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Digital signaling, signal filters and central tolerance in thymocytes ASHOK PRASAD, MIT, JULIE ZIKHERMAN, UCSF, JAYAJIT DAS, OSU, JEROEN ROOSE, UCSF, ARTHUR WEISS, UCSF and HHMI, ARUP CHAKRABORTY, MIT — T cells are characterized by the immense diversity of the antigen binding receptors (TCR's) they bear. TCR's carried by immature T cells (thymocytes) are made in the thymus by a stochastic process, followed by testing against self-peptides. Thymocytes that do not respond to self-peptides die through neglect (positive selection); those that respond too strongly die through apoptosis (negative selection). We present a new molecular explanation of this phenomenon via a computational model, which we also test by experiments. We show that Ras activation in thymocytes is characterized by the presence of a digital molecular switch due to a positive feedback loop in a Ras-activating enzyme. We also show how an important adaptor protein, LAT, acts as a filter, sending weak TCR signals along a pathway that leads to Ras activation via a graded mechanism, and sending stronger signals along another path that activates Ras via the molecular switch. Our model yields a new mechanism for digital signaling of the Erk protein in mammalian cells, and has important implications for autoimmunity.

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