Tumor cell-intrinsic STING pathway activation leads to robust induction of Type III Interferons and contributes to the anti-tumor activity elicited by STING agonism.

Abstract

The tumor cell-intrinsic STING pathway plays a critical role in inducing anti-tumor immunity by upregulating Type III IFN (IFNλ) and IFN-λ-induced genes within the tumor microenvironment in response to treatment with STING agonists. Therefore, targeting this pathway holds great promise as a tactic to improve the efficacy of current immunotherapies. However, the tumor cell intrinsic STING pathway is also essential for the anti-tumor activity of STING agonist antibody-drug conjugates (ADCs), which are currently in clinical trials. We previously demonstrated that tumor cell-targeted STING-agonist ADCs activated STING downstream of STING pathway activation in both tumor cells and immune cells, leading to potent anti-tumor activity in preclinical tumor models.

In this study, we investigated the mechanism by which tumor-targeted STING agonist ADCs activate the tumor cell intrinsic STING activity in tumor cells and immune cells, and how this activates IFNλ and Type III IFN production in vivo.

**Background**

- **Systematically administered**
- **Tumor targeted delivery of STING agonist**
- **Efficacy in a single dose across multiple tumor models**
- **Increased burden in multiple co-injected cell types**
- **Systematic induction of antiviral cytokines**
- **Drastically enhanced efficacy compared to a systemically administered free STING agonist**

**Proposed mechanism of action**

**Tumor cell-targeted immunosynthetic STING agonist ADCs**

- **Systematically administered**
- **Tumor targeted delivery of STING agonist**
- **Efficacy in a single dose across multiple tumor models**
- **Increased burden in multiple co-injected cell types**
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**RESULTS**

Tumor cell-targeted STING agonist ADCs exhibit significant activity in cancer cell / primary human immune cell co-cultures and in vivo tumor models.

**Figure 1.** Delivery of a STING agonist into tumor cells and secondary immune cells

**Figure 2.** Tumor cell-targeted STING agonist ADCs exhibit significant activity in cancer cell / primary human immune cell co-cultures and in vivo tumor models

**Figure 3A.** Consistent with the results shown in Fig. 3A, targeted ADC with wt Fc induced significant killing of both STING wt and STING ko tumor cells

**Figure 3B.** Tumor cell-targeted Fc mutant STING agonist ADCs exhibit significant activity in cancer cell / primary human immune cell co-cultures and in vivo tumor models

**Figure 3C.** STING agonist ADCs induce Type III Interferon activation in cancer cell / primary human immune cell co-cultures

**Figure 4.** Tumor cell-targeted STING agonist ADCs induce Type III Interferon activation in cancer cell / primary human immune cell co-cultures

**Figure 5.** Tumor cell-targeted STING agonist ADCs induce IFNλ production in tumor cell / primary human immune cell co-cultures

**CONCLUSIONS**

- The immunosynthetic STING ADC platform enables tumor-targeted delivery of a STING agonist with improved efficacy and selectivity compared to a free STING agonist.
- Antitumor activity of STING agonist ADCs involves activation of STING pathway in both immune cells and cancer cells.
- In the study we have demonstrated:
  - Tumor cell-intrinsic STING pathway can be activated in the presence of cues from immune cells.
  - Tumor cell-targeted STING agonist ADCs induce IFNλ production in cancer cells.
  - Tumor cell-targeted STING agonist ADCs may be a critical tool for induction of Type III IFN in vivo.

References