Targeted Delivery of Immune Agonists for Antitumoral Response of the Tumor Microenvironment

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Tumor-mediated immunosuppression allows tumors to hide from the immune system and avoid recognition. To reverse this suppressive microenvironment, antigen-presenting cells (APCs) and other innate/adaptive immune cells within the tumor can be targeted and activated from their senescent states. Cyclic diguanylate monophosphate (c-di-GMP), a drug that works within the cytosol of immune cells, is used to release inflammatory cytokines (IFN-ß) to recruit immune cells and initiate anti-tumor responses. However, therapy using freely injected drug is limited because c-di-GMP cannot easily cross cell membranes and is quickly cleared from the body. It is hypothesized that c-di-GMP loaded into a nanoparticle will more effectively deliver drug into the cytosol of immune cells, widespread within the tumor, resulting in more potent therapy. To demonstrate the therapeutic potential, macrophages were exposed to c-di-GMP loaded into nanoparticles in vitro. C-di-GMP nanoparticles boosted the secretion of cytokine IFN-ß from murine macrophages by 6-fold compared to free drug. To increase the particle specificity for suppressive immune cells, an antibody targeting the novel inhibitory immune-checkpoint protein V-domain Immunoglobulin Suppressor of T cell Activation (VISTA) was conjugated to the surface of a nanoparticle. Ongoing work looks to demonstrate the increased uptake of VISTA-targeting particles by a VISTA expressing cell line in vitro. This work demonstrates a potential new treatment that increases the efficacy of c-di-GMP by targeting and reversing immunosuppressive cell subtypes. Future work includes in vitro and in vivo studies optimizing the delivery of nanoparticles to tumor-associated immune cells and evaluating the therapeutic effects on tumor burden and overall survival.

Awards Won: