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REVIEW

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The possibility of cancer immune editing in gliomas. A critical review

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ABSTRACT

The relationship between anti-tumoral immunity and cancer progression is complex. Recently, immune editing has emerged as a model to explain the interplay between the immune system and the selection of genetic alterations in cancer. In this model, the immune system selects cancer cells that grow as these are fit to escape immune surveillance during tumor development. Gliomas and glioblastoma, the most aggressive and most common of all primary malignant brain tumors are genetically heterogeneous, are relatively less antigenic, and are less responsive to immunotherapy than other cancers. In this review, we provide an overview of the relationship between glioma's immune suppressive features, anti-tumoral immunity and cancer genomics. In this context, we provide a critical discussion of evidence suggestive of immune editing in this disease and discuss possible alternative explanations for these findings.

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Introduction

Burgeoning work of next-generation sequencing analysis has provided the framework to visualize the genomic landscape of cancer, these studies have revealed a remarkable genetic heterogeneity within lower-grade gliomas (LGG) and glioblastomas (GBM).[1-3] Gliomas elicit a strong immunosuppressive state through the expression of inhibitory ligands that induce anergy and apoptosis of cytotoxic lymphocytes, expression of immune checkpoints that impair the anti-tumoral immune response, and through eliciting tumoral infiltration by immunosuppressive cells.[4-7] There is also evidence of immune-cell infiltration following immunotherapy in human and murine gliomas,[8,9] in which bone marrow-derived dendritic cells play a role.[9] Despite these findings, immunotherapy for gliomas has not shown a significant efficacy in the clinical setting.[10-12] These facts rise the possibility that the dominance of tumor clones that evade immune recognition could be related to the emergence and selection of specific genetic alterations that confer cancer cells this feature during tumor progression. However, the possibility of immune editing during the progression of gliomas has not been explored. Herein we provide an overview of immune editing and some illustrative examples that suggest that this might be happening in gliomas.

The cancer immune editing concept

The first hints of immunity against cancer were given by Paul Ehrlich[13] and later supported by Burnet and Thomas.[14-16] However, in light of some studies that introduced doubts about the paradigm of immune control of cancer,[17-19] the attention of cancer immune surveillance gained broader recognition again more recently by experiments where mice devoid of T, B and NK cells or immune-regulatory cytokines were more susceptible to tumor formation than immunocompetent mice.[20-24] Particularly, the reviving of interest on tumor immunology arose from studies showing that cancer cells can escape immune recognition and destruction,[20,25,26] framing this mechanism as one of the hallmarks of cancer in the latest iteration of a comprehensive review of cancer biology by Hanahan and Weinberg in recent years.[27] The growing recognition of the immunological control of neoplasia prompted a more integrative concept of tumor-immune system interaction called cancer immune editing in which cancer immune-related phenotype is shaped by selection of tumor cells capable of avoiding recognition and killing by the immune system. Cancer immune editing has been conceptualized into three phases: **elimination**, a process in which the immune system recognizes and eradicates developing cancer cells before the latter can reach a clinical stage; **equilibrium**, a state of tumor latency in which tumor cells remain occult or sub-clinical, are not completely eradicated but do not increase in number; and **escape**, a phase in which tumor cells capable of evading immune recognition and eradication (i.e. edited cells) grow progressively into a clinical stage of cancer.[28,29] When this process is carried out in its entirety, tumor cell variants with a less immunogenic phenotype emerge resulting in cancer that cannot be eradicated by the immune system.[30,31] Comprehensive reviews have described the details

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of the evidence suggestive of the process of cancer immune editing.[30-32]

Immune editing in Gliomas: Elimination, equilibrium, and escape

Elimination

Clinical observations have provided the inference that the immune editing phases might be occurring in cancer patients. Particularly, the observation that immune suppressed patients with AIDS or transplant recipients receiving immunosuppressive therapies are more prone to some cancer types suggests the presence of the elimination phase in the immune competent population.[33-35] The innate and adaptive immune system eliminate an emergent cancer through several processes: some of the best characterized mechanisms include the tumoral expression of NKG2D ligands that are recognized by NK cells, the recognition of tumor-specific antigens by $CD4^+$ and $CD8^+$ T-cells, the production of pro-inflammatory and immunomodulatory cytokines that enhance immune anti-tumoral responses, and the induction of tumor cell apoptosis by immune effector cells.[28,30,31]

