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Analysis

New therapeutic targets and mechanisms of papillary thyroid carcinoma identified by multi-omics analysis

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Abstract

Introduction The treatment of papillary thyroid carcinoma (PTC) presents ongoing challenges, underscoring the need for novel therapeutic targets.

Methods This study employed proteomic MR analysis, utilizing publicly available data from genome-wide association studies (GWAS) and protein quantitative trait loci (pQTL) studies. We analyzed proteomic data from deCODE and the UK Biobank Protein Project (UKB-PP), along with GWAS data on papillary thyroid carcinoma (PTC) from the Finnish Consortium. This analysis was further supported by eQTL validation and bioinformatics differential analysis to identify potential therapeutic targets for PTC. Additionally, we explored possible downstream mechanisms of the target proteins through mediation analysis.

Results Our analysis identified two potential therapeutic targets associated with PTC, specifically, LY75 and S100A12. Mediation analysis further investigated their potential mechanistic role in the pathogenesis of PTC.

Conclusion Through multi-omics analysis, we identified new potential therapeutic targets for papillary thyroid carcinoma and investigated their possible underlying mechanisms affecting PTC.

Keywords Papillary thyroid carcinoma · Cis-pQTL · EQTL · Bioinformatics analyses · Mendelian randomization · Mediation

1 Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent form of thyroid cancer, accounting for the majority of cases. Despite advances in diagnostic techniques, approximately 20% of patients are diagnosed at an advanced stage. Traditional treatments, including surgery, radioactive iodine therapy, and thyroid-stimulating hormone suppression, often fall short in achieving complete remission. Additionally, targeted therapies for BRAF and RAS mutations have encountered resistance, compromising the efficacy of existing treatments [1]. Therefore, there is a critical need for innovative therapeutic approaches to address these limitations and improve patient survival rates.

Recent advancements in genomics, proteomics, and Mendelian randomization (MR) have significantly broadened the scope of oncological research, enabling the identification of novel targets in cancers such as prostate [2] and lung cancer

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[3]. However, the application of these technologies in thyroid cancer, particularly in the context of integrating protein quantitative trait loci (pQTL) data, mRNA expression quantitative trait loci (eQTL), and genome-wide association study (GWAS) results, remains largely unexplored.

Our study aimed to identify plasma proteins as potential therapeutic targets for PTC by analyzing pQTL data from the deCODE and UK Biobank databases, complemented by patient data from the Finnish consortium. A comprehensive analytical strategy was employed, which included initial and repeated analyses, retrocausality assessment, bioinformatics-based differential analyses, and additional validation of eQTL data from European ancestry cohorts. Moreover, mediation analysis was utilized to explore the potential downstream mechanisms of the identified target protein. This research provides new insights into the molecular basis of PTC and identifies promising therapeutic intervention pathways, enhancing our understanding of the disease and laying the groundwork for future targeted treatment strategies.

2 Methods

2.1 Research design

The overall research design is illustrated in Fig. 1. Our study employed a two-sample Mendelian Randomization (MR) analysis, utilizing cis-pQTL data for plasma proteins in blood as exposure factors and conducting a genome-wide association study (GWAS) of papillary thyroid carcinoma (PTC) as the outcome measure. This approach aimed to investigate the association between plasma proteins and PTC. Appropriate single nucleotide polymorphisms (SNPs) were selected as instrumental variables (IVs) based on stringent inclusion and exclusion criteria.

To enhance the reliability of our MR analysis, we conducted a series of sensitivity analyses. For plasma proteins that yielded significant MR results, we repeated the analyses, performed eQTL validation analyses, and conducted bioinformatics differential analyses. These multiple validation methods were employed to identify potential therapeutic targets for PTC. Additionally, we explored the possible downstream mechanisms of the target proteins through mediation analysis. The analytical approach was ethically sound, as all data utilized in this study had received prior approval and consent in their original studies.

