Near-infrared photoimmunotherapy augments the antitumor effect of in situ vaccine using a unique nanoparticulate Toll-like receptor 9 ligand

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Abstract

In situ vaccine (ISV), in which intratumorally injected immunostimulatory adjuvants activates innate immunity at the tumor site, utilizes tumor-derived patient-specific antigens, thereby allowing for the development of vaccine in patients themselves. They are expected to synergize with any other classes of cancer immunotherapies including PD-1 blockade. The primary goal of our division is clinical development of ISV that maximizes cancer immune activation by immunological intervention at tumor sites using a two-sided approach, i.e., "unique innate immunity-activating adjuvant" and "enhanced tumor destruction to release patient's own tumor antigens". Here, we present a novel approach in which near-infrared photoimmunotherapy (NIR-PIT) is incorporated into ISV injecting a unique nanoparticulate Toll-like receptor 9 ligand "K3-SPG". The combination of K3-SPG-ISV and NIR-PIT showed synergistic systemic antitumor effects and enhanced PD-1 blockade. Mechanistically, strong intratumoral upregulation of interferon-related genes and dependency on $CD8^+$ T cells were observed, suggesting the possible role of interferon and cytotoxic T cell responses in the induction of antitumor immunity. This combination induced immunological memory in therapeutic and neoadjuvant settings. Our study represents the first attempt to integrate NIR-PIT with ISV, offering a promising new direction for cancer immunotherapy.