A key question within the study of relationship between the immune system and the cancer genome is whether immune cells can recognize genetic alterations in the tumor. Recent studies have suggested this to be the case. For instance, the proliferation of hyperploid cancer cells alerts the immune system of developing cancer through the recognition of the abnormally exposed calreticulin on the cell surface, which renders polyploid cancer cells as targets of cytotoxic T-cells.[36] However, a recent analysis of TCGA data from 12 human cancer types showed that high levels of tumor aneuploidy is associated with decreased expression of genes encoding for markers of infiltrating cytotoxic immune cells, genes encoding for components of the T and B-cell receptor, genes mediating cytotoxic activities, genes related to the IFN-γ pathway, as well as genes associated with the maintenance of the immune response and the production of cytokines.[37] Moreover, a higher number of neoantigens resulting from non-silent mutations were found in highly aneuploid tumors compared to less aneuploid tumors, indicating that the former did not undergo immune editing during progression due to a reduced anti-tumoral imunity.[37] Highly aneuploid GBM and LGG did not reveal any decrease in the expression of genes involved in immune cytotoxic activities.[37] In any case, according to the immune editing model, if a particular cancer cell is not initially eliminated due to the fact that is not antigenic or given that it has acquired the ability to suppress anti-tumor immunity, it will prevail into the equilibrium phase.[28,30]

No studies provide any evidence to address whether the elimination phase is occurring in gliomas, that is, evidence of gliomas disappearing at a pre-clinical stage. Regardless of some reports suggesting a higher incidence of gliomas in immunosuppressed individuals,[38,39] in general, gliomas do not arise from immunosuppressed states as opposed to other cancers like non-Hodgkin lymphoma or Kaposís sarcoma.[34] Direct demonstration of the elimination phase in patients is particularly difficult as it would require evidence of tumor-infiltrating immune cells on preclinical stages of gliomas followed by the spontaneous disappearance of the tumors. To prove this, transgenic mouse gliomas have emerged as novel tools that can model the acquisition of many of the genetic alterations seen in human gliomas[40-42] and offer an opportunity to investigate whether gliomas at early stages of formation undergo infiltration by immune cells, a pre-requisite for the existence of the elimination phase. One of these studies analyzed early immune responses at occult stages of glioma development in a transgenic mouse glioma model of spontaneous cancer (*GFAP*-V^{12}HA-*ras*).[41] To induce the development of astrocytomas, the glial fibrillary acidic protein (GFAP) promoter was used to express the V^{12}HA-*ras* specifically in astrocytes. At 12 weeks, asymptomatic mice had infiltration of $CD4^+$ and $CD8^+$ T-cells in the tumor, suggesting that the immune system can detect a developing glioma at early stages. However, no evidence of spontaneous disappearance of these tumors was reported.[41] Whereas it is difficult to rule out elimination of gliomas by the immune system, there is no substantial evidence to suggest this phenomenon is taking place.

Equilibrium

The equilibrium phase was inferred from reports of transplant patients who developed metastases in a transplanted organ that was donated by a cancer patient.[43-45] Particularly, there have been reports of transplant recipients diagnosed with glioma metastases on the grafted organs after receiving liver, kidney or lung transplants from GBM donor patients, suggesting the possibility of an equilibrium phase in these tumors, at least with respect to systemic grafting of lesions.[39,46-48] In general, gliomas do not metastasize outside the central nervous system in spite of the fact that tumor cells have been found circulating in the blood stream.[49] In the context of these organ transplant case reports,[39,46-48] it appears that glioma cells in the donor patient may have been in a dormant state due to the host immune pressure, but after transplantation, these lesions grew in the organ that was transplanted into a host undergoing pharmacological immunosuppression. Another example of evidence suggestive of the existence of an equilibrium phase in brain tumors is that of a pediatric patient who was diagnosed with medulloblastoma at 17 months of age, who 10 years later was treated with immunosuppressive drugs for a lung transplant due to the development of chemotherapy-induced pulmonary fibrosis. 12 months after transplantation, liver metastases were detected revealing recurrence of the medulloblastoma in the histopathological report.[50]

Mouse models have suggested that adaptive immunity and T-cells in particular are responsible for controlling tumor growth during the equilibrium phase.[51,52] As opposed to NK cells, depletion of IFN-γ, $CD4^+$ and $CD8^+$ T-cells in mice treated with methyl-colantrene promoted the development of sarcomas.[51] In addition, depletion of $CD4^+$ and/or $CD8^+$ T-cells led to spontaneous lung metastases in a fibrosarcoma mouse model that do not develop these metastases in an immune competent setting.[52] These metastases were highly positive for MHC class I (MHC-I),[52] indicating the

importance of the interaction between MHC-I molecules and T-cell receptors in tumor dormancy/equilibrium maintenance.

Escape

In the escape phase, the immune system fails to limit tumor growth, and tumor cells capable of evading the immune recognition and elimination prevail into a clinically evident state.[28,30-32] The interaction between cancer and the immune system gives rise to a new group of tumor cells displaying reduced immunogenicity, and tumors that elicit an immunosuppressive microenvironment that endows them to survive and proliferate in the immunocompetent host.[28,53,54] Taking into account that the correct functionality of the MHC-I complex is required for an effective anti-tumoral immune response,[55] immune escape capabilities have been well associated with defects on MHC-I expression on tumor cells.[53,56] Relative reduction in expression of MHC-I by tumor cells can cause immune selection and outgrowth of a tumor clone resistant to immunotherapies.[57,58] Furthermore, recent evidence suggests a positive selection of loss-of-function mutations of HLA class I genes compared with mutations in non-HLA class I genes in a pan-cancer analysis.[59] This analysis showed few HLA class I mutations in human gliomas compared to other cancers. Nevertheless, an association between HLA class I mutations and upregulation of killer lymphocyte effector gene expression was found in several cancer types, including gliomas (Fig. 1).[59,60] This finding suggests that immune pressure exerted by lymphocyte cytolytic activity selects glioma cells harboring loss-of-function HLA class I mutations.[59,60] Moreover, the decreased expression of HLA class I and the antigen processing and presentation machinery (APM) components correlates with malignancy grade in human and murine GBM.[61,62] The reduction of HLA class I and II gene expression could be explained by the EGFR activation.[63] Indeed, inhibitory signals originated from the activation of EGFR have been proposed to affect the expression of the IFN-γ receptor complex, as well as to act on the promoter of HLA class I and II genes and MHC class II transactivator (CIITA) gene, a transcriptional activator of HLA class I and II genes.[63] This mechanism might explain the relative lymphocytic depletion of GBM of the classical subtype, which characteristically have EGFR amplification.[64] On the other hand, the sole expression of HLA class I molecules without loaded antigen due to dysfunctional APM has been described in astrocytomas as another potential escape mechanism that inhibits the anti-tumoral response of NK cells.[65] Given the relative uncommon frequency of HLA class I gene mutations in human gliomas in spite of the implications of these genes in tumor recognition by the immune system, we investigated the aggregate frequency of down-regulation, non-silent mutation or deletion of HLA class I and related APM genes across gliomas from TCGA. As a group, these genes are found affected by these inactivating alterations in 53.7% of GBM (n = 396) and 32.4% of LGG (n = 511), suggesting that gliomas commonly suffer hits of this pathway that is critical for immune recognition (Fig. 2). The evidence presented above indicates and further substantiates the idea of immune selection of glioma cell populations with HLA class I molecules presentation defects.

Cancer immune editing implications in glioma therapy

Immune checkpoint inhibitors have shown clinically relevant efficacy for some cancers such as melanoma and lung cancer, and have emerged as an innovative therapeutic approach within the field of oncology.[66-69] Particularly, tumors with high mutational load and mismatch repair (MMR) defects have been shown to vary among cancer types and correlate with good clinical responses to immune checkpoint inhibitors.[70-73] In this context, GBM patients with germline MMR defects and the accompanying hypermutator phenotype have shown striking and long-term responses to the PD1 inhibitor nivolumab.[74] Temozolomide, the chemotherapeutic standard of care of GBM, can generate mutations in the tumor that can lead to a hypermutator phenotype following treatment with this chemotherapy in 17% of cases.[75-78] Whereas high tumor mutational load and loss of MMR protein expression are infrequent,[79,80] the possibility of this phenotype/genotype being more responsive to immunotherapy rises interest for personalizing the use of this treatment modality for a subset of glioma patients.

Similar to the T-cell-dependent selection of tumor cells lacking highly immunogenic antigens during tumor progression,[81,82] the major implication of immune editing for glioma therapy is that

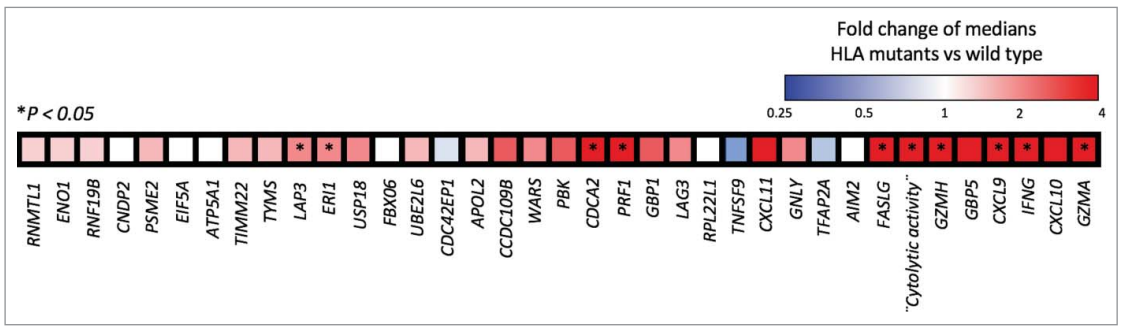

Figure 1. Heatmap displaying a differential gene expression in a color scale in HLA class I-mutant gliomas vs. wild-type HLA class I gliomas. Tumors harboring HLA class I mutations overexpress lymphocyte killer effector genes. As previously defined, "Cytolytic activity" is included as a single gene and determined by Granzyme A (*GZMA*) and Perforin (*PRF1*), two cytolytic genes expressed in activated CD8+ T-cells.[60] *$P < 0.05$ represents the significance of the association between the expression of each gene and HLA class I mutant-gliomas. [Adapted by permission from Springer Nature: Nature Biotechnology, Comprehensive analysis of cancer-associated somatic mutations in class I HLA genes, Shukla et al., copyright 2015][59].

