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Integrative multi-omics and Mendelian randomization identify WWOX and THBS2 as potential therapeutic targets in mature T/NK-cell lymphoma

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Abstract

Background Mature T/NK-cell lymphoma is a highly heterogeneous, aggressive non-Hodgkin lymphoma. Due to the lack of specific therapeutic targets, treatment outcomes for patients with relapsed/refractory (R/R) disease are limited, and survival rates are low. Therefore, there is an urgent need to explore specific therapeutic targets and treatment strategies based on molecular mechanisms.

Methods Multi-omics data including genome-wide association study (GWAS), cis-expression quantitative trait loci (cis-eQTL), and cis-protein quantitative trait loci (cis-pQTL) were integrated through Mendelian Randomization (MR) and Bayesian colocalization analyses to identify and validate potential therapeutic targets. Summary-data-based MR (SMR) analysis strengthened causal inference, while cis-methylation quantitative trait loci (cis-mQTL) data integration elucidated genetic regulatory mechanisms. Transcriptome analysis assessed target biological functions, and phenome-wide MR evaluated the risk-benefit profile of target interventions. Drug prediction and molecular docking assessed therapeutic potential of these targets.

Results WWOX was identified as a protective factor and THBS2 as a risk factor, both with strong colocalization support. SMR analysis revealed close associations between WWOX expression, DNA methylation, and disease risk. Transcriptome analysis indicated that WWOX and THBS2 participate in tumor proliferation, invasion, and immune regulation. Phenome-wide MR analysis suggested that tissue-specific targeting is crucial for THBS2 inhibition. Drug prediction preliminarily validated the therapeutic potential of epigenetic regulatory drugs.

Conclusions This study identifies WWOX and THBS2 as potential therapeutic targets for mature T/NK-cell lymphoma. Treatment strategies based on epigenetic reprogramming and immune microenvironment regulation targeting WWOX and THBS2 provide new directions for precision therapy of this refractory lymphoma.

Keywords Mature T/NK-cell lymphoma, Mendelian randomization, Quantitative trait loci, Therapeutic target

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Introduction

Mature T/NK-cell lymphomas are a highly heterogeneous group of aggressive non-Hodgkin lymphomas originating from mature T cells or natural killer (NK) cells. Their pathological subtypes mainly include extranodal NK/T-cell lymphoma (ENKTCL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), systemic anaplastic large cell lymphoma (sALCL), angioimmunoblastic T-cell lymphoma (AITL), and primary cutaneous T-cell lymphomas, among others [1]. These diseases are often characterized by complex diagnosis, strong invasiveness, and poor prognosis. The efficacy of traditional chemotherapy regimens for patients with mature T/NK-cell lymphomas is typically unsatisfactory. Although optimizing drug regimens can improve the effective remission rate in initially treated patients, long-term survival data remain pessimistic for patients with relapsed/refractory (R/R) and advanced disease, with an average overall survival of approximately 6 months [1–3]. In recent years, treatment strategies for mature T/NK-cell lymphomas have progressively shifted from monotherapy with conventional chemotherapy to multimodal approaches, including targeted therapy, immunotherapy, and combination regimens, demonstrating promising potential for sustained disease control [4–6]. Although molecular targeted therapy and immunotherapy have achieved certain breakthroughs, a unified standardized treatment protocol has not yet been established, and their efficacy has not fully surpassed the survival bottleneck of traditional chemotherapy. Overall, individualized and precision treatment based on molecular typing and genetic variations represents the future trend. There is an urgent need for in-depth research into the biological heterogeneity and pathogenesis of mature T/NK-cell lymphomas to explore more effective treatment strategies.

Mendelian Randomization (MR) is an effective statistical method in genetic epidemiology that infers causality using genetic variants, primarily single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) [7]. This approach adheres to Mendel's laws of inheritance, where genetic variants are randomly allocated during gamete formation, a process independent of postnatal environmental factors, thereby effectively controlling for confounding effects of the environment. Genome-wide association studies (GWAS) are a research method based on high-throughput genotyping technologies, aimed at identifying genetic variants significantly associated with specific phenotypes (such as diseases, traits, biomarkers, etc.) through genome-wide screening of large-scale population cohorts [8]. With the rapid growth of GWAS data and the widespread availability of related genetic data, MR analysis, utilizing the genetic variants associated with risk factors revealed by these data, has been widely applied in various fields including disease risk factor

identification, drug efficacy evaluation, and drug target development [9, 10]. For instance, by employing genetic variants related to systolic blood pressure within multiple antihypertensive drug target gene loci as genetic proxies for the drugs, MR analysis has demonstrated a negative association between the effects of these antihypertensive drugs and the risk of coronary atherosclerotic heart disease and stroke [9].

Through large-scale GWAS studies of plasma protein abundances, it is possible to identify plasma protein quantitative trait loci (pQTL), thereby recognizing genetic variants associated with protein abundances [11]. Similarly, by conducting association analysis between genotype data and gene expression data to determine expression quantitative trait loci (eQTL), the regulatory relationship between genetic variants and gene expression can be identified [12]. By integrating multi-omics data such as eQTL, pQTL, and GWAS, and employing MR analysis for causal inference, it is possible to identify target molecules associated with disease risk [13]. This provides crucial evidence for elucidating the pathogenesis of diseases, formulating prevention and treatment strategies, as well as developing drug targets. On this basis, we integrate multi-omics data and MR analysis to explore potential therapeutic targets for mature T/NK-cell lymphomas, aiming to provide new insights for enriching treatment strategies.

Methods

Overall design

The workflow and methods of this study are shown in Fig. 1. We determined the druggable genes by aggregating data from the Drug-Gene Interaction database (DGIdb v5.0.8) (<https://dgidb.org/>) and the list of potentially druggable genes identified by Finan et al. [14, 15]. Based on the target restriction of druggable genes, we integrated the cis-eQTL of druggable genes and the cis-pQTL of druggable plasma proteins with the GWAS data of mature T/NK-cell lymphoma for MR analysis to identify potential therapeutic targets. Subsequently, Bayesian colocalization analysis was conducted on the significant results obtained from the MR analysis to further identify potential therapeutic targets with evidence of colocalization. In conjunction with the methylation quantitative trait loci (mQTL) data for the target genes, we performed multi-step Summary-data-based MR (SMR) analyses and heterogeneity in dependent instruments (HEIDI) tests to further investigate the genetic regulatory mechanisms and enhance the credibility of causal inference. Furthermore, we employed transcriptome data to analyze the expression levels of target genes in tumor tissues and their correlation with the levels of tumor immune cell infiltration. Additionally, we conducted gene set enrichment analysis (GSEA) to elucidate the biological

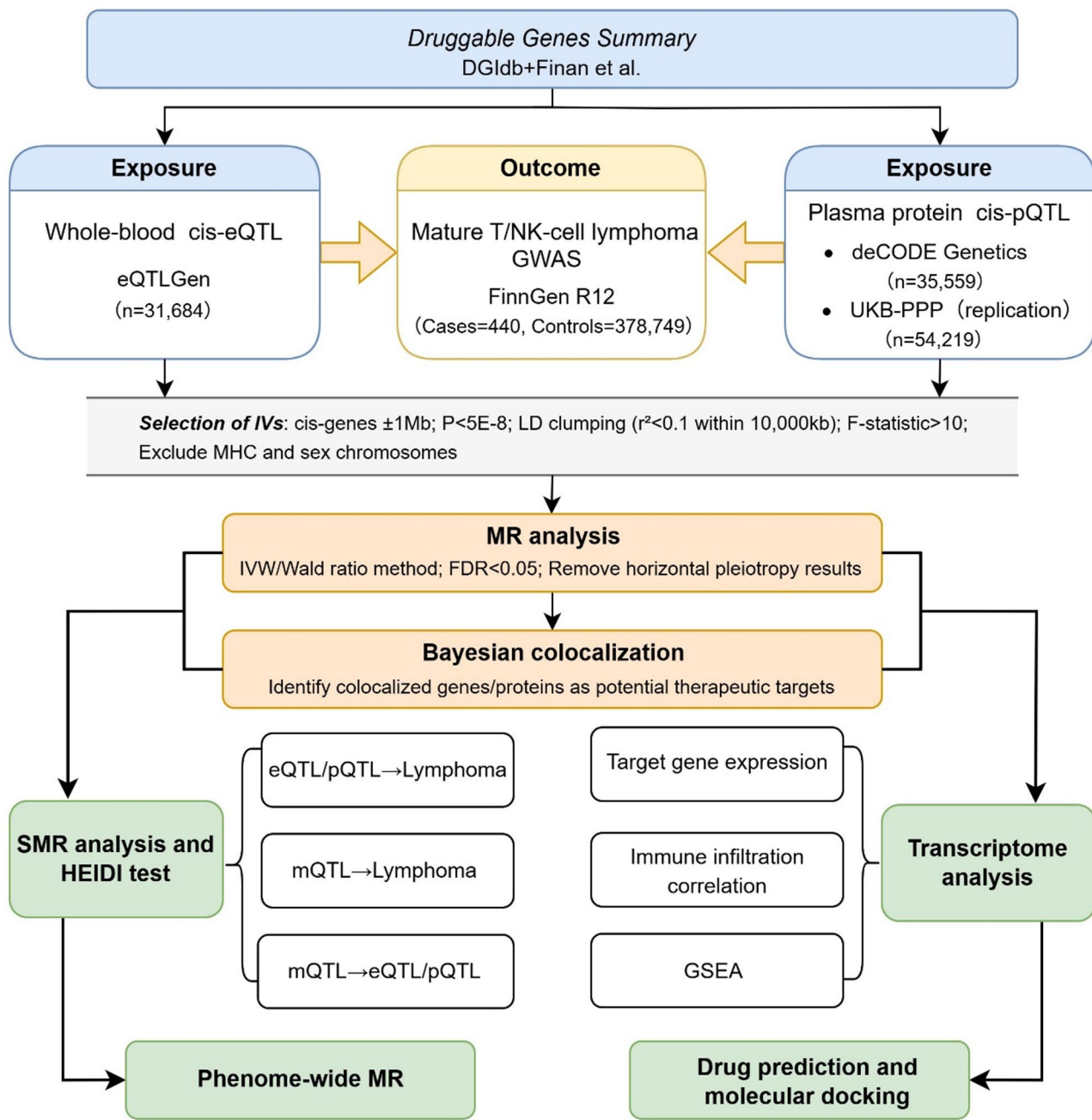


Fig. 1 Flowchart of the study design. cis-eQTL, cis-expression quantitative trait loci; cis-pQTL, cis-protein quantitative trait loci; GWAS, genome-wide association studies; IVs, instrumental variables; MR, Mendelian Randomization; SMR, Summary-data-based MR; HEIDI, heterogeneity in dependent instruments; mQTL, methylation quantitative trait loci; GSEA, gene set enrichment analysis

functions and potential pathogenic mechanisms of these target genes. Ultimately, the feasibility and development potential of potential therapeutic targets were further confirmed through phenome-wide MR analysis, drug prediction, and molecular docking. All data used in this study were derived from publicly available datasets, and the original studies have been approved by the respective ethics review committees. Therefore, our current analysis does not require further ethical approval.

