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Role of T cell metabolism in brain tumor development: a genetic and metabolic approach

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Abstract

Background Malignant brain tumors are among the most lethal cancers. Recent studies emphasized the crucial involvement of the immune system, especially T cells, in driving tumor progression and influencing patient outcomes. The emerging field of immunometabolism has shown that metabolic pathways play a pivotal role in regulating immune responses within the tumor microenvironment. This study aims to clarify the relationships between specific T cell phenotypes, circulating metabolites, and malignant brain tumors.

Methods We utilized a multiple mendelian randomization approach to investigate the associations between T cell phenotypes and malignant brain tumors, as well as the role of plasma metabolites in mediating these interactions. Instrumental variables were selected based on stringent criteria, and multiple mendelian randomization methods were utilized to identify causal pathways and metabolites potentially mediating these effects.

Results Our analysis identified significant associations between seven distinct T cell phenotypes, including various CD8 + and regulatory T cell subsets, and the presence of malignant brain tumors. We also identified 87 plasma metabolites correlated with these tumors. Notably, metabolites such as octadecanedioylcarnitine (C18-DC) and eicosanedioate (C20-DC) were implicated in modulating the risk of developing malignant brain tumors. Furthermore, metabolites such as 5-dodecenoate (12:1n7) and arachidonate (20:4n6) were found to influence tumor risk, particularly in relation to CD28 − CD8 + T cells.

Conclusion The study identifies key T cell phenotypes and plasma metabolites involved in the pathogenesis of malignant brain tumors, offering potential biomarkers and therapeutic targets for future interventions.

Keywords Malignant brain tumors, T cells, Plasma metabolites, Mendelian randomization

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Introduction

Malignant brain tumors rank among the most aggressive and lethal cancer, with limited therapeutic options and poor prognoses due to their subtle location and rapid progression [1, 2]. Recent studies have emphasized the role of the immune system, particularly T cells, in modulating tumor progression and patient outcomes [3, 4]. Antigen-primed T cells navigate through healthy tissues to locate their targets, accumulate within brain tumors, and perform cytotoxic functions with precise cellular accuracy; subsequently, they adapt to the tumor's evolving molecular landscape through epitope spreading and differentiate into memory T cells capable of preventing delayed tumor recurrence [5, 6]. These findings provided a rationale for the complex interactions between T cells and malignant brain tumors.

Immunometabolism— a field exploring the interaction between immune and metabolic processes — gaining prominence. Aberrant metabolic remodeling is at the root of many dysfunctional immune responses, while modulating cellular metabolism offers potential therapeutic strategies to enhance or suppress immune functions as needed [7]. Targeting metabolic pathways in T cells, such as the glycolytic pathway and pentose phosphate pathway, within the immunosuppressive microenvironment of malignant brain tumors, has demonstrated promise in clinical settings [7–9]. Specific metabolites, including branched-chain amino acids, fatty acids, and certain vitamins, have emerged as crucial regulators in various biological processes, including immune cell function and cancer metabolism [10, 11]. In the context of T cell activity, specific plasma metabolites may influence the risk and development of malignant brain tumors by modulating immune responses and tumor microenvironment interaction. Therefore, elucidating and understanding the causal relationship between T cells, metabolites, and malignant brain tumors could be very useful for the early identification, prevention, and management of malignant brain tumors in the future.

In this study, we aim to identify key metabolites that influence immune cell behavior and tumor development through Mendelian randomization (MR), a robust approach leveraging genetic variations as instrumental variables to infer causal relationships between exposures and outcomes, and we hope to discover potential biomarkers and therapeutic targets for this devastating disease.

Materials and methods

Study design

In this study, we first evaluated the relationship between 731 immune cell phenotypes across 7 panels and malignant brain tumors using two-sample MR. We then explored the potential mediating role of 1400 plasma metabolites in this association based on two-step MR (TSMR) and multivariable MR approaches (Fig. 1).

The study was performed according to the Reporting of Observational Studies in Epidemiology–Mendelian Randomization (STROBE-MR) checklist. All data used were derived from publicly available datasets with prior ethical approval.

