Design and Delivery of STING Mimicking Therapeutics for Cancer Immunotherapy

by

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Abstract

Stimulator of interferon genes (STING) is a promising therapeutic target to drive the immune system to eliminate cancer. However, STING agonists are commonly rendered ineffective in cancer cells by a loss of STING expression. Here we overcome STING loss in cancer by developing STING mimics: therapeutics that replicate the protein-protein interactions of STING to directly activate downstream kinase TANK-binding kinase 1 (TBK1) and transcription factor interferon regulatory factor 3 (IRF3) in the cytosol. In this thesis, we optimize the design of STING mimicking proteins, develop nanocarriers to deliver these proteins inside of cells, and apply this technology to treat ovarian cancer.

We report that cytosolic delivery of a soluble STING protein fragment (STINGΔTM) can strongly activate TBK1 and IRF3. This observation was unexpected as prior work suggested that addition of the ligand cGAMP was required to convert STINGΔTM into an active multimeric state. Our results show that in addition to facilitating transport across the cell membrane, complexation by nanocarriers can replace the need for an activating ligand by promoting multimerization of the STING fragment. We demonstrate that cytosolic STINGΔTM delivery is able to induce target immune signaling in multiple STING deficient cancer cell lines that do not respond to STING agonists. To apply this technology therapeutically, we develop a poly(β-amino ester) (PBAE) degradable polycation nanoparticle formulation to target ovarian cancer and deliver bioactive STINGΔTM protein to the cytosol. Screening experiments reveal that increasing PBAE hydrophobicity enables efficient protein encapsulation and intracellular delivery. Incorporating a polyanion in this formulation tunes the cell type specificity of STING signaling activation *in vitro*, with poly(L-glutamate) and poly(L-aspartate) preferentially activating signaling in ovarian cancer cells. In a mouse model of metastatic ovarian cancer, nanoparticles accumulate preferentially in tumors throughout the abdomen, slow tumor growth, and extend survival.

We then engineer a multivalent peptide-polymer conjugate material as a next generation STING mimic to improve potency and enable easier delivery to the cytosol. While previously developed STING mimicking therapeutics utilize nearly the full STING protein, we determine that the 180 amino acid ligand binding domain is not required to activate TBK1 and IRF3. Therefore, we design a molecule that includes only a 39 amino acid peptide from the STING C-terminal tail that contains interaction motifs for TBK1 and IRF3. Conjugation of multiple peptide copies to a negatively charged polymer backbone mimics the multivalent protein-protein interactions of the oligomerized STING signaling complex, activating TBK1 and IRF3 as well as the transcription of downstream genes in both STING proficient and STING silenced cancer cell lines. We optimize a lipid nanoparticle formulation to deliver this conjugate material, allowing for its application as an immunotherapy for ovarian cancer. Treatment with the STING mimicking conjugate material promoted the production of type I interferons, repolarization of myeloid cells to an anti-tumor phenotype, and recruitment of T cells to tumors in mice. This treatment ultimately led to tumor regression and improved survival extension in multiple mouse models of metastatic ovarian cancer.

Overall, this work introduces new strategies to engage intracellular signaling machinery by leveraging drug delivery technology and protein-protein interaction motifs from adaptor proteins. Beyond the demonstrated promise of STING mimics as a treatment for ovarian cancer, this work lays the groundwork to design future therapies against other difficult to drug targets.

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