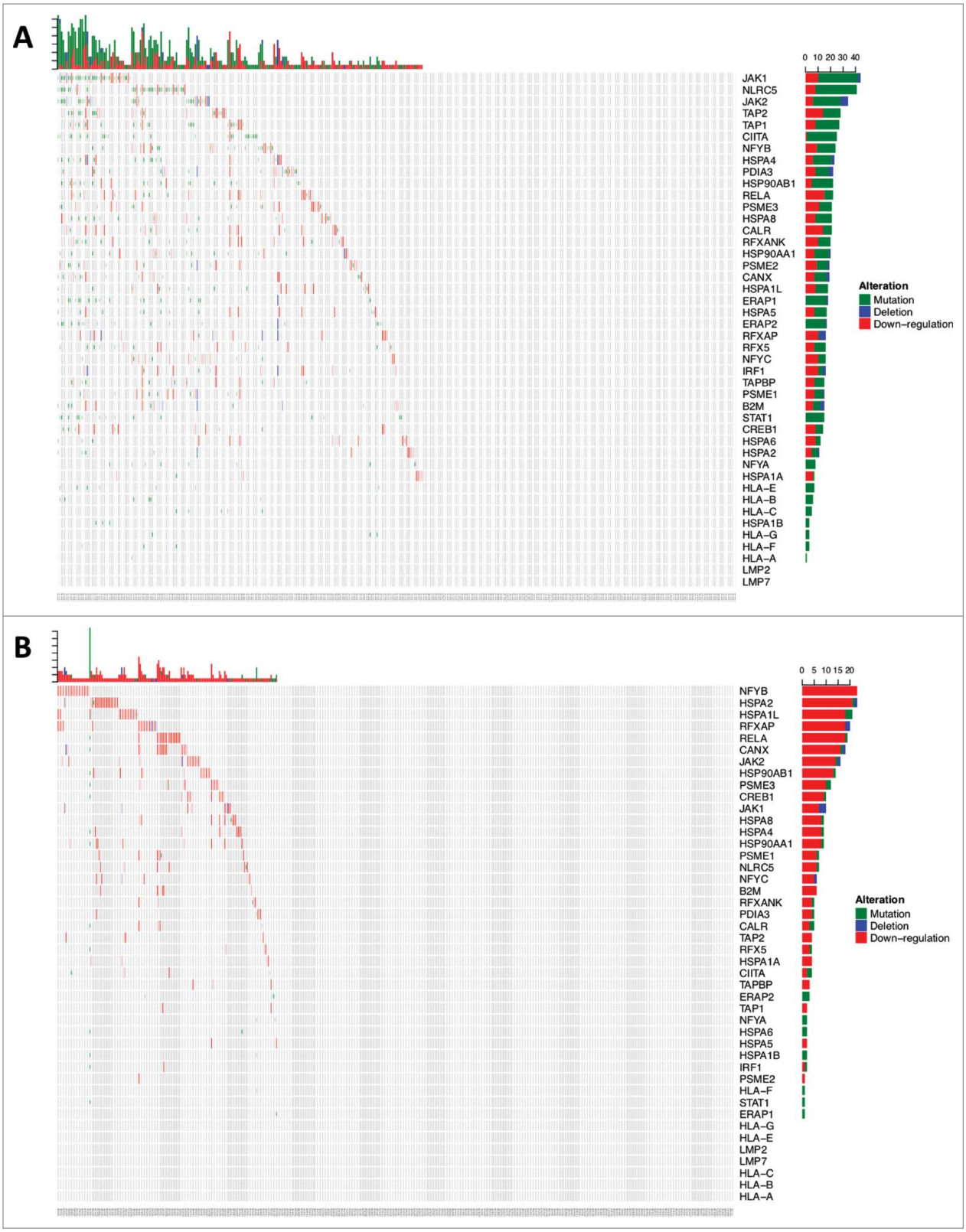

Figure 2a. (Continued).

