

Analysis of the correlation between inflammatory cytokines and glioblastoma A Mendelian randomization study

Feng Xuan, MB^{a,*}, Tian Lv, MB^b, Lin Zheng, MM^c, Shengjian Yu, MM^a, Mengjuan Ding, MB^d

Abstract

Epidemiological studies have demonstrated that inflammatory cytokines are associated with cancer development. However, the causal relationship between inflammatory cytokines and glioblastoma remains unclear. We used a two-sample Mendelian randomization approach to determine the potential causal effects of inflammatory cytokines on glioblastoma. Genome-wide association study summary statistics for 41 inflammatory cytokines were obtained from the University of Bristol database, and 91 inflammatory cytokines were acquired from the genome-wide association study catalog database. Genetic data on glioblastoma were downloaded from the FinnGen consortium (R10). Mendelian randomization analysis and Bayesian weighted Mendelian randomization analysis were performed to investigate the causal relationship between inflammatory cytokines and glioblastoma risk. A combination of Mendelian randomization (MR)-Egger, MR-Pleiotropy Residual Sum and Outliers, and Radial MR methods was employed to assess horizontal pleiotropy, which is a potential bias in MR studies. The Cochran Q test was used to quantify the degree of heterogeneity. Finally, we conducted a comprehensive meta-analysis to confirm the robustness of our findings. Increased levels of tumor necrosis factor β (odds ratio [OR] = 1.597, 95% CI: 1.143–2.230, P = .006) and interleukin-10 (OR = 1.452, 95% CI: 1.059–1.992, P = .021) were associated with an increased risk of glioblastoma. Conversely, higher levels of circulating fibroblast growth factor 21 (OR = 0.456, 95% CI: 0.276–0.754, P = .002) and macrophage inflammatory protein 1a (OR = 0.743, 95% CI: 0.558–0.990, P = .042) were associated with a decreased risk of glioblastoma. No significant causal effect on inflammatory cytokines from glioblastoma was detected, and no significant heterogeneity in instrumental variables or horizontal pleiotropy was observed. Our findings indicate that specific inflammatory cytokines may play a role in glioblastoma development, acting as either protective factors or risk factors. This offers valuable insights into the disease mechanism and suggests that targeting these cytokines could be a potential strategy for glioblastoma prevention and treatment.

Abbreviations: BWMR = Bayesian weighted Mendelian randomization, CCL3 = chemokine (C-C motif) ligand 3, FGF21 = fibroblast growth factor 21, GBM = glioblastoma, GWAS = genome-wide association study, IL-10 = interleukin-10, IVs = instrumental variables, IVW = inverse variance weighted, LD = linkage disequilibrium, MR = Mendelian randomization, OR = odds ratio, SNPs = single nucleotide polymorphisms, TNF α = tumor necrosis factor alpha, TNF β = tumor necrosis factor beta.

Keywords: genome-wide association study, glioblastoma, inflammatory cytokines, Mendelian randomization, tumor microenvironment

1. Introduction

Glioblastoma (GBM), a grade instrumental variable (IV) tumor, is the most common and aggressive brain tumor. It originates from glial cells of the central nervous system and accounts for approximately 49% of malignant brain tumors.^[1] Despite advances in surgical resection, radiotherapy, chemotherapy, and tumor treatment (TTFields), the prognosis for patients with GBM remains extremely poor,^[2] with a nearly 100% recurrence rate and a median overall survival of approximately 20 months.^[3] Only a limited number of patients are capable of surviving beyond the age of 5 years.^[4] Radiation exposure and some rare familial cancer syndromes such as neurofibromatosis type 1,^[5] Lynch syndrome,^[6] and Li-Fraumeni syndrome,^[7] are associated with an increased risk of GBM. However, the exact cause of GBM remains unclear. Early identification and prompt treatment are crucial for improving the outcomes of patients diagnosed with GBM. The medical community continues to prioritize research on the prevention of GBM to increase survival

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The datasets generated during and/or analyzed during the current study are publicly available.

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^a Department of Radiation Oncology, Zhuji Affiliated Hospital of Wenzhou Medical University, Shaoxing, China, ^b Department of Neurology, Zhuji Affiliated Hospital of Wenzhou Medical University, Shaoxing, China, ^c Department of Radiation Oncology, Taizhou Cancer Hospital, Wenling, China, ^d Department of Quality Management, Zhuji Blood Bank, Shaoxing, China.

^{*} Correspondence: Feng Xuan, Department of Radiation Oncology, Zhuji Affiliated Hospital of Wenzhou Medical University, Shaoxing, China (e-mail: xfeng8901@outlook.com).

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rates and enhance the quality of life of individuals afflicted by GBM.

Increasing evidence suggests that inflammatory cytokines play a crucial role in the development and progression of tumors and have a significant impact on the host antitumor response.^[8,9] These proteins can be categorized into different groups based on their roles, such as interleukins, interferons, chemokines, the tumor necrosis factor superfamily, colony-stimulating factors, and growth factors. Understanding the intricate connection between inflammatory cytokines and cancer has opened new avenues for investigation and potential therapeutic approaches. Given the significant impact of inflammatory cytokines on tumor development and the host antitumor response, there is increasing interest in targeting these molecules as a potential strategy for cancer treatment. Researchers are exploring ways to block pro-tumor cytokines and enhance the antitumor immune response. Moreover, some studies have demonstrated that altering the levels of certain cytokines within the tumor microenvironment can enhance the efficacy of existing anticancer therapies.

Mendelian randomization (MR) is a powerful epidemiological research method that can provide valuable insights into causal relationships between exposures and outcomes by using genetic variants as IVs.^[10,11] The use of genetic variation as a proxy for exposure in MR circumvents the limitations of traditional observational studies, allowing researchers to assess the causal effects of an exposure on an outcome without the confusion caused by reverse causality or residual confusion.^[12]

In this study, we extracted validated genetic variants from 2 published genome-wide association study (GWAS) summary datasets of 41 inflammatory cytokines^[13] and 91 inflammatory cytokines.^[14] We then performed MR analyses to test whether a range of circulating inflammatory cytokines could be causally associated with the risk of GBM (FinnGen R10) at onset. If MR studies identify certain inflammatory cytokines as having a causal relationship with GBM, this may help to develop new prevention and treatment strategies.

2. Methods

2.1. Study design

In our study, a bidirectional two-sample MR analysis was conducted to evaluate the causal relationships between 132 inflammatory cytokines and GBM, based on summary-level datasets from large-scale GWASs.

We used a two-sample MR analysis to evaluate the causal relationships between 132 circulating inflammatory cytokines and GBM. In the forward analysis, we used 132 inflammatory cytokines from the 2 databases as exposures and GBM as the outcome to explore the possibility that different inflammatory cytokines cause GBM. We evaluated the causal relationship between GBM and each inflammatory cytokine using a reverse analysis. Single nucleotide polymorphisms (SNPs) significantly associated with exposure were used as IVs.^[15,16] The selected IVs must satisfy 3 fundamental assumptions.^[17]

- (1) Relevance assumption: IVs are strongly correlated with exposure.
- (2) Independent assumption: IVs were not associated with any known confounders identified based on established biological and epidemiological knowledge regarding potential factors influencing the relationship between 132 inflammatory cytokines and GBM.
- (3) Exclusion restriction assumption: There is no correlation between IVs and outcomes, except for their possible connection with exposure.

The study design is illustrated in Fig. 1. We strictly adhered to the recommendations outlined in the Strengthening the Reporting of Observational Studies in Epidemiology Mendelian Randomization (STROBE-MR) framework (Table S1, Supplemental Digital Content, https://links.lww.com/MD/ O1000).^[18]

2.2. Data sources

All IVs utilized in this study were derived from the summaries of GWASs. The data on 41 inflammatory cytokines were derived from a meta-analysis including 8293 Finnish individuals from 3 separate population-based cohorts [the Cardiovascular Risk in Young Finns Study (YFS), FINRISK 1997, and FINRISK 2002], which was published in 2017 by Ahola-Olli et al.^[13] The University of Bristol provides publicly available GWAS summary statistics for each inflammatory cytokine (https://data. bris.ac.uk/data/dataset). GWAS summary statistics can also be downloaded from the IEU Open GWAS (accession numbers from ebi-a-GCST004420 to ebi-a-GCST004460) at https:// gwas.mrcieu.ac.uk (Table S2, Supplemental Digital Content, https://links.lww.com/MD/O1000). The 91 inflammatory cytokines under investigation were derived from a meta-analysis involving 11 cohorts of 14,824 participants of European ancestry published in 2023 by Jing Hua Zhao et al.^[14] The complete GWAS summary statistics for each cytokine were obtained from the OpenGWAS database (https://www.ebi.ac.uk/gwas/) under accession numbers GCST90274758-GCST90274848 (Table S3, Supplemental Digital Content, https://links.lww.com/MD/ O1000). The FinnGen consortium provided summary statistics for GBM at the genus level (https://finngen.gitbook.io/documentation/, Documentation for the R10 release). This study included 314,193 European individuals, of whom 253 were patients with GBM and 314,446 were controls. Population selection ensured the absence of overlap between the exposure and outcome datasets. The details of the GWASs are summarized in Table 1.

2.3. Instrument selection

To ensure that SNPs selected as IVs were strongly associated with exposure, we implemented the following steps based on the 3 core assumptions of the MR analysis.

First, the genome-wide significance criterion of $P < 5 \times 10^{-8}$ was employed to identify SNPs significantly linked to both GBM and inflammatory cytokines. As only a few SNPs were found for certain inflammatory cytokines and GBM when they were considered for exposure, we adopted a higher cutoff ($P < 1 \times 10^{-5}$).^[19]

Second, SNPs that showed potential linkage disequilibrium (LD) with an r^2 value of ≥ 0.001 and an LD distance of <10,000 kb were excluded to ensure the independence of SNPs using the clustering algorithm in the PLINK software (version v1.90) (https://www.cog-genomics.org/plink/1.9/).

Third, the LDtrait website (https://ldlink.nih.gov/?tab=ldtrait) was used to identify disease-related SNPs and to exclude SNPs associated with potential confounders.^[20]

Finally, we calculated the F-statistics for each SNP using the established formula.^[21] The R^2 value, which is indicative of the proportion of variance in the exposure variable explained by IV, was derived using the following formula:

$$R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2$$

The F-statistic, which further assesses the strength of the association between SNP and exposure, was calculated as follows:

$$F = \frac{R^2 \times (N-2)}{1-R^2}$$

Here, *EAF* denotes the effect allele frequency, β is the effect size of the association between the SNP and inflammatory cytokine, and N is the sample size of the GWAS from which



Figure 1. The study design of our study. (A) Three instrumental variable assumptions for Mendelian Randomization analysis; (B) the study design of two sample MR analysis.

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Baseline information for inflammatory cytokines and glioblastoma.

Traits	Catlog ID	Population	Year	Author	PMID	DOI
91 inflammatory proteins 41 inflammatory proteins Phenotype Brain glioblastoma	GCST90274758~GCST90274848 ebi-a-GCST004420~ebi-a-GCST004460 Consortium FinnGen (R10)	European European Population European	2023 2021 Year 2023	Zhao Jing Hua Marita Kalaoja Cases 253	37563310 33491305 Sample size 314,446	10.1038/s41590-023-01588-w 10.1002/oby.23060 Websites https://www.finngen.fi/en

the SNPs were derived. SNPs with an F-statistic exceeding the threshold of 10 were deemed to have a strong association with exposure and, therefore, qualified as suitable IVs for MR analysis. We further refined our selection by conducting a Steiger test after excluding weak IVs.

2.4. MR analysis and Bayesian weighted Mendelian randomization analysis

In our investigation of the genetic causality between inflammatory cytokines and GBM based on GWAS data, we conducted a two-sample MR analysis using a variety of commonly employed MR methodologies. The MR–Egger,^[22] weighted median,^[23] inverse variance weighted (IVW),^[24,25] weighted mode,^[26] constrained maximum likelihood-based Mendelian randomization^[27] and robust adjusted profile score^[28] models were used. The IVW method, which is known for its efficiency and high statistical power, was used to evaluate causal associations. The IVW findings were considered to be suggestive of a meaningful association if they achieved statistical significance (P < .05) and were supported by a consistent trend across other approaches in instances where other methods, such as the weighted median method and the MR-Egger method, failed to produce meaningful outcomes.

Bayesian weighted Mendelian randomization (BWMR) analysis serves as a valuable complement to traditional two-sample MR analysis. BWMR analysis enhances the stability and reliability of the final results using a Bayesian framework. Moreover, BWMR analysis enhances the conventional two-sample MR by providing a more robust estimation in the presence of heterogeneity and potential violations of the assumptions underpinning the IV analysis.^[29]

By employing a comprehensive array of MR methods, we assessed the genetic causality between inflammatory cytokines and GBM from multiple perspectives, ensuring that our research findings are both accurate and robust.

2.5. Sensitivity analyses

The Cochrane Q test was used to quantitatively evaluate heterogeneity among the Cochrane Q test (P < .05).^[25] Furthermore, we applied the MR-Egger intercept test (P < .05) to examine whether there was evidence of directional pleiotropy within the IVs.^[22] A significant deviation in the intercept from zero indicates directional pleiotropy.

Furthermore, we employed the MR-Pleiotropy Residual Sum and Outlier method^[30] to detect and eliminate outliers that could introduce horizontal pleiotropy. In the event that outliers were identified, the SNPs associated with them were excluded from subsequent analyses.

Our research utilized an innovative methodology by utilizing modified second-order weights to identify and subsequently eliminate outliers in the MR analysis. This was accomplished by utilizing the "RadialMR" package (https://github.com/WSpiller/ RadialMR) in the R programming environment. This method improves the robustness of the MR analysis by minimizing the potential impact of outliers, which could otherwise skew the results and lead to biased estimates of the causal effect.^[31]

To identify potentially heterogeneous SNPs, we conducted leave-one-out sensitivity analysis. This approach involved systematically removing each SNP from the analysis and observing its impact on the overall results.

