Title

IMMU-11. SPATIOTEMPORAL IMMUNOGENOMIC ANALYSIS OF THE T-CELL REPERTOIRE IN IDH-MUTANT LOWER GRADE GLIOMAS

Journal

Neuro-oncology, 21(Suppl 6)

ISSN

1522-8517

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Publication Date

2019-11-01

Peer reviewed

IMMU-10. ESTABLISHING EFFECTIVE MODELS FOR IMMUNOTHERAPY IN GBM

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The introduction of immunotherapies has been paradigm shifting for cancers that were previously a death sentence. However, preclinical/clinical studies on glioblastoma (GBM) have generated mixed outcomes in patients, likely due to its great heterogeneity of immune microenvironment, particularly the myeloid cell populations. Primary patient studies have been limited by a difficulty in performing longitudinal studies, uncontrolled environmental conditions, and genetic variability. There is also, unfortunately, a paucity of mouse models that effectively re-capitulate the immune microenvironment of the human disease. To address these difficulties, we have established the Qk/p53/Pten (QPP) triple knockout mouse model established in our lab. The QPP model uses a cre-lox system to induce Qk deletion on a Pten–/–; p53–/– background which helps NSCs maintain their stemness outside the SVZ in Nes-CreERT2;$Qki^{L/L}$ $Pten^{L/L}$ $p53^{L/L}$ mice, which develops glioblastoma with survival of ~105 days. We have preliminarily assessed the QPP tumors as a faithful model to study the immune response to GBM and found them to recapitulate human GBM with respect to differential response to checkpoint blockade therapy and myeloid and T-cells histopathologically, particularly regarding upregulation of Arginase-1 (Arg1). Arg1 is the canonical marker for tumor-associated macrophages (TAMs), which is a major population of myeloid cells that greatly infiltrate in human GBM, sometimes making up more than ~30% of all GBM cells. Given TAMs' prevalence in the tumor microenvironment and their upregulation of Arg1 in both human GBM and our QPP model, we are testing whether manipulation of Arg1 will impact TAM function and influence GBM growth. We are also evaluating arginine metabolism in TAMs effect on T cell function in GBM. Lastly, we have developed a genetically engineered mouse model to study the role of Arg1 knockout in a GBM context in-vivo. Our studies suggest that Arg1 plays an important role in GBM immune interaction.

IMMU-11. SPATIOTEMPORAL IMMUNOGENOMIC ANALYSIS OF THE T-CELL REPERTOIRE IN IDH-MUTANT LOWER GRADE GLIOMAS

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The design and evaluation of immunotherapies in *IDH*-mutant lower grade gliomas (LGG) is hindered by a poor understanding of the LGG T-cell repertoire. We present data on the temporal evolution, intratumoral spatial distribution, and prognostic value of the T-cell repertoire in *IDH*-mutant LGGs. We performed immunogenomic profiling using T-cell receptor beta-chain sequencing of 163 glioma and peripheral blood samples from 33 immunotherapy-naive glioma patients (22 astrocytomas, 11 oligodendrogliomas). T-cell repertoire evolution was analyzed in a subset of 26 patients (69 samples) with matched primary (WHO grade II) and recurrent (WHO grade II-IV) glioma samples. T-cell repertoire diversity was defined as the number of unique T-cell clonotypes by V-gene, J-gene, and CDR3 nucleotide sequences. Malignant transformed (Grade III or IV) recurrent gliomas demonstrated increased T-cell repertoire diversity compared to their patient-matched primary tumors (p=0.0023), but grade II recurrences did not show the same increased diversity (p=0.26). This increase in T-cell repertoire diversity was greater in patients who underwent transformation in the context of TMZ-associated hypermutation compared to spontaneously transformed counterparts (p=0.035). In grade II primary astrocytomas (n=17), T-cell repertoire diversity above the median (186 unique T-cell clonotypes per sample) was associated with worse transformation-free (HR=4.2, p=0.045) and overall survival (HR=6.4, p=0.025). Next, we evaluated intratumoral immune heterogeneity in 7 patients by sampling from up to 10 distinct and maximally-separated intratumoral sites per LGG (64 samples). Eighty-two to 96% of unique clonotypes within a given tumor were present only within a single sampled site. Despite this heterogeneity, six LGG patients harbored T-cell clonotypes present tumor-wide across all sampled sites within a given tumor. Ten of 24 (42%) tumor-wide T-cell clonotypes were enriched in the glioma compared to matched peripheral blood, suggesting glioma-specificity. Taken together, T-cell receptor profiling in LGGs may have utility both as a prognostic biomarker and to identify glioma-specific T-cells.