Exposure data acquisition and genetic instrumental variable screening

We obtained whole-blood cis-eQTL data from the eQTLGen Consortium (<https://eqtlgen.org/>). These data were derived from a meta-analysis of blood samples from 31,684 healthy individuals of European ancestry across 37 cohorts, covering 16,987 genes, with cis positions within 1 Mb for each gene [16]. We obtained cis-pQTL summary data for 4,907 plasma proteins from the

deCODE Genetics (<https://www.decode.com/summarydata/>), which based on a large-scale GWAS of 35,559 Icelanders [11]. Additionally, we acquired cis-pQTL data for 2,923 plasma proteins from the UK Biobank Pharma Proteomics Project (UKB-PPP, <http://ukb-ppp.gwas.eu/>) for replication validation [17]. All cis-pQTL data were extracted within 1 Mb of each gene's genome position. Subsequently, we selected cis-eQTL and cis-pQTL data associated with druggable genes for MR analysis. To satisfy the core assumptions of MR analysis, SNPs were screened and filtered according to the following criteria: (1) strong association with the exposure ($P < 5E-8$); (2) linkage disequilibrium (LD) clumping using the 1000 Genomes Project as the reference panel, with a threshold of $R^2 < 0.1$ and a window size of 10,000 kb; (3) minor allele frequency (MAF) > 0.01 ; (4) exclusion of SNPs located in the major histocompatibility complex (MHC) region (chromosome 6: 28 Mb-34 Mb) and the sex chromosomes; (5) exclusion of weak IVs with F-statistics < 10 [18]. The F-statistic was calculated as follows:

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

$$R^2 = \frac{2 \times \beta^2 \times EAF \times (1 - EAF)}{2 \times \beta^2 \times EAF \times (1 - EAF) + 2 \times SE^2 \times N \times EAF \times (1 - EAF)}$$

Where R^2 represents the proportion of exposure variance explained by the instrumental variable, N is the sample size, k is the number of IVs, EAF is the effect allele frequency, and β represents the effect size of each instrumental variable on the exposure.

MR analysis

We obtained the GWAS summary data for mature T/NK-cell lymphoma from the FinnGen consortium R12 release (<https://www.finnngen.fi/en>) [19]. This dataset included 440 cases and 378,749 controls. Using the 'TwoSampleMR' R package, we conducted MR analyses treating cis-eQTLs and cis-pQTLs separately as exposures to assess causal effects on mature T/NK-cell lymphoma risk. The inverse variance weighted (IVW) method (Number of SNPs > 1) and the Wald ratio method (Number of SNPs = 1) were the primary MR methods. The Benjamini-Hochberg (BH) method was applied to correct the P-values of the MR analysis results to control the false discovery rate (FDR). A significant causal association between the exposure factor and the outcome variable was indicated when the FDR-corrected P-value was less than 0.05. Other MR analysis methods, such as MR-Egger, Simple Mode, Weighted Median, and Weighted Mode, were used as supplementary reference methods for assessing the causal effect. Additionally, the MR-Egger

regression intercept test was employed to assess horizontal pleiotropy [20]. A significance of the intercept ($P < 0.05$) indicated the presence of horizontal pleiotropy. Furthermore, the Cochran's Q test was used to evaluate the heterogeneity of the IVs [21]. In the presence of significant heterogeneity ($P < 0.05$), random-effects IVW was used for MR analysis; otherwise, fixed-effects IVW was employed.

Bayesian colocalization

Bayesian colocalization, based on a Bayesian statistical framework, assesses whether two genetic traits (e.g., QTL and GWAS data) within a specific genomic region share a common causal variant [22]. This method evaluates four competing models (H0–H4) by calculating the posterior probability (PP) for each: H0, neither trait is associated with any SNP in the region; H1/H2, only one of the two traits is associated with SNPs in the region; H3, both traits are associated with SNPs in the region but are driven by distinct causal variants; and H4, both traits are associated with SNPs in the region and share the same causal variant. Having identified druggable target eQTLs and pQTLs significantly associated with mature T/NK-cell lymphoma risk via MR analysis, we assessed colocalization between these QTLs and the lymphoma using the 'coloc' R package. SNPs were extracted from genomic regions spanning ± 500 kb around the lead SNP within 1 Mb of each gene. Bayesian colocalization analysis was then performed via the 'coloc.abf()' function to compute the posterior probability for hypothesis H4 (PPH4). With prior probabilities set to $p1 = 1E-4$, $p2 = 1E-4$, and $p12 = 1E-5$, we considered a PPH4 > 0.5 as evidence of colocalization, indicating a shared causal variant between the druggable target and mature T/NK-cell lymphoma.

SMR and HEIDI analysis

SMR analysis was employed to assess causal relationships by testing for pleiotropic associations between molecular phenotypes (e.g., gene expression, protein abundances, or DNA methylation) and complex traits [23, 24]. This method utilizes the HEIDI test to determine whether observed associations are attributable to pleiotropy of a shared causal variant or confounding due to genetic linkage disequilibrium. To supplementally validate the causal associations of potential therapeutic targets for mature T/NK-cell lymphoma, we performed SMR and HEIDI test. These targets had been previously identified through MR and colocalization analyses. All analyses were conducted using the "smr" command-line tool (v1.3.1-linux). A putative causal effect of genetically predicted expression/protein level on mature T/NK-cell lymphoma risk was supported if both a significant SMR association ($P < 0.05$) and a non-significant HEIDI test for heterogeneity ($P > 0.01$) were observed. Furthermore, to elucidate

the complex genetic regulatory mechanisms linking gene expression and protein abundances to disease, we obtained whole-blood mQTL data from the GoDMC database (<http://mqtl.db.godmc.org.uk/>) [25]. We subsequently performed multi-step SMR analyses using cis-mQTLs of candidate therapeutic target genes to evaluate putative causal relationships between DNA methylation levels and mature T/NK-cell lymphoma risk.

Functional enrichment and immune infiltration correlations of target genes

We obtained raw bulk RNA microarray data (in CEL format) for GSE19067 (29 mature T/NK-cell lymphoma samples vs. 14 normal controls) and GSE90597 (66 EBV⁺ T/NK-cell lymphoma cases) from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>). Background correction, normalization, and log₂ transformation were performed using the Robust Multichip Average (RMA) algorithm via the ‘affy’ package. For genes represented by multiple probes, the mean expression value was calculated using ‘edgeR::aveReps()’. In the GSE19067 dataset, the Wilcoxon rank-sum test was employed to compare the expression of target genes between the case and control samples. The CIBERSORT algorithm was used to quantify the infiltration levels of 22 immune cell types within the tumor samples, and the Spearman correlation between target gene expression and immune cell abundance was calculated [26]. Subsequently, genes were ranked based on their genome-wide correlation with the target genes, and GSEA was performed using the ‘GSEA()’ function from the ‘clusterProfiler’ R package, based on the MSigDB “Hallmark” (v2024.1) gene sets [27]. Furthermore, the analysis was extended to KEGG pathway enrichment using the ‘gseKEGG()’ function. The ‘GseaVis’ package was utilized for the visualization of the results.

Phenome-wide MR analysis

To evaluate the drug safety and repurposing potential of therapeutic targets, we conducted a phenome-wide MR analysis across 1,403 diseases and traits, excluding mature T/NK-cell lymphoma. This analysis utilized GWAS summary statistics from the UK Biobank, as aggregated by the Lee Lab team (<https://pheweb.org/UKB-SAIGE/phenotypes>). Given that drugs primarily act on proteins, we focused on proteins that had been identified as potential therapeutic targets. We employed cis-pQTL for these targets, provided by deCODE Genetics, as the exposure variables in our analysis to simulate the regulatory effects on them. To ensure sufficient statistical power, we restricted our analysis to phenotypes with more than 400 cases. We then performed a replication analysis using plasma protein cis-pQTLs from the UKB-PPP for the phenotypic outcomes that showed significant

causal associations. Phenotypes validated through replication may be potential on-target side effects of therapeutic interventions.

Drug prediction and molecular docking

The Comparative Toxicogenomics Database (CTD, <https://ctdbase.org/>), which compiles extensive interactions among chemicals, genes, phenotypes, and diseases, was used to identify chemicals that regulate the expression of our target gene. Given the need for cautious interpretation of cross-species data, our analysis was restricted to interactions documented in human tissues. From this refined list, we then screened for chemicals with potential antitumor effects to select therapeutic candidates. For the selected candidates, we downloaded their 3D small-molecule structural files from the PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and obtained the corresponding receptor protein structure from the Protein Data Bank (PDB, <https://www.rcsb.org/>). Prior to docking, the receptor structure was prepared using PyMOL (v3.1.0), in which water molecules, co-crystallized ligands, and metal ions were removed. Subsequently, both the receptor and ligands were processed with AutoDockTools (v1.5.7) to add polar hydrogens and assign Gasteiger charges. We then performed molecular docking simulations using AutoDock Vina (v1.1.2) to predict the binding conformations [28]. Finally, the resulting docking poses were visualized and analyzed for key interactions using PyMOL.

Results

Blood eQTL-MR and colocalization analysis identify WWOX as a potential therapeutic target in mature T/NK-cell lymphoma

Using drug-gene interaction data from the DGIdb database, we identified 5,012 genes with known or potential drug interactions. Additionally, we extracted 4,463 druggable genes from the study by Finan et al. [15]. By integrating data from DGIdb and Finan et al., we compiled a combined list of 6,888 druggable genes (Fig. 2A). We then intersected the cis-eQTL genes from whole blood samples in the eQTLGen Consortium with the druggable gene list. Following the effective screening of IVs, we ultimately identified 56,237 IVs corresponding to 3,605 genes for use in the subsequent MR analysis (Additional file 1: Table S1). We performed MR analysis using the IVW and Wald ratio methods. The initial analysis identified 59 genes with expression levels significantly associated (FDR-corrected $P < 0.05$) with the risk of mature T/NK-cell lymphoma. Subsequently, we applied the MR-Egger regression intercept test to account for horizontal pleiotropy ($P < 0.05$). After excluding associations that showed evidence of horizontal pleiotropy, we identified 54 causal relationships between blood gene expression and mature