2.6. Meta-analysis

Finally, we evaluated the same inflammatory cytokine results from both databases after screening based on the "meta" package to confirm the reliability of the MR results. A randomeffects model was used when the heterogeneity of the results was significant ($I^2 \ge 50\%$ or P < .05), and a fixed-effects model was used when the results were not significant ($I^2 < 50\%$ and $P \ge .05$).^[19,32]

All the statistical analyses were performed using R version 4.3.3 (https://www.r-project.org/), along with the "TwoSampleMR," "RadialMR," and "MRPRESSO" packages. The data were visualized using the forestploter R package. The outcomes of the MR analysis were quantified using odds ratios with 95% confidence intervals, and a *P* value <.05 was considered to indicate statistical significance.

2.7. Ethics statement

Our research relied entirely on publicly available GWAS data that had already received ethical approval prior to its release. Because this study did not involve the collection of new data, it was not necessary to obtain additional ethical approval.

3. Results

3.1. The causal effect of inflammatory proteins on GBM

3.1.1. Selection of *IVs.* After rigorous selection and harmonization of IVs, 2330 SNPs linked to 91 inflammatory cytokines and 561 SNPs linked to 41 inflammatory cytokines were used as instruments for subsequent analysis, with all computed F-statistics above 10. Each selected IV had an F-statistic > 10, indicating strong IVs and absence of weak instrumental bias in the study (Tables S4 and S5, Supplemental Digital Content, https://links.lww.com/MD/O1000).

3.1.2. MR analysis and BWMR analysis. MR analysis of 132 inflammatory cytokines as exposure variables in GBM revealed 2 inflammatory proteins with a causal relationship with GBM (Tables S6 and S7, Supplemental Digital Content, https://links. lww.com/MD/O1000). The primary results of the main MR analyses are shown in Figs. 2–4.

According to the IVW results, elevated levels of fibroblast growth factor 21 (odds ratio [OR] = 0.456, 95% CI: 0.276– 0.754, P = .002) were associated with a reduced risk of GBM. In addition, increased levels of tumor necrosis factor β (OR = 1.597, 95% CI: 1.143–2.230, P = .006) may be linked to an increased risk of GBM. This result was corroborated by the BWMR analysis results for fibroblast growth factor 21 (FGF21) (OR = 0.444, 95% CI: 0.258–0.766, P = .004) and tumor necrosis factor beta (TNF-β) (OR = 1.624, 95% CI: 1.140–2.313, P = .007). Other supplementary methods for MR analysis corroborated similar trends and findings related to the impact of these inflammatory proteins on GBM.

3.1.3. Sensitivity analysis. In this study, a series of sensitivity analyses was conducted to evaluate the pleiotropy and heterogeneity of the MR results. Initially, Cochran Q test revealed no significant heterogeneity among the effect sizes of the included SNPs across the different studies, indicating good consistency in our analytical outcomes (Table 2). This implies that our results are uniform, thus enhancing the credibility of our findings. Subsequently, the MR-Egger intercept test was used to assess the presence of directional gene pleiotropy. The results did not indicate significant pleiotropy, reinforcing the notion that our IVs were generally unrelated to potential confounders, thereby supporting the trustworthiness of our study's results (Tables S8 and S9, Supplemental Digital Content, https://links.lww.com/MD/O1000). Furthermore, utilizing the MR-Pleiotropy Residual Sum and Outlier method and Radial MR analysis, we identified 142 outliers within our dataset (Tables S10 and S11, Supplemental Digital Content, https://links.lww.com/MD/O1000). To ensure the robustness and reliability of our MR analysis, we excluded these outliers

GWAS ID	Exposuer/Method	nSNP	b	se	OR(95% CI)			pval
GCST90274788	FGF21						1	
	IVW	25	-0.786	0.257	0.456 (0.276 to 0.754)			0.002
	BWMR	25	-0.811	0.278	0.444 (0.258 to 0.766)			0.004
	MR Egger	25	-0.88	0.575	0.415 (0.134 to 1.280)	-		0.140
	Weighted median	25	-0.629	0.378	0.533 (0.254 to 1.119)			0.096
	Weighted mode	25	-0.63	0.447	0.533 (0.222 to 1.280)			0.172
	RAPS	25	-0.787	0.274	0.455 (0.266 to 0.778)			0.004
	CML MR	25	-0.773	0.284	0.462 (0.264 to 0.806)			0.007
GCST90274795	IL-10							
	IVW	30	0.319	0.242	1.376 (0.856 to 2.213)	H	• • •	0.188
	BWMR	30	0.336	0.264	1.400 (0.834 to 2.349)			0.203
	MR Egger	30	0.762	0.504	2.143 (0.797 to 5.760)		-	→0.142
	Weighted median	30	0.449	0.354	1.566 (0.783 to 3.131)			→0.205
	Weighted mode	30	0.482	0.487	1.619 (0.623 to 4.210)			→0.331
	RAPS	30	0.389	0.26	1.476 (0.887 to 2.455)	H	• • • • • • • • • • • • • • • • • • • •	0.134
	CML MR	30	0.376	0.27	1.457 (0.858 to 2.475)		• • • • • • • • • • • • • • • • • • • •	0.164
GCST90274821	MIP 1a							
	IVW	29	-0.095	0.195	0.909 (0.620 to 1.334)	-		0.626
	BWMR	29	-0.122	0.208	0.885 (0.589 to 1.330)			0.556
	MR Egger	29	0.154	0.341	1.166 (0.598 to 2.273)			0.656
	Weighted median	29	-0.228	0.271	0.796 (0.468 to 1.354)		1	0.400
	Weighted mode	29	-0.302	0.354	0.739 (0.369 to 1.480)			0.401
	RAPS	29	-0.138	0.208	0.871 (0.579 to 1.311)			0.509
	CML MR	29	-0.121	0.217	0.886 (0.580 to 1.355)			0.577
ebi-a-GCST004425	TGF beta				,			
	IVW	8	0.468	0.17	1.597 (1.143 to 2.230)		·	0.006
	BWMR	8	0.485	0.18	1.624 (1.140 to 2.313)		· · · · · · · · · · · · · · · · · · ·	0.007
	MR Egger	8	0.434	0.354	1.544 (0.771 to 3.091)			
	Weighted median	8	0.334	0.229	1.397 (0.892 to 2.187)	H		0.144
	Weighted mode	8	0.35	0.281	1.419 (0.819 to 2.459)	-		0.253
	RAPS	8	0.453	0.185	1.573 (1.095 to 2.259)		· · · · · · · · · · · · · · · · · · ·	0.014
	CML MR	8	0.44	0.207	1.552 (1.034 to 2.329)		· · · · · · · · · · · · · · · · · · ·	0.034
ebi-a-GCST004434	MIP 1a				,			
	IVW	15	-0.383	0.203	0.682 (0.458 to 1.016)	· •	+	0.060
	BWMR	15	-0.365	0.217	0.694 (0.454 to 1.062)	·	; 	0.092
	MR Egger	15	-0.89	0.447	0.410 (0.171 to 0.985)			0.068
	Weighted median	15	-0.358	0.284	0.699 (0.400 to 1.220)			0.208
	Weighted mode	15	-0.758	0.517	0.469 (0.170 to 1.290)			0.165
	BAPS	15	-0.406	0.221	0.666 (0.432 to 1.027)		- 	0.066
	CML MB	15	-0.347	0.252	0.707 (0.431 to 1.158)			0.168
ebi-a-GCST004444	IL-10				,			
	IVW	15	0.416	0.216	1.516 (0.992 to 2.315)		· · · · · · · · · · · · · · · · · · ·	0.054
	BWMR	15	0.422	0.222	1.526 (0.987 to 2.359)			0.057
	MR Egger	15	0.09	0.467	1.095 (0.439 to 2.732)		•	0.850
	Weighted median	15	0.192	0.285	1.211 (0.692 to 2.120)			0.502
	Weighted mode	15	0.191	0.31	1.210 (0.660 to 2.220)			0.547
	RAPS	15	0.401	0.228	1,493 (0,954 to 2,335)			0.079
	CML MR	15	0.43	0.238	1.537 (0.964 to 2.450)			0.071
pval<0.05 was considered statistically	significant				(0 05	1	
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Figure 2. Forest plot for the significant associations. We mainly used the IVW method and BWMR. BWMR = Bayesian weighted Mendelian randomization; cML-MR = constrained maximum likelihood-based Mendelian randomization; FGF21 = fibroblast growth factor 21; IL10 = interleukin-10; IVW = inverse variance weighted; MIP 1a = macrophage inflammatory protein 1a; MR = Mendelian randomization; MRPresso = MR-pleiotropy residual sum and outliers; RAPS = Robust adjusted profile score; TGF beta = tumor necrosis factor β .

and subsequently reevaluated the genetic IVs in relation to the exposure and outcome variables. For example, when we investigated the causal link between interleukin-10 (IL-10) (from the EBI database) and GBM, the radial MR method successfully identified an outlier (SNP: rs4655953) (Fig. 5). The advantage of radial MR analysis lies in its ability to adapt to complex patterns in data and provide a flexible way to address pleiotropy issues, thereby enhancing the reliability and accuracy of our results. In addition, an approximately symmetric funnel

plot corroborated our findings, suggesting the robustness of our results. Finally, we performed a leave-one-out analysis of the data, and no specific SNPs were found to drive the association between inflammatory cytokines and GBM. The results of the analysis are presented as a forest plot (Fig. 6).

3.1.4. Meta-analysis. To further minimize the bias of the results due to different data sources, we performed a metaanalysis of the results of the same inflammatory cytokines

								_	
							Eukaryotic translation initiation factor 4E-binding protein 1 Adenosine Deaminase		0.95
							Artemin		
							Axin-1		0.75
							Caspase 8		
							Eotaxin		
							C-C motif chemokine 19		0.5
							C–C motif chemokine 23		
							C-C motif chemokine 25		0.05
							C-C motif chemokine 28		0.25
							Natural killer cell receptor 2B4		
							CD40L receptor		0.05
			*				T-cell surface glycoprotein CD5		
							CUB domain-containing protein 1		
							Macrophage colony-stimulating factor 1		
							Cystatin D		
							Fractaikine		
							C–X–C motif chemokine 10		
							C-X-C motif chemokine 11		
		Ŷ					C-X-C motif chemokine 5		
							C–X–C motif chemokine 9		
							Delta and Notch-like epidermal growth factor-related receptor		
							Protein S100-A12		
**	**				**	**	Fibroblast growth factor 21		
							Fibroblast growth factor 23		
							Fibroblast growth factor 5		
							Glial cell line-derived neurotrophic factor		
							Hepatocyte growth factor		
							Interferon gamma		
							Interleukin–10		
							Interleukin-10 receptor subunit beta		
							Interleukin-12 subunit beta		
							Interleukin–13		
							Interleukin–17A		
							Interleukin–17C		
		*					Interleukin–18		
							Interleukin–18 receptor 1 Interleukin–1–alpha		
							Interleukin-2		
							Interleukin-20		
							Interleukin-20 receptor subunit alpha Interleukin-22 receptor subunit alpha-1		
							Interleukin-24		
							Interleukin-2 receptor subunit beta		
							Interleukin–33 Interleukin–4		
							Interleukin–5		
							Interleukin-6		
							Interleukin–7 Interleukin–8		
							Latency-associated peptide transforming growth factor beta 1		
							Leukemia inhibitory factor		
							Leukemia inhibitory factor receptor		
							Monocyte chemoattractant protein 2		
							Monocyte chemoattractant protein-3		
							Monocyte chemoattractant protein-4		
							Matrix metalloproteinase-1		
							Matrix metalloproteinase-10		
	*		*		*		Neurotrophin_3		
							Osteoprotegerin		
							Oncostatin-M		
							Programmed cell death 1 ligand 1		
							Sterri celli factor SIR2-like protein 2		
							Signaling lymphocytic activation molecule		
							Sulfotransferase 1A1		
							S raw binding protein Transforming growth factor-alpha		
							Tumor necrosis factor		
							TNF-beta		
							Tumor necrosis factor receptor superfamily member 9		
							TNF-related apoptosis-inducing ligand		
							TNF-related activation-induced cytokine		
							Thymic stromal lymphopoietin		
							Urokinase-type plasminogen activator		
							Vascular endothelial growth factor A		
m.	Su.	MA	hoi	200	Pas	Cha			
	MA	150	- ^{'g} hie	-Ship	ۍ ^ت ې	" Mx	>		
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Figure 3. Heatmap of Mendelian randomization analysis of the causal effect of 91 inflammatory cytokines on glioblastoma. ***P < .001; **0.001 $\leq P < .01$; *0.01 $\leq P < .05$. BWMR = Bayesian weighted Mendelian randomization; cML-MR = constrained maximum likelihood-based Mendelian randomization; IVW = inverse variance weighted; RAPS = robust adjusted profile score.

from different database sources. Finally, 2 inflammatory cytokines, IL-10 (OR = 1.452, 95% CI: 1.059-1.992, P = .021) and MIP-1a (OR = 0.743, 95% CI: 0.558-0.990, P = .042), were screened out. The results are shown as forest plots (Fig. 7).