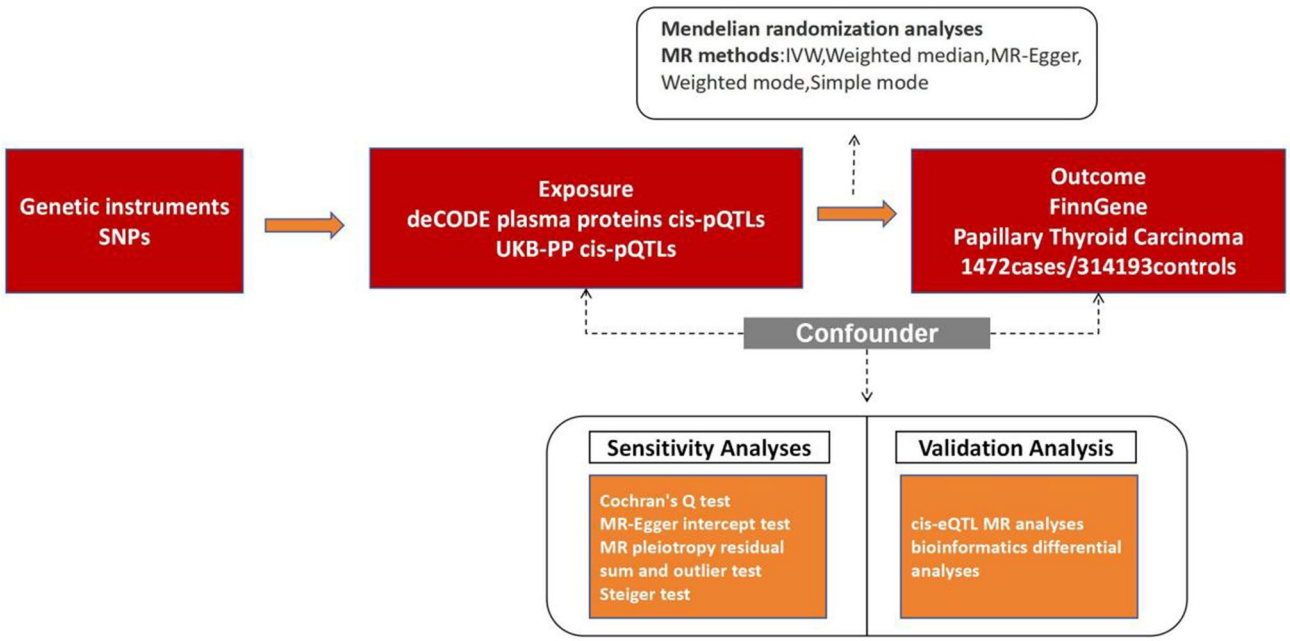

Fig. 1 Study workflow. MR: Mendelian randomization; eQTL: expression quantitative trait locus; pQTL: protein quantitative trait locus; IVW: inverse variance-weighted

2.2 Data sources

Proteome data were sourced from the deCODE database (https://www.decode.com/summarydata/) for the Icelandic population [4], as well as from the UK Biobank Pharmaceutical Proteomics Project (UKB-PPP) (https://www.synapse.org/Synapse:syn51364943/wiki/622119) [5]. Our selection criteria for protein quantitative trait loci (pQTL) were stringent, focusing specifically on cis-pQTL and extracting genetic variants located within 1000 kb of the coding sequence. These variants were selected due to their strong association with the gene expression of pathogenic proteins, thereby ensuring the specificity and relevance of our research, particularly in the context of papillary thyroid carcinoma.

Blood cis-eQTL data within 1 Mb of the central location of each gene were obtained from the eQTLGen Consortium [6]. The genes were identified within this 1 Mb range, with each variant exhibiting a minor allele frequency (MAF) greater than 0.01.

Additionally, we collected summary statistics for 731 immunological features (accession numbers: GCST0001391-GCST0002121) from the GWAS catalog database (https://www.ebi.ac.uk/gwas/), which included absolute counts (AC), median fluorescence intensity (MFI), morphological parameters (MP), and relative counts (RC). A comprehensive list of each immunological profile is provided in Table S1 [7].

PTC GWAS statistics were obtained from the Finnish Database Consortium, involving 1472 cases and 314,193 controls.

2.3 Instrumental variable (IV) selection

To ensure the reliability and accuracy of our results, it was essential to fulfill three key assumptions in Mendelian Randomization (MR) analysis: (1) the instrumental variable (IV) must be strongly associated with the exposure; (2) the IV must be independent of any confounding factors; and (3) there should be no horizontal pleiotropy, meaning the IV influences the outcome solely through the exposure and not through alternative pathways [8]. Based on these assumptions, a rigorous selection process was conducted for each gene included in our study.

Initially, single 5.0×10^{-8} nucleotide polymorphisms (SNPs) were selected using a uniform and stringent threshold, considering only those with a P value below the genome-wide significance threshold of. Subsequently, to derive a set of independent SNPs, we clustered SNPs associated with each druggable gene according to the 1000 Genomes Project European population, applying a linkage disequilibrium (LD) threshold of $r^2 < 0.1$ and an aggregation window of 10,000 kb [9]. Furthermore, SNPs that were incompatible between exposure and outcome were excluded, and the positive strand allele was inferred based on the frequency of the palindromic allele. In cases where allele frequencies were unavailable, palindromic SNPs were directly excluded. Finally, SNPs with F statistics below 10 were omitted to mitigate the risk of weak instrument bias [10].

