Simulations of the NK cell immune synapse reveal that activation thresholds can be established by inhibitory receptors acting locally

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***Short Abstract* — NK cell activation is regulated by a balance between activating and inhibitory signals. To address the question of how these signals are spatially integrated, we created a computer simulation of activating and inhibitory NK cell immunological synapse (NKIS) assembly. The simulations mimicked the observed molecule distributions in inhibitory and activating NKIS, and yielded several new insights, described below.**

***Keywords* — Immunological Synapse, Killer Inhibitory Receptors, Natural Killer cells, Computer simulations.**

I. BACKGROUND

NATURAL KILLER (NK) cells are lymphocytes that are able to lyse a variety of tumor targets and cells infected with intracellular bacteria, parasites or several types of viruses. The cytolytic capability of NK cells is enabled after ligation of NK cell activating receptors such as NKG2D, which binds the stress-inducible ligands [1]. NK cell activation is tightly regulated by inhibitory receptors (mainly Ly49 receptors in mice and KIR in humans) that limit and potentially terminate the response [2]. Inhibitory receptors mostly bind self MHC-I molecules, such that target cells that do not express, or have downregulated self MHC-I expression, are more likely to be killed by NK cells (the “missing self” hypothesis [3]). Bound inhibitory receptors recruit and activate protein tyrosine phosphatases that dephosphorylate key components for NK cell activation, thus blocking signaling from activating receptors [4]. The mechanism(s) by which signals are integrated in NK cells, and how exactly the balance between the two types of receptors determines NK cell function are, however, unclear. In particular, it is not clear whether signal integration occurs over the whole NK cell immunological synapse (NKIS), or is a more local process. Our aim in this study was to clarify the relationship between the integration of activating/inhibitory signals and the spatial dynamics of the NKIS.

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II. SIMULATION

Our model of the NKIS contains two parallel two-dimensional grids, representing the contact areas on the membranes of the two interacting cells – the NK and the Target cell grids. The grids contain some of the different cell surface molecules, and membrane microdomains, present in the NKIS. Molecules and lipid microdomains move around the grids in a random manner, which may be biased towards the center of the NKIS when the integrated signal exceeds the cell's activation threshold. Molecules may bind to, or disconnect from, their ligands on the opposite grid. The simulations implemented either a "quantity-based" inhibition model or a "distance-based" inhibition model.

III. RESULTS AND CONCLUSION

The total signal was found to be highly influenced by activating complex dissociation rates, but not by adhesion and inhibitory complex dissociation rates. Second, concerted motion of receptors in clusters significantly accelerates NKIS maturation. Third, the integrated signal behavior obtained when using the distance-based inhibition signal model was closer to the experimentally observed behavior, with an inhibition radius of the order of 3-10 molecules. Taken together, these data are consistent with a model in which inhibitory receptors act locally, i.e., that every bound inhibitory receptor acts on activating receptors within a certain radius around it. This work is published [5].

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