3.2. The causal effect of GBM on inflammatory proteins

To further investigate the reverse causal effects of GBM on 132 inflammatory cytokines, we performed reverse MR analysis conducted primarily using the IVW method. In this analysis, we identified only 8 SNPs that demonstrated a robust association

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** ** ** ** TNF-related apoptosis inducing ligand ** ** * Tumor necrosis factor beta Tumor necrosis factor alpha Tumor necrosis factor alpha 0.5 Image: Stromal-cell-derived factor 1 alpha 0.5 Image: Stromal-cell derived factor 1 Image: Stromal-cell factor 1 Image: Stromal-cell derived factor 1 Image: Stromal-cell factor 1 Image: Stromal-cell derived factor 1
** ** ** Tumor necrosis factor beta Tumor necrosis factor alpha 0.5 Image: Stem cell growth factor beta Image: Stem cell growth factor beta 0.5 0.5 0.5 Image: Stem cell growth factor beta Image: Stem cell growth factor beta 0.5 0.5 0.5 Image: Stem cell growth factor beta Image: Stem cell growth factor beta 0.5 0.5 0.5 Image: Stem cell growth factor beta Image: Stem cell growth factor beta 0.5 0.25 0.25 Image: Stem cell growth factor BB Image: Stem cell growth factor BB 0.5 0.05 0.25 Image: Stem cell growth factor growth factor BB Image: Stem cell growth factor BB 0.05 0.05 Image: Stem cell growth factor growth factor BB Image: Stem cell growth factor growth factor BB 0.05 Image: Stem cell growth factor growth factor BB Image: Stem cell growth factor BB 0.05 Image: Stem cell growth factor growth factor growth factor BB Image: Stem cell growth factor BB 0.05 Image: Stem cell growth factor BB Image: Stem cell growth factor BB Image: Stem cell growth factor BB 0.05 Image: Stem cell growth factor BB Image: Stem cell growth factor BB Image: Stem
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Image: Stromal-cell-derived factor 1 alpha 0.5 Image: Stromal-cell growth factor beta Stem cell growth factor beta Image: Stromal-cell growth factor beta Stem cell factor Image: Stromal-cell derived growth factor beta Interleukin-16 Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor bas Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor BB Image: Stromal-cell derived growth factor Macrophage colony stimulating factor Image: Stromal-cell derived growth chemoattractant protein-3 Monocyte chemoattractant protein-3 Image: Stromal-cell derived growth factor growth factor Image: Stromal-cell derived growth factor Image: Stromal-cell derived growth factor Image: Stromal-cell derived growth factor Image: Stromal-cell derin derived growth factor Ima
Image: Stem cell growth factor beta Image: Stem cell factor
Image: Stem cell factor Interleukin-16 Image: Stem cell factor Regulated on activation, normal T cell expressed and secreted Image: Stem cell factor Platelet-derived growth factor BB Image: Stem cell factor Macrophage inflammatory protein 1b Image: Stem cell factor Macrophage inflammatory protein 1a Image: Stem cell factor Monokine induced by gamma interferon Image: Stem cell factor Monocyte chemoattractant protein-3 Image: Stem cell factor Monocyte chemoattractant protein-1 Image: Stem cell factor Interleukin-12p70 Image: Stem cell factor Interleukin-13 Image: Stem cell factor Interleukin-13 Image: Stem cell factor Interleukin-12p70 Image: Stem cell factor Interleukin-13 Image: Stem cell factor Interleukin-17
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Macrophage inflammatory protein 1a 0.05 Macrophage inflammatory protein 1a 0.05 Macrophage colony stimulating factor Macrophage colony stimulating factor Macrophage colony stimulating factor Macrophage colony stimulating factor Macrophage colony stimulating factor Macrophage colony stimulating factor Macrophage colony stimulating factor Monocyte chemoattractant protein–3 Macrophage colony stimulating factor Monocyte chemoattractant protein–1 Interleukin–12p70 Interleukin–12p70 Interleukin–18 Interleukin–17
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Interleukin–18
Interleukin–17
Interleukin–13
Interleukin–10
Interleukin–8
Interleukin–6
Interleukin–1–receptor antagonist
Interleukin-1-beta
Hepatocyte growth factor
Interleukin-9
Interleukin–7
Interleukin–5
Interleukin–4
Interleukin–2 receptor antagonist
interieron gamma
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Figure 4. Heatmap of Mendelian randomization analysis of the causal effect of 41 inflammatory cytokines on glioblastoma. ***P < .001; **0.001 $\leq P < .01$; *0.01 $\leq P < .05$. BWMR = Bayesian weighted Mendelian randomization; cML-MR = constrained maximum likelihood-based Mendelian randomization; IVW = inverse variance weighted; RAPS = robust adjusted profile score.

Table 2	
Heterogeneity and pleiotropy analyses.	

		Heterogeneity	y test		н	orizontal pl	MRPresso				
	Cochrane Q				MR-Egger in	itercept	MR-PRESS	0 global	MR analysis		
Exposure	method Q		df	Р	Intercept	Р	RSSobs	Р	Causal Estimate	Р	
FGF21	MR Egger	21.424	23	.555	0.010	.856	23.073	.646	-0.786	.004	
GCST90274788	IVW	21.457	24	.612							
IL10	MR Egger	24.892	28	.634	-0.052	.325	27.479	.655	0.319	.174	
GCST90274795	IVW	25.896	29	.631							
MIP 1a	MR Egger	18.715	27	.880	-0.040	.380	21.172	.876	-0.095	.564	
GCST90274821	IVW	19.510	28	.882							
ΤGFβ	MR Egger	6.971	6	.324	0.010	.915	8.635	.514	0.468	.029	
ebi-a-GCST004425	IVW	6.986	7	.430							
MIP 1a	MR Egger	10.929	13	.617	0.092	.224	14.432	.582	-0.383	.067	
ebi-a-GCST004434	IVW	12.557	14	.562							
IL10	MR Egger	11.365	13	.580	0.044	.445	14.319	.615	0.416	.056	
ebi-a-GCST004444	IVW	11.984	14	.608							

FGF21 = fibroblast growth factor 21, IL10 = interleukin-10, IVW = inverse variance weighted, MIP 1a = macrophage inflammatory protein 1a, MR = Mendelian randomization, MRPresso = MR-Pleiotropy Residual Sum and Outliers, TGF β = tumor necrosis factor β .



Figure 5. Outliers identified by the radial MR analysis. (A) Fibroblast growth factor 21 on glioblastoma; (B) interleukin-10 on glioblastoma (91 cytokines); (C) macrophage inflammatory protein 1a on glioblastoma (91 cytokines); (D) tumor necrosis factor β on glioblastoma; (E) macrophage inflammatory protein 1a on glioblastoma (41 cytokines); (F) interleukin-10 on glioblastoma (41 cytokines). The purple portions signify the identified outliers by IVW and MR-Egger. The green portions signify the identified outliers by IVW.

with GBM. Only 90 inflammatory cytokines (from the EBI database) and 28 inflammatory cytokines (from the University of Bristol database) were successfully detected via MR analysis using the IVW method (Tables S12 and S13, Supplemental Digital Content, https://links.lww.com/MD/O1000). Ultimately, our findings did not provide evidence that GBM significantly influences the levels of these cytokines (Figs. 8 and 9).

4. Discussion

In this study, we explored the relationship between inflammatory cytokines and GBM based on genetic data from publicly available databases using MR analysis. Understanding the causal link between the levels of inflammatory cytokines and GBM is crucial for determining the underlying causes of this disease and for devising effective preventative and curative strategies. Further analysis revealed that, among the 132 inflammatory cytokines, low levels of FGF21 and high levels of TNF- β were associated with a greater risk of GBM. In addition, the results of the meta-analysis indicated that 2 additional inflammatory cytokines were associated with the risk of GBM. Low levels of MIP-1a and high levels of IL-10 correlated with a greater likelihood of developing GBM. In the reverse analysis, no causal relationship between GBM and inflammatory cytokines was found.

The tumor microenvironment plays a crucial role in cancer initiation and progression.^[33] Inflammatory cytokines, which are key components of the tumor microenvironment, are produced by various cell types, including tumor cells, immune cells, and stromal cells.^[34] Dysregulation of these genes can lead to chronic inflammation, which can either promote^[35] or inhibit tumor growth. Understanding the complex interplay between inflammatory cytokines and the tumor microenvironment is essential for developing targeted therapies that modulate the microenvironment and improve patient outcomes.^[36] MR studies have been applied to investigate the causal relationships between inflammatory cytokines and various cancers, including prostate cancer, breast cancer, colorectal cancer, lung cancer, and diffuse large B-cell lymphoma.^[37-40]

FGF21 is a multifaceted hormone with a complex role in the regulation of metabolism, energy expenditure, and glucose homeostasis.^[41] However, its role in cancer remains complex and context dependent.^[42] Several recent studies have shown that FGF21 is associated with the development and progression of cancers, such as liver cancer,^[43–46] lung cancer,^[47] thyroid cancer,^[48] and ovarian cancers.^[49] For example, in prostate cancer,



Figure 6. Results of the causal relationship between fibroblast growth factor 21, tumor necrosis factor β and glioblastoma. (A) Scatter plots of the causal relationship between fibroblast growth factor 21 and glioblastoma at using 7 different MR methods. (B) Funnel plots of fibroblast growth factor 21 on glioblastoma; (C) leave-one-out sensitivity analysis of fibroblast growth factor 21 on glioblastoma; (D) scatter plots of the causal relationship between tumor necrosis factor β and glioblastoma at using 7 different MR methods; (E) funnel plots of tumor necrosis factor β on glioblastoma; (F) leave-one-out sensitivity analysis of tumor necrosis factor β on glioblastoma; (F) leave-one-out sensitivity analysis of tumor necrosis factor β on glioblastoma.

Α				
	Exposure	Source	Odds Ratio	OR [95%–CI] P
	MIP1a MIP1a	University of Bristol database(41 cytokines) — EBI database(91 cytokines)		0.682 [0.458, 1.016] 0.0 - 0.815 [0.539, 1.232] 0.3
		Fixed effect model		0.743 [0.558, 0.990]
		Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $\chi_1^2 = 0.37$ ($p = 0.54$)		
		Test for overall effect: $z = -2.03$ ($p = 0.042$) 0.4	0.75 1	1.5
в		Test for overall effect: $z = -2.03$ ($p = 0.042$) 0.4	0.75 1	1.5
в	Exposure	Test for overall effect: $z = -2.03$ ($p = 0.042$) 0.4 Source	0.75 1 Odds Ratio	1.5 OR [95%–Cl] P
в	Exposure IL-10 IL-10	Test for overall effect: $z = -2.03$ ($p = 0.042$)0.4SourceUniversity of Bristol database(41 cytokines)EBI database(91 cytokines)	0.75 1 Odds Ratio	1.5 OR [95%–CI] F — 1.516 [0.992, 2.315] 0.0 — 1.376 [0.856, 2.213] 0.1

Figure 7. The forest plot shows the 2 sets of results from the analysis of inflammatory cytokines on glioblastoma using meta-analysis methods combined to assess the reliability of positive or potentially positive results. (A) Macrophage inflammatory protein 1a on glioblastoma. (B) Interleukin-10 on glioblastoma.

OutcomeOutcomeOutcomeOutcomeOutcomeOutcomeCGT1070701AutomeCGT000000000000000000000000000000000000								
Del 1000000000000000000000000000000000000	GWAS ID	Outcome	nSNP	b	se	OR(95% CI)		pval
number p< p<< p<< p<< p<< p<< p<< p<< p<< p< p< p<<	GCST90274758	Eukaryout translation initiation factor 4E-binding protein 1 Adenosine Deaminase	7	-0.002	0.012	0.998 (0.974 to 1.023) 1.002 (0.979 to 1.024)		0.891
CONSTRUCTAbe-1Construct	GCST90274759	Artemin	6	-0.002	0.012	0.991 (0.962 to 1.020)		0.561
CCTST02770Construction <td>GCST90274761</td> <td>Axin-1</td> <td>4</td> <td>0.018</td> <td>0.022</td> <td>1.018 (0.976 to 1.062)</td> <td></td> <td>0.410</td>	GCST90274761	Axin-1	4	0.018	0.022	1.018 (0.976 to 1.062)		0.410
CGTN20700CGNUPAL	GCST90274762	beta-nerve growth factor	6	0.006	0.013	1.006 (0.981 to 1.032)		0.635
CHENDEROYExamS-0.001000.00	GCST90274763	Caspase 8	7	-0.001	0.013	0.999 (0.974 to 1.024)		0.910
CGT1902704C-C mald denomine 19S0.0000.0011.0000.0010.0000.0010.000 <t< td=""><td>GCST90274764</td><td>Eotaxin</td><td>5</td><td>-0.002</td><td>0.017</td><td>0.998 (0.965 to 1.032)</td><td>·</td><td>0.897</td></t<>	GCST90274764	Eotaxin	5	-0.002	0.017	0.998 (0.965 to 1.032)	·	0.897
GGT192077 C- mod at answine 20 7 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 0.040 0.051 </td <td>GCST90274765</td> <td>C-C motif chemokine 19</td> <td>5</td> <td>0.008</td> <td>0.014</td> <td>1.008 (0.981 to 1.036)</td> <td></td> <td>0.566</td>	GCST90274765	C-C motif chemokine 19	5	0.008	0.014	1.008 (0.981 to 1.036)		0.566
0.6111002770 CC. mori dramewine 3 4 -0.00 0021 1020 0027 1000 0027 0.00 0.00 1000 0027 0.00	GCST90274766	C-C motif chemokine 20	7	0.004	0.013	1.004 (0.979 to 1.029)		0.772
04511022190 C-C mod memories 2 6 0.000 0.001 </td <td>GCST90274767</td> <td>C-C motif chemokine 23</td> <td>4</td> <td>-0.008</td> <td>0.018</td> <td>0.992 (0.957 to 1.028)</td> <td></td> <td>0.659</td>	GCST90274767	C-C motif chemokine 23	4	-0.008	0.018	0.992 (0.957 to 1.028)		0.659
CG11902/170 C-C. mod strendmar B -0.000 0001 0005 <	GCST90274768	C-C motif chemokine 25	6	0.003	0.013	1.003 (0.977 to 1.029)		0.834
Cd11102/277 C-C mod demokers 4 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.011 0.010 0.0111 0.	GCST90274769	C-C motif chemokine 28	7	-0.005	0.012	0.995 (0.972 to 1.018)		0.660
0.0.110.00.0000 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.0000 0.000 0.000	GCS190274770	C-C motif chemokine 4	4	0.010	0.017	1.010 (0.976 to 1.045)		0.577
Display Coulds, Resplay Display Display <thdisplay< th=""> Display Display</thdisplay<>	GCST90274771	Natural killer cell receptor 2B4	4	0.010	0.016	1.010 (0.980 to 1.042)		0.513
0.0.1102/0717 Locate Junce Systemster LOS 0.001	GCS190274772	CD40L receptor	6	-0.015	0.013	0.985 (0.960 to 1.010)		0.236
Del:Biology: Del:Biology: Del:Display: Del:Display:<	GCST90274773	T cell surface glycoprotein CD5	6	0.0011	0.013	1.011 (0.986 to 1.038)		0.392
DCST902777 Manusphage comy-stanualing bates 1 7 0.00	GCST90274774	CLIB domain_containing protein 1	5	-0.010	0.016	0.990 (0.968 to 1.032)		0.534
CGSTB02777 Opatin D Sol 2007 0.040 0.075 1.040 0.075 1.040 0.075 1.040 0.075 1.040 0.075 1.040 0.075 1.040 0.075 1.040 0.075 1.020 0.075 0.075 1.020 0.075	GCST90274776	Macronhage colony-stimulating factor 1	7	0.005	0.013	1.005 (0.979 to 1.031)		0.731
Display Functions B D.000 D.010 D.010 <thd.010< th=""> D.010 D.010 <t< td=""><td>GCST90274777</td><td>Cystatin D</td><td>5</td><td>0.004</td><td>0.015</td><td>1.004 (0.975 to 1.033)</td><td></td><td>0.806</td></t<></thd.010<>	GCST90274777	Cystatin D	5	0.004	0.015	1.004 (0.975 to 1.033)		0.806
CX-X-D rol 4 members 7 -0.07 0.07 0.085	GCST90274778	Fractalkine	8	0.006	0.012	1.006 (0.983 to 1.029)	·	0.618
CX-X-C mark dramoules 10 3 0.00 0.00 0.09 1.000 0.099 1.000 0.099 1.000 0.099 1.000 0.099 1.000 0.099 1.000 0.099 1.000 0.099 1.000 0.099 0.099 1.000 0.099	GCST90274779	C-X-C motif chemokine 1	7	-0.013	0.012	0.987 (0.963 to 1.011)		0.298
CCST002779 C.X-C. molt demokins 1 0 -0.08 0.014 0.928 0.989 0.94	GCST90274780	C-X-C motif chemokine 10	3	0.000	0.021	1.000 (0.959 to 1.043)	·	0.987
CS-N2-Cmid examples 7 -0.012 0.088 (0.084 to 10.02) CST0027478 C-X-C mid examples 8 0.000 0.021 1.000 (0.073 to 10.00) CST0027478 C-X-C mid examples 8 0.000 0.011 1.010 (0.873 to 10.00) CST0027478 Finchist growth factor 11 6 0.010 0.011 1.010 (0.885 to 10.05) CST0027478 Finchist growth factor 12 6 0.010 0.031 1.010 (0.885 to 10.05) CST0027478 Finchist growth factor 13 6 -0.002 0.021 0.010 (0.975 to 10.05) CST0027479 Finchist growth factor 14 0.000 0.010 0.010 (0.975 to 10.02) CST0027479 Finchista growth factor 14 0.000 0.010 0.010 (0.975 to 10.02) CST0027479 Finchista growth factor 14 0.000 0.011 0.010 (0.975 to 10.02) CST0027479 Finchista growth factor 14 0.000 0.011 0.010 (0.975 to 10.02) CST0027490 Interlevita-1-12 0.010 0.011 0.010 (0.975 to 10.02) CST0027400 <	GCST90274781	C-X-C motif chemokine 11	6	-0.008	0.014	0.992 (0.965 to 1.020)		0.585
CS-TBO27779C-X-C moli demokine 68-0.000.020.998 (0.971 b 10.00)	GCST90274782	C-X-C motif chemokine 5	7	-0.012	0.013	0.988 (0.964 to 1.012)		0.330
CGSTB027479C-X-C mol channelse is a point of anomalo is a point of a point	GCST90274783	C-X-C motif chemokine 6	8	-0.004	0.012	0.996 (0.974 to 1.020)		0.766
CGSTB027479Delta and Noth-like applemal growth factor -leikated respects0.001 <td>GCST90274784</td> <td>C-X-C motif chemokine 9</td> <td>3</td> <td>0.009</td> <td>0.020</td> <td>1.009 (0.971 to 1.050)</td> <td></td> <td>0.636</td>	GCST90274784	C-X-C motif chemokine 9	3	0.009	0.020	1.009 (0.971 to 1.050)		0.636
CGSTN027479 Problem S100-h12 6 0.010 0.011 0.1010 (0.848 to 1.080) CGSTN027479 Flochdast growth factor 21 3 005 0.023 0.969 (0.975 to 1.020) CGSTN027479 Flochdast growth factor 21 6 002 0.010 0.011 0.101 (0.885 to 1.040) CGSTN027479 Flochdast growth factor 23 6 002 0.010 0.011 0.010 (0.875 to 1.027) CGSTN027479 Flochdast growth factor 23 6 002 0.010 0.011 0.010 (0.875 to 1.025) CGSTN027479 Interlautin-10 Control 0.011 0.010 (0.875 to 1.025)	GCST90274785	Delta and Notch-like epidermal growth factor-related recepted	or5	0.001	0.014	1.001 (0.973 to 1.030)		0.925
CGSTB027/87 Fibolast growth factor 19 6	GCST90274786	Protein S100–A12	6	0.010	0.013	1.010 (0.984 to 1.036)		0.474
GCSTB027/89 Fibodball growth fictor 21 3 -0.05 0.985 0.982 0.985 0.982 0.985 0.982 0.985 0.982 0.985 0.982 0.985 <td< td=""><td>GCST90274787</td><td>Fibroblast growth factor 19</td><td>6</td><td>-0.004</td><td>0.013</td><td>0.996 (0.971 to 1.022)</td><td></td><td>0.780</td></td<>	GCST90274787	Fibroblast growth factor 19	6	-0.004	0.013	0.996 (0.971 to 1.022)		0.780
GCSTB0274799 Fibodball growth flactor 23 6 0.000 0.015 1.010 (0.985 to 1.035) GCSTB0274790 Fina-related tyrouine kinase 3 lgand 4 -0.002 0.056 (0.985 to 1.034) GCSTB0274791 Fina-related tyrouine kinase 3 lgand 4 -0.003 0.013 1.001 (0.976 to 1.026) GCSTB0274792 Interleukin-10 receptor subcht lghna 4 0.004 0.017 1.008 (0.976 to 1.045) GCSTB0274795 Interleukin-12 subcht lghna 3 -0.002 0.016 0.986 (0.987 to 1.045) GCSTB0274795 Interleukin-12 subcht lghna 5 -0.005 0.016 0.986 (0.987 to 1.034) GCSTB0274796 Interleukin-17C 7 0.001 0.017 1.016 (0.987 to 1.024)	GCST90274788	Fibroblast growth factor 21	3	-0.005	0.023	0.995 (0.952 to 1.040)	••	0.828
GCSTB027/89 Fibodball growth factor 5 6 -0.005 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.096 0.007 <th< td=""><td>GCST90274789</td><td>Fibroblast growth factor 23</td><td>6</td><td>0.010</td><td>0.013</td><td>1.010 (0.985 to 1.035)</td><td></td><td>0.440</td></th<>	GCST90274789	Fibroblast growth factor 23	6	0.010	0.013	1.010 (0.985 to 1.035)		0.440
GCSTB027479 Imme-shead by younk insues 3 gand 4 -0.00 0.02 0.956 (0.958 to 1.04) GCSTB027478 Hepatocycle growth factor 7 0.001 0.013 1.001 (0.976 to 1.026) GCSTB0274780 Interleukin-10 receptor subcut lapha 4 0.008 0.017 1.006 (0.976 to 1.045) GCSTB0274796 Interleukin-10 receptor subcut lapha 3 -0.002 0.016 0.966 (0.976 to 1.041) GCSTB0274796 Interleukin-12 subcut bata 3 -0.002 0.16 0.966 (0.976 to 1.024) GCSTB0274796 Interleukin-17C 7 0.001 0.971 (0.976 to 1.024)	GCST90274790	Fibroblast growth factor 5	6	-0.002	0.015	0.998 (0.969 to 1.027)		0.869
GCS1902/149/L Suat cell line-derived neutrophic factor 7 0.003 0.012 1.003 0.012 1.003 0.012 1.004 GCS1902/1499 Interkulkn-10 0 0.001 0.011 0.014 <td< td=""><td>GCST90274791</td><td>Fms-related tyrosine kinase 3 ligand</td><td>4</td><td>-0.005</td><td>0.020</td><td>0.995 (0.958 to 1.034)</td><td></td><td>0.797</td></td<>	GCST90274791	Fms-related tyrosine kinase 3 ligand	4	-0.005	0.020	0.995 (0.958 to 1.034)		0.797
GGS 1802/14783 Hepsatopic growth factor 7 0.001 0.013 1.001 (0.076 to 1.080) GGS 1802/14796 Interinukin-10 moegotor subunit batha 4 0.008 0.017 1.006 (0.076 to 1.081) GGS 1802/14796 Interinukin-10 moegotor subunit batha 5 0.004 0.016 0.086 (0.056 to 1.033) GGS 1802/14796 Interinukin-12 subunit batha 5 -0.002 0.115 0.986 (0.076 to 1.033) GGS 1802/14796 Interinukin-15 moegotor subunit batha 5 -0.002 0.116 0.986 (0.976 to 1.023) GGS 1802/1490 Interinukin-16 moegotor 1 4 0.010 0.116 (0.976 to 1.043) GGS 1802/1490 Interinukin-26 -0.005 0.016 0.989 (0.970 to 1.028) GGS 1802/1490 Interinukin-26 -0.001 0.101 (0.077 to 1.028)	GCST90274792	Glial cell line-derived neurotrophic factor	7	0.003	0.012	1.003 (0.979 to 1.027)		0.812
Occ3 1002/14/39 Interlukin-10 conceptor subunit alpha 5 0.024 0.0315 1.248 (0.034 16 1.048) OCS1 1002/14/99 Interlukin-20 conceptor subunit alpha 5 0.004 0.015 1.048 (0.075 to 1.035) OCS1 1002/14/99 Interlukin-13 5 -0.002 0.989 (0.085 to 1.035)	GCST90274793	Hepatocyte growth factor	7	0.001	0.013	1.001 (0.976 to 1.026)		0.962
GCS 1902/4799 Interlukika-10 cocport suburit bata 5 0.004 0.017 1.004 0.018	GCST90274795	Interleukin-10	5	0.024	0.015	1.024 (0.994 to 1.054)		0.113
Occ.150027497 Interfeuden-10 trebsport subunit beta 5 0.004 0.018 0.094 (0.57 ko 1.0.35) OCG.150027498 Interfeuden-13 5 0.007 0.015 0.995 (0.55 ko 1.0.35) OCG.150027498 Interfeuden-13 5 0.000 0.017 0.010 (0.98 ko 1.0.35) OCG.150027480 Interfeuden-17A 6 -0.005 0.014 0.017 (0.97 ko 1.0.28) OCG.150027480 Interfeuden-18 receptor 1 4 0.010 0.998 (0.97 ko 1.0.28) Interfeuden-18 receptor 1 4 0.010 0.017 (0.97 ko 1.0.44) OCG.150027480 Interfeuden-2 4 -0.004 0.018 (0.97 ko 1.0.44) OCG.150027480 Interfeuden-2 5 0.004 0.018 (0.07 ko 12 ko 1.0.44) Interfeuden-2 5 0.004 0.018 (0.07 ko 12 ko 1.0.44)	GCS190274796	Interleukin–10 receptor subunit alpha	4	800.0	0.017	1.008 (0.976 to 1.041)		0.629
00.013007/19/96 Interfeuden-12 subunit Deal 3 -0.002 0.016 0.026 (0.976 to 1.034) 00.01300724900 Interfeuden-15 receptor subunit alpha 5 -0.002 0.015 0.996 (0.977 to 1.023) 00.01300724900 Interfeuden-17C 7 0.001 0.014 0.996 (0.977 to 1.023) 00.01300724900 Interfeuden-18 comptor 1 4 0.001 0.017 1.010 (0.974 to 1.023) 00.01300724900 Interfeuden-18 comptor 1 4 0.001 0.017 1.010 (0.974 to 1.023) 00.01300724900 Interfeuden-3e comptor 1 4 0.001 0.017 1.010 (0.974 to 1.024) 00.01300724900 Interfeuden-2e comptor subunit alpha 4 0.007 0.020 1.007 (0.972 to 1.044) 00.01300724811 Interfeuden-2e comptor subunit alpha 1 0.007 0.000 1.001 (0.972 to 1.044) 00.01300724181 Interfeuden-2e comptor subunit belaw 7 0.014 0.014 1.001 (0.978 to 1.044) 00.01300724181 Interfeuden-2e 7 0.000 0.014 1.000 (0.978 to 1.024) 00.	GCS190274797	Interleukin–10 receptor subunit beta	5	0.004	0.015	1.004 (0.976 to 1.033)		0.771
