- Irem Yenidogan,
- Uri Tabori &
- Anirban Das

Immune checkpoint inhibitors in pediatric central nervous system tumors: biology, clinical experience, and translational pathways to precision immunotherapy

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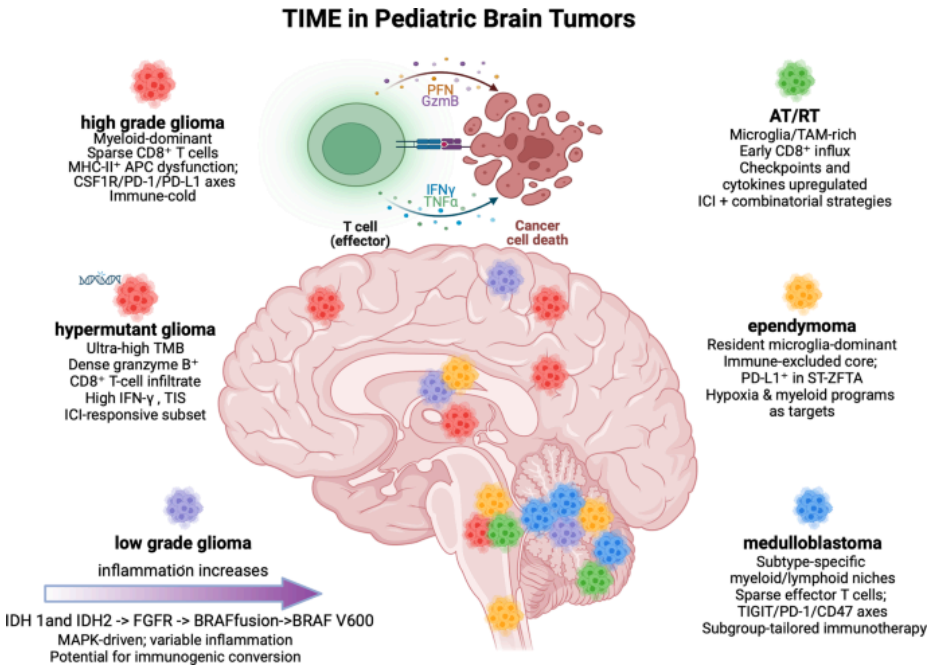

Abstract

Purpose

Immune checkpoint inhibitors (ICI) have transformed cancer therapy but remain of limited efficacy in pediatric central nervous system tumors, which are characterized by low tumor mutational burden, sparse antigen presentation, and profoundly immunosuppressive microenvironments.

Content

Across pediatric trials, ICI monotherapy targeting the PD-1/PD-L1 axis has largely failed to show substantive benefits, underscoring the need for biomarker-driven patient selection and the identification of synergistic vulnerabilities. Recent high-dimensional profiling reveals that pediatric central nervous system tumors are not uniformly “immune cold.” Subsets such as DNA replication-repair–deficient high-grade gliomas exhibit robust neoantigen burden and durable responses to PD-1 blockade, whereas data from other

tumor subsets including some gliomas, germ cell tumors and select medulloblastomas demonstrate potential latent immune reactivity. Translational strategies are being developed to overcome barriers impacting ICI efficacy by studying resistance mechanisms, some of which are unique to central nervous system tumors. Potentially useful strategies to improve ICI efficacy in childhood brain tumors may involve exploration of early or neoadjuvant use, targeting non-traditional checkpoints as combination treatments, metabolic and genomic targeting for immune reprogramming, advanced drug-delivery approaches, studying and modulating the gut microbiota, improve toxicity management by limiting systemic steroid use, and parallel innovations redefining immunotherapy response assessment using advanced imaging and liquid biopsies.

Conclusion

We provide an overview of the current checkpoint inhibitor landscape for pediatric brain tumors, highlight barriers and summarize possible approaches that can be efficaciously explored in future clinical trials.