2.4 Mendelian randomization analysis and sensitivity analysis

The Mendelian Randomization (MR) method was employed to investigate the causal relationship between cis-acting polymorphic quantitative trait loci (cis-pQTLs) and phenotypic trait changes (PTC). The inverse variance weighting (IVW) method served as the primary analytical tool, operating under the assumption that single nucleotide polymorphisms (SNPs) did not exhibit horizontal pleiotropy, which enhances the accuracy of causal effect assessments [11]. To reinforce the findings, supplementary analyses were conducted using MR-Egger, weighted median, simple mode, and weighted mode approaches. Although the IVW method is conservative, it is recognized for its robustness. Therefore, despite the presence of heterogeneity, the IVW method remained the primary approach, with results corroborated by supplementary methods. Initially, the Cochran's Q test was utilized to evaluate the heterogeneity of the results [12]. Subsequently, MR-Egger intercepts were calculated to identify potential biases arising from directional pleiotropy and null instrument variables [13]. Additionally, the MR-Pleiotropy Residuals and Outliers (MR-PRESSO) method was employed to detect and adjust for heterogeneous SNPs, aiming to minimize confounding effects that could impact MR estimates [14]. A leave-one-out (LOO) analysis was also performed to assess the robustness of the findings by examining the impact of each SNP on the overall results. These sensitivity analyses were conducted to identify and mitigate potential biases, thereby enhancing the reliability of the study outcomes. All Mendelian randomization analyses were conducted using R version 4.3.1 along with the software packages"Mendelian randomization","TwoSampleMR", and"MR-PRESSO".

2.5 Replicative analysis, validation analysis, and directionality test

To validate the preliminary findings, we repeated the analysis using an alternative set of cis-pQTL data from the UKB-PPP database. For the validation analysis, we selected eQTL data for genes that were consistent across both the initial and repeated analyses. Additionally, a Steiger test was performed to assess potential bias, aiming to enhance the credibility of the study and minimize the impact of reverse causality.

2.6 Differential analysis

Differential expression data for papillary thyroid carcinoma (PTC) were obtained from the TCGA and GETx databases using the GEPIA2 tool (http://gepia2.cancer-pku.cn/#index). The analysis aimed to identify genes exhibiting an absolute log fold change (log2 FC) greater than 0.5 and an adjusted p-value (adj.pval) of less than 0.05. This differential analysis further corroborated our conclusions regarding PTC expression.

2.7 Mediation analysis

A two-step mediation analysis was conducted to explore the potential downstream mechanisms of the target protein [15, 16]. Initially, two-sample Mendelian randomization (MR) was employed to evaluate the impact of the target protein on immune cell phenotypes (β1) and papillary thyroid carcinoma (PTC) (α). Subsequently, immune cell phenotypes associated with the target protein and its effects (β2) were identified. The total effect was decomposed into indirect (mediated) and direct (unmediated) effects. The indirect effect was calculated as the product of the direct effect on the mediator (β1) and the effect of the mediator on the outcome (β2) (Fig. 2). The percentage of the mediation effect was computed by dividing the indirect effect by the total effect.