DCG10027400 Interfeadurin-15 seceptor subunit alpha 5 -0.005 0.007 <td>GCS190274798</td> <td>Interleukin-12 subunit beta</td> <td>5</td> <td>-0.002</td> <td>0.018</td> <td>1.001 (0.963 to 1.035)</td> <td></td> <td>0.925</td>	GCS190274798	Interleukin-12 subunit beta	5	-0.002	0.018	1.001 (0.963 to 1.035)		0.925
SGL 3100/1000 Interfeadukin-119 telepion subunit apina 5 -0.002 0.014 0.996 (0.97106 1.023)	GCS190274799	Interleukin-13	5	0.001	0.017	1.001 (0.969 to 1.034)		0.940
DGUSTUDZIMUE Interlineduction 1/A 0	GCST90274800	Interleukin-17	5	-0.002	0.015	0.996 (0.970 to 1.028)		0.915
CGST9027400 Interleukin-16 6 0.007 0.013 1.007 (0.914 b) 1.024) Image: CGST9027400 GGST9027400 Interleukin-12 receptor 1 4 0.010 0.091 (0.918 b) 1.024) Image: CGST9027400 GGST9027400 Interleukin-2 4 -0.004 0.018 0.996 (0.926 b) 1.028) GGST9027400 Interleukin-20 receptor subunit alpha 4 0.007 0.018 1.007 (0.976 b) 1.044) GGST9027400 Interleukin-22 receptor subunit alpha 3 0.007 0.021 1.007 (0.976 b) 1.044) Image: CGST9027401 GGST90274810 Interleukin-2 receptor subunit alpha 3 0.007 0.021 1.014 1.015 (0.986 b) 1.049) Image: CGST9027411 Interleukin-2 receptor subunit beta 7 0.010 0.011 (0.01 (0.716 b) 1.049) Image: CGST9027411 Interleukin-3 GGST9027401 Interleukin-5 7 0.000 0.011 (0.01 (0.76 b) 1.069) Image: CGST9027411 Interleukin-3 GGST9027402 Interleukin-4 5 0.012 (0.96 (0.96 b) 1.069) Image: CGST90274411 Interleukin-5 GGS	GCST90274802	Interleukin-17C	7	0.003	0.014	1.001 (0.974 to 1.029)		0.941
GCST9027480 interleukin-16 receptor 1 4 0.010 0.017 1.010 (0.976 to 1.040) GCST9027480 Interleukin-1-apha 6 -0.001 0.015 0.969 (0.970 to 1.030) GCST90274807 Interleukin-2 4 -0.001 0.018 1.060 (0.976 to 1.030) GCST90274807 Interleukin-20 ceceptor subunit alpha 4 0.007 0.028 1.077 (0.972 to 1.044) GCST90274807 Interleukin-22 ceceptor subunit alpha 4 0.010 0.015 0.969 (0.970 to 1.07) GCST90274811 Interleukin-22 ceceptor subunit beta 7 0.014 0.014 1.014 (0.987 to 1.049) GCST90274811 Interleukin-33 4 0.014 0.014 1.014 (0.987 to 1.049) GCST90274814 Interleukin-3 7 0.012 0.018 1.012 (0.976 to 1.049) GCST90274816 Interleukin-3 7 0.030 0.014 1.003 (0.976 to 1.049) GCST90274816 Interleukin-3 -0.000 0.012 1.000 (0.976 to 1.026)	GCST90274803	Interleukin-18	6	0.007	0.013	1.007 (0.981 to 1.034)		0.594
GCST90274805 Interleukin-1-alpha 6 -0.001 0.015 0.999 (0.970 to 1.029) GCST90274806 Interleukin-20 4 -0.004 0.018 0.966 (0.9621 to 1.031) GCST90274806 Interleukin-20 receptor subunit alpha 4 0.007 0.018 1.007 (0.977 to 1.039) GCST90274801 Interleukin-22 receptor subunit alpha 3 0.007 0.020 (0.077 to 1.019) GCST90274812 Interleukin-22 receptor subunit beta 7 0.014 0.014 (0.167 to 1.019) GCST90274812 Interleukin-33 4 0.014 0.011 (0.018 (0.978 to 1.049) GCST90274812 Interleukin-5 7 0.000 (0.11 (0.03 (0.978 to 1.031))	GCST90274804	interleukin-18 receptor 1	4	0.010	0.017	1.010 (0.976 to 1.044)		0.578
GCST9027480 Interleukin-2 4 -0.004 0.018 0.996 0.982 to 1.037 GCST90274807 Interleukin-20 receptor subunit alpha 4 0.007 0.018 1.044 (0.271 to 1.049) GCST90274809 Interleukin-22 receptor subunit alpha 6 -0.014 0.107 (0.972 to 1.044) GCST90274811 Interleukin-24 receptor subunit beta 7 0.014 0.014 0.1012 0.038 to 1.040) GCST90274812 Interleukin-3 7 0.003 0.014 1.030 0.076 to 1.041) Interleukin-4 5 0.014 0.014 1.030 0.041 1.030 0.041 1.030 0.076 to 1.020)	GCST90274805	Interleukin-1-alpha	6	-0.001	0.015	0.999 (0.970 to 1.028)		0.921
GCST90224807 Interleukin-20 5 0.004 0.018 1.004 (0.972 to 1.039)	GCST90274806	Interleukin-2	4	-0.004	0.018	0.996 (0.962 to 1.031)		0.805
GCST90274809 Interleukin-22 receptor subunit alpha-1 3 0.007 0.020 1.007 (0.967 to 10.47) GCST90274801 Interleukin-22 receptor subunit alpha-1 3 0.007 0.020 1.007 (0.967 to 10.47) GCST90274811 Interleukin-24 receptor subunit beta 7 0.014 0.014 0.017 1.014 (0.980 to 10.42) GCST90274811 Interleukin-3 4 0.014 0.014 1.003 (0.976 to 1.049)	GCST90274807	Interleukin-20	5	0.004	0.018	1.004 (0.970 to 1.039)		0.825
GCST90274810 Interleukin-22 receptor subunit alpha-1 3 0.007 0.020 1.007 (0.976 to 1.047) + + + + + + + + + + + + + + + + + + +	GCST90274808	Interleukin-20 receptor subunit alpha	4	0.007	0.018	1.007 (0.972 to 1.044)		0.686
GCST90274810 Interleukin-24 6 -0.010 0.014 0.916 0.919 GCST90274811 Interleukin-33 4 0.014 0.014 1.014 0.986 1.042 GCST90274813 Interleukin-33 4 0.014 0.014 1.014 0.986 1.049 GCST90274813 Interleukin-5 7 0.000 0.011 1.002 0.976 1.049 GCST90274815 Interleukin-5 7 0.000 0.013 1.000 0.976 1.026 GCST90274816 Interleukin-7 7 0.000 0.115 0.996 0.976 1.026 GCST90274816 Interleukin-7 0.000 0.015 0.996 0.976 1.029 GCST90274816 Leukemia inhibitory factor 3 -0.000 0.11 0.001 0.998 0.988 0.989 0.970 1.029 GCST90274822 Monocycle chemoattractart protein 2 6 -0.002 0.011 0.998 0.988 0.970 1.016 0.9	GCST90274809	Interleukin-22 receptor subunit alpha-1	3	0.007	0.020	1.007 (0.967 to 1.047)		0.745
GCST90274811 Interleukin-2 receptor subunit beta 7 0.014 0.017 0.114 0.014 0.012 Image to the	GCST90274810	Interleukin-24	6	-0.010	0.015	0.990 (0.961 to 1.019)		0.489
GCST90274812 Interleukin-33 4 0.014 0.017 1.014 (0.90 to 1.049) GCST90274814 Interleukin-5 7 0.003 0.014 1.003 (0.976 to 1.031) GCST90274815 Interleukin-5 7 0.000 0.014 1.003 (0.976 to 1.036) GCST90274815 Interleukin-7 5 0.000 0.015 0.996 (0.976 to 1.026) GCST90274817 Interleukin-7 7 0.000 0.121 0.009 (0.976 to 1.026) GCST90274817 Interleukin-7 5 -0.007 0.016 0.999 (0.976 to 1.028) GCST90274812 Laukemai inhibitry factor 3 -0.002 0.014 0.998 (0.958 to 1.029) GCST9027482 Monocycle chemoattractart protein-1 5 -0.007 0.014 0.998 (0.958 to 1.029) GCST9027482 Monocycle chemoattractart protein-3 7 -0.008 0.014 0.998 (0.958 to 1.029) GCST90274828 Monocycle chemoattractart protein -4 5 -0.012 0.014 0.998 (0.958 to 1.029) GCST90274828 Macocycle chemoattractart protein -4 5	GCST90274811	Interleukin–2 receptor subunit beta	7	0.014	0.014	1.015 (0.988 to 1.042)		0.293
GCST90274813 Interleukin-4 5 0.012 0.016 0.172 (0.976 to 1.049) GCST90274815 Interleukin-5 7 0.003 0.014 1.000 (0.976 to 1.026) GCST90274815 Interleukin-6 7 0.000 0.015 0.996 to 1.026)	GCST90274812	Interleukin-33	4	0.014	0.017	1.014 (0.980 to 1.049)		0.424
GCST90224814 Interfeukin-5 7 0.000 0.011 1.000 (0.976 b 1.021) GCST902274815 Interfeukin-6 7 0.000 0.015 0.995 (0.966 b 1.026) GCST902274817 Interfeukin-7 7 0.000 0.012 1.000 (0.976 b 1.026) GCST902274817 Interfeukin-8 Anone secolated peptide transforming growth factor beta 1.6 0.000 0.012 0.996 (0.970 b 1.025) GCST902274821 Laukemia inhibitory factor receptor 5 -0.007 0.016 0.993 (0.983 b 1.039) GCST90274822 Monocycle chemoattractart protein-1 5 0.000 0.014 0.999 (0.970 b 1.026) GCST90274822 Monocycle chemoattractart protein-3 7 -0.000 0.014 0.999 (0.970 b 1.026) GCST90274825 Macrocyte chemoattractart protein-1 5 -0.010 0.991 (0.985 b 1.022)	GCST90274813	Interleukin-4	5	0.012	0.018	1.012 (0.976 to 1.049)		0.515
GCST90274815 Interleukin-6 7 0.000 0.011 1.000 (0.976 to 1.026) GCST90274816 Interleukin-7 5 0.000 0.012 0.000 (0.976 to 1.026) GCST90274817 Interleukin-8 7 0.000 0.015 0.999 (0.976 to 1.029) GCST90274818 Latkernai inhibitory factor 3 -0.002 0.016 0.999 (0.958 to 1.029) GCST90274820 Leukernai inhibitory factor receptor 5 -0.007 0.016 0.993 (0.958 to 1.029) GCST90274822 Monocycle chemoattractart protein -1 5 -0.007 0.014 0.998 (0.958 to 1.029) GCST90274822 Monocycle chemoattractart protein -3 7 -0.008 0.014 0.998 (0.955 to 1.019) GCST90274825 Macocycle chemoattractart protein -4 5 -0.012 0.017 0.998 (0.955 to 1.019) GCST90274826 Macocycle chemoattractart protein -3 7 -0.008 0.014 0.998 (0.955 to 1.019) GCST90274828 Macrocycle chemoattractart protein -3 5 -0.015 0.016 0.998 (0.957 to 1.05) GCST90274828 </td <td>GCST90274814</td> <td>Interleukin-5</td> <td>7</td> <td>0.003</td> <td>0.014</td> <td>1.003 (0.976 to 1.031)</td> <td></td> <td>0.829</td>	GCST90274814	Interleukin-5	7	0.003	0.014	1.003 (0.976 to 1.031)		0.829
GCST90274816 Interleukin7 5 -0.005 0.015 0.0968 (b 1.026)	GCST90274815	Interleukin-6	7	0.000	0.013	1.000 (0.976 to 1.026)		0.986
GCST90274817 Interlevien-6 7 0.000 0.012 1.000 (0.976 to 1.025) GCST90274819 Lattercy-associated peptide transforming growth factor beta 1 6 0.000 0.016 0.999 (0.970 to 1.029) GCST90274819 Leukemia inhibitory factor receptor 5 -0.007 0.016 0.998 (0.985 to 1.029) GCST90274822 Monocycle chemoattractart protein-1 5 0.000 0.014 0.998 (0.985 to 1.029) GCST90274822 Monocycle chemoattractart protein-3 7 0.000 0.014 0.999 (0.970 to 1.026) GCST90274824 Monocycle chemoattractart protein-3 7 0.000 0.011 0.099 (0.955 to 1.022) GCST90274825 Macrocycle chemoattractart protein-4 5 -0.016 0.016 1.016 (0.986 to 1.042) GCST90274825 Macrocycle chemoattractart protein-4 5 -0.016 0.016 1.016 (0.986 to 1.042) GCST90274825 Macrocycle chemoattractart protein-3 5 -0.016 0.011 1.007 (0.981 to 1.044) GCST90274825 Macrocycle chemoattractart protein -2 -0.007 0.110 0.996 (0.975 to 1.014)	GCST90274816	Interleukin-7	5	-0.005	0.015	0.995 (0.966 to 1.026)		0.767
GCST90274818 Laterxy-associated peptide transforming growth flador beta 16 -0.000 0.015 0.999 (0.958 to 1.029) GCST90274812 Leukemia inhibitory factor receptor 5 -0.007 0.016 0.998 (0.958 to 1.024) GCST90274821 Monocyte chemoattractant protein-1 5 0.001 0.014 0.998 (0.958 to 1.024) GCST90274822 Monocyte chemoattractant protein-2 6 -0.002 0.014 0.998 (0.958 to 1.024) GCST90274823 Monocyte chemoattractant protein-3 7 -0.002 0.014 0.999 (0.956 to 1.019) GCST90274825 Monocyte chemoattractant protein-4 5 -0.012 0.017 0.098 (0.956 to 1.019) GCST90274826 Macrocyte chemoattractant protein-4 5 -0.010 0.112 0.998 (0.956 to 1.014) GCST90274828 Macrophage inflammatory protein 1a 6 0.007 0.103 1.007 (0.958 to 1.044) GCST90274828 Neurturin 4 0.003 0.114 0.998 (0.967 to 1.015) GCST90274828 Neurturin 6 -0.000 0.110 0.997 (0.958 to 1.024)	GCST90274817	Interleukin-8	7	0.000	0.012	1.000 (0.976 to 1.025)		0.992
GCS 1902/4819 Leukemia inhibitory factor receptor 5 -0.007 0.016 0.998 (0.988 to 1.039)	GCST90274818	Latency-associated peptide transforming growth factor beta	16	-0.001	0.015	0.999 (0.970 to 1.029)		0.931
GCS 1902/4820 Leuxema inhibitory factor receptor 5 -0.007 0.016 0.998 to 10.24) Image: Construction of the construction o	GCST90274819	Leukemia inhibitory factor	3	-0.002	0.021	0.998 (0.958 to 1.039)		0.908
Substrate/refer wonscyte formoattrature protein 1 5 0.001 1.001 (0.978 to 1.029) GCST90274823 Monocyte chemoattrature protein 2 6 -0.002 0.14 0.996 (0.976 to 1.026) GCST90274823 Monocyte chemoattrature protein-4 5 -0.012 0.17 0.986 to 1.019) GCST90274825 Macrocyte chemoattratater protein-4 5 -0.012 0.17 0.986 to 1.048) GCST90274825 Macrocyte page inflammatory protein 1a 6 0.007 0.13 1.007 (0.981 to 1.034) GCST90274828 Matrix metalloproteinase-10 7 -0.010 0.101 0.999 (0.967 to 1.015) GCST90274828 Neurutrin 4 0.003 0.011 0.997 (0.957 to 1.014) GCST90274828 Neurutrin 6 -0.009 0.014 0.997 to 1.014) GCST90274829 Neurutrin 5 -0.006 0.016 0.994 to 1.044) GCST90274831 Oncostatin-M 6 -0.009 0.014 0.997 to 1.014) GCST90274832 Steme cell factor 5 -0.008 0.016 <td>GCST90274820</td> <td>Leukemia inhibitory factor receptor</td> <td>5</td> <td>-0.007</td> <td>0.016</td> <td>0.993 (0.963 to 1.024)</td> <td></td> <td>0.639</td>	GCST90274820	Leukemia inhibitory factor receptor	5	-0.007	0.016	0.993 (0.963 to 1.024)		0.639
