IM-12. RNA NANOPARTICLE VACCINES RE-PROGRAM HOST IMMUNITY IN FAVOR OF ENHANCED EFFECTOR RESPONSES AGAINST INTRACRANIAL MALIGNANCIES
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BACKGROUND: Pediatric brain tumors are the number one cause of solid cancer death in children, and thus necessitate the development of novel targeted therapeutics. To enhance the feasibility of cancer immunotherapy, off-the-shelf vaccination strategies have been proposed, but have proven to be only weakly immunogenic. Consequently we have designed a novel, translatable nanoparticle (NP) vaccine that can be embedded with immunomodulatory modifications to generate robust anti-tumor responses against murine models for glioblastoma (GBM) and medulloblastoma (MB). OBJECTIVES: We sought to assess if RNA-NP vaccines would induce superior immune responses against GBM and MB by stimulating intracellular pathogen recognition receptors (PRRs) while simultaneously downregulating regulatory pathways. RESULTS: We screened commercially available and clinically translatable NP formulations and determined that the cationic liposome DOTAP was the most superior NP for delivery of RNA to antigen presenting cells (APCs) in vitro and in vivo. Afterwards, we verified that these particles preserve RNA stability over time, and induce in vivo gene expression. These RNA-NPs elicited potent T cell immunity, superior to peptide vaccines formulated in Complete Freund’s Adjuvant (CFA) and induced anti-tumor efficacy in adoptive cellular therapy platforms in murine GBM and MB models. We showed dramatic upregulation of activation markers including CD80 and CD86 and demonstrated abrogation of regulatory markers such as programmed death-ligand1 (PD-L1) when RNA-NPs were administered in combination with anti-PD-L1 monoclonal antibodies. Finally, we demonstrated enhanced immune responses through incorporation of immunomodulatory RNAs encoding for pathogen associated molecular patterns (PAMPs) derived from hepatitis C. CONCLUSION: Since clinically translatable RNA-NP vaccines can deliver combinatorial therapies using a single delivery platform, they represent a novel platform for inducing potent nontoxic immunity against intracranial tumors that can be harnessed to provide a more effective and specific therapy critical in improving clinical outcomes for children affected by these malignancies.