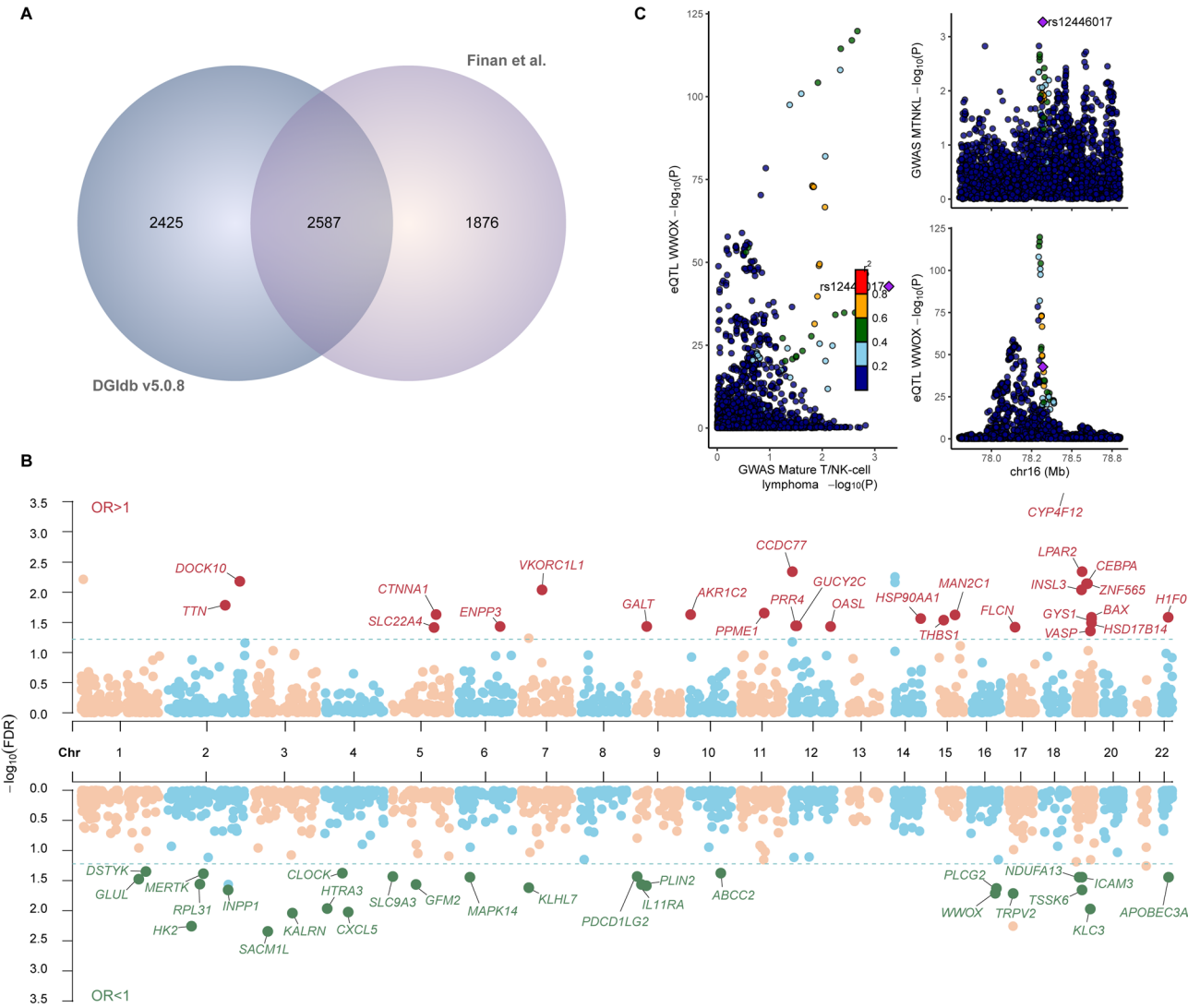


Fig. 2 Blood eQTL-MR and colocalization analysis identify WWOX as a potential therapeutic target in Mature T/NK-cell lymphoma. **(A)** The number of druggable genes summarized. **(B)** Blood eQTL-MR analysis reveals candidate therapeutic target genes for mature T/NK-cell lymphoma. **(C)** Bayesian colocalization of WWOX gene cis-eQTL with mature T/NK-cell lymphoma

T/NK-cell lymphoma risk (Table 1). Cochran’s Q test indicated significant heterogeneity among the IVs for the VASP gene ($P < 0.05$), and a random-effects IVW model was thus used for its analysis. Among the 54 candidate therapeutic targets, elevated genetically predicted expression of 27 genes was associated with increased risk of mature T/NK-cell lymphoma (odds ratio, $\text{OR} > 1$). Conversely, higher expression of the remaining 27 genes was linked to reduced risk ($\text{OR} < 1$), suggesting potential protective effects (Fig. 2B).

To investigate shared genetic mechanisms underlying mature T/NK-cell lymphoma and strengthen causal inference validity, we conducted Bayesian colocalization analysis for candidate target genes [29]. Among the 54 candidate targets, three genes were found to have $\text{PPH4} > 0.5$: WWOX (WW domain containing oxidoreductase;

PPH4 0.619), AKR1C2 (aldo-keto reductase family 1 member C2; PPH4 0.521), and ENPP3 (ectonucleotide pyrophosphatase/phosphodiesterase 3; PPH4 0.510) (Table 1). These findings suggest the presence of shared causal variants between these loci and mature T/NK-cell lymphoma. Given its stronger colocalization evidence ($\text{PPH4} > 0.6$), we prioritized WWOX as a therapeutic target candidate (Fig. 2C).

Plasma protein pQTL-MR and colocalization analysis identify THBS2 as a potential therapeutic target in mature T/NK-cell lymphoma

Directly linking protein expression levels to disease phenotypes enables more precise identification of potential drug targets. We thus performed pQTL-based MR

Table 1 Blood eQTL-MR and Bayesian colocalization analysis results in mature T/NK-cell lymphoma

Gene	nSNPs	OR (95%CI)	P-value	FDR	Pleiotropy P-value	Heterogeneity P-value	Colocalization PPH4
ABCC2	8	0.357 (0.198–0.646)	6.61E-04	0.042	0.276	0.489	0.069
AKR1C2	47	1.294 (1.131–1.480)	1.75E-04	0.023	0.362	0.479	0.522
APOBEC3A	27	0.734 (0.618–0.872)	4.35E-04	0.036	0.673	0.938	0.217
BAX	16	1.919 (1.356–2.714)	2.31E-04	0.026	0.521	0.349	0.065
CCDC77	38	1.456 (1.239–1.711)	5.03E-06	0.005	0.285	0.647	0.168
CEBPA	10	3.296 (1.896–5.732)	2.37E-05	0.007	0.503	0.732	0.054
CLOCK	15	0.543 (0.382–0.772)	6.65E-04	0.042	0.198	0.877	0.073
CTNNA1	64	1.214 (1.097–1.342)	1.62E-04	0.023	0.812	0.535	0.105
CXCL5	33	0.679 (0.564–0.817)	4.22E-05	0.010	0.245	0.877	0.216
CYP4F12	40	2.029 (1.632–2.522)	1.96E-10	< 0.001	0.859	0.183	0.453
DOCK10	34	1.464 (1.231–1.741)	1.64E-05	0.007	0.999	0.854	0.128
DSTYK	68	0.829 (0.744–0.924)	7.32E-04	0.045	0.827	0.992	0.114
ENPP3	5	3.428 (1.707–6.884)	5.33E-04	0.037	0.999	0.993	0.510
FLCN	19	1.632 (1.236–2.155)	5.58E-04	0.038	0.221	0.371	0.177
GALT	14	1.737 (1.271–2.375)	5.33E-04	0.037	0.350	0.632	0.124
GFM2	8	0.377 (0.223–0.637)	2.71E-04	0.027	0.556	0.563	0.272
GLUL	11	0.357 (0.202–0.630)	3.80E-04	0.033	0.818	0.120	0.060
GUCY2C	14	1.975 (1.349–2.893)	4.69E-04	0.036	0.926	0.900	0.367
GYS1	4	6.341 (2.335–17.218)	2.91E-04	0.028	0.660	0.639	0.358
H1FO	63	1.255 (1.112–1.416)	2.30E-04	0.026	0.569	0.996	0.310
HK2	42	0.716 (0.618–0.831)	1.02E-05	0.006	0.151	0.673	0.155
HSD17B14	11	1.740 (1.284–2.357)	3.57E-04	0.032	0.225	0.734	0.178
HSP90AA1	14	2.081 (1.404–3.083)	2.59E-04	0.027	0.113	0.400	0.164
HTRA3	4	0.242 (0.122–0.482)	5.42E-05	0.011	0.613	0.492	0.318
ICAM3	18	0.590 (0.439–0.792)	4.48E-04	0.036	0.095	0.338	0.112
IL11RA	28	0.667 (0.538–0.827)	2.21E-04	0.026	0.293	0.595	0.124
INPP1	19	0.575 (0.433–0.765)	1.44E-04	0.022	0.125	0.377	0.026
INSL3	20	1.644 (1.299–2.081)	3.54E-05	0.009	0.109	0.550	0.114
KALRN	9	0.315 (0.182–0.546)	3.80E-05	0.009	0.369	0.776	0.186
KLC3	14	0.415 (0.271–0.635)	5.04E-05	0.011	0.665	0.900	0.186
KLHL7	7	0.353 (0.204–0.611)	1.94E-04	0.024	0.447	0.342	0.183
LPAR2	41	1.485 (1.254–1.758)	4.50E-06	0.005	0.815	0.954	0.254
MAN2C1	67	1.228 (1.103–1.367)	1.85E-04	0.024	0.497	0.271	0.147
MAPK14	8	0.463 (0.300–0.713)	4.70E-04	0.036	0.569	0.775	0.056
MERTK	63	0.810 (0.718–0.914)	6.28E-04	0.041	0.984	0.429	0.448
NDUFA13	4	0.170 (0.063–0.458)	4.59E-04	0.036	0.510	0.647	0.269
OASL	41	1.398 (1.157–1.691)	5.33E-04	0.037	0.756	0.657	0.025
PDCD1LG2	9	0.549 (0.391–0.769)	5.03E-04	0.037	0.209	0.745	0.065
PLCG2	29	0.592 (0.451–0.779)	1.76E-04	0.023	0.626	0.847	0.048
PLIN2	44	0.729 (0.615–0.863)	2.57E-04	0.027	0.103	0.682	0.047
PPME1	2	32.325 (5.371–194.543)	1.47E-04	0.022		0.448	0.025
PRR4	39	1.389 (1.156–1.669)	4.43E-04	0.036	0.697	0.859	0.049
RPL31	17	0.630 (0.491–0.809)	2.91E-04	0.028	0.661	0.496	0.301
SACM1L	39	0.649 (0.539–0.781)	4.81E-06	0.005	0.506	0.982	0.088
SLC22A4	43	1.407 (1.158–1.708)	5.76E-04	0.038	0.157	0.438	0.042
SLC9A3	44	0.863 (0.794–0.938)	4.92E-04	0.037	0.713	0.901	0.035
THBS1	38	1.341 (1.143–1.573)	3.13E-04	0.029	0.524	0.994	0.026
TRPV2	9	0.317 (0.177–0.567)	1.07E-04	0.019	0.408	0.833	0.468
TSSK6	3	0.126 (0.043–0.366)	1.45E-04	0.022	0.647	0.754	0.269
TTN	3	25.895 (5.101–131.441)	8.64E-05	0.016	0.927	0.917	0.236
VASP	45	1.356 (1.137–1.617)	7.06E-04	0.044	0.256	0.013	0.195
VKORC1L1	20	1.805 (1.366–2.386)	3.28E-05	0.009	0.579	0.456	0.323

Table 1 (continued)

Gene	nSNPs	OR (95%CI)	P-value	FDR	Pleiotropy P-value	Heterogeneity P-value	Colocalization PPH4
WWOX	29	0.533 (0.388–0.734)	1.13E-04	0.019	0.163	0.677	0.619
ZNF565	14	2.308 (1.566–3.402)	2.39E-05	0.007	0.427	0.691	0.366

nSNPs, the number of single nucleotide polymorphisms used to estimate the causal effects; OR, odds ratio; CI, confidence interval; FDR, false discovery rate; PPH4, the posterior probability for hypothesis H4

Table 2 Plasma protein pQTL-MR and Bayesian colocalization analyses in mature T/NK-cell lymphoma

