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Meeting abstract

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Decision making in NK cells

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A balance of positive and negative signals that are transmitted by different surface receptors controls the effector functions of NK cells. To date our understanding about the integration of positive and negative signals and the decision-making process inside NK cells remains poor.

With the help of bioinformatic modelling we try to understand how NK cells first integrate antagonising signals and then compute a reliable killing decision. Gradual signal input through activating and inhibitory receptors is integrated to come to a "yes or no" decision by the NK cell to kill an attached target cell. Triggering of activating receptors leads to Src kinase activation and Vav-1 phosphorylation, whereas inhibitory receptors dephosphorylate Vav-1 via the phosphatase SHP-1. Therefore, we proposed in a first hypothesis, that Vav-1 is the decision making point in the signal transduction network. With this hypothesis we created a family of simplified models describing NK cell activation upon various stimuli. The predictions derived from these models were compared with experimental data. Our experiments showed that increased clustering of activating receptors lead to a rapid switch-like increase in Vav-1 phosphorylation. Similarly, titrating the engagement of inhibitory receptors resulted in switch-like dephosphorylation of Vav-1. Testing NK cell activity after various amounts of activating and inhibitory receptor engagement revealed a functional dominance of inhibitory receptors. Our current model is consistent with a central role of Vav-1 in the decision making process of NK cells and enables a novel insight into the integration of positive and negative signals during lymphocyte activation.