Activated human hepatic stellate cells induce myeloid derived suppressor cells from peripheral blood monocytes in a CD44-dependent fashion.

Abstract:
Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of cells associated with the suppression of immunity. However, little is known about how or where MDSCs are induced and from which cells they originate. The liver is known for its immune regulatory functions. Here, we investigated the capacity of human hepatic stellate cells (HSCs) to transform peripheral blood monocytes into MDSCs. We cultured freshly isolated human monocytes from healthy donors on primary human HSCs or an HSC cell-line and characterized the phenotype and function of resulting CD14(+)HLA-DR(-/low) monocytes by flow cytometry, quantitative PCR, and functional assays. We analyzed the molecular mechanisms underlying the induction and function of the CD14(+)HLA-DR(-/low) cells by using blocking antibodies or knock-down technology. Mature peripheral blood monocytes co-cultured with HSCs downregulated HLA-DR and developed a phenotypic and functional profile similar to MDSCs. Only activated but not freshly isolated HSCs were capable of inducing CD14(+)HLA-DR(-/low) cells. Such CD14(+)HLA-DR(-/low) monocyte-derived MDSCs suppressed T-cell proliferation in an arginase-1 dependent fashion. HSC-induced development of
CD14(+)HLA-DR(-/low) monocyte-derived MDSCs was not mediated by soluble factors, but required physical interaction and was abrogated by blocking CD44. Our study shows that activated human HSCs convert mature peripheral blood monocytes into MDSCs. As HSCs are activated during chronic inflammation, the subsequent local induction of MDSCs may prevent ensuing excessive liver injury. HSC-induced MDSCs functionally and phenotypically resemble those isolated from liver cancer patients. Thus, our data suggest that local generation of MDSCs by liver-resident HSCs may contribute to immune suppression during inflammation and cancer in the liver.