Expansion of immune suppressive myeloid cells in Cancer

Background

Myeloid derived suppressor cells (MDSC) consist of two distinct subsets, polymorphonuclear-MDSC (PMN-MDSC), and monocytic-MDSC (M-MDSC). The current paradigm considers PMN-MDSC and M-MDSC to differentiate from different granulocytic and monocytic lineages, respectively. In this study, we found that M-MDSC directly differentiates into PMN-MDSC and retinoblastoma gene (Rb1) products regulate their differentiation.

Methods

Morphology, phenotype, and function of PMN-MDSC differentiated from M-MDSC were evaluated using Giemsa staining and flow cytometry. Protein and gene expression level of Rb1 in MDSC subsets and myeloid cells were determined by western blot and real-time PCR. Transcriptional regulation of Rb1 in MDSC by histone modification was examined using ChIP assay.

Results

M-MDSC differentiate into dendritic cells and macrophages, whereas PMN-MDSC are terminally differentiated cells. Our study demonstrated that in cancer M-MDSC represent highly proliferative population of cells that differentiate not only to DC and macrophages but also to PMN-MDSC. Rb1, a central regulator of the cell cycle and cell differentiation, is known to be involved in monocytic and granulocytic lineage commitment. When examining Rb1 levels in freshly isolated cells, M-MDSC expressed high levels of Rb1 similar to those in dendritic cells, macrophages, and neutrophils isolated from naïve mice. In sharp contrast, PMN-MDSC had undetectable Rb1. Lack of Rb1 in mice with conditional deletion of the gene promoted an expansion of splenic CD11b+Ly6G+Ly6Clo cells, similar to the phenotype of PMN-MDSC in tumor-bearing mice. Lack of Rb1 in PMN-MDSC was caused by transcriptional repression of the gene. Inhibition of Rb1 expression in PMN-MDSC correlated with the level of histone acetylation of Rb1 promoter. Treatment of PMN-MDSC with inhibitors of histone deacetilases (HDAC) resulted in the increase in Rb1 expression suggesting that it may be controlled by histone modification. HDAC inhibitors abrogated differentiation of M-MDSC to PMN-MDSC in the presence of tumor explants conditioned medium.

Conclusion

Down-regulation of Rb1 plays a major role in accumulation of MDSC in cancer by regulating PMN-MDSC differentiation from M-MDSC. HDAC may be considered as potential targets for therapeutic regulation of MDSC.