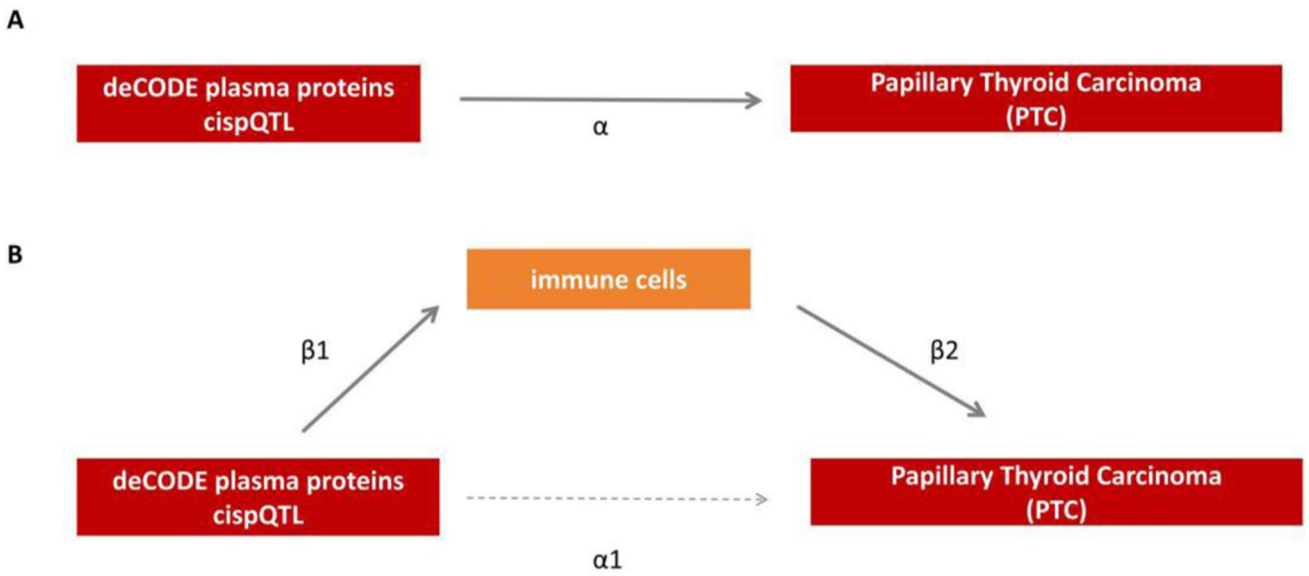

Fig. 2 Diagrams illustrating the associations examined in this study. **A** The total effect between plasma protein cis-pQTL and papillary thyroid carcinoma (PTC). α represents the total effect using genetically predicted plasma protein cis-pQTL as exposure and PTC as the outcome. **B** The total effect was decomposed into: (i) the indirect effect using a two-step approach (where β1 is the total effect of cis-pQTL on immune cells, and β2 is the effect of immune cells on PTC) and the product method (β1 × β2), and (ii) the direct effect α1 = α − β1 × β2. The proportion mediated was calculated as the indirect effect divided by the total effect

3 Results

3.1 Preliminary analysis and replicative analysis

We utilized 1614 available cis-acting QTL (cis-pQTL) data points from the deCODE database for our Mendelian Randomization analysis. After meticulously controlling theQuality of the instrumental variables (IVs), we employed the inverse variance weighting (IVW) method as our primary analytical approach. This analysis revealed 149 plasma proteins that may exert a causal influence on PTC (Table S2). In the replicative analysis, we accessed 1812 available cis-pQTL data points from the UK Biobank Protein Project (UKB-PP) database and re-evaluated the plasma proteins previously identified as having a causal effect on PTC in the preliminary analysis. This effort resulted in the identification of 35 proteins that were consistently determined to be causal in both the preliminary and replicative analyses. The results of the replicative analysis concerning these plasma proteins are elaborated upon in Table S3. Sensitivity analyses, including the Cochran Q test ($p > 0.05$) and the MR-Egger intercept test ($p > 0.05$), robustly indicate the absence of heterogeneity and pleiotropy. Additionally, Steiger's test demonstrated no evidence of reverse causality (Tables 1, 2).

3.2 Validation analysis

To investigate the effect of the target protein on papillary thyroid carcinoma (PTC), we further examined the relationship between gene expression levels and PTC by utilizing expression quantitative trait loci (eQTL) data from the eQTLGen Consortium database. A total of seven groups yielded positive results in the eQTL Mendelian randomization (MR) analysis (Fig. 3).

Table 1 Mendelian randomization results for cis-pQTL and eQTL significantly related to PTC

Protein	Mendelian randomization analysis				
	Method	p	Beta	OR	OR (95% CI)
deCODE cis-pQTL					
ENTPD5	IVW	4.87e−04	0.198	1.22	(1.09,1.36)
LY75	IVW	0.038	0.047	1.05	(1.00,1.09)
NPTX1	IVW	0.004	0.170	1.19	(1.05,1.33)
PPP1R14 A	IVW	0.015	0.308	1.36	(1.06,1.75)
S100 A12	IVW	0.048	− 0.324	0.72	(0.52,0.99)
SIGLEC5	IVW	0.033	− 0.041	0.96	(0.92,0.99)
SNAP29	IVW	0.041	− 0.719	0.49	(0.25,0.97)
UKB-PP cis-pQTL					
ENTPD5	IVW	0.006	0.179	1.20	(1.05,1.36)
LY75	IVW	2.62e−07	0.109	1.12	(1.07,1.16)
NPTX1	IVW	2.92e−07	0.203	1.22	(1.13,1.32)
PPP1R14 A	IVW	0.024	0.246	1.28	(1.03,1.58)
S100 A12	IVW	0.038	− 0.352	0.70	(0.50,0.98)
SIGLEC5	IVW	0.035	− 0.056	0.95	(0.90,0.99)
SNAP29	IVW	0.043	− 0.793	0.45	(0.21,0.98)
eQTLGen Consortium cis-eQTL					
ENTPD5	IVW	0.042	0.336	1.40	(1.01,1.94)
LY75	IVW	9.95e−06	0.209	1.23	(1.12,1.35)
NPTX1	IVW	0.007	− 1.101	0.33	(0.15,0.75)
PPP1R14 A	IVW	4.86e-04	0.303	1.35	(1.14,1.61)
S100 A12	IVW	0.011	− 0.104	0.90	(0.83,0.98)
SIGLEC5	IVW	0.015	− 0.107	0.90	(0.82,0.98)
SNAP29	IVW	0.015	− 0.104	0.90	(0.82,0.98)

