

USING ADAM17 INHIBITION TO BOOST HUMAN NATURAL KILLER CELL-MEDIATED ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

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Human natural killer (NK) cells are known to kill diseased cells through two different methods: direct killing and antibody-dependent cell-mediated cytotoxicity (ADCC). NK cells can be stimulated through a cascade triggered by toll-like receptor 9 (TLR9) agonism, which begins in neighboring (non-NK) white blood cells. This neighboring cell-based activation process allows for physiologically relevant levels of NK cell stimulation. Importantly, we found that stimulation in this manner only increases direct killing by human NK cells; ADCC did not change as a result of this stimulation approach. Our working hypothesis for the lack of change in ADCC relates to the fact that NK cells rely on CD16, a surface receptor, to carry out ADCC. Notably, activated NK cells cleave CD16 from their surface using ADAM17 sheddase as a mechanism to autoregulate their activity. In our experiments, we are combining a TLR9 agonist with an ADAM17 sheddase inhibitor. We expect this approach to allow for boosting both direct killing and ADCC, in contrast to what we found with TLR9 agonist treatment alone. Because the ADAM17 sheddase inhibitor is dissolved in a different solvent (DMSO) than the TLR9 agonist (H₂O), our first set of experiments are to determine how much of the DMSO solvent can be tolerated by human NK cells before either killing efficacy is impaired. Once this value is determined, we will know the maximum concentration of ADAM17 inhibitor that we can possibly use so that we can begin to develop our dose-response curves for this drug. Finally, we will combine the drugs together in our lab's recently described killing assay to assess the functional outcomes of the combined intervention. Our data to date for this aspect of the project will be presented. The project described was supported in part by an Institutional Development Award (IDeA) from the NIGMS of the National Institutes of Health under Grant # 5P20GM103427.