escape the immune system's response. Inhibitory protein CTLA-4 expressed by MDSCs in lymph node maintain hepatitis C infection. MDSCs cells have the ability to interact with these signals generated by common progenitor lymphoid cells and in this way the immune system cannot exercise its function.

Keywords: Hepatitis C; MDSCs; Immune system; CTLA-4

Introduction

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness.

HCV is a small, enveloped, positive single-stranded RNA virus that belongs to the *Flaviviridae* family, genus *Hepacivirus*. Analysis of viruses from plasma and from cell culture supernatant indicated that enveloped particles are icosahedral and 56-65 nm in diameter, while and the viral core is about 45 nm. Viral spikes on the membrane of the virion are about 6 nm and they are formed by heterodimers of E1 and E2 glycoproteins. In fact, the population of the extracellular HCV particles is heterogeneous. Particles are pleomorphic and size, buoyant density, and infectivity might differ significantly [1,2]. A large majority of particles is non-infectious. Interestingly, the buoyant densities of infectious particles isolated from serum and from cell culture medium are different. A significant amount of the particles are associated with cellular lipoproteins making that a hallmark mark of HCV [3,4].

Life cycle of the hepatitis C virus

The HCV life cycle is only partly understood; difficulties in establishing an *in vitro* model of replication and the complex network of cell surface molecules used to mediate viral entry have delayed comprehension of various molecular mechanisms [5,6].

Immune response in chronic hepatitis C

Immune responses to HCV are slow to develop even in infections that resolve without treatment. This delay may be due in part to HCV's effects on innate immune signaling, as discussed in the previous section. As HCV infection progresses to persistence, the initial, broadly directed HCV-specific CD4+ and CD8+ T cell response weakens. The number of epitopes targeted is reduced due to failure of epitope-specific T cell populations and to viral evolution. The waning of HCV-specific T cell function may be an adaptive response that reduces T cell-mediated tissue damage in conditions of persistent, high antigen load; reduced viral loads may permit T cells to recover their function [7].

In children vertical transmission is responsible for most "new infections", however, has an efficiency of only about 5% [8].

Risk of maternal-infant transmission is increased (up to 22%) by level of maternal HCV viral load such as HIV co infection.

Vertical transmission is almost always confined to women who have detectable HCV RNA. There is an extremely low risk of transmission with undetectable or intermittent viremia, even though the risk of infection in this clinical situation is as low as 0.3%.

Presumably, both intrauterine and intrapartum infections occur. The mode of delivery does not affect risk of HCV transmission. Membrane ruptures longer than six hours and internal fetal monitoring were associated with an increased risk of transmission. Current recommendations are that women with HCV without HIV co-infection can be advised to breast feed [9-12].

Following perinatal transmission of HCV, the constant rate of spontaneous clearance in children is reported to be between 10%–20% and usually occurs within the first 4 years of life [13].

Discussion

Hepatitis C causes acute and chronic infections, the fact that there is a category of babies infected at birth who succeed in eliminating HCV can provide us with important information about the immune system response.

We found that myeloid-derived suppressor cells (MDSCs), which is rarely seen in healthy adults, are present in large numbers in new-borns and their frequency decreases rapidly in the first months of life.

Myeloid-derived suppressor cells (MDSCs) throughout immunosuppressive function facilitates pregnancy successfully, contributing to maternal fetal-tolerance but myeloid-derived suppressor cells (MDSCs) will be responsible for tolerance of hepatitis C by the immune system as well.

The first step in initiation of the T-Cell response is to bring antigens by DC in lymph nodes, lymph nodes representing the common meeting point of Antigens with T Cells and B Cells. The adaptive immune system requires two signals to activate T cells against viral infections. Signal 1 is represented by Peptide HCV-MHC complex and signal 2 is represented by co-stimulatory molecule.

Most important co-stimulatory are B7-1(CD80) and B7-2 (CD86), which both bind to CD28. MDSCs interacts with these co-stimulatory molecules throughout immunosuppressive function of inhibitory protein CTLA-4 in lymph node.

In hepatitis C we see an inhibition of the immune system on T cells. Unlike hepatitis B, the manifestation of hepatitis C is maintained in the blood without any inhibitory factors in the tissue. This fact is confirmed by the conclusion that lowering the viral load in the blood of patients to an undetectable level is sufficient in most cases for elimination of the virus, hence demonstrating that inhibition of T cells is exclusively in the lymph node. MDSCs cells thrown CTLA 4 in lymph nodes allow chronic manifestation of Hepatitis C.

The presence of myeloid-derived suppressor cells (MDSCs) in the lymph node are responsible for maintaining the infection with hepatitis C by inhibiting co-stimulatory molecules. The inhibitory proteins generated by myeloid-derived suppressor cells (MDSCs) have higher affinity than the signals required for T cell activation and this coincides with tolerance.

The above theory might explain the HCV antigen tolerance in new-borns. It might be a possibility that the above theory, would have an impact on patients with chronic Hepatitis C that are not able to reach cure using the current antivirals treatment.

Conclusion

Myeloid derived suppressor cells (MDSCs) are responsible for maintaining chronic hepatitis C by inhibiting T cells in the lymphnode using the CTLA-4 inhibitory protein.

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