

King CG,<sup>\*†</sup> Kobayashi T,<sup>\*†</sup> Troy AE,<sup>§</sup> Chiffoleau E,<sup>‡</sup> Walsh M,<sup>\*†</sup> Walsh P,<sup>‡</sup> Shen H,<sup>§</sup> Turka LA,<sup>‡</sup> Choi Y<sup>\*†</sup>

Departments of <sup>\*</sup>Pathology and Laboratory Medicine, <sup>‡</sup>Medicine, <sup>§</sup>Microbiology and <sup>†</sup>Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, PA 19104

TNF family members are essential for the regulation of cell survival, differentiation and proliferation. T cells express a wide array of TNF receptors known to both positively and negatively regulate T cell responses including cell division, effector function, survival and memory development. TNF receptor engagement is believed to provide co-stimulatory signals that augment signal transduction pathways initiated by T cell receptor engagement. TRAF6 is an important signaling adaptor downstream from both TNFR family members and IL-1/Toll Like Receptors (TLRs). Although it has been well established that TRAF6 plays a critical role in the innate immune system, a role for TRAF6 in T cells has not been described. To address this, we generated mice with TRAF6 deletion specific to T cells (TT6). Initial analyses reveal that TT6 mice have approximately one half the number of T cells of littermate control mice, with an especially significant decrease in total CD8<sup>+</sup> T cell numbers. Upon stimulation *in vitro*, both CD4<sup>+</sup> and CD8<sup>+</sup> T cells hyperproliferate and CD4<sup>+</sup> T cells produce an excess of Th2 cytokines. TT6 mice have an accumulation of CD44<sup>hi</sup>, CD62L<sup>lo</sup> CD4<sup>+</sup> T cells in the periphery, elevated levels of immunoglobulin isotypes in the sera, and a marked expansion of B cells in the lymph nodes. H/E staining of organs from 4 month TT6 mice reveal mononuclear cell infiltrates in liver, lung and kidney. In addition, anti-DNA antibodies are detected in the sera of these mice. These preliminary findings indicate that TRAF6 deletion results in T cell intrinsic defects and may play a role in the maintenance of peripheral tolerance.