Protein	nSNPs	OR (95%CI)	P-value	FDR	Pleiotropy P-value	Heterogeneity P-value	Colocalization PPH4
CHIT1	112	1.210 (1.098–1.333)	1.19E-04	0.036	0.571	0.405	0.415
CXCL5	4	0.141 (0.052–0.384)	1.24E-04	0.036	0.538	0.692	0.212
FKBP7	35	0.583 (0.436–0.779)	2.73E-04	0.047	0.827	0.703	0.102
MMP8	12	0.377 (0.223–0.638)	2.80E-04	0.047	0.865	0.948	0.117
PCSK1	112	0.773 (0.681–0.877)	6.10E-05	0.036	0.545	0.754	0.335
SPON2	26	0.513 (0.361–0.730)	2.08E-04	0.047	0.143	0.614	0.113
THBS2	96	1.563 (1.360–1.797)	3.25E-10	<0.001	0.726	0.499	0.631

analysis to detect protein-level changes causally associated with mature T/NK-cell lymphoma and thereby uncover potential therapeutic targets. We intersected cis-pQTL plasma protein-coding genes from the deCODE Genetics with a list of druggable genes and screened for IVs using the method described above, ultimately identifying 38,646 IVs corresponding to 1,175 proteins for MR analysis (Additional file 1: Table S2). We identified seven plasma proteins causally associated with mature T/NK-cell lymphoma, following the selection of statistically significant MR results (FDR-corrected $P < 0.05$) and exclusion of proteins with horizontal pleiotropy ($P < 0.05$) (Table 2). Furthermore, no heterogeneity was detected among these significant associations through Cochran's Q test. Among the seven significantly associated proteins, THBS2 (thrombospondin 2) and CHIT1 (chitinase 1) had ORs > 1 , suggesting potential pro-tumorigenic effects. The remaining five proteins, including PCSK1 (proprotein convertase subtilisin/kexin type 1), CXCL5 (C-X-C motif chemokine ligand 5), FKBP7 (peptidyl-prolyl cis-trans isomerase FKBP7), SPON2 (spondin 2), and MMP8 (neutrophil collagenase), may exert protective effects against the development of mature T/NK-cell lymphoma (Fig. 3A). Additionally, the therapeutic target WWOX identified by eQTL-MR showed consistent significant causal association at the protein level (OR = 0.117, 95% confidence interval (CI): 0.024–0.559, $P = 7.2E-03$), but this association did not reach statistical significance after FDR correction (FDR-corrected $P = 0.160$).

To further enhance the reliability of causal associations, we conducted a replication analysis using plasma protein cis-pQTLs from the UKB-PPP for MR at the protein level. Applying the same screening strategy, we identified 31,991 IVs corresponding to 1,286 plasma proteins. After FDR correction and exclusion of horizontal pleiotropy, 13 plasma proteins showed significant causal associations with mature T/NK-cell lymphoma, with no heterogeneity

detected by Cochran's Q test (Additional file 1: Table S3). Among these, THBS2 (OR = 1.510, 95% CI: 1.215–1.878, FDR-corrected $P = 0.029$) and CHIT1 (OR = 1.328, 95% CI: 1.188–1.485, FDR-corrected $P = 4.15E-04$) were successfully replicated.

We performed Bayesian colocalization analysis on seven candidate therapeutic target proteins to investigate shared genetic variants with mature T/NK-cell lymphoma, thereby enhancing the robustness of causal inference. The analysis revealed substantial evidence for colocalization between THBS2 protein abundance and mature T/NK-cell lymphoma (PPH4 = 0.631), indicating a high probability that they share the same causal genetic variant (Fig. 3B). For further validation, THBS2 protein data were extracted from UKB-PPP and replicated the colocalization analysis, which similarly revealed high colocalization evidence (PPH4 0.645) (Fig. 3C). These results indicate that THBS2 protein may play a key role in the pathogenesis of mature T/NK-cell lymphoma and could be considered a potential therapeutic target.

SMR analysis of WWOX, THBS2, and their DNA methylation levels in mature T/NK-cell lymphoma

SMR analysis revealed that genetically predicted elevated expression of the WWOX gene was significantly associated with a reduced risk of mature T/NK-cell lymphoma ($P = 2.33E-03$, β -SMR = -1.082, HEIDI test $P > 0.01$). Further multi-step SMR analysis integrating cis-mQTL data revealed that the methylation levels of three CpG sites in the WWOX gene (cg10001715, cg00232445, and cg03216739) were associated with the risk of mature T/NK-cell lymphoma. Among these CpG sites, increased methylation at cg00232445 and cg03216739 was associated with a higher risk of mature T/NK-cell lymphoma and suppressed WWOX expression (Table 3; Fig. 4A and B). These findings support the hypothesis that methylation at specific CpG sites within the WWOX

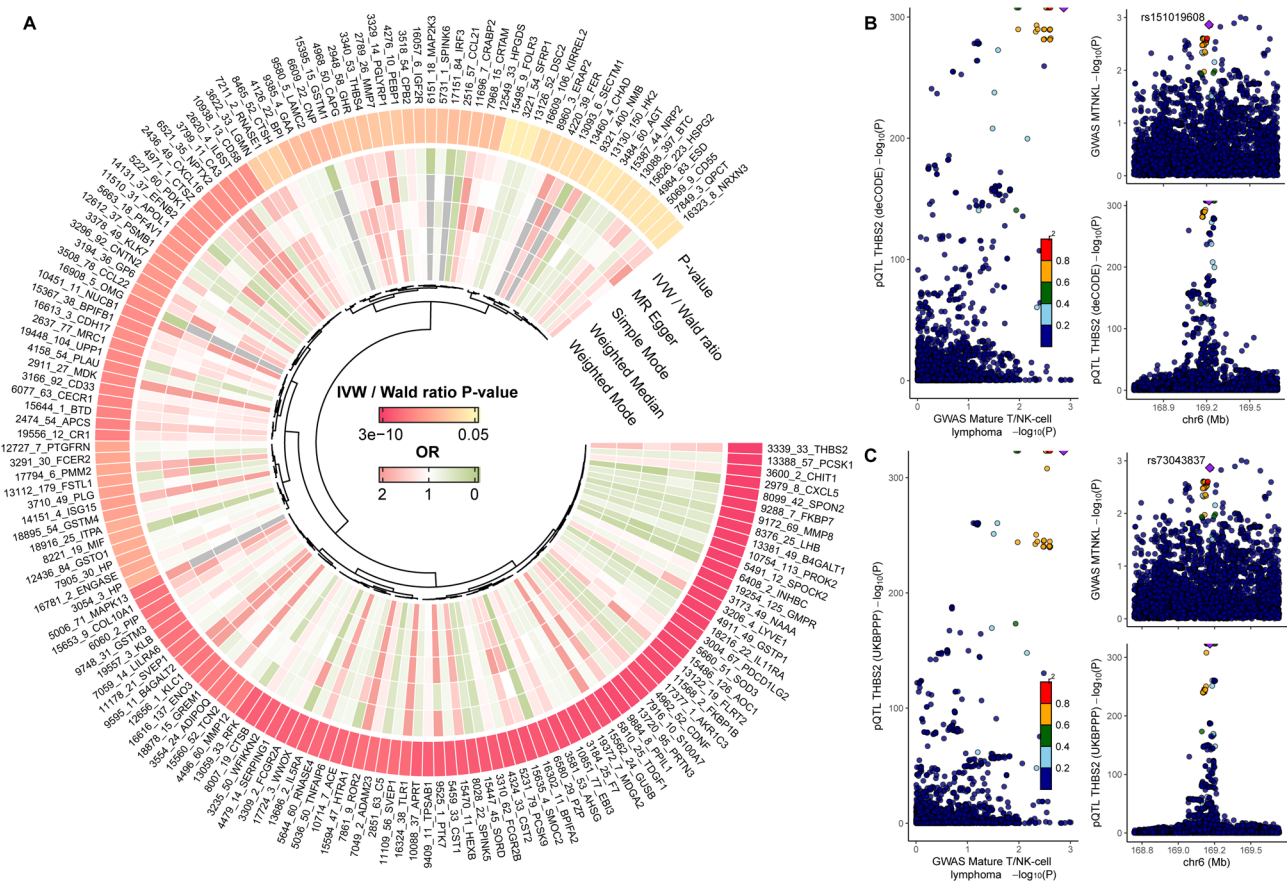


Fig. 3 Plasma Protein pQTL-MR and colocalization analysis identify THBS2 as a potential therapeutic target in Mature T/NK-cell lymphoma. **(A)** Plasma protein pQTL-MR analysis result visualization, outer circle shows the P-value significance of IVW/Wald ratio method, while inner circle displays the OR values of various MR analysis methods. **(B)** Bayesian colocalization of THBS2 cis-pQTL with mature T/NK-cell lymphoma using data from deCODE Genetics. **(C)** Replication validation of THBS2 cis-pQTL colocalization with mature T/NK-cell lymphoma using data from UKB-PPP

Table 3 Summary of SMR analysis results for integrated DNA methylation levels

Gene/protein	Exposure and outcome	CpG sites	β-SMR	P-SMR	P-HEIDI
WWOX	cis-eQTL→Lymphoma	/	-1.082	0.0023	0.268
	cis-mQTL→Lymphoma	cg10001715	0.379	0.0166	0.669
		cg00232445	1.360	0.0323	0.072
		cg03216739	1.972	0.0375	0.642
	cis-mQTL→cis-eQTL	cg10001715	-0.209	1.83E-27	1.92E-07
		cg00232445	-1.046	2.20E-20	0.047
		cg03216739	-0.593	1.93E-6	0.037
THBS2	cis-pQTL→Lymphoma	/	0.412	0.0014	0.389
	cis-mQTL→Lymphoma	cg25018403	1.029	0.0278	0.463
		cg21732383	-0.964	0.0290	0.558
		cg25631414	-0.245	0.0338	0.192
		cg13995916	0.527	0.0408	0.785
	cis-mQTL→cis-pQTL	cg25018403	2.063	1.20E-46	7.29E-31
		cg21732383	-1.007	1.11E-37	9.98E-15
		cg25631414	-0.442	5.11E-164	2.95E-150
		cg13995916	0.810	3.32E-75	1.67E-26

