Retinoic Acid Signaling in Thymic Epithelial Cells Regulates Thymopoiesis

Despite the essential role of thymic epithelial cells (TEC) in T cell development, the signals regulating TEC differentiation and homeostasis remain incompletely understood. In this study, we show a key in vivo role for the vitamin A metabolite, retinoic acid (RA), in TEC homeostasis. In the absence of RA signaling in TEC, cortical TEC (cTEC) and CD80loMHC class IIlo medullary TEC displayed subset-specific alterations in gene expression, which in cTEC included genes involved in epithelial proliferation, development, and differentiation. Mice whose TEC were unable to respond to RA showed increased cTEC proliferation, an accumulation of stem cell Ag-1hi cTEC, and, in early life, a decrease in medullary TEC numbers. These alterations resulted in reduced thymic cellularity in early life, a reduction in CD4 single-positive and CD8 single-positive numbers in both young and adult mice, and enhanced peripheral CD8+ T cell survival upon TCR stimulation. Collectively, our results identify RA as a regulator of TEC homeostasis that is essential for TEC function and normal thymopoiesis.