IMMU-12. IL13Ra2-CAR T CELLS STIMULATE ENDOGENOUS IMMUNE RESPONSES AGAINST MURINE GLIOBLASTOMAS

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Malignant gliomas (MG) are one of the deadliest cancers with very limited therapeutic options. Chimeric antigen receptor (CAR)-T cell therapy has emerged as a powerful strategy for B-cell malignancies and may offer new opportunities to improve outcomes for patients with MGs. Our team is clinically evaluating IL13Rα2-targeted CAR-T cells for the treatment of recurrent IL13Rα2-positive MGs [NCT02208362]. While this trial is ongoing, we have previously reported that one patient with recurrent multifocal glioblastoma achieved a complete response post-IL13Rα2-CAR-T therapy despite the non-uniform expression of IL13Rα2 on the tumor. The therapeutic response against IL13Rα2-negative cells suggests CAR-T cells may stimulate endogenous immune responses. To study the interplay between CAR-T cells and host immune subsets, we have established a syngeneic immunocompetent glioma model, which recapitulates the tumor microenvironment (TME) of patients. Murine IL13Rα2-CAR-T cells mediate potent antitumor activity against IL13Rα2-engineered KR158, a highly invasive murine glioma model. Interestingly, mice "cured" from CAR-T therapy, after rechallenge, can successfully reject the tumors. Furthermore, we demonstrate comparable response rate in mice bearing gliomas with mixed antigen expression (50%IL13Rα2+/50%IL13Rα2-) vs 100% IL13Rα2+. Characterization of the TME post-CAR-T therapy indicates activation of endogenous cytotoxic CD8 T and myeloid cells, and decrease in the frequency of T regulatory cells. Further analyses reveal that tumor-associated macrophages (TAMs) may be reprogrammed during CAR-T therapy to exhibit tumoricidal activity and may promote the activation of endogenous T cells (CD4/CD8 T cells) resulting in enhanced antitumor activity. Current studies are focusing on the characterization of host immune cells to identify the mechanisms involved in induction of host immune responses mediated by CAR-T cell therapy. Our data thus strongly suggest that CAR-T therapy has the potential to reshape the glioma microenvironment creating a context permissible to elicit effective endogenous antitumor immunity.

IMMU-13. MECHANISMS OF IMMUNOLOGICAL ESCAPE DURING ADOPTIVE CELLULAR THERAPY IN HIGH GRADE GLIOMA

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INTRODUCTION: Immunotherapy is remarkably effective, yet tumor escape is common. Herein, we investigated tumor escape after adoptive cellular therapy (ACT) in intractable glioma models. These studies revealed multiple mechanisms of escape including a shift in immunogenic tumor antigens, downregulation of MHC-I, and upregulation of checkpoint molecules. Despite these changes, we HYPOTHESIZED that a new population of escape variant-specific polyclonal T cells could be generated to target immune-escaped tumors through using tumor escape variant RNA. METHODS: We studied KR158B-luc glioma-bearing mice during treatment with ACT with polyclonal tumor-specific T cells. We tested the immunogenicity of primary and escaped tumors using T cell restimulation assays. We used flow cytometry and RNA profiling of whole tumors to further define escape mechanisms. To treat immune-escaped tumors, we generated escape variant-specific T cells through the use of escape variant total tumor RNA and administered these cells as ACT. RESULTS: Escape mechanisms included a shift in immunogenic tumor antigens, downregulation of major histocompatibility complex (MHC) class I by 50%, and upregulation of checkpoint molecules. This included activated T cells and NK cells from tumor-draining lymph nodes expressing 50% and 30% PD-1 after ACT. Importantly, polyclonal T cells specific for escape variants displayed greater recognition of escaped tumors than primary tumors. When administered as ACT, these T cells prolonged median survival of escape variant-bearing mice by 60% (24 to 33 days, p=.0003). The rational combination of ACT with PD-1 blockade prolonged median survival of escape variant glioma-bearing mice by 110% and was dependent upon NK cells and T cells as determined by cell depletion experiments. To prevent escape from primary tumors, we combined ACT with PD-1 blockade to yield 71% long-term cures in KR158B-luc-bearing mice. CONCLUSIONS: These findings suggest that the immune landscape of brain tumors is markedly different post-immunotherapy yet can still be targeted with immunotherapy.