Background Major therapeutic success of chimeric antigen receptor T cells (CART) in solid tumors is lacking. A possible strategy to increase efficacy and therapeutic response of CART in solid tumors could be the combined use with IMSA101, a newly developed stimulator of interferon genes (STING) agonist, to effectively modify the tumor microenvironment (TME) prior to engineered T cell administration.

Methods To test this approach, we established two syngeneic flank tumor models using immunocompetent C57BL/6 mice. Mice were either implanted with PDA7940b, an immunologically cold pancreatic ductal adenocarcinoma cell line derived from KPC mice, or with B16, an immunogenic melanoma cell line. Approximately one week after tumor cell injection, animals were treated with intratumoral (i.t.) IMSA101 alone, intravenous (i.v.) CART alone, the combination of i.t. IMSA101 and i.v. CART, or were left untreated as control. At the time point of peak CART expansion, the TME was analyzed by flow cytometry in addition to pathological assessment, immunohistochemistry, and RNA in situ Hybridization of bulk tumor tissue. RNA was extracted from intratumoral CART for gene expression and pathway enrichment analyses, and mouse serum was analyzed for cytokines. In addition, a xenograft flank tumor model was established using NSG mice and human PDA AsPC-1 cells to characterize cell-intrinsic effects of IMSA101 on human CART.

Results Tumor clearance was seen in all B16, as well as in some PDA7940b tumor-bearing mice when both treatments were combined. This resulted in significantly improved overall survival when compared to mice treated with CART alone or IMSA101 alone. More CART were detected in tumors of IMSA101+CART-treated mice when compared to mice treated with CART alone. Gene expression and pathway enrichment analyses of CART isolated from tumors showed activation and effector T cell signatures, as well as upregulated IL-18 pathway in the combination treatment group. Also, higher levels of IL-18 in serum and more IL-18 RNA in tumors of these mice were detected. Consistent with this, treatment of mice with IL-18 receptor knock-out CART impaired the anti-tumor response in mice receiving combination treatment. Minimal differences were observed in immunodeficient NSG mice, consistent with STING agonist-induced modulation of the TME improving antitumor CART-immunity.

Conclusions In summary, we found that i.t. administration of IMSA101 promoted CART trafficking into the tumor, induced intratumoral CART activation, and enhanced CART efficacy, which was facilitated through STING agonist-mediated IL-18 induction. These promising observations laid the foundation for advancing the combinatorial approach into a clinic setting which is currently being planned.

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