Super sector Number of the informating protein 2 0 -0.002 0.011 0.0199 Image of the informating protein 2 0 -0.008 0.014 0.0992 0.0955 1.020 Image of the informating protein 2 0 -0.008 0.014 0.0992 0.0955 1.020 Image of the informating protein 2 0.007 0.016 0.016 0.017 0.086 0.021 Image of the informating protein 2 0.007 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.021 0.090 0.022 Image of the informating protein 2 0.007 0.016 0.016 0.016 0.016 0.021 0.010 0.021	GCS190274821	Monocyte chemoattractant protein-1	5	0.001	0.014	1.001 (0.973 to 1.029)		0.957
CGCS190274825 Manocycle fundamina potentry 7 -0.012 0.011 0.028 (0.955 to 1.0.97) CGCS190274825 Macophage inflammatory protein 1a 6 0.007 0.018 (0.955 to 1.0.49) CGCS190274825 Matrix metalloproteinase-10 7 -0.010 0.017 (0.986 to 1.0.49) GGS190274825 Matrix metalloproteinase-10 7 -0.016 0.012 0.990 (0.967 to 1.015) GGS190274828 Neurturin 4 0.003 0.022 1.003 (0.956 to 1.0.49) GGS190274828 Neururin 4 0.003 0.021 0.980 (0.967 to 1.0.15) GGS190274820 Oncostatin-M 6 -0.007 0.110 0.977 (0.975 to 1.019) GGS190274823 Oncostatin-M 6 -0.008 0.016 0.992 (0.968 to 1.0.20) GGS190274833 Steme cell factor 5 -0.008 0.016 0.992 (0.968 to 1.0.24) GGS190274835 Signaling hymphocytic activation molecule 4 0.007 0.101 0.096 (0.968 to 1.0.24) GGS190274835 Signaling hymphocytic activation molecule 5 -0.016 <td>GCST90274822</td> <td>Monocyte chemoattractant protein 2</td> <td>7</td> <td>-0.002</td> <td>0.014</td> <td>0.992 (0.965 to 1.026)</td> <td></td> <td>0.882</td>	GCST90274822	Monocyte chemoattractant protein 2	7	-0.002	0.014	0.992 (0.965 to 1.026)		0.882
CGST90274826 Matrophage inflammatory protein 1a 6 0.007 0.018 0.004	GCST90274824	Monocyte chemoattractant protein=3	5	-0.008	0.017	0.988 (0.955 to 1.019)		0.496
GCS19027482 Matrix metalloproteinase-10 5 0.016 0.027 0.003 0.020 0.003 0.020 0.004 0.016 0.0275 0.109 0.016 0.0275 0.109 0.016 0.0275 0.109 0.016 0.0275 0.109 0.016 0.0275 0.016 0.0275 0.016 0.029 0.024 1 - - 0.016 0.029 0.024 - - - - 0.016 0.029 0.024 - - - - - 0.016 0.029	GCST90274825	Macrophage inflammatory protein 1a	6	0.007	0.013	1.007 (0.981 to 1.024)		0.593
GCST90274827 Matrix metalloproteinase-10 7 -0.010 0.012 0.999 (0.967 to 10.15) GCST90274828 Neurturin 4 0.003 0.020 1.005 (0.967 to 10.15) GCST90274828 Neurturin 4 0.003 0.020 1.005 (0.967 to 10.15) GCST90274828 Neurotrophin-3 5 -0.016 0.015 0.984 (0.955 to 10.19) GCST90274829 Oteoprotegerin 8 -0.000 0.011 0.997 (0.955 to 10.19) GCST90274830 Oncostatin-M 6 -0.000 0.014 0.998 (0.968 to 1.020) GCST90274833 StlRe-like protein 2 5 -0.008 0.016 0.999 (0.968 to 1.024) GCST90274835 Signaling hymphocytic activation molecule 4 0.007 0.110 0.997 (0.968 to 1.024) GCST90274835 Signaling hymphocytic activation molecule 4 0.007 0.110 0.996 (0.968 to 1.026) GCST90274835 Stathatoming protein 5 -0.016 0.16 0.996 (0.968 to 1.026)	GCST90274826	Matrix metalloproteinase-1	5	0.016	0.016	1.016 (0.986 to 1.048)		0.296
GCST90274828 Neurturin 4 0.003 0.024 1.003 (0.964 to 1.044) GCST90274829 Neurotrophin-3 5 -0.016 0.15 0.984 to 1.044) GCST90274829 Neurotrophin-3 5 -0.016 0.015 0.984 (0.955 to 1.014) GCST90274831 Oncostatin-M 6 -0.009 0.014 0.997 (0.955 to 1.019) GCST90274832 Programmed cell death 1 ligand 1 7 -0.007 0.011 0.999 (0.965 to 1.018) GCST90274833 Sitem cell factor 5 -0.008 0.016 0.992 (0.965 to 1.024) GCST90274835 Signaling lymphocytic activation molecule 4 0.007 0.019 0.994 (0.954 to 1.05) GCST90274835 Signaling rothin 5 -0.016 0.016 0.994 (0.954 to 1.05)	GCST90274827	Matrix metalloproteinase-10	7	-0.010	0.012	0.990 (0.967 to 1.015)		0.434
GCST90274829 Neurotrophin-3 5 -0.016 0.015 0.984 (0.955 to 1.014) GCST90274820 Oneostatin-M 6 -0.003 0.011 0.997 (0.975 to 1.019) GCST90274830 Oneostatin-M 6 -0.009 0.014 0.991 (0.955 to 1.018) GCST90274830 Stem cell death I ligand 1 7 -0.007 0.016 0.992 (0.968 to 1.020) GCST90274833 Stem cell death I ligand 1 7 -0.008 0.016 0.992 (0.968 to 1.020) GCST90274834 SiR2like protein 2 5 -0.008 0.016 0.992 (0.968 to 1.024) GCST90274835 SubtortantFersters 1.1 5 -0.016 0.016 0.994 (0.954 to 1.05) GCST90274837 STAM binding protein 5 -0.004 0.015 0.996 (0.964 to 1.026) GCST90274838 Transforming growth factor-alpha 6 0.000 0.013 1.000 (0.974 to 1.027) GCST90274843 Tumor necrosis factor receptor superfamily member 9 5 -0.040 0.015 0.996 (0.945 to 1.028) GCST90274844 TWHrelated activation-induce	GCST90274828	Neurturin	4	0.003	0.020	1.003 (0.964 to 1.044)		0.871
GCST90274830 Osteoprotegerin 8 -0.003 0.011 0.997 (9.975 to 1.019) GCST90274831 Oncostatin-M 6 -0.009 0.014 0.991 (0.965 to 1.018)	GCST90274829	Neurotrophin-3	5	-0.016	0.015	0.984 (0.955 to 1.014)		0.289
GGST90274831 Oncostatin-M 6 -0.009 0.014 0.991 (0.965 to 1.018)	GCST90274830	Osteoprotegerin	8	-0.003	0.011	0.997 (0.975 to 1.019)		0.781
GCST90224832 Programmed cell death 1 ligand 1 7 -0.007 0.013 0.983 (0.985 to 1.020)	GCST90274831	Oncostatin-M	6	-0.009	0.014	0.991 (0.965 to 1.018)		0.528
GCST90274833 Stem cell factor 5 -0.08 0.016 0.992 (0.961 to 1.024) GCST90274834 SilR2-like protein 2 5 -0.008 0.016 0.992 (0.961 to 1.024) GCST90274835 Signaling hymbrocytic activation molecule 4 0.007 0.019 0.992 (0.961 to 1.024) GCST90274835 Sugnaling hymbrocytic activation molecule 5 -0.016 0.161 0.984 (0.964 to 1.05) GCST90274837 StAM binding protein 5 -0.004 0.015 0.986 (0.966 to 1.026)	GCST90274832	Programmed cell death 1 ligand 1	7	-0.007	0.013	0.993 (0.968 to 1.020)		0.618
GCST90224834 SIR2-like protein 2 5 -0.008 0.016 0.992 (0.91 to 1.0.24)	GCST90274833	Stem cell factor	5	-0.008	0.016	0.992 (0.962 to 1.024)		0.620
GCST90274835 Signaling hymphocytic activation molecule 4 0.007 0.011 1.007 (0.99 to 1.046) GCST90274835 Suldtrandfreese 1A1 5 -0.016 0.016 0.996 (0.996 to 1.046) GCST90274837 STAM binding protein 5 -0.016 0.016 0.996 (0.996 to 1.026) GCST90274837 Transforming growth factor-alpha 6 0.000 0.013 1.000 (0.974 to 1.027) GCST90274843 Tumor necrosis factor 8 0.002 0.013 1.002 (0.974 to 1.028) GCST90274840 TWF-related actor receptor superfamily member 1 3 -0.004 0.017 0.996 (0.964 to 1.036) GCST90274843 TWF-related activation-induced cytokine 5 -0.004 0.017 0.996 (0.964 to 1.036) GCST90274843 TWF-related activation-induced cytokine 6 0.000 0.015 1.000 (0.974 to 1.027) GCST90274843 TWF-related activation-induced cytokine 5 0.004 0.016 1.004 (0.971 to 1.030) GCST90274844 TWF-related activation-induced cytokine 5 0.004 0.016 1.002 (0.978 to 1.028)<	GCST90274834	SIR2-like protein 2	5	-0.008	0.016	0.992 (0.961 to 1.024)		0.622
GCST90274836 Sulfortransferase 1A1 5 -0.016 0.016 0.984 (0.965 to 1.026) GCST90274837 STAM binding protein 5 -0.004 0.015 0.996 (0.966 to 1.026) GCST90274837 STAM binding protein 6 0.000 0.015 0.996 (0.966 to 1.026)	GCST90274835	Signaling lymphocytic activation molecule	4	0.007	0.019	1.007 (0.969 to 1.046)		0.727
GCST90274837 STAM binding protein 5 -0.004 0.015 0.969 (0.968 to 1.026)	GCST90274836	Sulfotransferase 1A1	5	-0.016	0.016	0.984 (0.954 to 1.015)		0.314
GCST90274838 Transforming growth factor-alpha 6 0.000 0.013 1.000 (0.974 to 1.027)	GCST90274837	STAM binding protein	5	-0.004	0.015	0.996 (0.966 to 1.026)		0.776
GCST90274839 Tumor necrosis factor 8 0.002 0.011 1.002 (0.976 to 1.028) GCST90274841 Tumor necrosis factor receptor superfamily member 9 5 -0.006 0.021 0.994 (0.954 to 1.028) GCST90274841 Tumor necrosis factor receptor superfamily member 9 5 -0.004 0.017 0.996 (0.964 to 1.029) GCST90274842 Tumor necrosis factor receptor superfamily member 14 7 -0.007 0.014 0.996 (0.967 to 1.021) GCST90274844 TNF-related activation-induced cytokine 5 0.004 0.015 1.000 (0.971 to 1.030) GCST90274844 TNF-related activation-induced cytokine 5 0.004 0.016 1.004 (0.973 to 1.035) GCST90274845 Tumor necrosis factor ligand superfamily member 12 7 0.003 0.013 1.002 (0.976 to 1.028) GCST90274844 Tumor necrosis factor ligand superfamily member 12 7 0.003 0.013 1.002 (0.976 to 1.028) GCST90274844 Urokinase-type plasminopen activator 6 -0.005 0.014 0.996 (0.986 to 1.029) GCST90274844 Urokinase-type plasminopen activator <t< td=""><td>GCST90274838</td><td>Transforming growth factor-alpha</td><td>6</td><td>0.000</td><td>0.013</td><td>1.000 (0.974 to 1.027)</td><td></td><td>0.992</td></t<>	GCST90274838	Transforming growth factor-alpha	6	0.000	0.013	1.000 (0.974 to 1.027)		0.992
GCST90274840 TNF-rolated activation-induced cytokine 5 -0.006 0.021 0.994 (0.984 to 1.036)	GCST90274839	Tumor necrosis factor	8	0.002	0.013	1.002 (0.976 to 1.028)		0.907
GCST90274841 Tumor necrosis factor receptor superfamily member 9 5 -0.004 0.017 0.966 (0.964 to 1.029)	GCST90274840	TNF-beta	3	-0.006	0.021	0.994 (0.954 to 1.036)	• • • •	0.783
GCS190274842 tumor necross tactor ligand superfamily member 14 7 -0.007 0.014 0.993 (0.976 to 1.021) GCS190274844 TNF-related activation-induced cytokine 5 0.004 0.016 1.004 (0.973 to 1.030) GCS190274845 TNF-related activation-induced cytokine 5 0.004 0.016 1.004 (0.973 to 1.035) GCS190274847 Trumic stromal lymphopoletin 8 0.002 0.11 1.002 (0.978 to 1.028) GCS190274844 Tumor necrossitactor ligand superfamily member 12 7 0.003 0.013 1.003 (0.978 to 1.028) GCS190274844 Urokinase-type plasminogen activator 6 -0.005 0.014 0.989 (0.988 to 1.023)	GCST90274841	iumor necrosis factor receptor superfamily member 9	5	-0.004	0.017	0.996 (0.964 to 1.029)		0.791
GCST90274844 TNF-related activation-induced cytokine 5 0.004 0.015 1.000 (0.971 to 1.030) GCST90274844 TNF-related activation-induced cytokine 5 0.004 0.016 1.004 (0.973 to 1.035) GCST90274845 Thymic stromal hymphopolein 8 0.002 0.013 1.002 (0.976 to 1.028) GCST90274845 Tumor necrosis factor ligand superfamily member 12 7 0.003 0.013 1.003 (0.978 to 1.028) GCST90274847 Urokinase-type plasminogen activator 6 -0.005 0.014 0.996 to 1.023)	GCS190274842	rumor necrosis factor ligand superfamily member 14	7	-0.007	0.014	0.993 (0.967 to 1.021)		0.635
GCS19027484 Tumor recosis factor ligand superfamily member 12 0.002 0.013 1.002 (0.978 to 1.028) GCS190274844 Tumor recosis factor ligand superfamily member 12 7 0.003 0.013 1.002 (0.978 to 1.028) GCS190274847 Urkinase-type plasminogen activator 6 -0.005 0.014 0.988 to 1.023)	GCS190274843	TNE-related apoptosis-inducing ligand	6	0.000	0.015	1.000 (0.971 to 1.030)		0.991
GCS190274847 Urokinase-type plasminopen advator 6 -0.005 0.011 1.002 (0.978 to 1.026) GCS190274847 Urokinase-type plasminopen advator 6 -0.005 0.014 0.998 to 1.029) GCS190274847 Urokinase-type plasminopen advator 6 -0.005 0.014 0.998 to 1.029)	GCST00274844	There is a cuvation-induced cytokine	5 8	0.004	0.016	1.004 (0.973 to 1.035)		0.821
GCST90274847 Urokinase-type plasminogen activator 6 -0.005 0.014 0.996 to 1.029) GCST90274847 Urokinase-type plasminogen activator 6 -0.005 0.014 0.996 to 1.029)	GCST00274845	Tumor necrosis factor ligand suppression member 10	7	0.002	0.013	1.002 (0.976 to 1.028)		0.897
COST0027-077 Growing accepting internation 0 = -0.003 0.014 0.395 (0.306 0 1.025)	GCST00274846	Linokinase_type plasminorep activator	6	_0.003	0.013	0.995 (0.968 to 1.029)		0.803
	GCST00274047	Vascular endothelial growth factor A	8	-0.005	0.014	0.003 (0.000 t0 1.023)		0.700
	0001302/4040	vascular endomenal grown idelof A	0	-0.007	0.012	0.350 (0.371 10 1.017)		0.5/9
0.95 1 1.05							0.95 1 1.05	