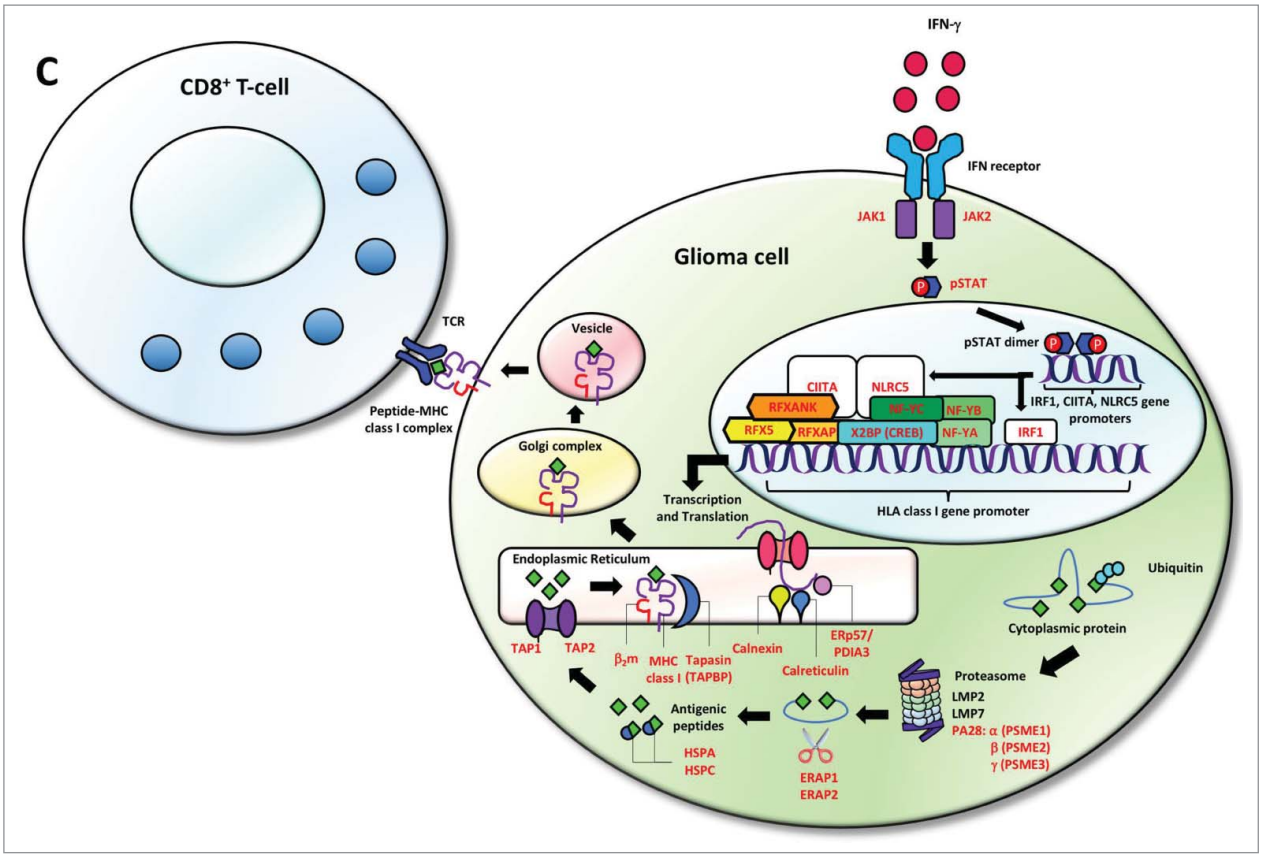

Figure 2b. Cumulative HLA class I and APM defects across gliomas from TCGA. (A) 213/396 GBM and (B) 166/511 LGG samples were found to have alterations in the formation of the HLA class I peptide complex that enable glioma cells to escape immune recognition by $CD8^+$ T-cells. (C) Highlighted in red are the components showing different types of alterations in antigen processing and presentation ranging from defects in the IFN-γ pathway (JAK1, JAK2, STAT1) and the HLA class I enhanceosome (NLRC5, CIITA, IRF1, RFX5, RFXANK, RFXAP, X2BP, NF-Y) that mediate the transcriptional activation of HLA class I genes; PSME1, PSME2, PSME3 genes coding for the alpha, beta, and gamma subunits that make up the proteasome activator complex PA28 for peptide generation; ERAP1 and ERAP2 that trim longer precursor of antigenic peptides; HSPA and HSPC that chaperones the peptides to their loading on the MHC class I in the endoplasmic reticulum; and TAP1, TAP2, TAPBP, calreticulin, calnexin, PDIA3, β_2-microglobulin and HLA class I genes that participate in the formation of the MHC class I peptide complex.