Source of data

The genetic data related to malignant brain tumors were obtained from the FinnGen consortium (https://www.finngen.fi/en), with the selected dataset bearing the identifier C3_BRAIN_EXALLC, encompassing 1070 patients with malignant neoplasm of brain and 345,118 control patients, sourced from the R11 version of FinnGen [12]. A total of 731 immune phenotypes were analyzed in this study, encompassing various categories of immunological traits. These included absolute cell (AC) counts (n=118), median fluorescence intensities (MFI) as markers of surface antigen expression (n=389), morphological parameters (MP) (n=32), and relative cell (RC) counts (n=192). These features spanned diverse immune cell subsets, including B cells, conventional dendritic cells (cDCs), mature T cell stages, monocytes, myeloid cells, TBNK (T cells, B cells, and natural killer cells), and regulatory T cells, assessed across MFI, AC, and RC panels. The MP traits specifically covered cDCs and TBNK panels. The original genome-wide association study (GWAS) on immune traits was performed using data from 3,757 European individuals with no overlapping cohorts. Genotyping was conducted using high-density arrays, capturing approximately 22 million single nucleotide polymorphisms (SNPs), which were subsequently imputed with a Sardinian sequence-based reference panel [13]. Plasma metabolite GWAS data were derived from the Canadian Longitudinal Study on Aging, which included 8,299 participants. This dataset covered 1,091 plasma metabolites and 309 metabolite ratios [14]. The GWAS for plasma metabolites was similarly performed on European individuals, ensuring no cohort overlap with other datasets.

Instrumental variable selection

In the MR analysis, we used SNPs strongly correlated with immune cell phenotypes and blood metabolite levels as instrumental variables, uniformly using a threshold of $P<1\times10^{-5}$ [15, 16]. Subsequently, SNPs exhibiting linkage disequilibrium were excluded according to the criteria of R^2<0.001 and an interval of 10,000 kb, after which weak instrumental variables were eliminated according to the F-statistic<10 [17].

