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Therapeutic Application of Myeloid-Derived Suppressor Cells (MDSC) in Dry Eye Disease

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Abstract

Purpose : To assess the immunosuppressive functions and therapeutic potential of locally administered MDSC in an established murine model of dry eye disease (DED).

Methods : MDSC ($CD11b^+Gr\text{-}1^+$) were isolated from cultured bone marrow cells via magnetic sorting. These cells were then co-cultured for 24 hours with DC ($CD11b^+$ MHC-II^+ from draining lymph nodes (DLN) of DED mice), Th17 cells ($CD4^+IL\text{-}17^+$ from GFP-tagged IL-17 reporter DED mice), or Treg ($CD4^+CD25^+FoxP3^+$ from DED mice) in a 1:1 ratio. The frequency of each cell type and expression levels of MHC-II (in DC), IL-17 (in Th17 cells), and FoxP3 (in Treg) were assessed with flow cytometry. DED mice were injected with $5x10^4$ MDSC and control groups received PBS or $CD11b^+Gr\text{-}1^-$ cells ($5x10^4$ cells) on day 4. On day 14, DLN and conjunctiva were collected for flow cytometry analysis of DC, Th17 cells, and Treg. CFS scores were measured at baseline and on days 4, 7, 10, and 14 to evaluate DED severity.

Results : We observed significantly lower frequencies of MHC-II^{hi} DC(p=0.0004) and MHC-II expression levels(p=0.0045) on culturing these cells with MDSC vs. DC cultured alone. We also observed significantly lower Th17 cell frequencies(p<0.0001) and their IL-17 expression levels(p<0.0001) vs. Th17 cells cultured alone. In contrast, higher Treg frequencies(p=0.0472) and FoxP3(p=0.0074) expression levels were observed on culturing with MDSC vs. Treg cultured alone. Moreover, injecting MDSC in DED mice resulted in significantly lower DC(p=0.0002) and Th17 cells(p<0.0001) frequencies compared to PBS-treated mice. Additionally, the expression levels of MHC-II by DC(p=0.0035) and IL-17 by Th17 cells(p<0.0001) were significantly lower compared PBS-

treated mice, and comparable to naïve mice. We observed that injecting DED mice with $CD11b^{+}Gr\text{-}1^{-}$ cells did not have a significant suppressive effect on DC and Th17 frequencies and their expression of MHC-II and IL-17. Treg isolated from MDSC-treated DED mice showed higher expression level of FoxP3 compared to both the PBS-treated(p=0.0016) and $CD11b^{+}Gr\text{-}1^{-}$ treated DED controls(p=0.0018). DED was suppressed in mice injected with MDSC compared to those that received PBS or $CD11b^{+}Gr\text{-}1^{-}$, evident from significantly lower CFS scores on days 7, 10, and 14.

Conclusions : These data establish immunosuppressive functions of MDSC in immune mediated DED, underlining the potential therapeutic application of these cells in treating refractory disease.

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