Effects of Nrf2 Activator Dimethyl Fumarate on CD8 and CD4 Effector Functions

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The Keap1Nrf2 Pathway, responds to oxidative by signaling to the MHS1 complex to activate CD8 and CD4 T-cells via APCs. CD4 and CD8 T-cells function in conjunction to fight invading pathogens during infections and cancers. CD8 T-cells are activated and differentiated into cytotoxic T-lymphocytes (CTLs) programmed for targeted killing of infected cells by releasing granules. Similarly, CD4 release proteins known as cytokines to activate other immune cells' and CD8 T-cells' assigned task during an immune response. Dimethyl-Fumarate, an FDA-approved Nrf2 activating drug, has shown promising results in particular Multiple Sclerosis treatments. However, DMF's exact mechanisms are not yet fully known. We hypothesize that DMF induced Nrf2 negatively affects the adaptive immune response. To conduct our study, we isolated splenocytes from C57BL/6 (B-6) mice which contain T-cells, treated them with two different concentrations of DMF and compared their cell numbers and immune functions to those in a 'normal' condition, media without an Nrf2 activator, as our control group. Upon Flow cytometry analysis, we observed lower cell number and lowered Granzyme B and Perforin granule production in CD8 T-cells treated with DMF. Furthermore, CD4 and CD8 cells treated with DMF had lower secretion of interferon-gamma (IFN- γ) cytokine. Our findings suggest that Nrf2 downregulates specific cytokine production in CD4 and CD8 T-cells and cytotoxic function of CD8 T-cells, inhibiting the inflammatory immune response. This inhibition of T-cell immune responses by Nrf2 might contribute to DMF's efficacy in treating MS. Future studies may examine what other effector functions are affected by DMF and how the related effector functions contribute to MS alleviation.