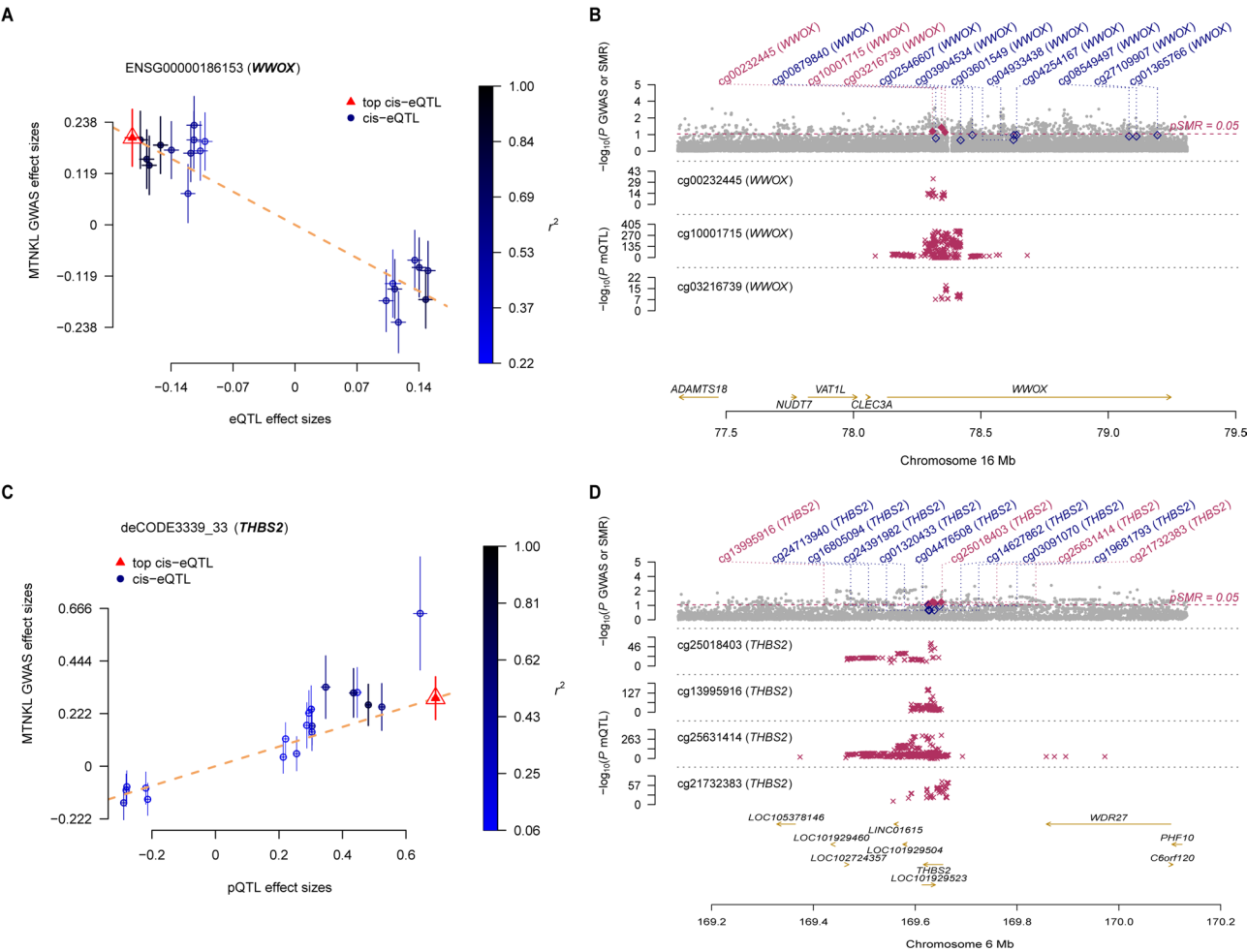


Fig. 4 SMR analysis of WWOX (A, B), THBS2 (C, D), and their DNA methylation levels in mature T/NK-cell lymphoma

gene promotes mature T/NK-cell-lymphoma by suppressing WWOX expression. SMR analysis of THBS2 showed that higher protein abundance was associated with an increased risk of mature T/NK-cell lymphoma ($P=1.41E-03$, β -SMR=0.412, HEIDI test $P>0.01$), aligning with prior MR findings. Methylation at four CpG sites in THBS2 (cg25018403, cg21732383, cg25631414, and cg13995916) was linked to mature T/NK-cell lymphoma risk (Table 3; Fig. 4C and D). However, the HEIDI test ($P<0.01$) rejected a direct causal effect of methylation at these CpG sites on THBS2 protein abundance. Further research is required to identify the causal variants mediating this association.

Immune infiltration and functional enrichment analysis of WWOX and THBS2

To assess the gene expression of potential therapeutic targets, we analyzed the GSE19067 dataset using the Wilcoxon rank-sum test and found that WWOX expression in lymphoma cells was significantly lower than in normal cells, while THBS2 expression was significantly

higher (Fig. 5A). We performed immune cell infiltration analysis based on the GSE90597 dataset to investigate the roles of WWOX and THBS2 in the tumor immune microenvironment. Using the CIBERSORT algorithm and Spearman's correlation analysis, we found that WWOX gene expression in T/NK-cell lymphoma was significantly positively correlated with CD8 T cell infiltration, while THBS2 gene expression was positively correlated with activated NK cell infiltration. Notably, WWOX and THBS2 show significant differences in M1 and M2 macrophage infiltration levels. Specifically, increased WWOX expression was associated with decreased M2 macrophage infiltration; conversely, increased THBS2 expression was associated with reduced M1 macrophage infiltration (Fig. 5B and C). These findings suggest that they may play distinct roles in regulating immune cell infiltration.

We performed single-gene GSEA for WWOX and THBS2 to investigate their biological functions in mature T/NK-cell lymphoma and the signaling pathways involved. In the GSE19067 dataset, enrichment

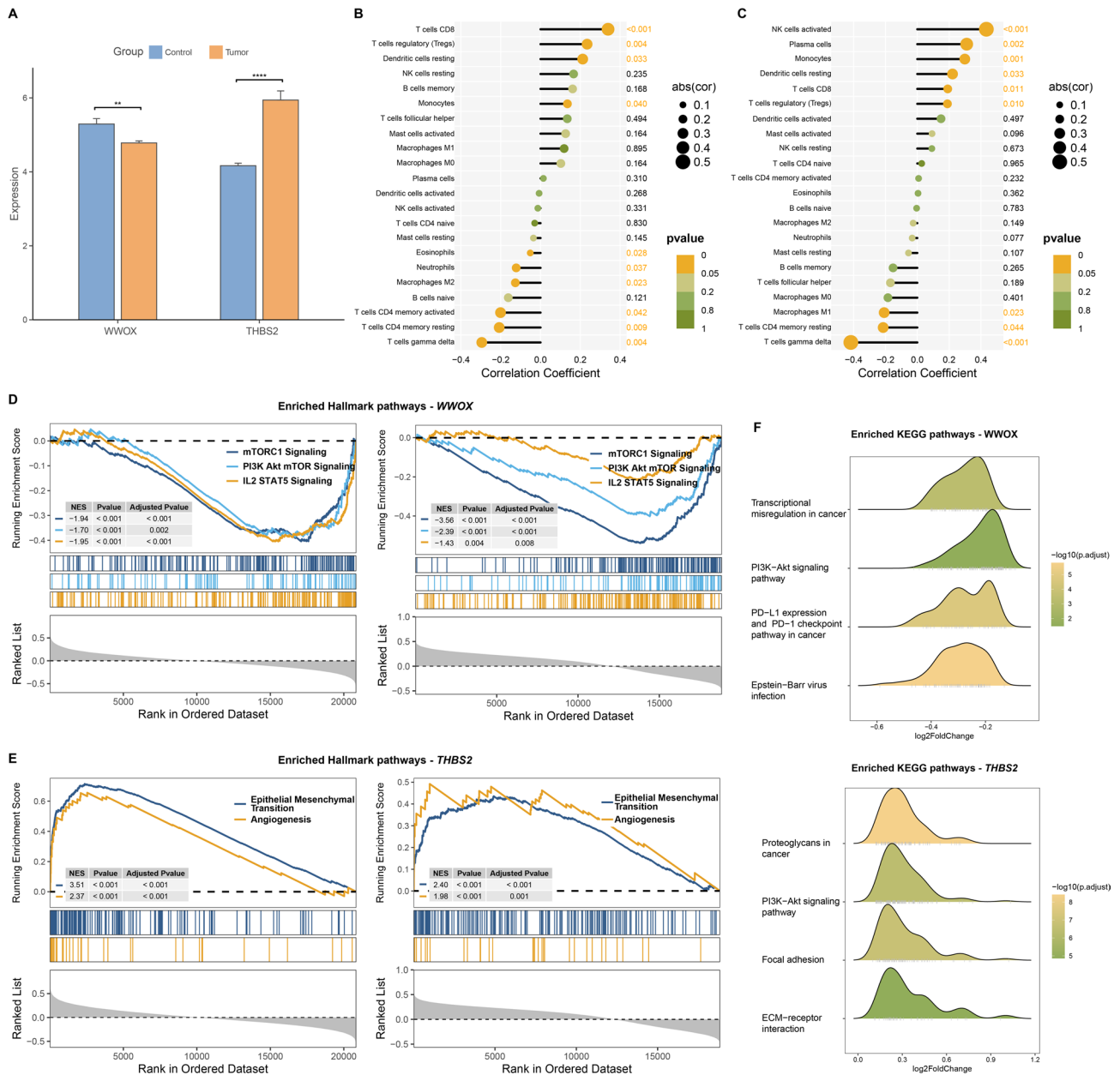


Fig. 5 Immune infiltration and functional enrichment analysis of WWOX and THBS2. **(A)** Expression of WWOX and THBS2 in mature T/NK-cell lymphoma. **(B-C)** Correlation between immune cell infiltration and gene expression: **(B)** WWOX; **(C)** THBS2. **(D-E)** Single-gene GSEA of WWOX **(D)** and THBS2 **(E)** in mature T/NK-cell lymphoma. Left panels: GSE19067 dataset; Right panels: GSE90597 validation dataset. **(F)** Single-gene GSEA of WWOX and THBS2 based on KEGG pathway analysis. In **(A)**, data are presented as mean $\pm$ SEM, and P-values were calculated by Wilcoxon rank-sum test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

analysis based on the “Hallmark gene set” revealed that gene sets associated with WWOX expression showed significant negative enrichment in the mTORC1 signaling pathway, PI3K/Akt/mTOR signaling pathway, and IL2/STAT5 signaling pathway (NES < -1 , FDR-corrected $P < 0.05$) (Fig. 5D). These results suggest that WWOX may suppress tumor progression by inhibiting cell proliferation-related signaling pathways. In contrast, gene sets associated with THBS2 expression were significantly

enriched in pathways such as epithelial-mesenchymal transition (EMT) and angiogenesis (NES > 1 , FDR-corrected $P < 0.05$), suggesting that THBS2 may mediate tumor invasion and metastasis (Fig. 5E). We validated these findings using GSEA on the GSE90597 dataset. Additionally, we performed KEGG-based GSEA to investigate the roles of WWOX and THBS2 in biological processes. The results showed that WWOX expression was significantly negatively correlated with the enrichment of

pathways such as transcriptional misregulation in cancer, PI3K/Akt signaling pathway, PD-1/L1 immune checkpoint, and EBV infection. In contrast, THBS2 expression was significantly positively correlated with the enrichment of pathways such as proteoglycans in cancer, PI3K/Akt signaling pathway, focal adhesion, and extracellular matrix receptor interaction (Fig. 5F). These findings further elucidate the distinct biological functions of WWOX and THBS2 in lymphoma pathogenesis.

Phenome-wide MR analysis of WWOX and THBS2 targeting effects

Using 1,403 phenotypic GWAS datasets from the Lee laboratory, we identified 853 phenotypes for MR analysis by excluding those with ≤ 400 cases and removing phenotypes including mature T/NK-cell lymphoma. We used cis-pQTLs for WWOX and THBS2 proteins from deCODE Genetics as exposure variables to evaluate the potential effects of targeting these proteins on other phenotypes. Following FDR correction for multiple testing, no significant causal associations were observed between WWOX and the 853 phenotypes, indicating that WWOX inhibition may not lead to widespread adverse effects (Fig. 6A; Additional file 1: Table S4). Replication was not feasible due to the absence of WWOX in the UKB-PPP cis-pQTL dataset. Additionally, THBS2 demonstrated significant causal associations with 99 phenotypes in deCODE data, 63 of which were successfully replicated in UKB-PPP (Additional file 1: Table S5). Focusing on strong effects ($OR > 1.2$ or $OR < 0.8$), we identified that higher THBS2 abundance increased risk for conditions such as salivary gland disease and psoriatic arthritis ($OR > 1.2$), suggesting protective effects of THBS2 inhibition. Conversely, lower THBS2 abundance was associated with higher risk for cellulitis of the trunk and iris diseases ($OR < 0.8$), implying potential adverse reactions associated with reduced THBS2 abundance (Fig. 6B). Collectively, THBS2 inhibition may have dual effects, underscoring the need for tissue-specific targeting strategies to mitigate these risks.

