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Epigenetic Reprogramming with DNMT Inhibitors: A Multi-Mechanistic Approach to Enhance Immunotherapy in Glioblastoma

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Commentary

Although adoptive T cell therapies and immune checkpoint blockades have been successfully implemented in various cancers, no immunotherapy agents have yet reached FDA approval for glioblastoma (GBM). GBM harbors a uniquely immunosuppressive tumor microenvironment that presents significant barriers to effective immunotherapy. Key hallmarks of the GBM microenvironment include the exclusion of lymphoid cells from the tumor core and the predominance of immunosuppressive tumor-associated macrophages [1-3]. This limited immune cell infiltration into an inhibitory tumor immune microenvironment combined with low mutational burden results in the added complexity of identifying specific and durably-expressed tumor-associated antigens in a heterogenous tumor cell population [4-7]. These obstacles have resulted in variable response rates of current immunotherapies in GBM that starkly contrast to other cancers where these strategies have demonstrated strong clinical efficacy.

Previous studies have demonstrated the potential for epigenetic engineering to remodel the tumor microenvironment for targeted immunotherapies against solid tumors [8-10]. While histone deacetylase inhibitors (HDACi) and Enhancer of Zeste Homolog 2 inhibitors (EZH2i) have demonstrated similar antigenic upregulation in malignant neoplasms, DNA methyltransferase inhibitors (DNMTi) remain the most well studied small molecule epigenetic agents with strong potential as an adjunct to immunotherapy in solid tumors [11]. Specifically, our group recently published a mechanistic rationale to epigenetically prime human gliomas to immunotherapeutic targeting using clinically achievable doses of the FDA-approved DNMTi, Decitabine (DAC) [12]. Through analysis of tumor-intrinsic epigenetic and transcriptional mechanisms at single cell resolution, we demonstrated that DAC concomitantly induced tumor antigens, reactivated human endogenous retroviruses, and stimulated interferon signaling. Notably, this epigenetic remodeling was correlated with improved T cell functionality and increased cytolytic activity against primary GBM cells *in vitro*.

In this commentary, we synthesize recent work that supports epigenetic remodeling with DNMTi to sensitize immunogenically cold and heterogenous solid tumors to immunotherapy. We summarize previous efforts using DAC to induce targetable tumor antigens, to enhance immunology through epigenetic reactivation of human endogenous

retroviruses (hERV) with downstream stimulation of IFN pathways and apoptosis receptors, and to remodel the GBM tumor microenvironment through epigenetic reprogramming of infiltrating lymphoid and myeloid immune cells. In doing so, we argue that epigenetically priming the tumor microenvironment demonstrates the potential to overcome many of the current obstacles inhibiting successful immune therapies in GBM.

DNMTi Induces Targetable Tumor Antigen

Current approaches utilizing DNMTi epigenetic remodeling have concentrated on the induction of cancer testis antigens (CTA) for adoptive T cell targeting. Endogenously expressed in many cancer types, CTA are a family of proteins that are expressed normally in germinal spermatogonia and downregulated in somatic tissue via *de novo* DNA methylation and other epigenetic programs [8]. In certain immunogenic tumors, aberrant expression of these proteins has been identified for targeting by engineered T cells, with New York esophageal squamous cell carcinoma 1 (NY-ESO-1) considered to be the most immunogenic [13-18]. Indeed, NY-ESO-1 and other well-studied CTA are currently being assessed in a variety of adoptive T cells and cancer vaccine clinical trials in numerous cancer types [19-25].

Despite the potential for tumor specificity and epitope immunogenicity, current adoptive T cell approaches targeting single CTA in GBM have not been successful to date. Single-antigen therapies are susceptible to antigen escape and engineered T cells struggle to overcome the inhibitory tumor-immune microenvironment within some solid tumors [26]. Moreover, in cold tumors resistant to immune therapies like GBM, NY-ESO-1 and other CTA are not frequently endogenously expressed [27]. Indeed, high intratumoral heterogeneity, low mutational burden, and inconsistent antigen expression in glioma patients compound the challenge of targeting GBM-specific tumor antigens. For example, while not classically a CTA, IL13Ra2 expression is restricted to testis in normal tissue and is a well-studied GBM-specific antigen with endogenous expression in the tumor tissue of 75% of glioma patients. However, adoptive chimeric antigen receptor (CAR) T cell therapies targeting IL13Ra2 in GBM have struggled to overcome intratumoral heterogeneity, adapt to antigen escape, and resist immunosuppressive changes in the tumor microenvironment [5,28]. Indeed, tissue analysis from GBM tumors resected after IL13Ra2 CAR T therapy demonstrated that the antigen was eliminated, but tumor growth persisted [29]. Moreover, intraventricular IL13Ra2 CAR T infusion resulted in observable increases in cytokines and immune cells in cerebral spinal fluid, however these enhancements again were unable to overcome the immunosuppressive microenvironment in GBM and prevent relapse in glioma patients receiving therapy [5]. Similar results were observed in CAR T targeting EGFRviii which demonstrated elimination of antigen despite tumor persistence [6]. Therefore, the need to identify, induce, and target multiple antigens that can remodel an immunosuppressive tumor microenvironment in GBM is particularly important.

Cancer testis antigens (CTA) are particularly susceptible to epigenetic induction. Previous work from our group and others have shown that clinically achievable doses of DAC induces durable expression of CTA in GBM tumor tissue but not normal tissue for immunotherapeutic targeting [30-34]. We administered a DAC dose approved by the FDA for myelodysplastic syndrome that was detectable in cerebral spinal and achieved durable expression of NY-ESO-1 upregulation 65-days following initial exposure to DAC [34-36]. Consistent with previous studies demonstrating re-establishment of T cell mediated apoptosis via Fas/Fas Ligand after DAC treatment in glioma, we observed that targeting of these DAC-treated glioma cells with NY-ESO-1 TCR engineered $CD8^+$ cells stimulated polyfunctional antitumor, antiviral, and T helper cytokine repertoire that further enhanced the clearance of NY-ESO-1–expressing tumor cells [30]. Single-cell RNA sequencing of DAC treated serum-free patient-derived gliomaspheres demonstrated that ~70% of tumor cells expressed one or more CTA. Moreover, CTA were upregulated across all clusters despite interpatient and intrapatient heterogeneity marked by mesenchymal, classical, proneural, or cycling cellular clusters.

We speculated that the simultaneous induction of multiple CTA can potentially prime glioma to polyvalent antigen targeting [12]. Preclinical studies of tandem or trivalent CARs targeting multiple antigens IL13Ra2, HER2, and EphA2 in GBM mitigated antigen escape in orthotopic xenograft models of GBM and future work will need to demonstrate the feasibility of this strategy in an immune competent model [37,38]. Moreover, we hypothesize that epigenetic priming with DNMTi can be repeated with DAC being readministered following antigen dropout to re-express targetable antigen. Taken together, the induction of targetable CTA for polyclonal antigen adoptive T cell targeting supports a promising strategy for immunotherapy against GBM.

DNMTi Activates Human Endogenous Retroviruses

Beyond the induction of CTA, recent studies have begun to characterize the pleiotropic epigenetic and transcriptomic effects of DNMTi, with particular focus on how these effects can be leveraged to enhance immunotherapy. Many of these studies have highlighted the reactivation of human endogenous retroviruses (hERV). These transposable elements are fragments of exogenous viruses that have incorporated into the human genome over millions of years. Aberrant activation of these retroviral elements has been implicated in many disease pathologies, including multiple cancer types [39,40]. Until recently, the reactivation of hERV has been difficult to study, and their impact on downstream immune pathways and disease pathologies remain complex.

Previous studies have identified a role for DNA demethylation in the regulation of hERV expression which subsequently activates innate immune pattern recognition receptors (PRR) for downstream inflammatory signaling. Administration of DNMTi in solid tumors has been shown to reactivate hERVs which triggers antiviral interferon responses via Toll-Like Receptor 3 (TLR3) pathways and enhances the tumor's sensitivity to immune checkpoint therapies [41]. In primary GBM cells specifically, we identified significantly upregulated hERV after DAC treatment that positively correlated with downstream type I interferon (IFN) signaling. Consistent with previous studies in glioma, we observed enhanced MHC-I expression after DAC treatment that correlated with IFN signaling instead of direct MHC-I demethylation [30]. Similar findings have been observed in clear cell renal cell carcinoma where increased hERV signatures and associated type I IFN signaling via RIG-I have been predictive of immunotherapy [42]. In small-cell lung cancer, interferon inducible endogenous retroviruses engaged the PRRs Mitochondrial Antiviral Protein (MAVS) and Stimulator of Interferon Genes (STING), resulting in feed-forward innate immune signaling and resultant T cell infiltration [43]. We speculate that similar enhancement of IFN signaling may occur in glioma to alter the cellular composition of the tumor immune microenvironment and overcome the epigenetic mechanisms of T cell exhaustion in glioma [3,44,45].

Interestingly, recent studies have questioned the role of interferon signaling as an inhibitor rather than an enhancer of immunotherapeutic efficacy. We previously reported that TLR3 agonist, Poly-ICLC, in conjunction with dendritic cell vaccination induced enhanced interferon signaling that was associated with prolonged survival and delayed tumor progression in a randomized phase II clinical trial for the treatment of recurrent GBM [44]. These findings underscore the essential role of interferon in initiating robust anti-tumor immunity by enhancing antigen presentation, promoting T cell recruitment, and increasing MHC class I expression.

However, chronic inflammation secondary to type I IFN signaling has been associated with T cell exhaustion and resistance to immune checkpoint blockade (ICB) therapy in multiple solid tumors. Indeed, recent studies characterizing the use of a Janus kinase inhibitor (JAKi), Ruxolitinib, to inhibit downstream IFN signaling in combination with ICB has demonstrated enhanced efficacy in Hodgkin lymphoma and non-small cell lung cancer patients who had previously failed ICB [46,47]. Immunologically cold tumors need some IFN signaling to mount an effective immune response, however the role of IFN is less defined than previously thought [48]. In the context of DNMTi therapy and hERV activation in GBM, it will be crucial to carefully balance the activation of IFN signaling to avoid tipping the immune response toward exhaustion. Strategic dosing regimens or combinatorial approaches will need to be carefully considered to briefly pulse IFN and avoid chronic activation. Ongoing studies are being performed to better characterize the immunologic consequences of IFN signaling downstream of DNMTi and hERV activation in GBM.

Despite the contrasting effect of interferon stimulation in immunotherapeutic response, modulation of the glioma tumor immune microenvironment through epigenetic reactivation of hERV joins established viral strategies for the treatment of GBM. Oncolytic viruses have long been studied for their ability to stimulate host immune response in GBM and cytomegalovirus-specific $CD8^+$ T cell responses have been induced in GBM patients treated after autologous tumor-lysate pulsed dendritic cell vaccination [49,50]. Future work will need to mechanistically establish the specific hERV upregulation and downstream interferon activation in glioma.

DNMTi Reprograms Immune Cells

Although most studies on DNMTi have focused on tumor-intrinsic epigenetic and transcriptional alterations, emerging research highlights the impact of DNMTi on immune cell function. In tumor-reactive effector cells, *de novo* hypermethylation programs have been associated with exhausted T-cell phenotypes that limit the efficacy of ICB [51]. Encouragingly, administration of DAC prior to ICB in a chronic LCMV *in vivo* model overcame *de novo* exhaustion-associated hypermethylated regions within *IFN-g* and *Myc* loci that rejuvenated exhausted CD8 T cells [52]. Moreover, low dose DAC priming prior to adoptive transfer of effector T cells into *in vivo* tumor models demonstrated enhanced anti-tumor properties, suggesting epigenetic protection from an exhausted T cell phenotype [53,54]. Specifically in GBM, a recent study demonstrated that hypermethylation of a regulatory transcription factor AP-2a is associated with increased expression of PD-L1 [55]. Furthermore, DAC re-expressed AP-2a in the tumor parenchyma to sensitize glioma to anti-PD-1 ICB *in vivo* [55].

The impact of DNMTi on tumor-infiltrating myeloid cells, which constitute most of the infiltrating immune cells in the GBM parenchyma, is less well-defined. Indeed, *in vivo* studies using a murine ovarian cancer model have identified that, secondary to type I IFN enhancement, DNMTi decreased the proportion of tumor-promoting M2 macrophages characterized by expression of scavenger receptors and indoleamine 2,3-dioxygenase activity and increased anti-tumor M1 characterized by production of TNF, IL-1, and IL-2 macrophages [56-58]. However direct *in vitro* DNMTi treatment of macrophages promoted M2 markers CD206 and ALOX15 while decreasing IL-1B, TNF-a, IFNg, and IL-10 production in a granuloma-like *Mycobacterium tuberculosis* model [59]. While the study of DNMTi on tumor-associated lymphocytes and myeloid demonstrates promise, future study of the direct DNMTi effect on the lymphoid and myeloid compartments in the GBM microenvironment remains critical.

Advances in our understanding of the epigenetic contribution to the immunologic milieu in GBM and other solid tumors continue to highlight the necessity for effective immunotherapeutic enhancement. We theorize that minimizing cell cycle inhibition and cytotoxic effects

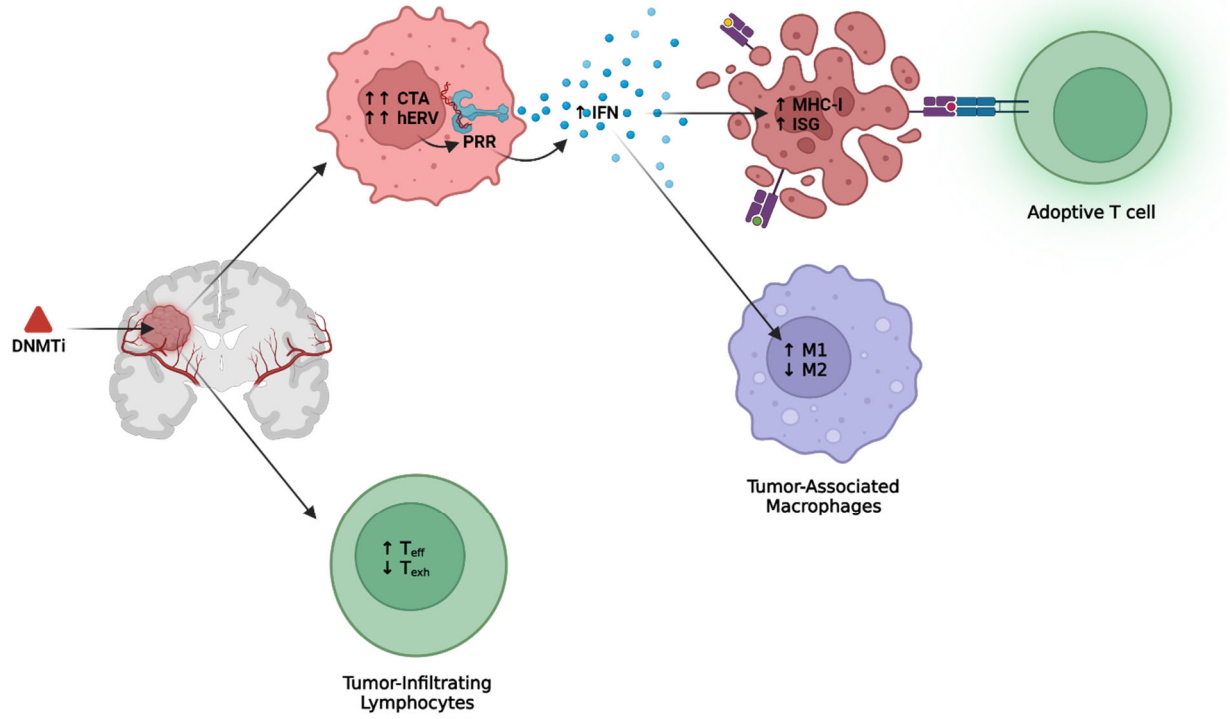

Figure 1: DNMTi enhancement of adoptive T cell therapy and microenvironment in GBM. Created with Biorender.com.

with lower doses and longer administration of DNMTi would enhance immunotherapies in GBM and there are now depot injection forms of drug as well as oral forms that might make this immune adjunct strategy more feasible [60]. The capacity of DNMTi to induce targetable antigens in solid tumors is well-established and this manuscript has reviewed novel strategies that include enhancing tumor-intrinsic interferon signaling and epigenetically reprogramming effector cells, which collectively may overcome the immunosuppressive microenvironment characteristic of GBM. While future preclinical studies will need to directly characterize DAC-mediated effects in the GBM tumor-immune microenvironment within the context of established immunotherapies, we are encouraged by this exciting progress in the study of DNMTi as a promising strategy to induce epigenetic reprogramming capable of enhancing immune therapy for GBM.

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