Table 2 Sensitivity analysis and directionality test on candidate target proteins

Protein	SNP	Steiger direction	Steiger P value	Heterogeneity	Pleiotropy
deCODE cis-pQTL					
ENTPD5	rs10151810	TRUE	3.51E−172	0.954	0.784
LY75	rs10205876	TRUE	3.63E−268	0.166	0.696
NPTX1	rs79744555	TRUE	0	0.71	0.051
PPP1R14 A	rs71354995	TRUE	5.44E−90	0.612	0.374
S100 A12	rs3014874	TRUE	2.15E−100	0.527	0.063
SIGLEC5	rs11394995	TRUE	0	0.169	0.344
SNAP29	rs192565874	TRUE	5.43E−27	0.645	0.4972
UKB-PP cis-pQTL					
ENTPD5	rs28458356	TRUE	1.58E−290	0.69	0.061
LY75	rs114113847	TRUE	0	0.756	0.331
NPTX1	rs11150745	TRUE	2.12E−195	0.961	0.059
PPP1R14 A	rs71354995	TRUE	5.22E−132	0.816	0.479
S100 A12	rs3014874	TRUE	2.19E−154	0.181	0.244
SIGLEC5	rs12459648	TRUE	1.62E−187	0.801	0.134
SNAP29	rs5759874	TRUE	5.19E−18	0.978	0.889
eQTLGen Consortium cis-eQTL					
ENTPD5	rs118113209	TRUE	3.19E−63	0.461	0.676
LY75	rs1344631	TRUE	4.22E−299	0.423	0.998
NPTX1	rs34177980	TRUE	8.77E−20	0.09	0.977
PPP1R14 A	rs4803999	TRUE	2.65E−176	0.823	0.543
S100 A12	rs11580993	TRUE	0	0.291	0.064
SIGLEC5	rs11084096	TRUE	5.20E−194	0.872	0.991
SNAP29	rs13053754	TRUE	0	0.849	0.879

3.3 Difference analysis

We queried the differential expression data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GETx) databases via their respective websites, setting the absolute value of log2 fold change (log2 FC) to be greater than 0.5 and the adjusted p-value to be less than 0.05. We identified 9856 differentially expressed genes (Table S5). Based on the requirement that the influence of cis-pQTL and eQTL1 on PTC should align with the level of differential expression, we ultimately identified two potential target proteins: S100 A12 and LY75. Their differential expression in tumors (Fig. 4) underscores their potential as therapeutic targets.

3.4 Mediation analysis

Initially, we identified several immune cell phenotypes associated with PTC through Mendelian randomization analysis (Table S6). Subsequently, we examined the relationship between the LY75 and S100 A12 proteins and the phenotypes of these immune cells using MR analysis (Table S6). Finally, we calculated the mediating proportion of immune cells that mediate the causal effect of plasma proteins on PTC (Table 3).

4 Discussion

Our study aimed to identify potential therapeutic targets for papillary thyroid carcinoma (PTC) through a comprehensive analysis. We meticulously evaluated the association between plasma proteins and PTC via a series of replication, sensitivity, and validation analyses. Our findings indicated that S100 A12 and LY75 could serve as promising

