Immunotherapies that mobilize CD8 T cells have revolutionized cancer therapy in recent years. A likely limitation of CD8 T cells in immunotherapy is that many tumors display few neoantigens and/or lack MHC I expression. Natural killer cells have emerged as exciting targets for new generations of immunotherapeutics. We investigated innate cues necessary for mobilizing spontaneous anti-tumor responses against tumors in mice and identified the cGAS-STING pathway as a critical pathway that is activated by cancer cells and mobilizes both NK cell and T cell mediated tumor rejection. Cyclic dinucleotides (CDNs) are STING agonists that, when injected into tumors, superactivate cellular immunity. We investigated the efficacy of CDNs in mobilizing anti-tumor activity in 6 independent gene edited models of MHC I-deficient tumors. Due to the absence of MHC I, CD8 T cells played no role in these responses. When transplanted syngeneic tumors of all 6 models were established and then treated intratumorally with CDNs (a single treatment, or in some cases 3 early treatments), tumor rejection rapidly ensued, which was NK-dependent and independent of CD8 T cells. In 5 of 6 MHC I-deficient tumor models tested, CDN therapy resulted in the indefinite survival of between 30% and 100% of the animals, with no evidence of residual tumors, suggesting the animals were cured. In one model (MHC I-deficient B16 melanoma cells) early rejection of the tumors was followed by relapse in all of the animals. Tumor rejection induced by CDNs was IFN-I-dependent, and conditional knockout experiments indicated that IFN-I acted directly on NK cells but also indirectly on DCs. After CDN therapy, DCs in the draining lymph nodes upregulated IL-15/IL-15R complexes on the membrane, and tumor rejection was blocked by neutralizing IL-15/IL15R. These data suggested that CDNs induce trans-presentation of IL15 by DCs to NK cells to support the tumor rejection response. CDN-induced tumor rejection was markedly enhanced by combining CDNs with IL-2 superkine (“super2”, in collaboration with C. Garcia), resulting in long-term tumor free survival in nearly all of the mice in the MHC I-deficient B16 and MC-38 models, indicating striking synergy between CDNs and super2. Our results suggest great potential for combining agonists of innate immune responses with superkines for treating cancers that are invisible to CD8 T cells, including MHC I-deficient cancers and potentially cancers with low neoantigen expression.