

Current landscape of immunotherapy for CNS tumors

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Background

Immunotherapy has emerged as a powerful tool in the oncologist's armamentarium, with durable clinical benefit observed across several malignancies, including melanoma^{1,2} and cancers of the lung,³ breast,^{4,5} and GI tract⁶ from checkpoint inhibitors. Despite this success, similar results have not yet been observed in central nervous system (CNS) tumors despite considerable efforts.^{7,8} This is thought to be largely due to unique challenges including an immunosuppressive microenvironment, our lack of understanding of CNS immunobiology generally, and the significant intra-tumoral heterogeneity of CNS tumors like glioblastoma.⁹ In response to these challenges, significant efforts have focused on better understanding the immunosuppressive mechanisms within these tumors to identify new immunotherapeutic vulnerabilities.^{10,11} Combination approaches, wherein multiple redundant immunosuppressive mechanisms are targeted simultaneously, have emerged as a promising approach.^{9,12} Similarly, novel techniques including engineered adoptive T-cell therapy have recently shown extreme promise in small cohorts of patients,^{13,14} as have oncolytic virus-based approaches.^{15–17} Despite this optimism, no standard-of-care treatment paradigms for brain tumors includes immunotherapy to date. Considerable ongoing research efforts are therefore needed in the preclinical, translational, and clinical stages to realize the potential of these personalized treatments in neuro-oncology. In this special edition, the current state of neuro-oncologic immunotherapy is covered through 7 review papers written by experts in the field. Reviews are divided by theme, with a focus on the basic science of brain tumor immunology, translational approaches to guide trial design, and the evidence behind current immunotherapeutic modalities.

Basic Science

"Within and Beyond the Tumor: Mechanisms of glioblastoma-induced immunosuppression"—Puvindran et al.

"The glioma microenvironment and its impact on antitumor immunity"—Hansen et al.

To understand the challenges of immunotherapy in glioblastoma, it is critical to first discuss the mechanisms underlying its immunosuppressive physiology.¹⁸ In this first section, two papers serve to comprehensively review the current knowledge of glioma immunology. First, *Puvindran et al.* provide a broad overview of the multiple mechanisms underlying glioblastoma-induced immunosuppression. Tumor-intrinsic factors including PD-L1 upregulation, MHC downregulation, a relatively low mutational burden, significant intra-tumoral heterogeneity, and a permissive metabolome that is hostile to anti-tumor immune cells are discussed. Contributions from the tumor microenvironment are also examined including T-cell exhaustion and the immunosuppressive role of tumor–neuron interactions. Finally, the relevance of systemic immune derangements (peripheral immunosuppression) is reviewed. The specific role of the tumor microenvironment is then meticulously discussed by *Hansen et al.* with a focus on each element that may impede the success of immunotherapy. The role of neoplastic cells and their low mutational burden, as well as non-neoplastic components including immunosuppressive myeloid cells, stromal cells, and neurons are each covered. The importance of the extracellular matrix and tumor metabolism on shaping its microenvironment is also considered. The authors conclude by discussing potential avenues through which the immunosuppressive microenvironment of glioma can be tackled to allow for increasingly effective immunotherapies. Overall, this section offers a broad

overview of the many mechanisms of glioma immunosuppression, providing rationale for multiple promising immunotherapeutic approaches.

Translational Science

“Biomarkers of immunotherapy response in neuro-oncology”—Landry et al.

“Immunologic Specificity in Glioblastoma: Antigen Discovery and Translational Implications”—Hill et al.

Bridging the gap between bench and bedside, this section serves to review important translational topics in the immunotherapy of CNS tumors. First, the current landscape of CNS immunotherapy biomarkers is reviewed by Landry et al., focusing specifically on brain metastases, glioblastoma, and meningioma given their diverse biology and relatively high prevalence. While several biomarkers, including PD-L1 expression, tumor mutational burden, RNA-based signatures, radiomic features, and liquid biopsy have shown early promise, additional work is needed to robustly validate these existing tools and simultaneously explore other modalities such as genomics and epigenomics to allow for increasingly personalized care. The inclusion of validated biomarkers into future clinical trials also offers the potential to address much of the heterogeneity that has impeded their success to date. With a focus on translational therapeutic research, Hill et al. provide a comprehensive review of the state of antigen discovery as an avenue for personalized immunotherapy. Topics including tumor-associated antigens, cancer germline antigens, and the role of therapy on antigen expression are covered, and the authors outline an approach to identifying tumor-specific antigens and determining their antigenicity. The translational potential of these approaches via therapeutics such as TCR engineering and vaccines is also reviewed.

Therapeutic Approaches

“The landscape of immune checkpoint inhibitor clinical trials in glioblastoma: a systematic review”—Schonfeld et al.

“Translational Advancements in Tumor Vaccine Therapies for Glioblastomas”—Bernstock et al.

“Cellular Immunotherapies for Central Nervous System Cancers”—Scott et al.

The final section of this special edition focuses on specific immunotherapeutic modalities that have generated optimism in glioblastoma to date. Most glioblastoma immunotherapy clinical trials to date have focused on the use of immune checkpoint inhibitors, which are systematically reviewed by Schonfeld et al. While none have demonstrated survival benefits compared to the current standard of care, the authors note that combination strategies have demonstrated early promise and should be the focus of ongoing and future clinical trials. They also highlight the importance of robust biomarkers and increased standardization across trials to help address the limitations associated with neuro-oncology clinical trials. Subsequently, Bernstock et

al. review the role of tumor vaccines in glioblastoma immunotherapy, which have gained increasing popularity in recent years. The many flavors of this approach, including peptide and multi-peptide vaccines, dendritic cell vaccines, and vaccines targeting heat shock proteins, nucleic acids, vascular endothelial growth factor receptor, and stem cells are each discussed in detail. The authors conclude by providing an overview of glioblastoma vaccine trials to date. As in the case of checkpoint inhibitors, vaccines targeting single epitopes have not demonstrated improvement in overall survival, but multi-target approaches have shown early promise and should form the basis of larger clinical trials. Finally, Scott et al. provide a comprehensive overview of cellular immunotherapy (mainly chimeric antigen T/NK cells) in CNS oncology, with a focus on glioblastoma, H3K27M-altered diffuse midline glioma, medulloblastoma, and CNS lymphoma. Multiple targets have shown significant promise in recent early-phase clinical trials including IL-13ra2 and EGFR/EGFRvIII in glioblastoma^{13,14} and GD2 in H3K27M altered midline glioma,¹⁹ with several additional targets showing promise in preclinical models. The authors discuss important potential mechanisms of treatment failure, such as an immunosuppressive tumor microenvironment, intra-tumoural heterogeneity, antigen escape, and T-cell exhaustion; each of which requires dedicated attention to continue improving upon our current approaches.

Conclusions

Immunotherapy has revolutionized the field of oncology by offering survival benefits across several cancers. Its translational value in neuro-oncology has been comparatively delayed, owing to unique challenges associated with CNS disease. In this special edition, the current state of the field is reviewed and avenues for future study are discussed. Despite limited success to date, recent studies offer new promise and provide hope to patients with these devastating malignancies.

Conflict of interest statement

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