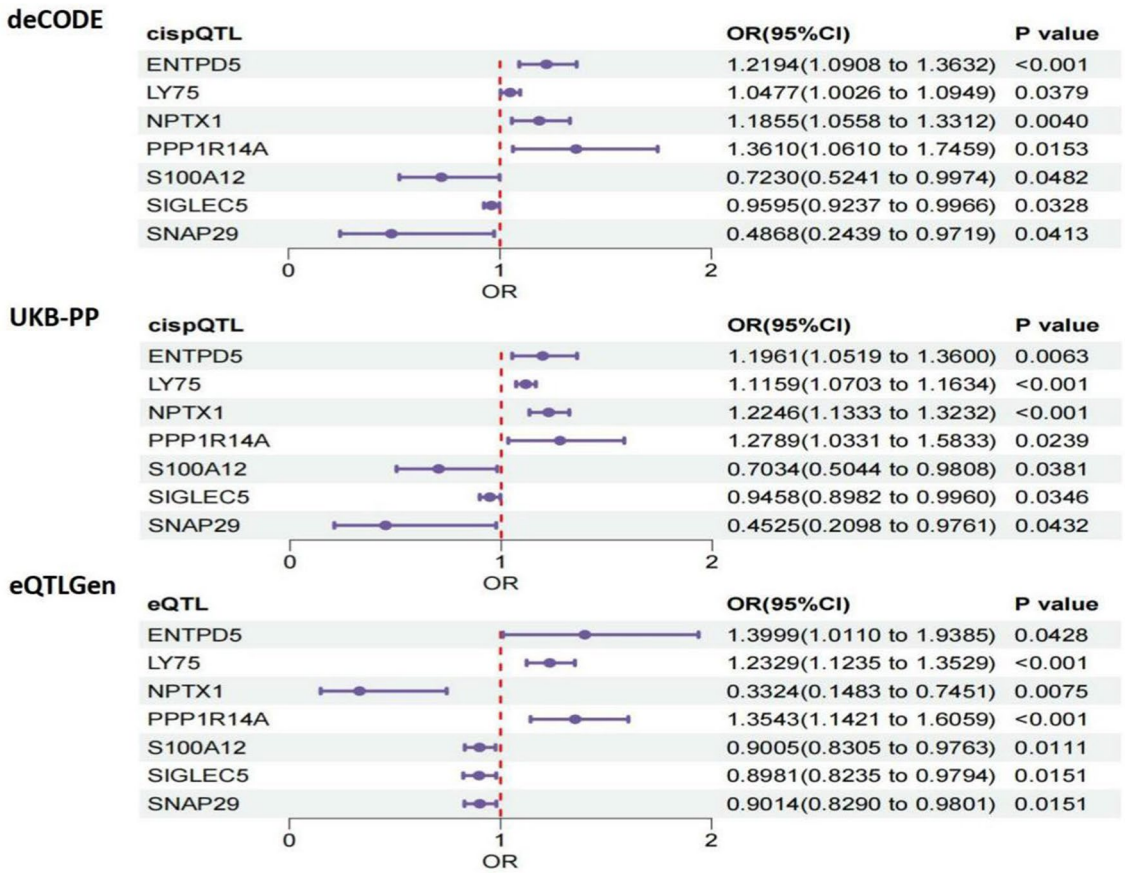

Fig. 3 Significant MR results in preliminary analysis, replicative analysis, and validation analysis

therapeutic targets for PTC. Furthermore, through mediation analysis, we elucidated the potential downstream mechanisms by which these plasma proteins may influence the occurrence and progression of PTC.

The expression of S100 A12 exhibits distinct characteristics across various tumor types, with its heterogeneity influenced by a complex interplay among the inflammatory microenvironment, receptor interactions, and a multifaceted regulatory network. In the majority of solid tumors, S100 A12 expression is positively correlated with inflammation levels, contributing to tumor progression by attracting immune cells and modulating cell migration. Conversely, in immunosuppressive tumors, S100 A12 expression is significantly reduced, highlighting a bidirectional feedback loop between the tumor microenvironment and the tumor itself [17]. Functional studies have revealed that S100 A12 can exert both oncogenic and antitumor effects, depending on its receptor interactions and subcellular localization. When associated with the RAGE receptor, S100 A12 promotes carcinogenic signals, including those involved in tumor proliferation and metastasis [18, 19]. However, in scenarios where S100 A12 is localized to the nucleus or inhibits calcium signaling, it may counteract tumor development [20–22]. This functional versatility is closely associated with its homodimeric conformation and the specific subcellular regions it occupies [23]. Our study demonstrated that S100 A12 expression was significantly lower in papillary thyroid carcinoma (PTC) tissues compared to normal tissues. This observation, combined with cis-pQTL and eQTL Mendelian randomization analyses, suggests that plasma S100 A12 levels may exert an inhibitory effect on PTC. This potential inhibitory role of S100 A12 in PTC could be attributed to its specific distribution within the PTC microenvironment, where it may contribute to a tumor-suppressive phenotype by blocking key signaling pathways, such as calcium-dependent proliferation signals. In the context of PTC's unique immunosuppressive state or genetic mutations like BRAF, these findings could provide novel insights into the pathogenesis and treatment strategies for this disease.

