(TAMs). We tested whether systemically administered resiquimod modulated TAMs in a genetic Sonic hedgehog (SHH) medulloblastoma model, and whether this modulation would be therapeutically beneficial. We generated mice with medulloblastoma by crossing hGFAP-Cre and SmoM2 mouse lines. The resulting hGFAP-Cre/SmoM2 (G-Smo) mice developed medulloblastoma with 100% frequency and showed a median survival of 14.5 days (n=12). Treatment with 3 doses of resiquimod at postnatal days 10, 12 and 14 reduced tumor size and increased median survival to 37 days (n=10) (p=0.003508). Cellular studies showed that resiquimod altered TAM phenotype, rapidly inducing expression of the inflammatory marker VCAM1, and more slowly increasing TAM populations. Responses to the 3-dose regimen were ultimately limited by recurrence and all mice eventually died of tumor progression. Continued resiquimod therapy with every other day dosing was less effective than the 3-dose regimen, suggesting that TAM responses to resiquimod are dynamic and change with prolonged exposure. Our data show that innate immunity, mediated by TAMs and stimulated by TLR-7/8 agonist therapy, can produce a significant anti-tumor effect in medulloblastoma. The common expression of TLR-7/8 on TAMs in patient-derived medulloblastoma samples and in the mouse model suggests that resiquimod may produce similar anti-medulloblastoma effects in humans. Further studies are needed to define the mechanism of the anti-tumor effect in detail, to determine the optimal dose regimen, and to determine if resiquimod can combine effectively with additional adjuvant therapies to produce curative effects.

IMMU-06. DELTA-24-RGD EXPRESSING POSITIVE IMMUNE MODULATORS SHOW ANTI-DIPG EFFECT AND INCREASE TUMOR IMMUNE INFILTRATION

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Diffuse Intrinsic Pontine Gliomas (DIPG) are aggressive pediatric brain tumors that arise in the pons of children, being the leading cause of pediatric death caused by cancer. We have previously demonstrated that Delta-24-RGD administration is safe and efficacious in DIPG preclinical models, indicating that it could be a good candidate as therapeutic approach for DIPG. However, our data underscore that there is still room to improve the anti-DIPG effect obtained with Delta-24-RGD. For that purpose, we have constructed three new virus by engineering Delta-24-RGD with different T cell activators: 4-1BBL (Delta-24-ACT), OX40-L (Delta-24-RGDOX) and GITRL (Delta-24-GREAT), to further increase the immune response generated by the viral effect. *In vitro*, the three virus were able to infect murine and human DIPG cell lines, produce oncolytic effect in a dose-dependent manner and express the corresponding functional ligand (4-1BBL, OX40L or GITRL) in the membrane of infected cells (almost 100% of cells expressing them at 10 MOIs). As expected, viral replication was optimal in human cell lines but semipermissive in murine cells. *In vivo*, the intratumoral administration of armed oncolytic viruses was safe and significantly increased survival of mice bearing orthotopic DIPG murine tumors, leading to long-term survivors. In addition, we analyzed the effect of the virus in the tumor microenvironment by flow cytometry and immunohistochemistry, which indicated that there was a significant increase of immune infiltration in brains of treated mice. Moreover, the immune infiltrated showed a functional active phenotype. Although deeper characterization is needed, these data show that the incorporation of a positive immune modulator into Delta-24-RGD could improve the oncolytic effect of the virus by boosting the immune response, while maintaining a safe profile in immunocompetent models offering a feasible option treatment for DIPG.

IMMU-07. "STROKE MIMICS" ARE NOT BENIGN IN IMMUNOCOMPROMISED CHILDREN

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Objective: To determine the clinical variances between strokes and stroke mimics in a pediatric immunocompromised population that consists of children with central nervous system (CNS) and non-CNS malignancies and a history of solid organ transplantation. Methods: We performed a retrospective cohort analysis of stroke alert activations in patients with high-grade gliomas, low-grade gliomas, atypical teratoid rhabdoid tumors, rare CNS tumors, B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, osteosarcoma, and solid organ transplants at St. Louis Children's Hospital between February 2013 and September 2019. We categorized final diagnoses as strokes or stroke mimics. We classified diagnoses as a neurologic emergency if the diagnosis necessitated changes in management. Results: Out of 217 stroke alerts, 31 alerts occurred for 28 patients meeting inclusion criteria. All final diagnoses constituted neurologic emergencies, including: stroke (39%), chemotherapy-related neurotoxicity (29%), tumor progression (19%), and seizures/posterior reversible encephalopathy syndrome (13%). Patients meeting inclusion criteria with strokes and stroke mimics presented similarly, with the exception of altered mental status, which was more prevalent in patients with strokes than stroke mimics ($p = 0.03$). One child received hyperacute thrombectomy for stroke. Only 58% of children with stroke mimics had complete resolution of their presenting neurologic symptoms. Children with strokes and stroke mimics had similar mortality incidences of 33% and 37%, respectively. Conclusions: Although all acute neurologic changes in immunocompromised children are not strokes, stroke mimics in this population are neither benign nor self-limited and carry long-term neurologic morbidity and mortality. This study highlights the utility of an acute stroke evaluation infrastructure and the need for acute and long-term neurology involvement in the care of these patients.

IMMU-08. MICROENVIRONMENT MODULATION BY TIM-3 BLOCKADE IMPROVES THE OUTCOME OF PRECLINICAL DIPG MODELS

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Diffuse Midline Gliomas (DMGs), encompassing Diffuse Intrinsic Pontine Gliomas (DIPGs), are the most aggressive pediatric brain tumors. Their meagre survival has not changed despite the combination of radiotherapy with targeted therapies emphasizing the urgent need for effective treatments. Recent research suggested that the DIPG tumor microenvironment is neither highly immunosuppressive nor inflammatory. These analyses showed the lack of infiltrating lymphocytes and the abundance of CD11b+ cells. TIM-3 (HAVCR2) is a member of the T-cell immunoglobulin and mucin domain protein family which is expressed on multiple immune cell types including T cells, T_{regs}, NK cells, monocytes, dendritic cells and microglia, where it potently regulates not only adaptive immunity but also innate immunity. Therefore, the central hypothesis of this study is that TIM-3 inhibitors could stimulate a cytotoxic immune effect and challenge several components in the tumor microenvironment including microglia, thereby providing a potential effective treatment for DMGs. In silico assessment of TIM-3 expression in a DIPG datasets showed a robust expression of this gene. Moreover, single-cell sequencing analyses of DIPG biopsies uncover its expression on tumor cells, especially in the OPCs compartment. In vivo efficacy studies showed that treatment with anti-TIM-3 antibody significantly increase the overall survival in two DIPG immunocompetent orthotopic animal models (doubling the median), lead to long-term survivors (50%) and showed immune memory. Analyses of $CD45^+$ populations in the tumor microenvironment showed a significant increase in B, NK and $CD8^+$ cells corresponding with a T-cell activate phenotype in treated-mice. The potential therapeutic involvement of NK cells was certified using nude mice and functional studies. Involvement of microglia in currently being analysed. In summary, these data underscore TIM-3 as a potential target DIPGs and uncover the potential involvement of NKs and other immune mechanisms in the efficacy of anti-TIM-3 therapy.

IMMU-09. MODULATING THE MYELOID POPULATION IN DIPG MODELS WITH ONCOLYTIC VIRUS AND COMPLEMENT INHIBITORS SHOWS THERAPEUTIC EFFICACY

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