INTERLEUKIN-21 ENHANCES NATURAL KILLER CELL ACTIVATION IN RESPONSE TO ANTIBODY-COATED TARGETS

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Natural killer (NK) cells express an activating receptor for the Fc portion of IgG (FcγRIIIa) that mediates antibody-dependant cellular cytotoxicity (ADCC) and the production of immune modulatory cytokines in response to antibody (Ab)-coated targets. Interleukin (IL)-21, a member of the common gamma chain family of cytokines, has anti-tumor activity in murine models that depends in part on its ability to stimulate NK cells and promote the secretion of interferon-gamma (IFN-γ). We hypothesized that the FcR-mediated NK cell response to immobilized IgG would be enhanced by the administration of IL-21. Purified human NK cells cultured with IL-21 and immobilized IgG or human breast cancer cells coated with a therapeutic monoclonal Ab (trastuzumab) secreted large amounts of IFN-γ. Increased secretion of TNF-α and the chemokines IL-8, MIP-1α, and RANTES was also observed under these conditions. NK cell IFN-γ production was dependent on distinct signals mediated by the IL-21 receptor and the FcR and was abrogated in NK cells from STAT1-deficient mice. Supernatants derived from NK cells that had been stimulated with IL-21 and monoclonal Ab (mAb)-coated breast cancer cells were able to drive the migration of naïve and activated T cells in an in vitro chemotaxis assay. IL-21 also enhanced NK cell lytic activity against Ab-coated tumor cells. Co-administration of IL-21 and Ab-coated tumor cells to immunocompetent mice led to synergistic production of IFN-γ by NK cells. Furthermore, the administration of IL-21 augmented the effects of an anti-HER2/neu mAb in a murine tumor model. These findings demonstrate that IL-21 significantly enhances the NK cell response to Ab-coated targets and suggest that IL-21 would be an effective adjuvant to administer in combination with anti-tumor mAbs.