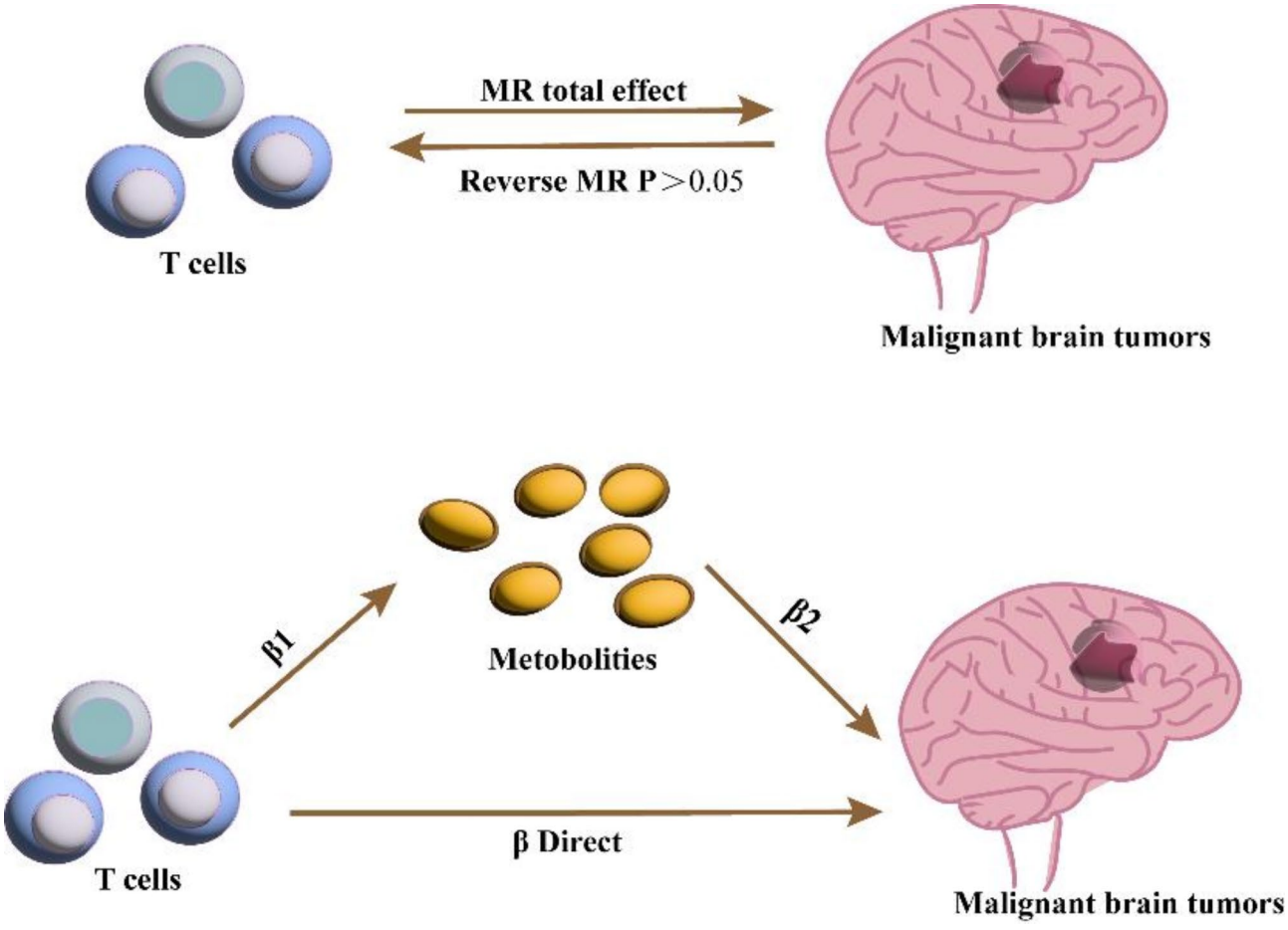

Fig. 1 The mediation analysis: exposure-T cell; outcome- malignant brain tumors; mediator-plasma metabolites

Statistical analysis

Five different MR analysis methods were used to assessed the causal relationship between exposure and outcome: Inverse Variance Weighted (IVW), Weighted Median, Simple Mode, Weighted Mode, and MR-Egger, and IVW was served as the primary method [18]. The MR-Egger intercept test and MR-Pleiotropy Residual Sum and Outlier were used to evaluate horizontal pleiotropy, and Cochran Q test was used to perform heterogeneity assessment [19, 20]. Finally, A sensitivity analysis was performed using "leave-one-out" method to evaluate the influence of individual SNPs on the causal relationship. Utilizing the TSMR method, we first computed the overall effect of immune cell phenotypes on malignant brain tumors (β0), the casual impact of immune cell phenotypes on metabolites (β1), and the casual impact of metabolites on malignant brain tumors (β2), followed by the calculation of the mediated effect (β1*β2), with the direct effect being represented as $\beta\ 3=\beta0-\beta1*\beta2$ [21]. All analyses were carried out using R software version 4.4.1.

Results

Genetic causality between immune cell phenotypes and malignant brain tumors

We identified 17,854 SNPs associated with immune cell phenotypes based on the established significance thresholds and F-statistic criteria (Supplement Table 1). Seven T cell phenotypes were consistently associated with malignant brain tumors across five different MR methods, as determined by consistent odds ratios (OR<1 or OR>1). Preliminary analysis using the IVW method revealed significant associations for the following phenotypes: Human Leukocyte Antigen (HLA) DR on HLA DR+CD8+T cell, CD127- CD8+T cell Absolute Count, Naïve CD8+T cell Absolute Count, Naïve CD8+T cell %T cell, CD28- CD8+T cell %CD8+T cell, Secreting CD4 regulatory T cell Absolute Count, and Resting CD4 regulatory T cell Absolute Count. Of these, six T cell phenotypes showed a negative correlation with malignant brain tumors, while one showed a positive correlation. The robustness of these findings was confirmed through pleiotropy tests, heterogeneity tests ($P>0.05$) and leave-one-out sensitivity analysis (Table 1).