Screening and molecular docking analysis of anti-tumor compounds targeting WWOX and THBS2

Based on CTD chemical-gene interaction data and the causal effects of WWOX and THBS2 on mature T/NK-cell lymphoma pathogenesis, we screened for chemical compounds that potentially upregulate WWOX expression and downregulate THBS2 expression. The screening was further restricted to compounds exhibiting confirmed antitumor activity. The compounds potentially increasing WWOX expression include Vorinostat, Valproic Acid, Sunitinib, Jinfukang, and Arsenic Trioxide. Those potentially reducing THBS2 expression include Vorinostat, Valproic Acid, JQ1, Ifosfamide,

GSK1210151A, and Calcitriol (Additional file 1: Table S6). Except for the inorganic compound arsenic trioxide and the complex traditional Chinese medicine Jinfukang, all other drugs underwent molecular docking analysis with WWOX or THBS2 proteins (Fig. 7). Molecular docking results revealed that Vorinostat, Valproic Acid, and Sunitinib exhibited binding energies of -5.7 , -4.2 , and -6.5 kcal/mol with WWOX protein, respectively. All three compounds formed polar interactions with the ALA-9 and GLY-10 amino acid residues, additionally involving ARG-7, GLN-18, and ASP-11 residues. These findings suggest that ALA-9 and GLY-10 residues of WWOX may represent conserved binding sites. Similarly, for THBS2 protein, Vorinostat, Valproic Acid, JQ1, Ifosfamide, GSK1210151A, and Calcitriol demonstrated binding energies of -6.7 , -4.8 , -7.4 , -5.3 , -8.0 , and -7.9 kcal/mol, respectively. They form polar interactions with multiple amino acid residues, with LYS-1166 recurring in multiple docking simulations, suggesting it may represent a conserved binding site.

Discussion

Currently, clinical therapies for mature T/NK-cell lymphoma still face multiple challenges, including limited chemotherapy options, high drug resistance, restricted targeted therapy choices, significant molecular heterogeneity, and the absence of personalized treatment strategies guided by precise biomarkers, resulting in slow progress in improving patient survival outcomes [30]. There is an urgent need to develop more effective novel targeted drugs and optimize personalized treatment strategies. Traditional observational studies have limitations in target screening and drug development, including susceptibility to confounding factors, ambiguous causal relationships, and selection and information bias. Molecular typing and genetic association analysis provide robust support for precision medicine, representing a trend in future therapeutic development. Notably, among the new drugs approved by the U.S. Food and Drug Administration in 2021, 66% have pharmacological targets that are supported by genetic association evidence with their indications or closely related phenotypes [31]. GWAS have identified numerous genetic variants associated with diseases and complex traits, providing abundant valuable data for understanding the genetic mechanisms of complex diseases. MR analysis utilizes genetic variants as instrumental variables to simulate natural randomized controlled trials, enabling more reliable assessment of potential disease risks as well as the efficacy and safety of drug treatments. By integrating GWAS with multi-omics data and employing MR for causal inference, researchers can achieve more comprehensive insights into the genetic mechanisms of complex diseases, effectively identify disease risk factors and

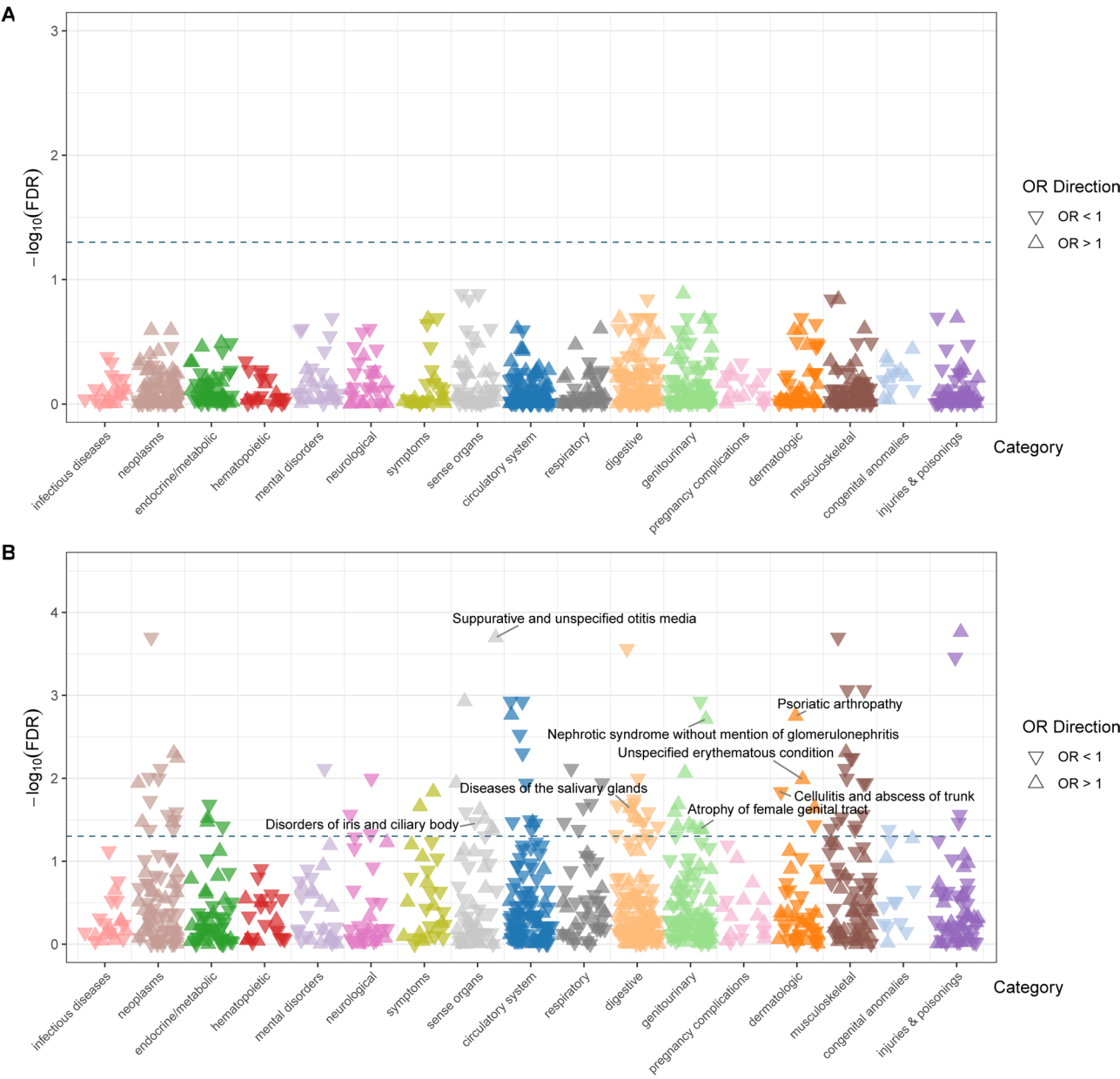


Fig. 6 Phenome-wide MR Analysis of Plasma Proteins WWOX (A) and THBS2 (B) from deCODE Genetics

potential therapeutic targets, and provide robust support for personalized diagnosis and precision medicine.

Based on a druggable gene set, this study integrated GWAS, cis-eQTL, and cis-pQTL data to systematically assess causal relationships between gene expression, protein abundance, and mature T/NK-cell lymphoma. Through MR analysis, we initially identified 54 gene expression targets and 7 plasma protein targets significantly associated with the disease. Further Bayesian colocalization analysis revealed that WWOX (at the gene level) and THBS2 (at the protein level) show substantial evidence of colocalization ($\text{PPH4} > 0.6$). Notably, the successful replication of THBS2 in an independent plasma

protein cohort (UKB-PPP) supports its potential as a robust therapeutic target. Additionally, we preliminarily validated the cis-eQTL-identified WWOX target at the plasma protein level ($P = 7.2\text{E-}03$). This association did not withstand FDR correction, emphasizing the importance of integrating tissue-specific pQTL data and conducting functional validation in future studies.

The WWOX gene is located in the chromosomal region 16q23.3-q24.1, spanning the fragile site FRA16D. It encodes a WW domain-containing oxidoreductase that participates in regulating multiple signaling pathways, influencing tumor development and progression [32]. Recent studies have increasingly established

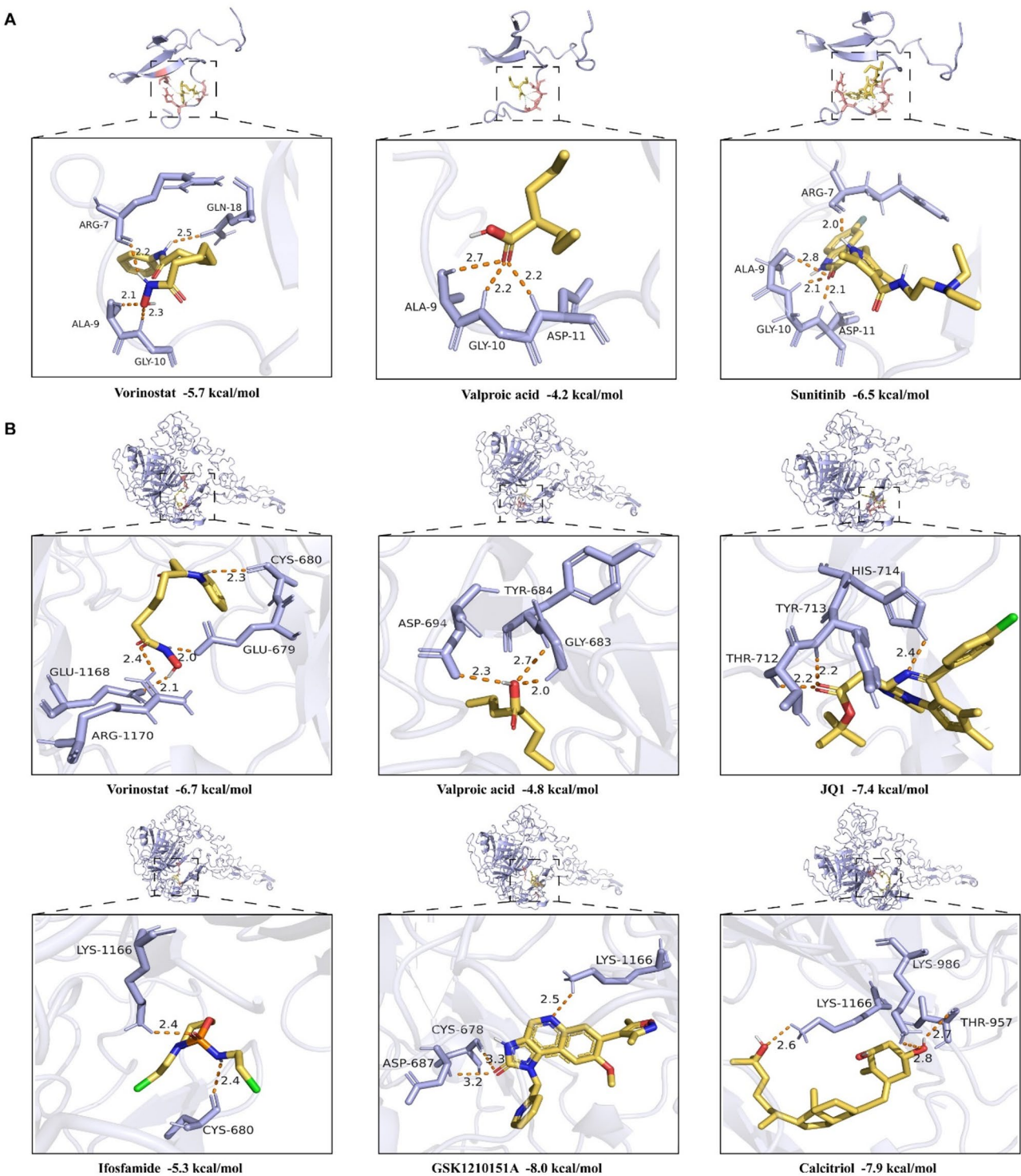


Fig. 7 Molecular docking of the predicted drugs with WWOX (A) and THBS2 (B) receptor protein