Our study found that LY75 was significantly overexpressed in papillary thyroid carcinoma (PTC) tumor tissues. This finding aligns with previous research that identified the oncogenic properties of LY75 in various solid tumors [24, 25]. However, this study represents the first systematic verification of the positive causal relationship between LY75 expression levels and PTC progression, achieved through cis-pQTL and eQTL Mendelian Randomization analyses. Notably, as a multifunctional molecule with both immune regulatory and signal transduction functions, LY75 likely drives tumor

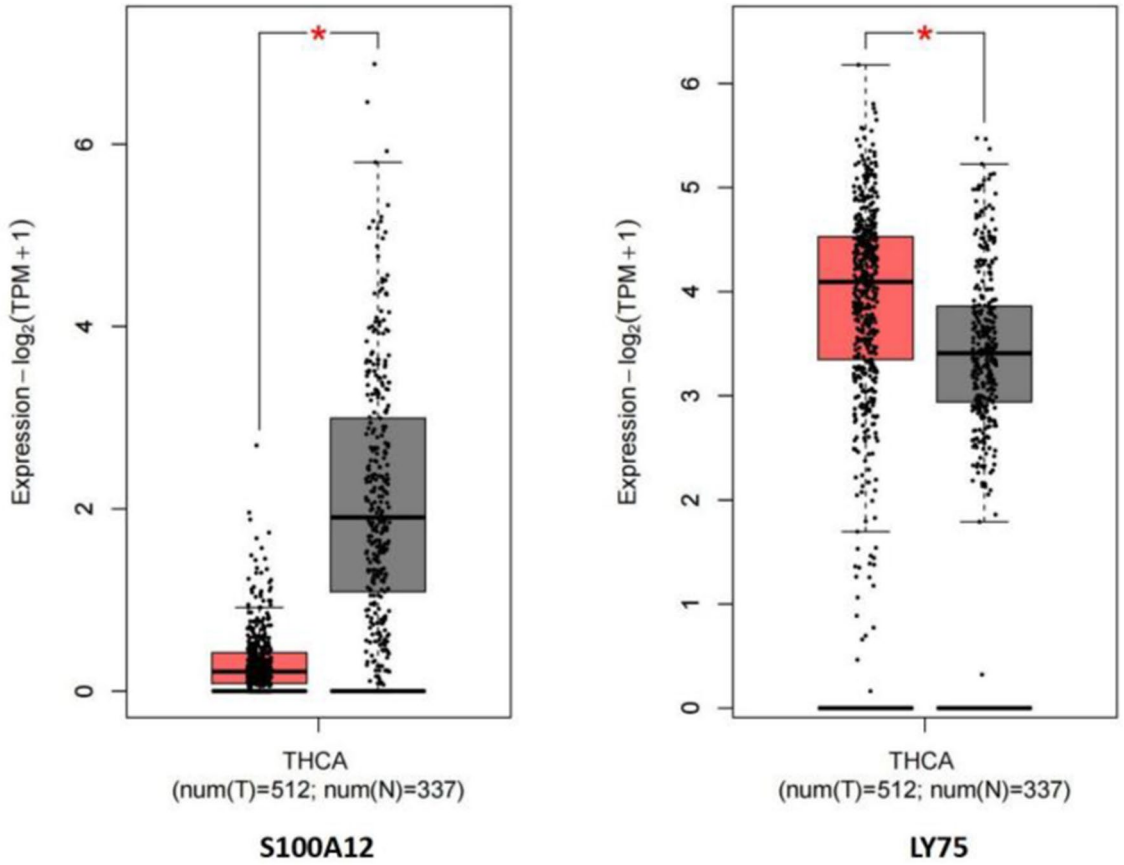

Fig. 4 Differential expression of S100 A12 and LY75 in PTC based on TCGA and GETx databases

Table 3 Mediation effects of immune cells on the total effect between plasma proteins and PTC

Exposure	Mediator	α	β1	β2	Proportion mediated β1*β2/α
LY75	CD8 dim NKT AC	0.0466	− 0.0315	− 0.1935	13%
	CD14 on CD14 + CD16 + monocyte		− 0.0342	− 0.3375	25%
S100 A12	CD25 hi %CD4 + Treg	− 0.3243	− 0.248	0.3023	23%

progression through dual mechanisms. On one hand, it may create an immunosuppressive microenvironment by interacting with immune cells within the tumor microenvironment. On the other hand, its overexpression can significantly activate the Wnt/β-catenin signaling pathway [26], a fact supported by the downstream gene expression profile observed in our study. Aberrant activation of this pathway has been shown to induce epithelial-mesenchymal transition (EMT), facilitating the acquisition of invasive and metastatic capabilities by cancer cells [27]. In contrast to previous studies, our research not only confirmed the elevated expression of LY75 in PTC but also explored its association with the disease in greater depth. These findings provide a novel foundation for the potential application of the LY75 protein in the diagnosis and treatment of PTC.

