> Cancer Immunol Immunother. 2018 Sep;67(9):1407-1416. doi: 10.1007/s00262-018-2193-1. Epub 2018 Jul 5.

Anti-ADAM17 Monoclonal Antibody MEDI3622 Increases IFNγ Production by Human NK Cells in the Presence of Antibody-Bound Tumor Cells

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PMID: 29978334 PMCID: PMC6126979 DOI: 10.1007/s00262-018-2193-1

Free PMC article

Abstract

Several clinically successful tumor-targeting mAbs induce NK cell effector functions. Human NK cells exclusively recognize tumor-bound IgG by the FcR CD16A (FcγRIIIA). Unlike other NK cell activating receptors, the cell surface density of CD16A can be rapidly downregulated in a cis manner by the metalloproteinase ADAM17 following NK cell stimulation in various manners. CD16A downregulation takes place in cancer patients and this may affect the efficacy of tumor-targeting mAbs. We examined the effects of MEDI3622, a human mAb and potent ADAM17 inhibitor, on NK cell activation by antibody-bound tumor cells. MEDI3622 effectively blocked ADAM17 function in NK cells and caused a marked increase in their production of IFNγ. This was observed for NK cells exposed to different tumor cell lines and therapeutic antibodies, and over a range of effector/target ratios. The augmented release of IFNγ by NK cells was reversed by a function-blocking CD16A mAb. In addition, NK92 cells, a human NK cell line that lacks endogenous FcγRs, expressing a recombinant non-cleavable version of CD16A released significantly higher levels of IFNγ than NK92 cells expressing equivalent levels of wildtype CD16A. Taken together, our data show that MEDI3622 enhances the release of IFNγ by NK cells engaging antibody-bound tumor cells by blocking the shedding of CD16A. These findings support ADAM17 as a dynamic inhibitory checkpoint of the potent activating receptor CD16A, which can be targeted by MEDI3622 to potentially increase the efficacy of anti-tumor therapeutic antibodies.

Keywords: Antibody; Cancer; Cytokine; Cytotoxicity; Immunotherapy; NK cell.

Conflict of interest statement

Compliance with ethical standards.
Disclosure of potential conflicts of interest.
The authors declare that they have no conflict of interest.