RasGRP-dependent feedback regulation of Sos contributes to digital ERK responses and efficient lymphocyte activation

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Abstract: Recent work suggests that calcium fluxes can be stimulated by a few agonists, and this response is analog in nature. In contrast many other downstream responses require a larger threshold number of agonists (i.e., digital response). We have previously demonstrated that RasGRP-Sos crosstalk is the basis for optimal Ras-ERK activation in lymphocytes. Here we describe the results of synergistic computational and experimental studies which demonstrate that a positive feedback mechanism involved in the Sos-catalyzed activation of Ras results in a threshold for efficient downstream signaling during membrane proximal signaling events. Our results also show that clonal cells subjected to the same amount of stimulation partition in to two subpopulations (characterized by strong and weak ERK activation) because this feedback regulation leads to a bistable response. Our computational analysis predicts that a consequence of this positive feedback regulation is an emergent hysteretic behavior that allows stimulated T cells to sustain a high level of signaling even when the stimulus falls below the original activation threshold. This feature could confer stability of T cell activation to fluctuations in the stimulus or TCR levels. We are currently testing this with various experimental approaches.