

Expression of a Recombinant High Affinity IgG Fc Receptor by Engineered NK Cells as a Docking Platform for Therapeutic mAbs to Target Cancer Cells

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PMID: 30574146 PMCID: [PMC6291448](#) DOI: [10.3389/fimmu.2018.02873](#)

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Abstract

Anti-tumor mAbs are the most widely used and characterized cancer immunotherapy. Despite having a significant impact on some malignancies, most cancer patients respond poorly or develop resistance to this therapy. A known mechanism of action of these therapeutic mAbs is antibody-dependent cell-mediated cytotoxicity (ADCC), a key effector function of human NK cells. CD16A on human NK cells has an exclusive role in binding to tumor-bound IgG antibodies. Though CD16A is a potent activating receptor, it is also a low affinity IgG Fc receptor (FcγR) that undergoes a rapid downregulation in expression by a proteolytic process involving ADAM17 upon NK cell activation. These regulatory processes are likely to limit the efficacy of tumor-targeting therapeutic mAbs in the tumor environment. We sought to enhance NK cell binding to anti-tumor mAbs by engineering these cells with a recombinant FcγR consisting of the extracellular region of CD64, the highest affinity FcγR expressed by leukocytes, and the transmembrane and cytoplasmic regions of CD16A. This novel recombinant FcγR (CD64/16A) was expressed in the human NK cell line NK92 and in induced pluripotent stem cells from which primary NK cells were derived. CD64/16A lacked the ADAM17 cleavage region in CD16A and it was not rapidly downregulated in expression following NK cell activation during ADCC. CD64/16A on NK cells facilitated conjugation to antibody-treated tumor cells, ADCC, and cytokine production, demonstrating functional activity by its two components. Unlike NK cells expressing CD16A, CD64/16A captured soluble therapeutic mAbs and the modified NK cells mediated tumor cell killing. Hence, CD64/16A could potentially be used as a docking platform on engineered NK cells for therapeutic mAbs and IgG Fc chimeric proteins, allowing for switchable targeting elements and a novel cancer cellular therapy.

Keywords: ADCC; FcR; NK cell; antibody; immunotherapy.