IL-21 Ameliorates Liver Inflammation by Enhancing MDSCs Activity in Chronic HBV Infection

731

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Introduction

In chronic HBV infection, despite the non-cytopathogenic nature of the virus, inadequate immune responses often lead to persistent inflammation. Addressing hepatitis might be achievable by dampening the activity of inflammatory cells during active hepatitis. Myeloid-derived suppressor cells (MDSCs), a heterogeneous population consisting of granulocytic MDSCs (gMDSCs) and monocytic MDSCs (mMDSCs), exhibit immunosuppressive functions. Research has focused on MDSCs in acute liver inflammation, associating them with protective roles. In the context of chronic HBV infection, aberrant IL-21 responses have been implicated in liver injury. Despite the diverse functions of IL-21 in HBV infection, its specific effects on the expansion and immunosuppressive functions of MDSCs remain unidentified. Further exploration of the interplay between IL-21 and MDSCs could provide insights into potential therapeutic strategies for alleviating chronic HBV-induced inflammation.

Hypothesis

We propose a hypothesis suggesting that interleukin (IL)-21 might possess the ability to mitigate liver inflammation through the modulation of myeloid-derived suppressor cells (MDSCs) and their suppressive impact on T cell responses.

Results

1. Circulating MDSCs were expanded with immunosuppressive activity in patients with chronic HBV infection.

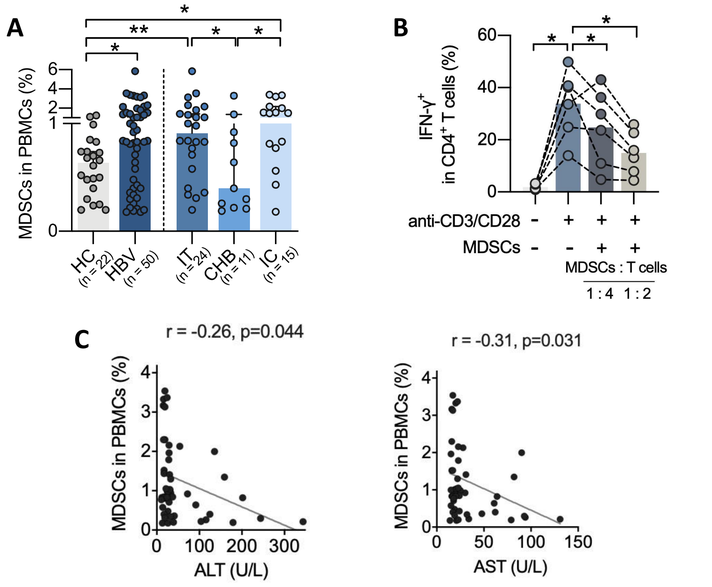


Figure 1. (A) Comparison of circulating MDSCs frequencies between HCs (n=22) and patients with chronic HBV infection (n=50). Patients with chronic HBV infection were classified into the immune tolerant carrier (IT; n = 24), hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB; n = 11), and inactive carrier (IC; n = 15) groups according to the American Association for the Study of Liver Diseases guidelines. **(B)** Sorted circulating MDSCs from patients with chronic HBV infection were cocultured with autologous purified CD4+ T cells in the presence of soluble anti-CD3 (5μg/mL) and anti-CD28 (5μg/mL) for 3 days; summary data on the frequency of IFN-γ+ in CD4+ T cells are shown. **(C)** Correlations between MDSC frequency and serum levels of ALT and AST in chronic HBV infected patients (n=50).

2. gMDSCs accumulate in the liver with inflammation in HBV infection.

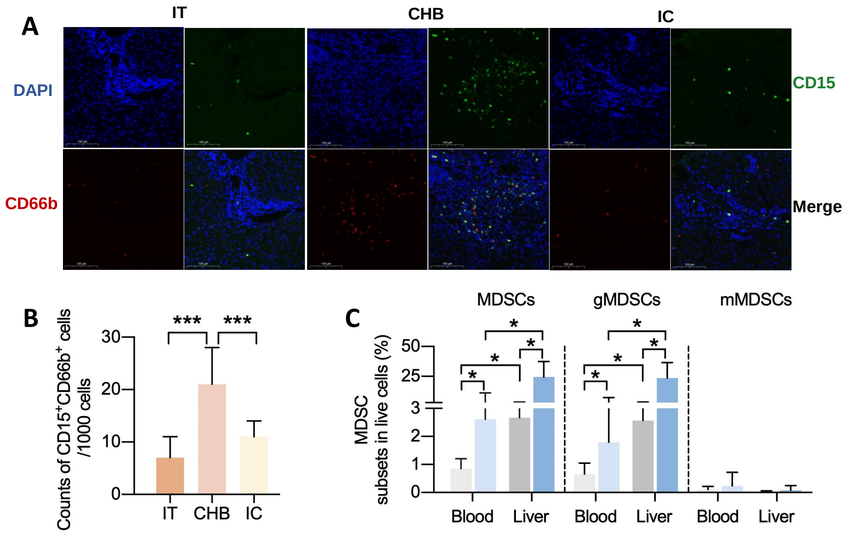


Figure 2. (A) Illustration of representative immunofluorescence analysis featuring CD15 (in green), CD66b (in red), and DAPI (for nuclei in blue) in the livers of IT, CHB, and IC patients. Scale bars: 100 μm. **(B)** Quantitation of CD15 and CD66b double-positive cells was performed using ImageJ software. **(C)** Comparison of the frequencies of MDSC subsets in paired blood and liver samples from patients with HBV-related HCC (n=9) and non-HBV infected patients with cavernous hemangioma (n=4).

