Optimization of oncolytic adenovirus-mediated antitumor immune efficacy

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Oncolytic adenovirus (Ad), which selectively replicate in cancer, is emerging as a promising new modality for the treatment of cancer and it has several advantageous attributes over non-replicating Ads. Oncolytic Ad possesses an inherent ability to multiply, lyse infected cancer cells, and spread to surrounding cells. Although oncolytic adenovirus is capable of inducing antitumor immune response even in the absence of therapeutic transgenes, arming the oncolytic Ad with immune stimulatory transgenes (cytokines, chemokines, and ligands) significantly improves the virus' ability to induce robust immune response against the tumor.

Currently, intratumoral injection of an oncolytic Ad remains the conventional administration route in clinical trials. Nonetheless, the locally administered Ad disseminates to the surrounding nontarget tissues and has short biological activity due to immunogenicity of Ad, which inadvertently promotes rapid clearance and insufficient intratumoral retainment of therapeutics. To address these limitations, we developed biocompatible and biodegradable hydrogels to enhance the therapeutic efficacy of oncolytic Ads. A hydrogel-based intratumoral delivery of oncolytic Ads prolonged intratumoral virion retention and lowered nonspecific shedding to normal tissues. Notably, hydrogel systems attenuated Ad-associated antiviral immune response, while preserving the viruses' ability to induce robust antitumor immune response. Importantly, a single hydrogel matrix enabled efficient co-delivery of both oncolytic Ad and therapeutic dendritic cells, resulting in superior antitumor immune response and tumor growth control than combination of these treatments in the absence of hydrogel. Collectively,

hydrogel-based delivery of oncolytic Ad can prime immunologically unresponsive 'cold' tumor microenvironment to a 'hot' environment that potentiats antitumor immune response by the virus as well as other immunotherapeutics.

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