Diverse facets of MDSC in different phases of chronic HBV infection: Impact on HBV-specific T-cell response and homing

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Abstract

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Background and Aims

Chronic HBV infection (CHI) is associated with a diverse natural history that includes immune-tolerant (IT), HBeAg-positive chronic hepatitis B (CHB) (EP-CHB), inactive carrier, and HBeAg-negative CHB (EN-CHB) phases. A hallmark of CHI is impairment of HBV-specific T-cell response. Recently, myeloid-derived suppressor cells (MDSCs) have emerged as key regulator of T cells, and their properties are sculpted by their microenvironment. Here, we investigated the distinctive features of MDSCs during CHI, identified factors responsible for their functional discrepancies, and studied their impact on HBV-specific T-cell response and homing. Influence of antiviral therapy on MDSC profile and T-cell response was also assessed.

Approach and Results

Flow cytometric analysis indicated that MDSCs in EP-CHB/EN-CHB patients had profound suppressive ability, expressing arginase 1 (Arg1)/inducible nitric oxide synthase (iNOS)/programmed death ligand 1 (PD-L1)/cytotoxic T lymphocyte–associated protein 4 (CTLA-4)/CD40 at significantly greater levels relative to healthy controls (HC). However, in IT, only $Arg1^+$ MDSCs and in inactive carrier, $iNOS^+$ and $PD\text{-}L1^+$ MDSCs were higher than HC. In vitro assays demonstrated that high HBsAg titer in IT/CHB induced $Arg1^+$ MDSC. Furthermore, elevated serum TNF-α and IL-4 in CHB potentiated Arg1/PD-L1/CD40/CTLA-4 expression, whereas increased IL-1β in CHB/IC triggered the expansion of $PD\text{-}L1^+$ MDSCs and $iNOS^+$ MDSCs. MDSCs, sorted from CHB/IC, greatly attenuated IL-2/interferon gamma (IFN-γ) production by HBV-specific $CD8^+/CD4^+$ T cells, the effect being more pronounced in CHB. However, MDSCs of IT minimally affected the cytokine production by T cells. Adding Arg1-/iNOS-inhibitor restored only IFN-γ production, while neutralizing PD-L1 recovered both IL-2 and IFN-γ secretion by T cells. Moreover, MDSCs from IT/CHB disrupted virus-specific T-cell trafficking by down-regulating chemokine receptor type 5 on them via TGF-β signaling. One year of tenofovir therapy failed to normalize MDSC phenotype and HBV-specific T-cell response.

Conclusions

Diversity of MDSCs during CHI affects HBV-specific T-cell response and homing. Hence, therapeutic targeting of MDSCs could boost anti-HBV immunity.