3. Excess IL-21 enhances the immune-suppressive activity of MDSCs *in vitro*.

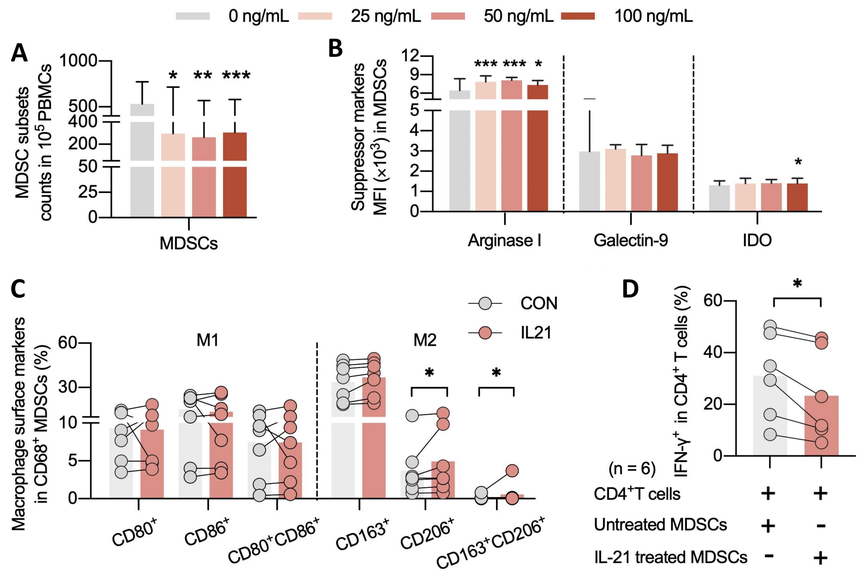


Figure 3. (A) Various IL-21 concentrations were used for coculturing with PBMCs for 20 h (n = 30). The MDSCs numbers were counted. **(B)** Production of suppressor markers in MDSCs after treatment with IL-21. **(C)** Percentages of M1-like and M2-like macrophage phenotypes in purified MDSCs after IL-21 administration (50ng/mL) for 20 h (n=7). **(D)** IFN-γ of purified CD4+ T cells cocultured with the IL-21 (50 ng/mL) treated or untreated autologous MDSCs.

4. IL-21 enhances the suppressive activity of MDSCs in a mice model with HBV expression.

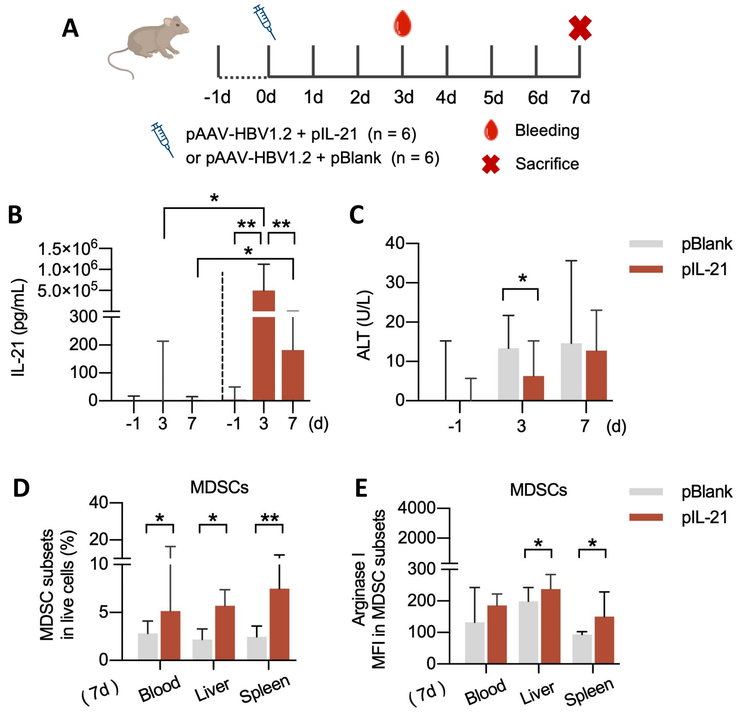


Figure 4. (A) Schematic representation of hydrodynamical injection (HDI) of pAAV-HBV1.2 in combination with pIL-21 (n=6) or pBlank (n=6). Analyses of serum IL-21 **(B)** and ALT **(C)** levels at the indicated time points. Measurement of MDSC frequency **(D)** and Arginase I expression **(E)** in blood, liver, and spleen at day 7 after HDI.

Conclusions

Our study highlights the robust immune-suppressive activity of MDSCs, which can be enhanced by exogenous IL-21, and their potential role in protecting against liver inflammation in chronic HBV infection. These findings provide a novel perspective on the involvement of IL-21 in the negative regulation of intrahepatic inflammation and have implications for the development of immunotherapeutic strategies to optimize the available anti-inflammatory hepatinica in chronic HBV infection.

Acknowledgements

We thank all doctors and nurses at Nanfang Hospital, Southern Medical University for their work. This work was supported by National Natural Science Foundation of China (82022007 and 81971933) and Guangdong Basic and Applied Basic Research Foundation (2023A1515010227).

Disclosures

All authors have no disclosures to declare.