Table 1 MR analysis of immune cells and malignant brain tumors

Exposure	Method	Nsnp	Beta	Se	*P* value	Pleiotropy	Heterogeneity
HLA DR on HLA DR+CD8+T cell	IVW	20	-0.216	0.082	0.0085	0.576	0.498
CD127-CD8+T cell Absolute Count	IVW	13	-0.207	0.079	0.0087	0.448	0.805
Naïve CD8+T cell Absolute Count	IVW	28	-0.034	0.014	0.0146	0.795	0.278
Naïve CD8+T cell %T cell	IVW	28	-0.030	0.012	0.0152	0.282	0.858
CD28-CD8+T cell %CD8+T cell	IVW	23	-0.199	0.085	0.0190	0.655	0.934
Secreting CD4 regulatory T cell Absolute Count	IVW	23	-0.058	0.027	0.0290	0.599	0.060
Resting CD4 regulatory T cell Absolute Count	IVW	25	0.122	0.062	0.0473	0.449	0.337

Genetic causality between plasma metabolites and malignant brain tumors

We identified 33,254 SNPs associated with plasma metabolites based on the same thresholds and F-statistic criteria (Supplement Table 2). Using MR methods, 87 plasma metabolites were found to be significantly associated with malignant brain tumors, comprising 77 known metabolites and 10 unknown metabolites, such as phosphate to sulfate ratio, arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio, 1-oleoyl-GPE (18:1) levels, retinol (Vitamin A) levels, 1-methylnicotinamide levels, phosphate to 5-oxoproline ratio, 5-dodecenoate (12:1n7) levels, arachidonate (20:4n6) levels and 1-linoleoyl-GPE (18:2) levels. Among the known plasma metabolites, 32 were associated with an increased risk of malignant brain tumors, while 45 showed a negative correlation with malignant brain tumors (Supplement Table 3).

Mediated effects of plasma metabolites on T cell-malignant brain tumors risk

To investigate the mediated effect of plasma metabolites on the association between T cells and malignant brain tumors, we first performed MR analysis from T cell phenotypes to plasma metabolites using 7 selected T cell phenotypes as exposure factors and the 77 plasma metabolites as outcomes: we then analyzed the determination of the effect size β2 from metabolites to malignant brain tumors using the same methods. Finally, we identified 6pairs of metabolites that serve as mediators in the relationship between T cell phenotypes and malignant brain tumors (Fig. 2).

Octadecanedioylcarnitine (C18-DC) and Eicosanedioate (C20-DC) were found to negatively modulate malignant brain tumors concerning Naïve CD8+T cell Absolute Count and Naïve CD8+T cell %T cell (Mediated effect, ME=-0.00370, -0.00336, -0.00317, -0.00271; Mediated proportion, MP=10.8%,11.2%, 9.2%, 9.0%) (Table 2). 5-dodecenoate (12:1n7) levels, Arachidonate (20:4n6) levels, and Glycerol to glycerol 3-phosphate ratio exhibited negative regulatory effect on malignant brain tumors with respect to CD28−CD8+T cell % CD8+T cell (ME=-0.02637, -0.01340, -0.01672; MP=13.2%, 6.7%, 8.4%) (Table 2). Glyco-beta-muricholate negatively regulated malignant brain tumors in conjunction with HLA DR on HLA DR+CD8+T cell and CD127- CD8+T cell Absolute Count (ME=--0.00867, -0.00948; MP=4.0%, 4.6%), among others (Table 2).

Discussion

In our study, we identified a causal relationship between seven T cell phenotypes and malignant brain tumors. Mediation analysis using TSMR and multivariate MR methods revealed that six of these T cell phenotypes are potentially linked to malignant brain tumors through eight known plasma metabolites, with 5-dodecenoate (12: 1n7) exhibiting the highest mediation proportion (13.2%).

Our study highlights the mediating role of eicosanoids, a lipid mediator derived from polyunsaturated fatty acids (PUFAs) metabolism, in the causal relationship between T cells and malignant brain tumors. In the tumor microenvironment, eicosanoids can exert pro- or anti-tumorigenic effects, depending on their concentration and interactions with specific cell types. For example, prostaglandin E2, a prominent derivative of arachidonate, has been recognized for its ability to inhibit the cytotoxic functions of T cells via G protein-coupled receptors or nuclear receptors, thus promoting cell proliferation, angiogenesis, and immune evasion; arachidonate (20:4n6) metabolites may indirectly affect the metabolic requirements and functions of T cells by modulating glutamine metabolism or glycolytic pathways [22, 23]. The balance between pro-inflammatory and immunosuppressive eicosanoids can greatly affect the effectiveness of T cell-driven tumor elimination, potentially leading to increased disease aggression and a diminished effectiveness of immunotherapy treatments [24–26]. For example, in the context of glioblastoma multiforme, eicosanoids can enhance the expression of matrix metalloproteinases, enzymes that degrade the extracellular matrix, allowing tumor cells to invade surrounding tissues and even migrate to distant sites [25, 27]. Targeting eicosanoid signaling could be a promising therapeutic strategy for malignant brain tumors, and cyclooxygenase-2 or lipoxygenase inhibitors, or antagonists of specific eicosanoid receptors, has shown promise in inhibiting tumor growth and improving patient outcomes in clinical trials [28, 29]. However, further studies are needed to elucidate

