

# **Prostaglandin E<sub>2</sub> induces the expression of functional inhibitory CD94/NKG2A receptors in human CD8<sup>+</sup> T lymphocytes by a cAMP-dependent protein kinase A type I pathway**

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## **Abstract**

The CD94/NKG2A heterodimer is a natural killer receptor (NKR), which inhibits cell-mediated cytotoxicity upon interaction with MHC class I gene products. It is expressed by NK cells and by a small fraction of activated T cells, predominantly of CD8<sup>+</sup> phenotype. Abnormal upregulation of the CD94/NKG2A inhibitory NKR on cytotoxic T cells (CTLs) could be responsible for a failure of immunosurveillance in cancer or HIV infection. In an attempt to identify the mechanisms leading to inhibitory NKR upregulation on T cells, we analyzed the expression of the CD94/NKG2A heterodimer on human CTLs activated with anti-CD3 mAb in the presence of PGE<sub>2</sub> or with 8-CPT-cAMP, an analogue of cyclic AMP. As previously described, anti-CD3 mAb-mediated activation induced the expression of CD94/NKG2A on a small fraction of CD8<sup>+</sup> T cells. Interestingly, when low concentrations of PGE<sub>2</sub> or 8-CPT-cAMP were present during the culture, the proportion of CD8<sup>+</sup> T cells expressing CD94/NKG2A was 2 to 5-fold higher. This upregulation was partially prevented by the PKA type I inhibitor, Rp-8-Br-cAMP. We also report that cAMP induces upregulation of NKG2A at the mRNA level. We further demonstrated that cross-linking of CD94 on CD8<sup>+</sup> T cells expressing the CD94/NKG2A heterodimer inhibits their cytotoxic activity in a bispecific antibody redirected lysis assay. Our findings clearly demonstrate that the PGE<sub>2</sub>/cAMP/PKA type I axis is involved in the expression of CD94/NKG2A receptor on human CD8<sup>+</sup> T lymphocytes.