WWOX as a tumor suppressor gene, with frequent gene loss or reduced expression observed in various malignancies, including lung and breast cancers [32]. The genomic instability of the FRA16D region is significantly associated with WWOX expression loss, and WWOX

deficiency is considered one of the driving factors in tumorigenesis, correlating with poor prognosis [33]. The antitumor effects of WWOX have been confirmed by multiple studies. WWOX inhibits the proliferation of breast cancer cells by suppressing the IL-6/JAK2/STAT3

signaling pathway [34]. WWOX can be activated by toosendanin, inhibiting the proliferation and metastasis of liver cancer cells through its effects on the IL-6/JAK2/STAT3 and Wnt/ β -catenin signaling pathways [35]. Furthermore, WWOX induces ferroptosis in liver cancer cells by regulating NRF2/FPN1 and p53/SAT1 pathways [36]. WWOX also plays a significant immunomodulatory role in the tumor microenvironment, inhibiting macrophage migration and M2 polarization by suppressing oleic acid secretion from liver cancer cells, thereby blocking immune escape and enhancing anti-PD-1 therapy efficacy [37]. PTCL with higher genomic complexity exhibits recurrent deletions of WWOX and other p53-related genes, contributing to adverse prognosis [38]. Although the mechanism of WWOX in mature T/NK-cell lymphoma remains to be elucidated, the protective effect demonstrated by genetic causal association analysis, combined with its broad tumor suppressor functions, suggests that WWOX may be a potential therapeutic target for this lymphoma.

THBS2 is a homotrimeric glycoprotein secreted by various cell types, including fibroblasts, endothelial cells, and immune cells, and belongs to the extracellular matrix protein family. Indeed, THBS2 plays a complex and often promotional role in tumors, widely participating in angiogenesis, EMT, and immune microenvironment remodeling, thereby influencing tumor invasion and metastasis. Although THBS2 can act as an endogenous angiogenesis inhibitor in specific tumors (such as gastric cancer and pancreatic neuroendocrine tumors) by binding to CD36, CD47, and integrin β 1 to inhibit endothelial cell functions, its effects are often dual [39–41]. THBS2 promotes tumor proliferation and invasion through multiple mechanisms. Specifically, THBS2 binds to α 3 β 1 integrin and CD36 to mediate the growth and metastasis of pancreatic ductal carcinoma cells [42]. THBS2 also promotes the differentiation of vascular endothelial cells into tumor-associated lymphatic vessels in intrahepatic cholangiocarcinoma, exacerbating malignant progression [43, 44]. Furthermore, by binding to specific receptors, THBS2 activates the PI3K/Akt/mTOR pathway, thereby promoting EMT and the formation of vasculogenic mimicry, which mediates tumor proliferation and invasion [45–47]. The intratumoral THBS2 protein level is primarily attributed to a specific subpopulation of cancer-associated fibroblasts (CAFs), namely THBS2 + CAFs, which can be activated by the TGF- β 1/Smad2/3 signaling pathway and secrete high levels of THBS2 [42]. THBS2 + CAFs are also closely associated with an immunosuppressive microenvironment and therapeutic resistance [48, 49]. In our study, THBS2 is identified as an important factor increasing the risk of mature T/NK-cell lymphoma, and it holds promise as a potential therapeutic target for this type of lymphoma.

In this study, we further validated the identification of WWOX and THBS2 as potential targets through SMR and HEIDI tests, supporting the causal roles of both genes in the risk of mature T/NK-cell lymphoma. Notably, we found that elevated methylation at specific WWOX CpG sites (cg00232445 and cg03216739) correlates with both downregulated gene expression and increased mature T/NK-cell lymphoma risk, suggesting DNA methylation may contribute to this malignancy via epigenetic WWOX regulation. Further transcriptomic analysis revealed decreased WWOX expression and increased THBS2 expression in mature T/NK-cell lymphoma, suggesting their close involvement in the pathogenesis of the disease. Immune infiltration correlation analysis showed that WWOX expression was negatively correlated with M2 macrophage polarization and positively correlated with CD8 T cell infiltration, consistent with the characteristics of anti-PD-1 therapy responders in liver cancer, indicating that WWOX may improve the tumor microenvironment and promote immune response [37]. Conversely, THBS2 expression correlated with decreased infiltration of M1 macrophages that exhibit anti-tumor immune activity. GSEA analysis revealed that WWOX and THBS2 showed differential enrichment in the PI3K/Akt/mTOR pathway. Given the known role of the PI3K/Akt pathway in regulating macrophage activation and polarization, WWOX and THBS2 may influence macrophage polarization through this pathway [50]. In addition, WWOX may exert antitumor effects by inhibiting the IL-6/STAT3 and IL-2/STAT5 pathways, while THBS2 may be associated with EMT and angiogenesis. These findings provide new insights for the development of strategies based on WWOX epigenetic regulation and targeting THBS2 for anti-angiogenesis or EMT inhibition.

Through phenome-wide MR analysis, we evaluated the potential safety and risks of WWOX and THBS2 interventions. The results showed that WWOX had no significant association with most non-target phenotypes, suggesting that WWOX-targeted therapy may have fewer adverse effects. However, its tissue specificity may not be fully revealed by MR analysis of circulating proteins, and the absence of WWOX data in the UKB-PPP dataset limited validation. THBS2 exhibits complex effects, with its inhibition potentially beneficial for psoriatic arthritis and nephrotic syndrome but increasing the risk of trunk cellulitis and iris disease. These diverse effects may be attributed to THBS2's multifaceted role in promoting fibrosis, regulating inflammatory microenvironments, and participating in peripheral immune defense [51]. Although the UKB-PPP data enhances credibility, the overlap with phenotypic data samples may introduce false positives. Notably, despite the weak association effects indicated by OR values, reducing THBS2 protein levels may increase

the risk of brain, bladder, and cervical cancers. The heterogeneity of THBS2 effects may be associated with the presence of CAFs within tumors. Systemic inhibition may carry off-target risks, whereas developing strategies targeting THBS2 + CAFs could help improve specificity [49].

Based on analysis of the CTD database, we identified two classes of epigenetic drugs, histone deacetylase inhibitors (HDACi) and bromodomain and extra-terminal (BET) inhibitors. Among these, HDACi (Vorinostat and Valproic Acid) can simultaneously upregulate WWOX expression and downregulate THBS2 expression, while BET inhibitors (JQ1 and GSK1210151A) primarily downregulate THBS2 expression. Molecular docking analyses demonstrated the strong binding affinity of these drugs with their target proteins. Vorinostat, approved for the treatment of cutaneous T-cell lymphoma, has also shown significant efficacy against PTCL-NOS with SMARCB1 deletion [52]. Valproic acid, an antiepileptic drug, also functions as an HDAC inhibitor, demonstrating potential value in lymphoma treatment [53]. BET inhibitors have demonstrated antitumor activity against multiple lymphomas in preclinical studies, but their role in mature T/NK-cell lymphoma and their effects on THBS2 require further investigation [54]. In addition, we found that ALA-9/GLY-10 on the WWOX protein and LYS-1166 on the THBS2 protein can form polar bonds with multiple drugs, suggesting that they may be key sites for drug binding. Epigenetic modulation strategies offer new therapeutic approaches for mature T/NK-cell lymphoma, but their biological significance and clinical translational value require validation through functional experiments and further research.

Although the integration of multi-omics data with MR analysis provides a powerful tool for systematically screening therapeutic targets for diseases, this study still has several limitations. Firstly, due to data availability constraints, genetic causal inference was only conducted in populations of European ancestry, while these causal effects or regulatory mechanisms may differ significantly in other ethnic groups (such as African or Asian populations), and there may even be population-specific functional variants, thereby affecting the generalizability and clinical translation potential of the research conclusions. Secondly, given that mature T/NK-cell lymphoma is a relatively rare subtype of non-Hodgkin's lymphoma, the available data and case numbers are limited, and the lack of independent validation cohorts increases the risk of insufficient statistical power and erroneous conclusions. Furthermore, although strict measures have been taken to reduce the risk of statistical bias, MR, Bayesian colocalization, and SMR analyses may still be influenced by potential confounding factors and horizontal pleiotropy, which could lead to bias in the results.

Overall, this study reveals the potential of WWOX and THBS2 as therapeutic targets for mature T/NK-cell lymphoma, providing molecular-level insights for the development of precision treatment strategies. Future research should further validate the biological mechanisms of candidate targets through in vitro and in vivo experiments to compensate for the limitations of computational analysis and optimize targeted strategies to overcome current treatment bottlenecks.

Abbreviations

NK	Natural killer
R/R	Relapsed/refractory
MR	Mendelian Randomization
SNPs	Single nucleotide polymorphisms
IVs	Instrumental variables
GWAS	Genome-wide association studies
pQTL	Plasma protein quantitative trait loci
eQTL	Expression quantitative trait loci
DGIdb	Drug-Gene Interaction database
mQTL	Methylation quantitative trait loci
SMR	Summary-data-based MR
HEIDI	Heterogeneity in dependent instruments
GSEA	Gene set enrichment analysis
UKB-PPP	UK Biobank Pharma Proteomics Project
MAF	Minor allele frequency
MHC	Major histocompatibility complex
IWV	Inverse variance weighted
BH	Benjamini-Hochberg
FDR	False discovery rate
PPH4	Posterior probability for hypothesis H4
CTD	Comparative Toxicogenomics Database
OR	Odds ratio
CI	Confidence interval
EMT	Epithelial-mesenchymal transition
CAFs	Cancer-associated fibroblasts
HDACi	Histone deacetylase inhibitors
BET	Bromodomain and extra-terminal

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12967-025-07301-9>.

Supplementary Material 1

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Author contributions

YQ and YH designed the study. YQ wrote the first draft of the manuscript. YH reviewed and edited the manuscript. JW, YZH, YZ, YL, ZL contributed to the investigation and resources. All authors read and approved the final manuscript.