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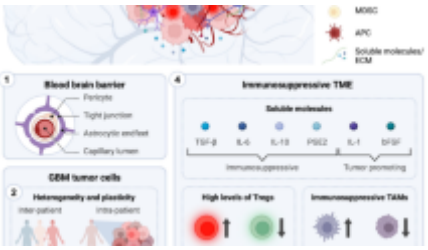

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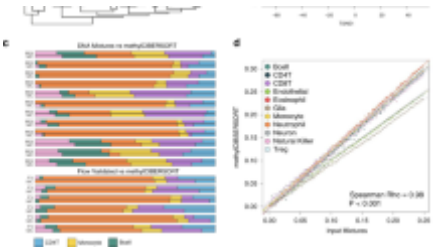

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Data availability

No datasets were generated or analysed during the current study.

Abbreviations

APC:
Antigen-presenting cell

AT/RT:
Atypical teratoid rhabdoid tumor

BBB:
Blood–brain barrier

CED:
Convection-enhanced delivery

cfDNA:
Cell-free DNA

CNS:
Central nervous system

CRS:
Cytokine release syndrome

ctDNA:
Circulating tumor DNA

CTLA-4 :
Cytotoxic T-lymphocyte–associated protein 4

DIPG:
Diffuse intrinsic pontine glioma

DMG:
Diffuse midline glioma

DNMT:
DNA methyltransferase

FUS:

Focused ultrasound

GBM:

Glioblastoma

GCT:

Germ cell tumor

H3K27M:

Lys27Met mutation in histone H3

HGG:

High-grade glioma

HLA:

Human leukocyte antigen

ICI:

Immune checkpoint inhibitors

IDO1:

Indoleamine 2,3-dioxygenase 1

IFN:

Interferon

IL:

Interleukin

iRANO:

Immunotherapy response assessment in neuro-oncology

irAE:

Immune-related adverse event

LGG:

Low-grade glioma

MAPK:

Mitogen-activated protein kinase

MHC:

Major histocompatibility complex

MMRd:

Mismatch repair deficient

mTOR:
Mechanistic target of rapamycin

NGGCT:
Non-germinomatous germ cell tumor

NK:
Natural killer

OS:
Overall survival

PedCAP:
Pediatric cytotoxicity and antigen presentation signature

PD-1:
Programmed cell death protein 1

PD-L1:
Programmed death-ligand 1

PFA:
Posterior fossa group A

PFS:
Progression-free survival

PI3K:
Phosphoinositide 3-kinase

RANO:
Response assessment in neuro-oncology

RRD:
Replication repair deficient

SCFA:
Short-chain fatty acid

SEPP1:
Selenoprotein P

SHH:
Sonic hedgehog

TAM:
Tumor-associated macrophage

TAP:

Transporter associated with antigen processing

TGF-β :

Transforming growth factor beta

TIME:

Tumor immune microenvironment

TIS:

Tumor Inflammation Signature

TMB:

Tumor mutational burden

VEGF:

Vascular endothelial growth factor

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Author information

Authors and Affiliations

1. Division of Hematology/Oncology, The Hospital for Sick Children, Room 10-14-049, 175 Elizabeth St, Toronto, ON M5G 2G3, Canada

   Irem Yenidogan, Uri Tabori & Anirban Das

2. The Arthur and Sonia Labbatt Brain Tumor Research Center, Toronto, Canada

   Uri Tabori & Anirban Das

3. Department of Paediatrics, University of Toronto, Toronto, Canada

   Uri Tabori & Anirban Das

Contributions

Irem Yenidogan conceived and drafted the manuscript, performed the literature review, and synthesized the clinical and translational evidence. Uri Tabori and Anirban Das contributed to the conceptual framework, provided critical expert revisions, and supervised manuscript development. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Corresponding author

Correspondence to Anirban Das.

Ethics declarations

Use of generative AI

Portions of the text in this manuscript were refined with the assistance of ChatGPT (GPT-4, OpenAI, version 2025-10). The tool was used exclusively to improve the clarity, grammar, and readability of language originally written by the authors and to help structure certain sections for improved flow. It was not used to generate original scientific content, data, analysis, images, or conclusions, and all outputs were critically reviewed, verified, and edited by the authors to ensure accuracy and integrity.

Competing interests

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- Pediatric central nervous system tumors
- Immune checkpoint inhibition

- Tumor immune microenvironment
- Mismatch repair–deficient / replication repair–deficient glioma
- Biomarker-guided precision immunotherapy