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**REGULATION OF NATURAL KILLER (NK) CYTOTOXICITY BY
HLA CLASS I-SPECIFIC INHIBITORY RECEPTORS**

by

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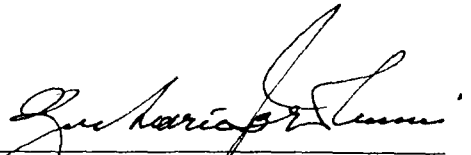
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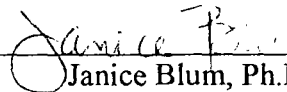
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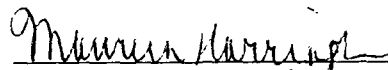
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ABSTRACT

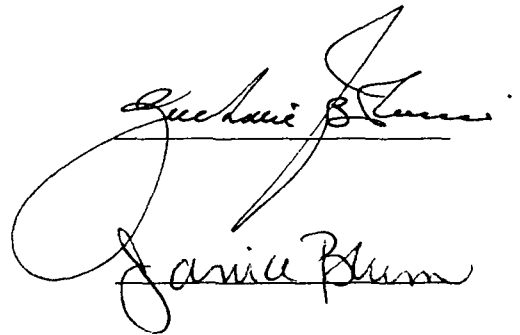
Natural killer (NK) cells constitute part of the immune system and provide protection by mediating cytotoxicity against virus-infected or transformed cells that lack “self” HLA Class I molecules, as described by the “missing-self” hypothesis. HLA Class I-specific NK receptors transduce inhibitory signals to block NK cytotoxic activity and therefore the absence of an inhibitory signal allows NK cells to remove such aberrant cells. Two types of inhibitory receptors exist, C-type lectins and killer inhibitory receptors (KIRs). The inhibitory signaling pathway has not been fully elucidated and whether the two inhibitory receptor types utilize distinct or differentially regulated pathways is unknown.

To investigate the inhibitory signaling pathways, the NK-like YTINDY cell line was transfected to express p58.2 KIR (YT/C143 transfectant) or CD94/NKG2A C-type lectin (YT/CD94 transfectant). We observed a significant down-regulation of total cytotoxicity, which includes perforin/GranzymeB and FasL-mediated pathways, in response to Class I in YT/C143 but not in YT/CD94. Our results suggest that the absence of inhibition in YT/CD94 may be due to low p56^{lck} or SHP-1 expression or to the possible expression of CD94/NKG2C activating receptor. Furthermore, the functional inhibitory signal observed in YT/C143 suggests that p56^{lck} is not required in p58.2 signaling and that another *src* tyrosine kinase may play a compensatory role.

Next, we made the novel observation that FasL-mediated cytotoxicity in YT/C143 and CD94/NKG2A-expressing LAK cells was down-regulated in response to Class I. Using the CD94/NKG2A-expressing NKL cell line, we showed that FasL mRNA and surface expression was up-regulated through simultaneous ligation of two activating

receptors, 2B4 and LFA-1. Additional CD94/NKG2A ligation, however, did not block the induced FasL expression.

In summary, the YTINDY NK-like cell line was successfully transfected and the cytotoxicity of the p58.2-expressing YT/C143 transfectant was down-regulated by Class I despite low p56^{lck} expression levels. In contrast, the CD94/NKG2A-expressing YT/CD94 transfectant was not inhibited by Class I, indicating that inhibitory signals transduced through these two receptors are distinct. We also showed that FasL-mediated cytotoxicity is down-regulated by HLA Class I in NK cells, an important new finding that may shed light on how certain tumors or virus-infected cells evade the immune system.


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Murren Karing



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