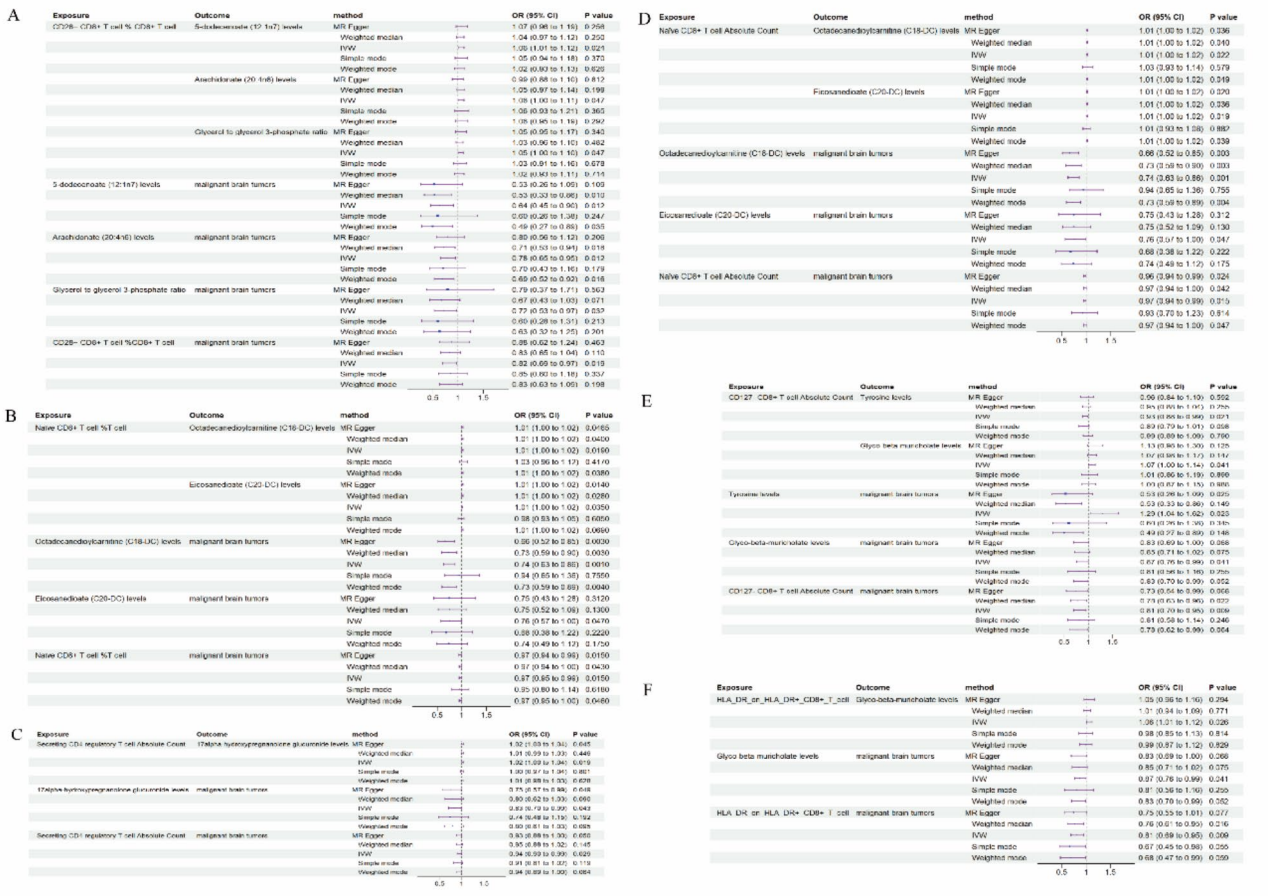

Fig. 2 A forest plot of the six sets of plasma metabolites exhibiting "T cell phenotype-malignant brain tumors" mediating effects. OR, odds ratio; CI, confidence interval. (**A**) CD28 – CD8 + T cell % CD8 + T cell-5-dodecenoate (12:1n7) /Arachidonate (20:4n6)/Glycerol to glycerol 3-phosphate ratio-malignant brain tumors. (**B**) Naïve CD8 + T cell %T cell-Octadecanedioylcarnitine (C18-DC)/Eicosanedioate (C20-DC)-malignant brain tumors. (**C**) Secreting CD4 regulatory T cell Absolute Count-17alpha-hydroxypregnanolone glucuronide-malignant brain tumors. (**D**) Naïve CD8 + T cell Absolute Count-Octadecanedioylcarnitine (C18-DC)/Eicosanedioate (C20-DC)-malignant brain tumors. (**E**) CD127- CD8 + T cell Absolute Count-Tyrosine/Glyco-beta-muricholate-malignant brain tumors. (**F**) HLA_DR_on_HLA_DR+_CD8+_T_cell-Glyco-beta-muricholate-malignant brain tumors

Table 2 Mendelian randomization analyses of the causal effects between T cells, plasma metabolites and malignant brain tumors

T cell	Metabolite	Outcome	Mediated Effect	Mediated proportion
Naïve CD8 + T cell Absolute Count	Octadecanedioylcarnitine (C18-DC) levels	malignant brain tumors	-0.00370	10.8%
	Eicosanedioate (C20-DC) levels	malignant brain tumors	-0.00317	9.2%
Naïve CD8 + T cell %T cell	Octadecanedioylcarnitine (C18-DC) levels	malignant brain tumors	-0.00336	11.2%
	Eicosanedioate (C20-DC) levels	malignant brain tumors	-0.00271	9.0%
CD28 – CD8 + T cell % CD8 + T cell	5-dodecenoate (12:1n7) levels	malignant brain tumors	-0.02637	13.2%
	Arachidonate (20:4n6) levels	malignant brain tumors	-0.01340	6.7%
	Glycerol to glycerol 3-phosphate ratio	malignant brain tumors	-0.01672	8.4%
HLA_DR_on_HLA_DR+_CD8+_T_cell	Glyco-beta-muricholate levels	malignant brain tumors	-0.00867	4.0%
Secreting CD4 regulatory T cell Absolute Count	17alpha-hydroxypregnanolone glucuronide levels	malignant brain tumors	-0.00344	5.9%
CD127- CD8 + T cell Absolute Count	Tyrosine levels	malignant brain tumors	-0.0182	8.8%
	Glyco-beta-muricholate levels	malignant brain tumors	-0.00948	4.6%

the complexities of eicosanoid signaling in brain tumor microenvironments and to develop targeted therapies that minimize adverse effects.

