Abstract

Gliomas, like other solid tumors, restrict immune recognition of aberrant cancer cells. Further complicating this, pediatric cancers also have lower mutation rates than adult tumors making them more difficult to generate an immunotherapeutic response. This proposal addresses three mechanisms contributing to immune resistance in pediatric tumors: 1) low mutational activity, 2) antigen presentation in an immunosuppressive environment, and 3) MHC downregulation. We have developed a multimodal virus-based vaccine platform that uses the virus’s natural ability to recruit immune cells and break immune tolerance to improve immune activity against the tumor. By encoding tumor associated self-antigens within the viral genome so that they are expressed during infection our results show that we can convert the antiviral response into an anti-tumor response. The studies described in our proposal seek to improve our virus-based multi-modal vaccine approach to overcome immune resistance in one of the most difficult to treat solid tumors, malignant glioma.

Hypothesis

Engineered viral modifications that enhance native and adoptive immune cell activity will improve durable anti-tumor activity in treatment-resistant pediatric gliomas.

Background

Fig 1 C134 is a next generation virus that evades translational arrest and stimulates early tIFN and chemokine signaling (Cassady 2017). In some tumor models, oHSV treatment stimulates tumor specific T cells that recognize and suppress tumor growth after virus infection has resolved (Ghoneim and Cassady, CIR, 2018). Other tumors however are less responsive and OV therapy induces an antiviral rather than tumor specific response. Pediatric Tumors have low mutational loads and are less immune responsive. Pediatric Tumors may be improving virotherapeutic response in cold tumors

Aim 1 OVERVIEW

Aim 1: Improve the Immune-mediated Anti-Tumor Response Through Virus-based Tumor Associated Antigen Expression

Aim 2 OVERVIEW

Aim 2: Promote antigen presentation and a durable anti-tumor immune response

Aim 3 OVERVIEW

Aim 3: Enhance antitumor activity by improving cytokine/ cellular therapy recruitment and activity

Fig 2 OV-based tumor associated antigen (TAA) expression improves anti-tumor activity and overall survival in an immunotherapy resistant EphA2(+)/C57BL/6 based glioma

Fig 4 Myeloid targeting domains incorporated in the virus expressed antigen improve anti-tumor immunity and suppresses tumor growth on re-challenge.

Fig 6 Phase I clinical studies show that antiviral Type 1 IFN and adoptive immune cell responses correlate with OV-mediated survival. Immunoodiated tumors (e.g. MHC I downregulated) may suppress virus-TAA therapy. We postulate that oHSV cytokine & chemokine expression in combination with adoptive cellular therapy will overcome these restrictions.

Aim 3 Studies will:
- Evaluate OV-based cytokine and chemokine effect with native immune cell activity
- Improve adoptive cellular therapy (NK and CAR-NK) recruitment and anti-tumor activity using oHSV-based chemokine and cytokine expression (in collaboration with Dr. Lee and Dr. Cairo)

Fig 7 Treatment with a C134 based ILL2 expressing virus improves survival in Balb/c mice with DBT malignant glioma brain tumors.

Fig 5 Phage binding studies identified a consensus 12mer peptide domain that binds GPNMB (a surface protein involved in macrophage polarization and T cell activation). By incorporating this 12 AA sequence into the expressed antigen, we postulate that this will both improve EphA2 uptake by antigen presenting cells and improve T cell immunity against the viral expressed TAA

Impact

If successful, this flexible multimodal viral vaccine platform will harness and direct both native and adoptive cellular therapeutics against low mutational load immunotherapy-resistant tumors

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