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Modeling of T-Cell Signaling: Anergy versus Proliferation

T-cells are activated by interactions between the T-cell receptor (TCR) and peptides bound to the major histocompatibility complex (MHC). The activation of TCRs initiates several signaling pathways that are necessary for the proper cellular response to the presented peptides. We investigated the activation of the Erk Protein by means of a data-based mathematical model, focusing on the feedback mechanisms within this pathway that could explain the observed kinetics. T-cells were stimulated by antibodies cross-linked in solution (sAbs) as well as by antibodies immobilized on microbeads (iAbs). The stimulation with sAbs shows a strong, but transient signal whereas the iAbs stimulus leads to a sustained signal that results in a strong activation of Erk. The stronger stimulus (sAbs) results in the weaker activation of Erk, which indicates that the activation of Erk is regulated by feedback. We developed a mathematical model based on ordinary differential equations, which promotes LAT as an important element of the feedback mechanisms. Depending on the input signal LAT reaches different states of phosphorylation. By splitting the signal at LAT level feedback can be regulated by those different states of LAT. First simulations with this model show that the experimental-observed dynamics can be explained much better than with a simpler model of the pathway that also includes feedback, but no signal splitting at LAT.