Figure 8. Forest plot of MR analysis of causal effects of glioblastoma on 90 inflammatory cytokines from EBI database (91 cytokines). MR = Mendelian randomization.

FGF21 promotes autophagy in LNCaP cells by inhibiting the phosphatidylinositol 3-kinase-Akt kinase-mammalian target of rapamycin (PI3K-Akt-mTOR) pathway. It also inhibits the migration and invasion of prostate cancer cells.^[50] However, its role in GBM has not been reported to date, and our study reveals for the first time the importance of FGF21 as a key factor in GBM. This finding provides a new outlook for the potential clinical application of FGF21 drugs for the treatment of GBM, which should be investigated in future studies.

TNF- β , also called lymphotoxin- α , a member of the tumor necrosis factor superfamily, is a cytokine produced by lymphocytes.[51,52] Although much is known about the importance of

GWAS ID	Outcome	nSNP	b	se	OR(95% CI)		pval
ebi-a-GCST004420	CTACK	3	0.010	0.044	1.010 (0.927 to 1.101)		0.816
ebi-a-GCST004421	beta-nerve growth factor	2	-0.006	0.043	0.994 (0.914 to 1.081)		0.892
ebi-a-GCST004423	Macrophage Migration Inhibitory Factor	3	-0.009	0.037	0.991 (0.921 to 1.066)	·	0.813
ebi-a-GCST004426	Tumor necrosis factor alpha	2	0.014	0.054	1.014 (0.912 to 1.127)		0.793
ebi-a-GCST004427	Stromal-cell-derived factor 1 alpha	2	0.014	0.038	1.014 (0.942 to 1.092)	· · · · · · · · · · · · · · · · · · ·	0.707
ebi-a-GCST004429	Stem cell factor	2	0.016	0.028	1.017 (0.963 to 1.073)	· · · · · · · · · · · · · · · · · · ·	0.553
ebi-a-GCST004430	Interleukin-16	2	0.001	0.043	1.001 (0.920 to 1.088)		0.987
ebi-a-GCST004432	Platelet-derived growth factor BB	4	-0.012	0.022	0.988 (0.946 to 1.031)	—	0.571
ebi-a-GCST004433	Macrophage inflammatory protein 1b	2	-0.022	0.035	0.978 (0.914 to 1.048)		0.533
ebi-a-GCST004435	Monokine induced by gamma interferon	4	0.004	0.033	1.004 (0.942 to 1.070)	·•	0.903
ebi-a-GCST004436	Macrophage colony stimulating factor	2	-0.007	0.065	0.993 (0.874 to 1.129)	⊢−−−−−	0.920
ebi-a-GCST004438	Monocyte chemoattractant protein-1	2	-0.002	0.035	0.998 (0.932 to 1.069)	·	0.960
ebi-a-GCST004439	Interleukin-12p70	2	-0.003	0.035	0.997 (0.931 to 1.067)	· · · · · · · · · · · · · · · · · · ·	0.925
ebi-a-GCST004441	Interleukin-18	2	-0.027	0.042	0.973 (0.896 to 1.057)	·	0.521
ebi-a-GCST004442	Interleukin-17	2	-0.010	0.037	0.990 (0.920 to 1.065)	·	0.786
ebi-a-GCST004446	Interleukin-6	3	-0.005	0.029	0.995 (0.939 to 1.054)		0.869
ebi-a-GCST004447	Interleukin-1-receptor antagonist	2	-0.013	0.054	0.987 (0.887 to 1.098)	·	0.805
ebi-a-GCST004449	Hepatocyte growth factor	3	-0.002	0.029	0.998 (0.943 to 1.057)	⊢	0.956
ebi-a-GCST004450	Interleukin-9	2	-0.015	0.053	0.986 (0.888 to 1.094)	••	0.784
ebi-a-GCST004451	Interleukin-7	2	0.012	0.055	1.012 (0.909 to 1.127)		0.826
ebi-a-GCST004452	Interleukin-5	2	0.002	0.055	1.002 (0.900 to 1.115)	++	0.974
ebi-a-GCST004453	Interleukin-4	4	0.000	0.026	1.000 (0.951 to 1.052)	⊢ +	0.994
ebi-a-GCST004454	Interleukin-2 receptor antagonist	4	0.013	0.033	1.013 (0.950 to 1.080)		0.697
ebi-a-GCST004455	Interleukin-2	2	-0.001	0.043	0.999 (0.918 to 1.087)	F	0.980
ebi-a-GCST004456	Interferon gamma	2	0.003	0.036	1.003 (0.934 to 1.076)	·	0.944
ebi-a-GCST004458	Granulocyte-colony stimulating factor	2	-0.024	0.036	0.976 (0.911 to 1.047)		0.503
ebi-a-GCST004459	Fibroblast growth factor basic	2	-0.032	0.036	0.969 (0.902 to 1.040)		0.384
ebi-a-GCST004460	Eotaxin	2	0.004	0.028	1.004 (0.950 to 1.061)		0.885
pval<0.05 was considered statistically sig	gnificant					0.95 1 1.05	
						protective factor risk factor	

Figure 9. Forest plot of MR analysis of causal effects of glioblastoma on 28 inflammatory cytokines from University of Bristol database (41 cytokines). MR = Mendelian randomization.

tumor necrosis factor alpha (TNF-α) in carcinogenesis, data on TNF-β are very limited. Similar to TNF-α, several studies have demonstrated that TNF-β can regulate proliferation, survival, invasion, migration, and colony formation in colorectal and ovarian cancers.^[53,54] The potential mechanism is that TNF-β activates the NF-κB signaling pathway to induce cancer cell proliferation and invasion.^[55-57] Several reports have shown that resveratrol blocks NF-κB activation, inhibits the cell cycle, and induces apoptosis in various tumors and colorectal cancer cells.^[58,59] Furthermore, Buhrmann demonstrated that Calebin A component of Curcuma longa, could inhibit TNF-β-induced NF-κB-mediated malignancy in CRC cells in vitro.^[60] Our findings reveal a causal relationship between TNF-β and GBM, and the use of TNF-β blockade strategies may be a potential treatment for GBM.

Chemokines, as cardinal regulators of immune cell trafficking, play a pivotal role in inflammation and orchestrate the intricate immune landscape within the tumor microenvironment.^[61] Analogous to their role in inflammation, chemokines mediate the recruitment of immune cells to the tumor niche, exerting both direct and indirect effects on tumor cells.^[62] MIP-1a (Chemokine (C-C motif) ligand 3 [CCL3])^[63] is a small secreted protein belonging to the C-C chemokine subfamily.^[64,65] Its impact on tumorigenesis is complex, exhibiting both protumorigenic and antitumorigenic effects, depending on the context. They can promote angiogenesis, tumor growth, and metastasis by attracting immunosuppressive cells or by stimulating the release of growth factors. Conversely, they can also recruit immune effector cells to the tumor microenvironment, potentially enhancing antitumor immunity. The chemotactic effect of CCL3 enhances antitumor immunity by promoting dendritic cell homing to the tumor microenvironment.[66] Additionally, CCL3mediated NK cell recruitment is crucial for further bolstering

the CD8-positive antitumor response.^[67] This study revealed the genetic correlation between MIP-1a and GBM, providing valuable insights for future research on the pathogenesis and pharmacological intervention of GBM.

The number of studies on the role of IL-10 in tumor diseases has gradually increased; however, its role in tumorigenesis and progression remains highly controversial.[68] Some studies have shown that IL-10 may also exert antitumor effects through certain mechanisms, such as promoting CD8+ T-cell proliferation and activation, and enhancing their antitumor ability.^[69] Li Tang et al demonstrated that CAR-T cells expressing IL-10 resist dysfunction and mediate durable clearance of solid and metastatic tumors, including colon, breast, melanoma, and pancreatic cancers.^[70] However, other studies have shown that elevated IL-10 levels suppress T cell-mediated killing of tumor cells and that blocking IL-10 in animal models improves the ability of the immune system to eliminate tumor cells.^[71,72] Additionally, research indicates that IL-10 can create an immunosuppressive environment by inhibiting the activation of antigen-presenting cells (APCs), leading to inhibitory effects on T cells and ultimately inducing tumor immune escape.[73] Our study demonstrated that higher IL-10 levels promote GBM development. However, the role of IL-10 in the tumor microenvironment is complex and multifaceted. However, further studies are required to elucidate the mechanism by which IL-10 promotes GBM growth.

In this study, we investigated the causal relationship between inflammatory cytokines and GBM using an integrated approach involving MR analysis and BWMR. MR analysis is favored for its superior ability to circumvent confounding factors and mitigate the impact of ethical biases compared with conventional epidemiological statistical methods, thereby enhancing the reliability of our findings over those of prior research. Furthermore, to bolster the robustness of our study outcomes, we selected the most recent and extensive GWAS data from Open GWAS databases, which feature the largest sample cohorts available.

Although this investigation offers valuable insights into the potential causal associations between inflammatory cytokines and GBM, it is essential to recognize several limitations. First, the sample size for the GBM GWAS data in our analysis was relatively modest, which may have compromised the statistical power of our MR approach. A smaller sample size can lead to wider confidence intervals and a reduced capacity to detect modest causal effects, potentially resulting in over- or underestimation of the effect sizes. To address the strength of the IVs, we employed the F-statistic, including only IVs with values exceeding 10 in subsequent analyses. Although this step enhances the reliability of our results by mitigating weak instrument bias, it does not fully eliminate the limitations imposed by the modest sample size. Consequently, these findings should be cautiously interpreted. Second, the broader threshold applied in our analysis could have increased the risk of false positives. Third, our findings should be interpreted with caution because of the complexity of cytokine signaling pathways and the limitations of our sample size. Validation in a larger cohort is essential to confirm these results. Fourth, all the GWAS data in this study were derived from European populations. Although this approach has minimized the confounding effects of population stratification, it also underscores the necessity of validating causal conclusions in other non-European cohorts, such as those of Asian descent. Finally, larger-scale GWAS and more comprehensive MR studies are required to enhance the robustness and applicability of our findings. Incorporating multi-omics data, such as proteomics and transcriptomics, could further clarify the mechanistic contributions of inflammatory cytokines in GBM, providing a stronger foundation for these preliminary observations.

