STING-AGONIST ADCs TARGETING TUMOR-ASSOCIATED ANTIGENS COORDINATE IMMUNE-MEDIATED KILLING OF ANTIGEN-NEGATIVE CANCER CELLS

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Background The tumor microenvironment is a complex, multi-cellular system, composed not only of malignant cancer cells but also of a diversity of stromal cells including vascular cells, immune cells, and fibroblasts that support tumorigenesis. Antigens expressed on these cells tend to be widely expressed across a range of malignancies, presenting unique opportunities for development of anti-cancer therapies.

Methods We have previously demonstrated that STING-agonist antibody-drug conjugates (Immunosynthen ADCs) targeting tumor cell antigens induce target-dependent anti-tumor immune responses in vitro and in vivo. To that effect, we hypothesized that Immunosynthen ADCs targeting tumor-associated antigens would coordinate immune-mediated killing of cancer cells not expressing the tumor-associated antigens (antigen-negative cancer cells) and induce anti-tumor activity.

Results Herein, we demonstrate that targeting tumor-associated antigens with STING-agonist ADCs activate the STING pathway in immune cells via Fcγ receptor-mediated uptake. In addition, due to the intrinsic ability of certain tumor-associated cells to activate the STING pathway, STING-agonist ADCs targeting those cells can induce STING signaling in both the targeted cells and the immune cells, which constitutes a therapeutic advantage of ADCs that activate the STING pathway. In triple co-cultures of antigen-positive tumor-associated cells, antigen-negative cancer cells, and immune cells, the STING-agonist ADC specifically induced potent cell killing of the antigen-negative cancer cells with minimal impact on the immune and tumor-associated cells, thus representing a non-traditional, yet highly effective mechanism of ADC targeting. In vivo efficacy studies showed that STING-agonist ADCs developed for two tumor-associated antigens induced complete, sustained tumor regressions in syngeneic tumor models and exhibited immunological memory after rechallenge. CD8+ T cells contributed to the anti-tumor activity of the STING-agonist ADCs.

Conclusions In summary, Immunosynthen STING-agonist ADCs targeting tumor-associated antigens represent a novel approach for ADC-mediated cancer immunotherapy and enable the multifaceted activation of the STING pathway in a tumor-targeted manner beyond tumor antigens.

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