OR.107. TIM-1 Plays a Crucial Role in the Expansion of Autopathogeneic T-Cells and Regulation of Autoimmunity [abstract only]

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OR.107. TIM-1 Plays a Crucial Role in the Expansion of Autopathogeic T-Cells and Regulation of Autoimmunity

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T-cell immunoglobulin and mucin (TIM) family Members are differentially expressed on Th1 and Th2 cells. Polymorphisms of TIM-1 have been associated with susceptibility to asthma; however, its role in regulating autoimmunity has not been studied. Here, we have used an agonistic anti-TIM-1 antibody (Ab, Clone 3B3) which has previously been shown to costimulate T-cell activation and expansion, to analyze the role of TIM-1 in the development and regulation of experimental autoimmune encephalomyelitis (EAE). Treatment with 3B3 dramatically enhances the severity of
EAE as well as the frequency of encephalitogenic CD4+ T-cells and the production of IFN-γ and IL-17 by these cells. Furthermore, administration of 3B3 breaks self-tolerance and induces EAE in the disease resistant B10.S strain. We have utilized another anti-TIM-1 Ab (RMT1-10) that does not costimulate T-cell activation in vitro. In contrast to 3B3, treatment with RMT1-10 inhibits the development of EAE and reduces the frequency of encephalitogenic CD4+ T-cells with a commensurate decrease in the production of IFN-γ and IL-17. Treatment with RMT1-10 causes CD4+ T-cells to produce more IL-4 and IL-10. We provide evidence that both 3B3 and RMT1-10 bind to the same epitope in the Ig domain of TIM-1, but the binding affinity of 3B3 is much higher than that of RMT1-10. These data suggest that TIM-1 engagement with the agonistic Ab, along with TcR ligation, costimulates T-cell expansion with pro-inflammatory IFN-γ and IL-17 production resulting in the breakdown of self-tolerance and development of autoimmunity, whereas blocking anti-TIM-1 Ab causes a decrease in the autopathogenic Th1/ThIL-17 responses. This study demonstrates that TIM-1 is a key cell surface molecule that regulates effector T-cell response and depending on how the molecule is engaged, autoimmune responses can be either enhanced or inhibited in vivo.