5. Conclusion

In conclusion, the MR analysis revealed a causal relationship between specific inflammatory cytokines and GBM. Specifically, TNF- β and IL-10 have been identified as risk factors for GBM, whereas FGF21 and MIP-1a are recognized as protective factors against this disease. Notably, a reverse investigation revealed that GBM is not associated with elevated levels of inflammatory cytokines. These targeted inflammatory cytokines may provide a promising strategy for the treatment and prevention of GBM. Further research is needed to confirm these findings and elucidate the underlying biological mechanisms involved.

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Author contributions

Conceptualization: Feng Xuan, Tian Lv, Lin Zheng. Data curation: Feng Xuan, Mengjuan Ding. Formal analysis: Shengjian Yu, Mengjuan Ding. Investigation: Tian Lv, Lin Zheng. Methodology: Feng Xuan, Tian Lv, Lin Zheng. Project administration: Feng Xuan. Resources: Shengjian Yu, Mengjuan Ding. Software: Feng Xuan, Shengjian Yu, Mengjuan Ding. Supervision: Feng Xuan.

- Validation: Tian Lv, Lin Zheng, Shengjian Yu.
- Visualization: Feng Xuan, Shengjian Yu, Mengjuan Ding.

- Writing original draft: Feng Xuan, Tian Lv, Lin Zheng, Shengjian Yu, Mengjuan Ding.
- Writing review & editing: Feng Xuan.

References

- [1] Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: a review. JAMA. 2023;329:574–87.
- [2] Rong L, Li N, Zhang Z. Emerging therapies for glioblastoma: current state and future directions. J Exp Clin Cancer Res. 2022;41:142.
- [3] Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maint enance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA. 2017;318:2306–16.
- [4] Alexander BM, Cloughesy TF. Adult glioblastoma. J Clin Oncol. 2017;35:2402–9.
- [5] Romo CG, Piotrowski AF, Campian JL, et al. Clinical, histological, and molecular features of gliomas in adults with neurofibromatosis type 1. Neuro Oncol. 2023;25:1474–86.
- [6] Poumeaud F, Valentin T, Vande Perre P, et al. Special features of sarcomas developed in patients with Lynch syndrome: a systematic review. Crit Rev Oncol Hematol. 2023;188:104055.
- [7] Smith CJ, Perfetti TA, Chokshi C, Venugopal C, Ashford JW, Singh SK. Risk factors for glioblastoma are shared by other brain tumor types. Hum Exp Toxicol. 2024;43:9603271241241796.
- [8] Lan T, Chen L, Wei X. Inflammatory cytokines in cancer: comprehensive understanding and clin ical progress in gene therapy. Cells. 2021;10:100.
- [9] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539–45.
- [10] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using obser vational data. J Am Soc Nephrol. 2016;27:3253–65.
- [11] Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epide miological studies. Hum Mol Genet. 2014;23:R89–98.
- [12] Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. Nat Rev Methods Primers. 2022;2:6.
- [13] Ahola-Olli AV, Würtz P, Havulinna AS, et al. Genome-wide association study identifies 27 loci influencing concentra tions of circulating cytokines and growth factors. Am J Hum Genet. 2017;100:40–50.
- [14] Zhao JH, Stacey D, Eriksson N, et al. Genetics of circulating inflammatory proteins identifies drivers of im mune-mediated disease risk and therapeutic targets. Nat Immunol. 2023;24:1540–51.
- [15] Widding-Havneraas T, Zachrisson HD. A gentle introduction to instrumental variables. J Clin Epidemiol. 2022;149:203–5.
- [16] Palmer TM, Lawlor DA, Harbord RM, et al. Using multiple genetic variants as instrumental variables for modifiab le risk factors. Stat Methods Med Res. 2012;21:223–42.
- [17] Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. JAMA. 2017;318:1925–6.
- [18] Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology U sing mendelian randomization: the STROBE-MR statement. JAMA. 2021;326:1614–21.
- [19] Chen X, Zhang S, Wu X, Lei Y, Lei B, Zhao Z. Inflammatory cytokines and oral lichen planus: a Mendelian randomizati on study. Front Immunol. 2024;15:1332317.
- [20] Lin SH, Brown DW, Machiela MJ. LDtrait: an online tool for identifying published phenotype associations in linkage disequilibrium. Cancer Res. 2020;80:3443–6.
- [21] Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40:755–764.
- [22] Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44:512–25.
- [23] Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40:304–14.
- [24] Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG; EPIC- InterAct Consortium. Using published data in Mendelian randomization: a blueprint for effic ient identification of causal risk factors. Eur J Epidemiol. 2015;30:543–52.
- [25] Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37:658–65.

- [26] Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46:1985–98.
- [27] Xue H, Shen X, Pan W. Constrained maximum likelihood-based Mendelian randomization robust to both correlated and uncorrelated pleiotropic effects. Am J Hum Genet. 2021;108:1251–69.
- [28] Yu K, Chen X-F, Guo J, et al. Assessment of bidirectional relationships between brain imaging-derive d phenotypes and stroke: a Mendelian randomization study. BMC Med. 2023;21:271.
- [29] Zhao J, Ming J, Hu X, Chen G, Liu J, Yang C. Bayesian weighted Mendelian randomization for causal inference based on summary statistics. Bioinformatics. 2020;36:1501–8.
- [30] Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and disea ses. Nat Genet. 2018;50:693–8.
- [31] Bowden J, Spiller W, Del Greco MF, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial r egression. Int J Epidemiol. 2018;47:2100.
- [32] Imran TF, Khan AA, Has P, et al. Proprotein convertase subtilisn/kexin type 9 inhibitors and small inter rfering RNA therapy for cardiovascular risk reduction: a systematic review and meta-analysis. PLoS One. 2023;18:e0295359.
- [33] Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther. 2021;221:107753.
- [34] Jiang X, Wang J, Deng X, et al. The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res. 2020;39:204.
- [35] Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity. 2019;51:27–41.
- [36] Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. Nat Rev Clin Oncol. 2022;19:237–53.
- [37] Li S, Xu Y, Zhang Y, et al. Mendelian randomization analyses of genetically predicted circulating levels of cytokines with risk of breast cancer. npj Precis Oncol. 2020;4:25.
- [38] Bouras E, Karhunen V, Gill D, et al. Circulating inflammatory cytokines and risk of five cancers: a Mendeli an randomization analysis. BMC Med. 2022;20:3.
- [39] Yu J, Fu L, Zhang Z, et al. Causal relationships between circulating inflammatory cytokines and di ffuse large B cell lymphoma: a bidirectional Mendelian randomization s tudy. Clin Exp Med. 2023;23:4585–95.
- [40] Ma M, Zheng Z, Li J, He Y, Kang W, Ye X. Association between the gut microbiota, inflammatory factors, and colo rectal cancer: evidence from Mendelian randomization analysis. Front Microbiol. 2024;15:1309111.
- [41] Lu W, Li X, Luo Y. FGF21 in obesity and cancer: New insights. Cancer Lett. 2021;499:5–13.
- [42] Sui Y, Chen J. Hepatic FGF21: its emerging role in inter-organ crosstalk and cancers. Int J Biol Sci. 2022;18:5928–42.
- [43] Yang C, Lu W, Lin T, et al. Activation of Liver FGF21 in hepatocarcinogenesis and during hepatic s tress. BMC Gastroenterol. 2013;13:67.
- [44] Singhal G, Kumar G, Chan S, et al. Deficiency of fibroblast growth factor 21 (FGF21) promotes hepatocellu lar carcinoma (HCC) in mice on a long term obesogenic diet. Mol Metab. 2018;13:56–66.
- [45] Hu Y, Liu H-X, Jena PK, Sheng L, Ali MR, Wan Y-JY. *miR-22* inhibition reduces hepatic steatosis via FGF21 and FGFR1 induction. JHEP Rep. 2020;2:100093.
- [46] Kim J, Lee S, Lee M-S. Suppressive effect of autocrine FGF21 on autophagy-deficient hepatic T umorigenesis. Front Oncol. 2022;12:832804.
- [47] Yu X, Li Y, Jiang G, et al. FGF21 promotes non-small cell lung cancer progression by SIRT1/PI3K/AK T signaling. Life Sci. 2021;269:118875.
- [48] Kang YE, Kim JT, Lim MA, et al. Association between circulating fibroblast growth factor 21 and aggres siveness in thyroid cancer. Cancers (Basel). 2019;11:1154.
- [49] Zhong Q, Wang L, Cheng M, Yang H. Fibroblast growth factor 21 is related to cisplatin resistance in ovar ian cancer. Chin Med J (Engl). 2022;135:1500–2.

- [50] Dai H, Hu W, Zhang L, et al. FGF21 facilitates autophagy in prostate cancer cells by inhibiting the PI3K-Akt-mTOR signaling pathway. Cell Death Dis. 2021;12:303.
- [51] Aggarwal BB, Kohr WJ, Hass PE, et al. Human tumor necrosis factor. Production, purification, and characterization. J Biol Chem. 1985;260:2345–54.
- [52] Aggarwal BB, Moffat B, Harkins RN. Human lymphotoxin. Production by a lymphoblastoid cell line, purificat ion, and initial characterization. J Biol Chem. 1984;259:686–91.
- [53] Lau T-S, Chung TK-H, Cheung T-H, et al. Cancer cell-derived lymphotoxin mediates reciprocal tumour-stromal int eractions in human ovarian cancer by inducing CXCL11 in fibroblasts. J Pathol. 2014;232:43–56.
- [54] Buhrmann C, Yazdi M, Popper B, et al. Resveratrol chemosensitizes TNF-β-induced survival of 5-FU-treated colorectal cancer cells. Nutrients. 2018;10:888.
- [55] Bharti AC, Aggarwal BB. Chemopreventive agents induce suppression of nuclear factor-kappaB leading to chemosensitization. Ann N Y Acad Sci. 2002;973:392–5.
- [56] Dejardin E, Droin NM, Delhase M, et al. The lymphotoxin-beta receptor induces different patterns of gene expre ssion via two NF-kappaB pathways. Immunity. 2002;17:525–35.
- [57] Müller JR, Siebenlist U. Lymphotoxin beta receptor induces sequential activation of distinct NF -kappa B factors via separate signaling pathways. J Biol Chem. 2003;278:12006–12.
- [58] Buhrmann C, Shayan P, Kraehe P, Popper B, Goel A, Shakibaei M. Resveratrol induces chemosensitization to 5-fluorouracil through up-re gulation of intercellular junctions, Epithelial-to-mesenchymal transit ion and apoptosis in colorectal cancer. Biochem Pharmacol. 2015;98:51–68.
- [59] Buhrmann C, Shayan P, Goel A, Shakibaei M. Resveratrol regulates colorectal cancer cell invasion by modulation of focal adhesion molecules. Nutrients. 2017;9:1073.
- [60] Buhrmann C, Popper B, Kunnumakkara AB, Aggarwal BB, Shakibaei M. Evidence that calebin A, a component of curcuma longa suppresse s NF-B mediated proliferation, invasion and metastasis of human colore ctal cancer induced by TNF-β (lymphotoxin). Nutrients. 2019;11:2904.
- [61] Vilgelm AE, Richmond A. Chemokines modulate immune surveillance in tumorigenesis, metastasis, and response to immunotherapy. Front Immunol. 2019;10:333.
- [62] Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cance r immunotherapy. Nat Rev Immunol. 2017;17:559–72.
- [63] Ntanasis-Stathopoulos I, Fotiou D, Terpos E. CCL3 signaling in the tumor microenvironment. Adv Exp Med Biol. 2020;1231:13–21.
- [64] Maurer M, von Stebut E. Macrophage inflammatory protein-1. Int J Biochem Cell Biol. 2004;36:1882–6.
- [65] Menten P, Wuyts A, Van Damme J. Macrophage inflammatory protein-1. Cytokine Growth Factor Rev. 2002;13:455–81.
- [66] Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20:7–24.
- [67] Allen F, Bobanga ID, Rauhe P, et al. CCL3 augments tumor rejection and enhances CD8⁺ T cell infi ltration through NK and CD103⁺ dendritic cell recruitment V IA IFNγ. Oncoimmunology. 2017;7:e1393598.
- [68] Mannino MH, Zhu Z, Xiao H, Bai Q, Wakefield MR, Fang Y. The paradoxical role of IL-10 in immunity and cancer. Cancer Lett. 2015;367:103–7.
- [69] Ouyang W, O'Garra A. IL-10 Family cytokines IL-10 and IL-22: from basic science to clinical translation. Immunity. 2019;50:871–91.
- [70] Zhao Y, Chen J, Andreatta M, et al. IL-10-expressing CAR T cells resist dysfunction and mediate durable cl earance of solid tumors and metastases. Nat Biotechnol. 2024;42:1693–704.
- [71] Tanikawa T, Wilke CM, Kryczek I, et al. Interleukin-10 ablation promotes tumor development, growth, and metastasis. Cancer Res. 2012;72:420–9.
- [72] Mocellin S, Marincola F, Rossi CR, Nitti D, Lise M. The multifaceted relationship between IL-10 and adaptive immunity: putting together the pieces of a puzzle. Cytokine Growth Factor Rev. 2004;15:61–76.
- [73] Mittal SK, Roche PA. Suppression of antigen presentation by IL-10. Curr Opin Immunol. 2015;34:22–7.