

Regulation of T-cell differentiation and proliferation by the Myc antagonist Mnt

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The Myc family of proteins are closely associated with cell growth and proliferation and contribute to tumorigenesis when deregulated. Myc family proteins require heterodimerization with Max in order to bind DNA specifically and activate transcription. Max interacts with several other Myc-related proteins that repress transcription and have been proposed to act as Myc antagonists. We recently showed that mouse embryo fibroblasts lacking one of these genes, *Mnt*, exhibit many of the hallmark characteristics of cells that overexpress Myc. Further, when conditionally deleted in breast tissue, mammary carcinomas formed. Here we have extended these studies to conditionally delete *Mnt* in T-cells. Surprisingly, we find that the thymus is dramatically smaller and the spleen and liver are significantly larger in mice at 6 and 8 weeks of age. The decreased size of the thymus correlates with a significant reduction in cell number, but not in cell size. Using the viable dye CFSE, we show that *Mnt* deficiency causes a severe proliferation block in a subset of thymocytes. Additionally, Annexin staining shows that *Mnt* deficiency causes a strong increase in thymocyte apoptosis. We postulate that these defects contribute to the small thymus size. In addition to these changes, loss of *Mnt* caused a significant block in T-cell differentiation at the double negative 3 (DN3). Finally, the enlarged (and disorganized) spleen in these mice correlates with increased proliferation of B-cells, and B-cells are wild-type for *Mnt*. Taken together, these results suggest that the absence of *Mnt* in T-cells changes the ratio of T-cell sub-populations significantly and this imbalance in T-cell ratios leads to massive proliferation in B-cell population. These results reveal a unique regulatory role for *Mnt* in T-cell development and homeostasis.