The role of ERK activation during thymic development

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It is unknown how the contrasting events of positive and negative selection can lead to the distinct biological outcomes of life or death. An increasing body of evidence suggests that the duration of ERK signaling plays a role in thymocyte selection. However, it remains unclear whether the differences in ERK duration can be reproduced in vivo. We propose to define the kinetics and duration of ERK activation between positive and negative selection in intact thymic tissues using fetal thymic organ cultures and intracellular staining for pERK. Intact thymic tissues cultured under negative selection conditions induce maximum pERK activation at 2 minutes and then pERK phosphorylation quickly declines to baseline levels. Positive selection stimulates a weaker peak activation of pERK at 2 minutes, yet after an initial decrease at 24 hours, pERK activation increases and is sustained through 72 hours. The expression patterns of Egr-1 and Id3, downstream ERK effectors, correlate with the kinetics of pERK. Positive selection induces a weak yet sustained expression of Egr-1 while negative selection stimulates a strong, transient Egr-1 expression. These results demonstrate an in vivo molecular mechanism by which thymocytes can differentiate between positive and negative selection through the duration of pERK signaling.