

POSTER PRESENTATION

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Direct activation of STING in the tumor microenvironment partially overcomes immune tolerance in neu-N transgenic mice

Jeremy Foote^{1*}, James M Leatherman², Todd D Armstrong², Laureen Ojalvo³, David Kanne⁴, Elizabeth M Jaffee⁵, Tom Dubensky⁴, Leisha Emens³

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STING signaling induces interferon- β production by intratumoral dendritic cells (DCs), driving T cell priming within the tumor microenvironment. However, the impact of antigen-specific tolerance on this process is not well studied. We therefore examined the efficacy of *in situ* tumor delivery of a potent STING-activating CDN ligand (ML-RR-S2 CDA) in both non-tolerant parental FVB/N and the immune tolerant neu-N transgenic mice bearing established HER-2⁺ breast tumors. In non-tolerant FVB/N mice, single agent intratumoral ML-RR-S2 CDA injection induced complete tumor regression of both the injected tumor and a contralateral uninjected tumor, while also protecting mice from a subsequent tumor challenge. In contrast, intratumoral injection of ML-RR-S2 CDA alone in neu-N mice modestly delayed tumor growth. Furthermore, in contrast to our prior data that low dose cyclophosphamide could increase vaccine-induced immunity and tumor-free survival in neu-N transgenic mice, the sequential delivery of low dose cyclophosphamide with ML-RR-S2 CDA did not delay tumor outgrowth relative to ML-RR-S2 CDA alone. We therefore explored biomarkers of both STING pathway activation and T cell activity within the TME of FVB/N and neu-N transgenic mice. Intratumoral ML-RR-S2 CDA injection resulted in both high levels of IFN β production in the TME of tumor bearing FVB/N mice, and the induction of a durable population of HER-2-specific CD8⁺ T cells. In contrast, intratumoral ML-RR-S2 CDA injection resulted in low levels of IFN β production in the TME of tolerant neu-N transgenic mice, and the induction of few HER-2-specific

CD8⁺ T cells. Phenotypic analyses of tumor infiltrating leukocytes within the TME of untreated neu-N mice revealed increased expression of PD-1 on CD8⁺ T cells and PD-L1 on myeloid cells. Moreover, about 25% of HER-2⁺ tumor cells derived from the TME also expressed PD-L1. The addition of PD-L1 blockade to low dose cyclophosphamide in sequence with intratumoral ML-RR-S2 CDA resulted in a greater delay of tumor growth than intratumoral ML-RR-S2 CDA injection alone in neu-N transgenic mice, but did not clear any mouse of tumor. These findings suggest that multiple mechanisms of immune tolerance limit the ability of STING pathway activation to lead to HER-2 specific-CD8⁺ T cell activation and tumor regression in tolerant neu-N transgenic mice.

Authors' details

¹Department of Molecular and Comparative Pathobiology, Johns Hopkins School of Medicine, Baltimore, MD, USA. ²Johns Hopkins University, Baltimore, MD, USA. ³Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA. ⁴Aduro Bio Tech, Berkley, CA, USA. ⁵The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA.

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¹Department of Molecular and Comparative Pathobiology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Full list of author information is available at the end of the article