Consistent with previous studies, the reduction and impaired functions of CD8+cytotoxic T cells (CTLs) infiltration was pivotal in the pathogenesis of malignant brain tumors, such as glioblastoma, medulloblastoma and meningioma [30, 31]. Given the immunosuppressive tumor microenvironment and the low metabolic demands of circulating naïve T cells, we focused on their potential to differentiate into effective CTLs. As expected, it was CD8+T cells that were causally associated with malignant brain tumors in this study, including HLA DR on HLA DR+CD8+T cell, CD127- CD8+T cell, and CD28- CD8+T cell. Glioblastoma stem cells express HLA ligands, and human glioblastoma cell lines exhibit novel HLA peptides derived from cancer-testis antigens, which are therapeutic targets in ongoing clinical trials for glioblastoma [32, 33]. Metabolites like glyco-beta-muricholate influence intestinal flora and may exert effects via the brain-gut axis by activating bile acid receptors such as farnesoid X receptor and G protein-coupled bile acid receptor 5 [34, 35]. Tyrosine, a precursor for the synthesis of catecholamines and thyroid hormones, is necessary for T cell receptor signaling via protein phosphorylation, and dysregulated tyrosine metabolism is implicated in glioma aggressiveness and therapeutic resistance [36–39]. Therefore, understanding the causal mechanisms linking tyrosine metabolism to immune regulation and tumorigenesis could provide new avenues for therapeutic interventions targeting tyrosine-related pathways. Additionally, it is important to highlight that HLA DR+CD8$^+$ T-cells is not a routinely studied immune subpopulation. Lisowska et al. identified CD8$^+$ HLA-DR$^+$ T-cells as a subpopulation of T cells that are inactivated during chronic kidney disease [40], and Zhu et al. reported that CD8$^+$ HLA-DR$^+$ T-cells were positively correlated with total HIV DNA during inhibitory antiretroviral therapy [41]. These studies suggest that CD8$^+$ HLA-DR$^+$ T-cells are an indicator of immune activation, particularly in inflammatory related conditions. CD28- CD8+T cells, a distinct subset of regulatory T cells, are abundant in glioblastoma patients [42], and play a role in inhibiting T cell activation, reducing proinflammatory cytokine secretion from activated T cells, and inducing apoptosis of activated T cells in vitro [43]. Glycerol-3-phosphate biosynthesis is an endogenous NAD+regeneration pathway that inhibits neuroinflammation [44], however, no studies between 5-dodecenoate (12:1n7) levels and neural tumors have been found. Therefore, more research is needed to understand the mediating metabolites that play a role in the causal relationship between CD28- CD8+T cells and malignant brain tumors.