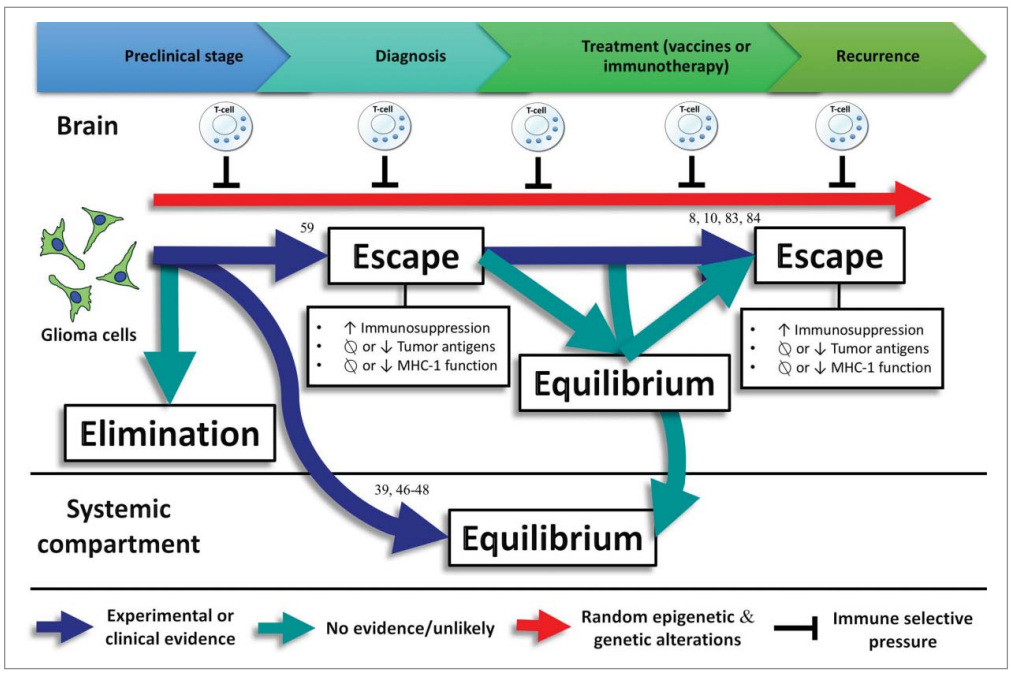

Figure 3. Experimental or clinical evidence regarding immune editing in gliomas with numbers representing the references related to this evidence. No evidence exists about the elimination phase in gliomas. Commonly, gliomas do not spread outside the central nervous system. However, glioma metastases have been detected in transplanted organs of immunosuppressed transplant recipients, suggesting that the equilibrium phase is taking place in the systemic compartment[39,46-48] Associations between loss-of-function HLA class I mutations and upregulation of lymphocyte killer effector genes,[59] as well as HLA class I and APM defects have been found in gliomas, evidencing the escape phase. In addition, loss of glioma-specific antigens after using targeted immunotherapies lead to a negative selection of tumor variants cells expressing these antigens.[8,10,83,84]

immunotherapies designed to target tumor-specific antigens often fail, as there are tumor clones that will be selected for the lack of expression of these antigens or defects in antigen presentation. In a phase II clinical trial evaluating EGFRvIII-targeted vaccination in glioma patients, it was found that EGFRvIII expression was lost at tumor recurrence.[10,83] Additionally, recent reports testing chimeric antigen receptor (CAR)-engineered T-cells targeting the cancer-associated antigens interleukin-13 receptor alpha 2 (IL13Rα2) and EGFRvIII have shown promising results in GBM patients with recurrent disease.[8,84] Although regression of multifocal GBM was achieved in one particular patient, recurrent lesions at new brain sites emerged with minimal to absent expression of IL13Rα2.[84] In the study evaluating CAR T-EGFRvIII, 5 of 7 GBM patients whom tumor was available for evaluation after CAR T-cells infusion had a decrease in the expression of EGFRvIII.[8] Thus, recurrent tumor lesions lacking glioma-specific antigens suggest the possibility that antigen loss variants were selected to grow during immunotherapy. Because of this mechanism of immune editing and the intrinsic molecular heterogeneity of gliomas, different strategies for immunotherapy should be used in order to target multiple antigens to mitigate antigen escape and avoid tumor recurrence.[85-87]

If immune editing is occurring during glioma progression, perhaps transient manipulation of the selection pressure elicited by the immune system might lead to more immunogenic tumors that might be more susceptible to immunotherapies. A scheme summarizing the existing evidence of immune editing in gliomas is shown (Fig. 3).

Conclusions

Gliomas are notorious for the multiple mechanisms of immune suppression and lack of response to immunotherapy compared to other cancers. Gliomas are molecularly complex and have several genetic and epigenetic alterations that are recurrently seen during tumor progression. Whereas some of these offer a tumor growth advantage, others might have been selected by the anti-tumoral immunity. This is an interesting possibility that has not been systematically investigated in gliomas. Hopefully, further research addressing the possibility of immune editing in gliomas will lead to manipulation of this process and more efficient immunotherapy strategies transforming the way these patients are treated.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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