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The Role of Anti-Viral Immune Responses on the Therapeutic Efficacy of Oncolytic Virotherapy for High-Grade Gliomas

Dong Ho Shin, BA (Advisor: Juan Fueyo, MD)

Currently, there is no effective treatment for high-grade gliomas resistant to conventional treatments. Oncolytic viruses offer a new treatment modality by selectively replicating in cancer cells and inducing anti-tumor immunity. Oncolytic adenovirus Delta-24-RGD has shown safety and efficacy in clinical trials for high-grade gliomas. Efforts to improve the efficacy of oncolytic virotherapy have primarily focused on increasing the immunogenicity of the virus, either by incorporating immune-stimulating transgenes or combining with immune checkpoint blockades. However, such strategies may inadvertently trigger heightened immune responses against viral antigens, which may not always translate into increased responses against tumor antigens. Data from a clinical trial using Delta-24-RGD have revealed that high titers of neutralizing antibodies developed against adenovirus serotype 5 are associated with reduced patient survival. Moreover, analysis of tumor-infiltrating lymphocytes from another clinical trial revealed that patients developed dominant T-cell immune responses against viral antigens rather than tumor antigens. We hypothesized that protecting oncolytic adenoviruses from humoral and cellular immune responses will enhance the efficacy of virotherapy. Here, we utilized sera collected from patients who participated in a completed clinical trial involving Delta-24-RGD for recurrent malignant gliomas. Approximately 40% of these patients developed neutralizing antibodies one month after virus administration. Multiple virus injections resulted in 82% of patients developing antibodies, compared to 41% for those who received a single injection. In an immunocompetent mouse model of gliomas, antibodies were present within brain tumors following intratumoral virus injections and were colocalized with viral proteins. Consequently, neutralizing antibodies limited the therapeutic efficacy of Delta-24-RGD delivered intratumorally to gliomas. Importantly, we engineered a chimeric virus with hexon hypervariable regions from adenovirus serotype 43 that evaded neutralizing antibodies developed in patients and mice. This chimeric virus demonstrated

improved therapeutic efficacy in glioma-bearing mice with immunity against adenovirus serotype 5 compared to Delta-24-RGD. Furthermore, we identified dominant viral epitopes recognized by CD8+ T-cells against Delta-24-RGD in mice and designed nanoliposomes encapsulating these epitopes. Intravenously injected nanoliposomes localized to the liver, specifically to CD11b+ antigen presenting cells. Injection of nanoliposomes induced cargo antigen-specific immune tolerance, thereby reducing anti-viral immune responses. Analysis of the transcriptome from isolated T-cells revealed clonal deletion and anergy as mechanisms involved in the induction of immune tolerance. Reduced immune responses to viral antigens increased immune responses against tumor antigens in a mouse model of glioma. This shift in immune responses occurred without affecting the entire T-cell population, highlighting the specificity of the immune tolerance. In turn, increased anti-tumor immunity translated to improved therapeutic efficacy of oncolytic adenovirus against gliomas. These two strategies demonstrate that protecting the therapeutic virus from the host immune system has the potential to significantly enhance the efficacy of oncolytic virotherapy, presenting a promising new treatment strategy for patients with high-grade gliomas.

Advisory Committee:
Juan Fueyo, MD, Chair
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Ji Young Yoo, PhD