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Development of a peptide vaccine platform for brain tumor immunotherapy that incorporates adjuvant CD27 stimulation for enhanced T cell immunity

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lioblastoma (GBM) is the most common malignant primary brain tumor and the most fatal, despite aggressive multimodal Ustandard of care. Immunotherapy with peptide vaccines derived from tumor antigens allows tumor-specific killing while sparing normal brain. However, the broad success of peptide vaccines is limited by their ability to induce potent CD8+ T cell responses. Immunomodulatory antibodies that promote co-stimulatory signaling, offer a broad adjuvant strategy for potentiating peptideinduced immunity. This research evaluates the mechanism by which an immunomodulatory agonist antibody specific for the T cell co-stimulatory molecule CD27 enhances the immune response to peptide vaccination for brain tumor immunotherapy. CD27 is constitutively expressed on naïve T cells, and signaling through this pathway during concomitant antigen presentation promotes T cell proliferation and survival and upregulation of pro-inflammatory cytokines. Furthermore, CD27 stimulation decreases the threshold of T cell activation to low-affinity antigens, suggesting a role for this pathway in promoting robust antitumor immunity. Celldex Therapeutics has developed a clinically-relevant high-affinity human-anti-human CD27 monoclonal antibody (ahCD27) that induces potent human T cell responses and prolongs survival in human CD27 transgenic mice bearing subcutaneous tumors. Here, we evaluate $\alpha hCD27$ as a vaccine adjuvant against a model tumor antigen. We show that $\alpha hCD27$ enhances the vaccineinduced T cell response and prolongs survival of mice bearing intracranial tumors in a T cell-dependent fashion. Interestingly, we demonstrate that the enhanced ahCD27-mediated vaccine-induced CD8+ T cell response is dependent upon CD27 stimulation on antigen-specific CD4+ T cells generated via MHC class II epitopes provided by the vaccine, indicating that the vaccine composition considerably influences the adjuvant potential of ahCD27. We demonstrate that this mechanistic information can be leveraged to develop a synthetic peptide vaccine platform targeting both CD4+ and CD8+ T cells against clinically-relevant antigens, such that the adjuvant potential of ahCD27 is optimally exploited.

Biography

Katherine Riccione has completed her Bachelor of Science in Biological Engineering at the University of Georgia and Master of Science in Biomedical Engineering from Duke University. She is currently working as a Graduate Research Assistant at the Duke Brain Tumor Immunotherapy Program, under the guidance of Dr. John Sampson. She is a National Science Foundation Graduate Research Fellow and recipient of the National Institute of Health's Ruth L Kirschstein National Research Service Award. Her current research focuses on the development of an immunomodulatory antibody as an adjuvant for brain tumor vaccines.

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