ORAL IMMUNIZATION WITH LISTERIA-BASED CANCER VACCINES ELICITS PROTECTIVE GASTROINTESTINAL FOCUSED IMMUNITY IN AN ORTHOTOPIC TRANSPLANTATION MODEL OF COLORECTAL CANCER

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Background: Gastrointestinal (GI) cancers, including colorectal, small intestine, and pancreatic cancer, pose a significant global public health challenge. Although effective in the short term, conventional treatment modalities such as surgery, radiotherapy, and chemotherapy often fail to provide lasting solutions. In this context, cancer vaccines have recently emerged as a promising avenue for immunotherapy, offering the potential to eradicate tumors while establishing durable protection. Listeria monocytogenes (Lm)-based cancer vaccines have emerged as a viable strategy to elicit a potent anti-tumors immunity. Intravenous (i.v.) delivery of Lm-based cancer vaccines can elicit a potent CD8 T cell response against tumors. Nevertheless, despite some promising outcomes reported in clinical trials, further refinements are needed to enhance the efficacy of this approach. Since our prior investigations have revealed that infecting mice with foodborne Lm induces GI focused CD8 T cell responses that are both qualitatively and quantitatively superior when compared to those induced by i.v. infection, we determined whether oral Lm immunization could protect mice against a model of colorectal cancer.

Methods: A modified Lm strain was used to orally immunize mice by consumption of vaccine-inoculated bread. Lm vaccines were attenuated by deletion of the ActA and InlB virulence genes and modified to facilitate murine intestinal epithelial invasion by mutating InlA. We orally immunized mice with attenuated Lm vaccines, then evaluated the CD8 T cell response in gut and lymphoid tissues during the effector phase, at memory homeostasis, and after recall. We utilized multi-color flow cytometry to assess the immunogenicity of oral Lm vaccines. Sham or immunized mice received orthotopic transplantation of 1x10^6 MC38-ova colorectal cancer cells and tumor burden was visualized by colonoscopy.

Results: Oral immunization with InlA^ΔActA ΔInlB Lm-ova vaccines induced widely disseminated effector and memory CD8 T cell responses. Vaccine elicited CD8 T cells were fully functional as measured by IFNg and TNF production. Oral Lm vaccines also induced durable memory CD8 T cells that recalled to target antigens. Oral immunization with InlA^ΔActA ΔInlB Lm-ova vaccines was safe. Mice did not lose weight after immunization and Lm remained confined to the gastrointestinal tissues. Finally, oral Lm immunization provided prophylactically protection against colorectal cancer, with a tumor rejection rate of 92%.

Conclusions: Attenuated Lm is highly immunogenic and safe when administered orally. Oral immunization with highly-attenuated Lm provides prophylactic protection. Therapeutic efficacy is currently being evaluated.

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