Localized STING Agonist via Liposome-MDP Hydrogel Composites with Combined Systemic α-PD-1 and α-CTLA-4 Improves Immunotherapy Responses in Oral Cancer

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Objectives

Despite decades of conventional multi-modality treatments for patients with locoregionally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), five-year survival rates remain just over 60%, driving the need for novel treatment strategies such as immunotherapy. Most HNSCC patients treated with systemic single-agent checkpoint inhibitors do not respond, due to the immunosuppressive tumor immune microenvironment (TIME). Therefore, a localized delivery platform that allows for the controlled release of immunomodulators to maximize effectiveness and limit systemic side effects is needed. We investigated a localized intratumorally-injected multidomain peptide (MDP) hydrogel encapsulating liposomes loaded with a Stimulator of Interferon Genes (STING) agonist, cyclic di-nucleotide (CDN). This was combined with systemic delivery of immune checkpoint inhibitors, anti-programmed cell death protein-1 (α-PD-1) and anti-cytotoxic T-lymphocyte-associated antigen-4 (α-CTLA-4). We hypothesized liposomal CDN-MDP hydrogel composites would enhance drug-delivery pharmacokinetics, localizing and extending the release of immunomodulators intratumorally and stimulating anti-effector immunocytes with systemic delivery of α-PD-1 and α-CTLA-4 to target the immune-excluded TIME in our preclinical model of oral cancer.

Methods

C57BL/6 mice were injected with ROC1 oral cancer cells in the oral maxillary vestibule. ROC1 tumor-bearing mice were treated with six intratumoral delivery of CDN, single intratumoral delivery of CDN, single intratumoral delivery of liposomal CDN-MDP hydrogel composites or saline, and conventional intra-peritoneal delivery of α-PD-1 and α-CTLA-4.

Results

ROC1 tumor-bearing mice treated with liposomal CDN-MDP hydrogel composites and systemic injections of α-PD-1+α-CTLA-4 experienced tumor regression and extended survival compared to liposome-CDN and systemic injections of α-PD-1+α-CTLA-4 ($p<0.002$), single intratumoral CDN and systemic injections of α-PD-1+α-CTLA-4 ($p<0.002$) and untreated groups ($p<0.0002$).

Conclusions

Our results demonstrate the effectiveness of the liposomal CDN-MDP hydrogel composites to treat an immunosuppressive orthotopic model of oral cancer. Immunotherapy response was improved with liposomal CDN-MDP hydrogel composites and systemic injections of α-PD-1+α-CTLA-4.

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