POWERFUL SYNERGISTIC EFFECTS OF A STING AGONIST AND THE IL-2 SUPERKINE, H9, IN ELICITING NK AND T CELL RESPONSES AGAINST MHC I- AND MHC I+ TUMORS

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Background Most current cancer immunotherapies are based on mobilizing CD8 T cell responses. However, many types of tumors evade CD8 T cell recognition by displaying few or no antigens, or losing expression of MHC I. These considerations underlie the need for complementary therapies that mobilize other antitumor effector cells, such as NK cells, which preferentially kill MHC I-deficient cells. Cyclic dinucleotides (CDNs) activate the cGAS-STING pathway of the innate immune system and are candidates as immunotherapy agents. Intratumoral CDN injections induce type I IFNs and other mediators that amplify the CD8 T cell response and induce tumor regression [1]. CDN therapy also induces long-term tumor regressions in some MHC I-deficient tumor models, mediated primarily by NK cells [2].

Methods To extend the efficacy of CDN therapy, we combined the IL-2 superkine, H9, or half-life extended H9, with CDNs to target and activate NK cells in the tumor microenvironment and prevent or delay the onset of NK cell desensitization [3,4]. In these studies, we utilized B16-F10 and MC38 tumor cells lacking B2m to examine effects of the combination therapy on MHC I-deficient tumor growth as well as to examine the activation of NK cells by flow cytometry and cytotoxicity assays. We also utilized B16-F10 WT and the spontaneous tumor model, MCA, to assess the effect of the combination therapy on MHC I+ tumors.

Results Here we show that H9 synergized with CDN therapy to mobilize much more powerful antitumor responses against MHC I-deficient tumors than CDN alone. The responses were mediated by NK cells and in some cases CD4 T cells, and were accompanied by increased recruitment to and sustained activation of NK cells in the tumor. This combination therapy regimen activated NK cells systemically, as shown by antitumor effects distant from the site of CDN injection and enhanced cytolytic activity of splenic NK cells against tumor cell targets ex vivo. Finally, the same combination therapy regimen synergistically mobilized powerful CD8 T cell responses in the case of MHC I+ tumor cells, suggesting the generality of the approach. The approach was effective against primary sarcomas, as well, especially when combined with checkpoint therapy, leading to tumor regressions and long-term survival of many mice with MCA-induced sarcoma.

Conclusions Overall, our work demonstrates the impact of a novel combination therapy in mobilizing powerful NK and T cell-mediated antitumor activity, providing important justification for evaluating this approach for treating cancers that are refractory to available treatment options.

REFERENCES