Within the population of tumor-specific tumor-infiltrating lymphocytes, Tregs are identified as a pro-tumorigenic subset, and their direct interaction with tumor-specific CTLs is a major focus for immune monitoring protocols in current immunotherapeutic strategies. In gliomas and medulloblastomas, Treg expansion, mediated by pathways such as mTOR and indoleamine deoxygenase expression, contributes to immunosuppression, shortened survival, and earlier recurrence [45–47]. 17alpha-hydroxypregnanolone glucuronide, a neurosteroid derivative, can affect central nervous system functions via glucuronidation process, such as modulating the activity of neurotransmitter receptors [48, 49]. Activated CD4+T cells are primarily dependent on glucose as their oxidative fuel, and Treg cells are partially dependent on glucose transporters for expansion and survival [50, 51]. The modulation of Treg activity by 17alpha-hydroxypregnanolone glucuronide may occur through its interaction with steroid hormone receptors expressed on Tregs. This interaction could enhance Treg proliferation or the expression of immunosuppressive cytokines, such as IL-10 and TGF-β, thereby contributing to an immunosuppressive environment.

Our study represents the first attempt to employ MR analysis to investigate the causal relationship between T cells and malignant brain tumors using the most comprehensive and up-to-date GWAS data, and to employ mediation analysis to explore the potential nonlinear association of plasma metabolites. However, our study still faces several limitations. Firstly, although the FinnGen database has advantages in data timeliness, its focus on a specific ethnic group and its dataset size limit the generalizability of our findings. Secondly, the causal relationship between T cells and malignant brain tumors is likely influenced by multiple mediating factors, and there may still be unidentified confounders that could introduce bias into our results. In addition, some of the immune subgroups we reported, such as CD8$^+$ HLA-DR$^+$ T-cells, have been rarely studied in tumors before, although this may limit the generality of this study, it also suggests that the potential role of the immune subgroups in tumors is worth exploring. Finally, our use of malignant brain tumors as a composite outcome rather than focusing on specific tumor types may reduce the specificity of our conclusions, but because of the tumor-suppressive properties of the brain microenvironment, an overall picture of the interaction between central nervous system tumors and the immune system is critical to understanding the potential mechanisms of malignant brain tumors.

Conclusion

In conclusion, our study provides genetic evidences of the causal relationships between T cell phenotypes, plasma metabolites, and malignant brain tumors. We identified a

reduction in CTLs infiltration and highlighted the potential role of eicosanoid compounds in malignant brain tumors. These findings may provide new insights into metabolic pathways that could be targeted to enhance the efficiency of T cell-based immunotherapies for brain tumors.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-04015-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Not applicable.

Author contributions
Bo Yang and Enshan Feng conceptualized and designed the study. Bo yang and Zhenyu Li carried out the initial analyses, drafted the initial manuscript and revised the manuscript. Peiliang Li and Bo Liang collected data and carried out the initial analyses.Yuhan Liu carried out the initial analyses. Enshan Feng coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability
The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The data used in this study were from publicly available datasets for which ethical approval has been obtained.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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