Quantitative and temporal requirements revealed for Zap70 catalytic activity during T cell development.

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Public Summary:
The activity of the tyrosine phosphorylating enzyme Zap70 is crucial for T cell development, but the quantitative and temporal requirements for its function in thymocyte development are not known. Using a chemical-genetic system to selectively and reversibly inhibit Zap70 catalytic activity, we show that although thymocytes can commit to negative selection after only 1 hour of Zap70 signaling, positive selection requires a minimum of 36 hours. Our data indicate that the temporal pattern and cumulative amount of signaling may be as important as signal amplitude in effecting positive vs. negative selection. This study also demonstrates surprising heterogeneity between synchronously differentiating thymocytes expressing identical T-cell receptors.

Scientific Abstract:
The catalytic activity of Zap70 is crucial for T cell antigen receptor (TCR) signaling, but the quantitative and temporal requirements for its function in thymocyte development are not known. Using a chemical-genetic system to selectively and reversibly inhibit Zap70 catalytic activity in a model of synchronized thymic selection, we showed that CD4(+)CD8(+) thymocytes integrate multiple, transient, Zap70-dependent signals over more than 36 h to reach a cumulative threshold for positive selection, whereas 1 h of signaling was sufficient for negative selection. Titration of Zap70 activity resulted in graded reductions in positive and negative selection but did not decrease the cumulative TCR signals integrated by positively selected OT-I cells, which revealed heterogeneity, even among CD4(+)CD8(+) thymocytes expressing identical TCRs undergoing positive selection.