



**Karolinska
Institutet**

Institutionen för Mikrobiologi, Tumör- och Cellbiologi

MHC class I molecules in Natural Killer cell education and tolerance

AKADEMISK AVHANDLING

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ABSTRACT

The immune system needs to respond to danger but remain tolerant to normal cells and tissues. Natural killer cells achieve tolerance to self by the use of inhibitory receptors recognizing MHC class I molecules on healthy cells. Only NK cells expressing such inhibitory receptors for self-MHC class I molecules are allowed to be fully functional through a process of education. Here we have studied this process of education and the nature of the MHC class I mediated influence. We have found that MHC class I molecules exert a quantitative rather than a binary influence on NK cells. This means that NK cells are not “on” or “off” but also everything in-between. We have also found MHC class I molecules to regulate NK cells at multiple levels, such as setting the threshold for activation and determining the quality of NK cell responses to stimulation. Also the formation of the NK cell repertoire is regulated by MHC class I. We propose that this reflects a process in which NK cells continuously sense MHC class I and other relevant inputs and adapt to them. This could serve to maintain NK cell sensitivity to relative changes in stimuli also in a context that is highly dynamic. We have termed this the Rheostat model for NK cell education.

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