Intratumoral STING Activation with T-cell Checkpoint Modulation Generates Systemic Antitumor Immunity

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Abstract

Coordinated manipulation of independent immune regulatory pathways in the tumor microenvironment-including blockade of T-cell checkpoint receptors and reversal of suppressive myeloid programs-can render aggressive cancers susceptible to immune rejection. Elevated toxicity associated with combination immunotherapy, however, prevents translation of the most efficacious regimens. We evaluated T-cell checkpoint-modulating antibodies targeting CTLA-4, PD-1, and 4-1BB together with myeloid agonists targeting either STING or Flt3 in the TRAMP-C2 model of prostate cancer to determine whether low-dose intratumoral delivery of these agents could elicit systemic control of multifocal disease. Intratumoral administration of the STING agonist cyclic di-GMP (CDG) or Flt3 Ligand (Flt3L) augmented the therapeutic effect of systemic triple checkpoint modulation and promoted the cure of 75\% of mice with bilateral TRAMP-C2; however, when all agents were administered locally, only CDG mobilized abscopal immunity. Combination efficacy correlated with globally enhanced ratios of CD8\textsuperscript{+} T cells to regulatory T cells (Treg), macrophages, and myeloid-derived suppressor cells, and downregulation of the M2 marker CD206 on tumor-associated macrophages. Flt3L improved CD8\textsuperscript{+} T-cell and dendritic cell infiltration of tumors, but was diminished in efficacy by concomitant Treg expansion. Although intratumoral CDG/checkpoint therapy invokes substantial ulceration at the injection site, reduced CDG dosing can preserve tissue integrity without sacrificing therapeutic benefit. For high-order combinations of T-cell checkpoint antibodies and local myeloid agonists, systemic antibody administration provides the greatest efficacy; however, local administration of CDG and antibody provides substantial systemic benefit while minimizing the potential for immune-related adverse events.

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