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| Title: | Elucidating the role of myeloid derived suppressor cells in virus induced immunity and immunopathology |
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| Abstract: | A balanced immune response contributed by stimulatory and inhibitory cellular and molecular mediators are critical for restoring immune cell homeostasis following infection. While the immunoregulatory activities of adaptive immune cells of CD4 lineage have been adequately established during the pathogenesis of viral infections, the contribution of myeloid cells remains less explored. This study aimed to decipher the role of myeloid-derived suppressor cells (MDSCs) in limiting herpesvirus and influenza A virus (IAV) induced tissue immunopathology. In the first part, the phenotype of MDSCs was defined in animals ocularly infected with herpes simplex virus 1 (HSV1) that causes an immunoblinding disease known as herpetic stromal keratitis (HSK). CD11b+GR1lo-int cells and not CD11b+Gr1hi cells suppressed the proliferation and cytokine production by stimulated CD4 T cells. Furthermore, in vitro differentiated MDSCs upon adoptive transfer reduced the severity of HSK by interfering with the migration of effector T cells to corneal stroma and by promoting endogenous regulatory T cells (Tregs) response. MDSCs not only induced de novo conversion of non-Tregs into Tregs but also stabilized the expression of FoxP3, a master regulator in pre-committed Tregs. In the second part, we demonstrated the therapeutic value of MDSCs in reducing immunopathology caused by a respiratory virus (IAV) infection. MDSCs helped reduce the proliferation of T cells and CTL responses in the lungs in the recipient animals. Surprisingly, MDSCs also promoted the differentiation of virus-specific memory CD8 T cells that controlled re-infection better. The responding CD8 T cells in the presence of elevated MDSCs showed higher expression levels of molecules such as CD127, TCF-7, EOMES, BCL-2, and ID-3 that are associated with memory transition of effector cells. The preferential memory formation occurred irrespective of the virus infection and the clonality of CD8+ T cells. These data suggested that MDSCS can provide an anti-inflammatory environment to the host, control T cell-mediated tissue immunopathology and enhance memory CD8 T cell generation following virus infection. Therefore, the therapeutic potential of MDSCS can be harnessed as a multi-pronged strategy to achieve a favourable outcome of viral infections. |
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