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Data availability

The data sources used in this analysis and supporting the conclusions of this study have been described in the main text or included in the supplementary files.

Declarations

Ethics approval and consent to participate

This study utilized publicly available datasets, which do not require additional ethical approval. All data were accessed in accordance with the respective database policies.

Consent for publication

All authors have reviewed the final version of the manuscript and approve its publication, including any associated images or data.

Competing interests

The authors declare no competing interest.

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References

- Jia J, Wang X, Song Z, Meng S, Fei Y, Yu J, et al. A retrospective analysis of mature T- and NK-cell lymphomas. *Cancer Biol Med*. 2024;21:223–9.
- Lim SH, Hong JY, Lim ST, Hong H, Arnoud J, Zhao W, et al. Beyond first-line non-anthracycline-based chemotherapy for extranodal NK/T-cell lymphoma: clinical outcome and current perspectives on salvage therapy for patients after first relapse and progression of disease. *Ann Oncol Off J Eur Soc Med Oncol*. 2017;28:2199–205.
- Bellei M, Foss FM, Shustov AR, Horwitz SM, Marcheselli L, Kim WS, et al. The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, international T-Cell project. *Haematologica*. 2018;103:1191–7.
- Gao Y, He H, Li X, Zhang L, Xu W, Feng R, et al. Sintilimab (anti-PD-1 antibody) plus Chidamide (histone deacetylase inhibitor) in relapsed or refractory extranodal natural killer T-cell lymphoma (SCENT): a phase Ib/II study. *Signal Transduct Target Ther*. 2024;9:121.
- Macapagal SC, Bennani NN. Nodal peripheral T-cell lymphoma: Chemotherapy-free management, are we there yet? *Blood Rev*. 2023;60:101071.
- Cwynarski K, Iacoboni G, Tholouli E, Menne T, Irvine DA, Balasubramaniam N, et al. TRBC1-CART cell therapy in peripheral T cell lymphoma: a phase 1/2 trial. *Nat Med*. 2025;31:137–43.
- Birney E. Mendelian randomization. *Cold Spring Harb Perspect Med*. 2022;12:a041302.
- Wang MH, Cordell HJ, Van Steen K. Statistical methods for genome-wide association studies. *Semin Cancer Biol*. 2019;55:53–60.
- Gill D, Georgakis MK, Koskeridis F, Jiang L, Feng Q, Wei W-Q, et al. Use of genetic variants related to antihypertensive drugs to inform on efficacy and side effects. *Circulation*. 2019;140:270–9.
- Georgakis MK, Gill D. Mendelian randomization studies in stroke: exploration of risk factors and drug targets with human genetic data. *Stroke*. 2021;52:2992–3003.
- Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrismisdottir EL, et al. Large-scale integration of the plasma proteome with genetics and disease. *Nat Genet*. 2021;53:1712–21.
- GTEX Consortium. The GTEx consortium atlas of genetic regulatory effects across human tissues. *Science*. 2020;369:1318–30.
- Kreitmaier P, Katsoula G, Zeggini E. Insights from multi-omics integration in complex disease primary tissues. *Trends Genet TIG*. 2023;39:46–58.
- Cannon M, Stevenson J, Stahl K, Basu R, Coffman A, Kiwala S, et al. DGLdb 5.0: rebuilding the drug-gene interaction database for precision medicine and drug discovery platforms. *Nucleic Acids Res*. 2024;52:D1227–35.
- Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, et al. The druggable genome and support for target identification and validation in drug development. *Sci Transl Med*. 2017;9:eaag1166.
- Vösa U, Claringbould A, Westra H-J, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet*. 2021;53:1300–10.
- Sun BB, Chiou J, Traylor M, Benner C, Hsu Y-H, Richardson TG, et al. Plasma proteomic associations with genetics and health in the UK biobank. *Nature*. 2023;622:329.
- Burgess S, Thompson SG, CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40:755–64.
- Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, et al. Finn-Gen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613:508–18.
- 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.
- Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36:1783–802.
- Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet*. 2014;10:e1004383.
- Wu Y, Zeng J, Zhang F, Zhu Z, Qi T, Zheng Z, et al. Integrative analysis of omics summary data reveals putative mechanisms underlying complex traits. *Nat Commun*. 2018;9:1–14.
- Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet*. 2016;48:481–7.
- Min JL, Hemani G, Hannon E, Dekkers KF, Castillo-Fernandez J, Luijk R, et al. Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation. *Nat Genet*. 2021;53:1311–21.
- Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods*. 2015;12:453–7.
- Wu T, Hu E, Xu S, Chen M, Guo P, Dai Z, et al. ClusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *Innov Camb Mass*. 2021;2:100141.
- Trott O, Olson AJ. AutoDock vina: improving the speed and accuracy of Docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem*. 2010;31:455–61.
- Rasooly D, Peloso GM, Giambartolomei C. Bayesian genetic Colocalization test of two traits using Coloc. *Curr Protoc*. 2022;2:e627.
- Flower A, Xavier AC, Cairo MS. Mature (non-anaplastic, non-cutaneous) T-/NK-cell lymphomas in children, adolescents and young adults: state of the science. *Br J Haematol*. 2019;185:418–35.
- Ochoa D, Karim M, Ghousaini M, Hulcoop DG, McDonagh EM, Dunham I. Human genetics evidence supports two-thirds of the 2021 FDA-approved drugs. *Nat Rev Drug Discov*. 2022;21:551–551.
- Schrock MS, Huebner K. WWOX: a fragile tumor suppressor. *Exp Biol Med* Maywood NJ. 2015;240:296–304.
- Aqeilan RI, Abu-Remaih M, Abu-Odeh M. The common fragile site FRA16D gene product WWOX: roles in tumor suppression and genomic stability. *Cell Mol Life Sci CMLS*. 2014;71:4589–99.
- Chang R, Song L, Xu Y, Wu Y, Dai C, Wang X, et al. Loss of Wwox drives metastasis in triple-negative breast cancer by JAK2/STAT3 axis. *Nat Commun*. 2018;9:3486.
- Yang T, Xu R, Huo J, Wang B, Du X, Dai B, et al. WWOX activation by Toosendanin suppresses hepatocellular carcinoma metastasis through JAK2/Stat3 and Wnt/ β -catenin signaling. *Cancer Lett*. 2021;513:50–62.
- Yang T, Zhang S, Nie K, Peng X, Huo J, Fu X, et al. WWOX-mediated p53/SAT1 and NRF2/FPN1 axis contribute to toosendanin-induced ferroptosis in hepatocellular carcinoma. *Biochem Pharmacol*. 2025;233:116790.
- Liu S, Yang S, Xu M, Zhou Q, Weng J, Hu Z, et al. WWOX tuning of oleic acid signaling orchestrates immunosuppressive macrophage polarization and sensitizes hepatocellular carcinoma to immunotherapy. *J Immunother Cancer*. 2024;12:e010422.
- Ong SY, Zain JM. Aggressive T-cell lymphomas: 2024: updates on diagnosis, risk stratification, and management. *Am J Hematol*. 2024;99:439–56.
- Sun R, Wu J, Chen Y, Lu M, Zhang S, Lu D, et al. Down regulation of Thrombospondin2 predicts poor prognosis in patients with gastric cancer. *Mol Cancer*. 2014;13:225.
- Jiao H, Zeng L, Zhang J, Yang S, Lou W. THBS2, a microRNA-744-5p target, modulates MMP9 expression through CUX1 in pancreatic neuroendocrine tumors. *Oncol Lett*. 2020;19:1683–92.
- Lawler PR, Lawler J. Molecular basis for the regulation of angiogenesis by thrombospondin-1 and -2. *Cold Spring Harb Perspect Med*. 2012;2:a006627.
- Nan P, Dong X, Bai X, Lu H, Liu F, Sun Y, et al. Tumor-stroma TGF- β 1-THBS2 feedback circuit drives pancreatic ductal adenocarcinoma progression via

- integrin $\alpha\beta3$ /CD36-mediated activation of the MAPK pathway. *Cancer Lett.* 2022;528:59–75.
43. Carpino G, Cardinale V, Di Giamberardino A, Overi D, Donsante S, Colasanti T, et al. Thrombospondin 1 and 2 along with PEDF inhibit angiogenesis and promote lymphangiogenesis in intrahepatic cholangiocarcinoma. *J Hepatol.* 2021;75:1377–86.
44. Corbella E, Fara C, Covarelli F, Porreca V, Palmisano B, Mignogna G, et al. THBS1 and THBS2 enhance the in vitro Proliferation, Adhesion, migration and invasion of intrahepatic cholangiocarcinoma cells. *Int J Mol Sci.* 2024;25:1782.
45. Huang J, Wang C, Hou Y, Tian Y, Li Y, Zhang H, et al. Molecular mechanisms of Thrombospondin-2 modulates tumor vasculogenic mimicry by PI3K/AKT/mTOR signaling pathway. *Biomed Pharmacother Biomedecine Pharmacother.* 2023;167:115455.
46. Qi L, Sun B, Yang B, Lu S. CEBPB regulates the migration, invasion and EMT of breast cancer cells by inhibiting THBS2 expression and O-fucosylation. *Hum Mol Genet.* 2023;32:1850–63.
47. Luo Q, Wang J, Zhao W, Peng Z, Liu X, Li B, et al. Vasculogenic mimicry in carcinogenesis and clinical applications. *J Hematol Oncol J Hematol Oncol.* 2020;13:19.
48. Yang H, Sun B, Fan L, Ma W, Xu K, Hall SRR, et al. Multi-scale integrative analyses identify THBS2 + cancer-associated fibroblasts as a key orchestrator promoting aggressiveness in early-stage lung adenocarcinoma. *Theranostics.* 2022;12:3104–30.
49. Zhou X, Han J, Zuo A, Ba Y, Liu S, Xu H, et al. THBS2 + cancer-associated fibroblasts promote EMT leading to oxaliplatin resistance via COL8A1-mediated PI3K/AKT activation in colorectal cancer. *Mol Cancer.* 2024;23:282.
50. Vergadi E, Ieronymaki E, Lyroni K, Vaporidi K, Tsatsanis C. Akt signaling pathway in macrophage activation and M1/M2 polarization. *J Immunol Baltim Md* 1950. 2017;198:1006–14.
51. Zhang N, Wu X, Zhang W, Sun Y, Yan X, Xu A, et al. Targeting thrombospondin-2 retards liver fibrosis by inhibiting TLR4-FAK/TGF- β signaling. *JHEP Rep Innov Hepatol.* 2024;6:101014.
52. Fischer A, Albert TK, Moreno N, Interlandi M, Mormann J, Glaser S, et al. Lack of SMARCB1 expression characterizes a subset of human and murine peripheral T-cell lymphomas. *Nat Commun.* 2024;15:8571.
53. Espinoza-Zamora JR, Labardini-Méndez J, Sosa-Espinoza A, López-González C, Vieyra-García M, Candelaria M, et al. Efficacy of hydralazine and valproate in cutaneous T-cell lymphoma, a phase II study. *Expert Opin Investig Drugs.* 2017;26:481–7.
54. Bertoni F, Stathis A. Bromodomain and Extra-Terminal domain inhibitors for lymphoid malignancies. *Curr Opin Hematol.* 2019;26:273.

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