The interplay between immune components and tumor progression in papillary thyroid carcinoma (PTC) revealed novel regulatory axes in this study. Monocyte subsets and innate lymphocytes exhibited context-dependent roles: CD14 + CD16 + monocytes with reduced CD14 expression demonstrated tumor-protective effects, corroborating previous observations of immune-mediated restraint in early-stage cancers [28, 29]. Mechanistically, CD14 functioned as a critical immunoregulatory node, facilitating pathogen recognition and coordinating anti-tumor responses through T/B-cell activation and inflammatory cytokine release [30, 31]. Strikingly, CD8 low NKT cells similarly conferred protection, likely

through granzyme B/perforin-dependent tumor lysis and IFN-γ-mediated dendritic cell priming—a mechanism aligning with conserved NKT functions in immune surveillance [32]. In contrast, expanded Treg cell infiltration in advanced PTC correlated with disease severity, reflecting their immunosuppressive impact via CTLA-4/CD25-mediated suppression of effector T cells [33]. This imbalance fostered a tolerogenic tumor microenvironment (TME), enabling immune evasion—a hallmark of worse prognosis observed across multiple carcinoma types [34]. Our mediation analysis established LY75 as a driver of PTC progression through dual mechanisms: suppressing CD14 expression in CD14 + CD16 + monocytes and inhibiting CD8 low NKT cell cytotoxicity. These LY75-mediated effects diminished monocyte-derived pro-inflammatory responses while impairing NKT-mediated tumor cell clearance, collectively promoting an immune-permissive TME. Conversely, S100 A12 exerted protective effects by antagonizing CD25 hiCD4+ Treg activity, potentially through calcium-dependent apoptosis induction and CD25 downregulation—mechanisms previously implicated in S100 A12-mediated Treg suppression in other cancer models [35]. These findings delineate a dynamic immune axis in PTC pathogenesis: LY75 fosters immune evasion by crippling monocyte/NKT surveillance, while S100 A12 counters immunosuppression via Treg inhibition. Therapeutically, targeting LY75-CD14 crosstalk could restore myeloid anti-tumor functions, whereas harnessing S100 A12's immunomodulatory capacity may alleviate Treg-mediated suppression. Together, these insights advance the rational design of microenvironment-focused immunotherapies for thyroid malignancies.

To date, numerous MR studies have been published on thyroid cancer, encompassing factors such as thyroid-stimulating hormone [36], trace elements [37], and telomere length [38]. However, our research represents the first to employ combined pQTL and eQTL data in MR analysis for the study of thyroid papillary carcinoma, a specific subtype of the disease. A key advantage of our study was the use of two independent cis-pQTL databases for analysis, a dual strategy that bolstered the reliability of our results. The consistency of findings from two distinct databases independently supported our conclusions, significantly enhancing their credibility. This cross-validation approach, widely accepted in scientific research, is an effective method to enhance the stability and accuracy of results. Moreover, we validated our findings using eQTL data, which not only reinforced our confidence in the results but also provided supplementary evidence. Our approach was further strengthened by integrating tumor differential analysis into bioinformatics, ensuring that our findings were not limited by the constraints of a single database or analysis method. In terms of study design, we implemented stringent screening criteria to ensure the accuracy and effectiveness of the instrumental variable (IV) selection process. By adhering to these rigorous standards and validating key assumptions, we aimed to minimize bias and achieve reliable results in multifactorial association analyses. These meticulous steps were crucial for safeguarding the scientific validity and integrity of our findings, thereby enhancing the overall quality of our research. The two identified biomarkers were statistically significant across all analyses, indicating their potential pivotal roles in the pathogenesis of PTC. These findings could be instrumental in discovering other potential therapeutic targets or diagnostic tools in future studies. In summary, our study offers valuable insights into the in-depth investigation of PTC through innovative methods and rigorous analysis. Additionally, we delved into the potential mechanism of action of the target protein through mediation analysis.

Despite the significant progress made in our study, several limitations have been identified that necessitate further investigation and should be addressed in future research. Firstly, while our analysis of the cis-pQTL data from the TCGA database revealed a correlation between high LY75 expression and PTC, and identified S100 A12 as a potential suppressor, these findings have not been experimentally validated in either laboratory experiments or clinical trials. This underscores the need for subsequent clinical studies to confirm the potential therapeutic implications of these findings prior to their application in the development of new PTC treatments. Secondly, the study did not elucidate the specific mechanism by which S100 A12 exerts its suppressive effects in PTC, nor the detailed role of LY75 in tumor progression. Further research is required to explore these mechanisms in depth, which will be crucial for the development of targeted therapeutic strategies. Additionally, our reliance on eQTL and qQTL data derived from blood samples may have limited our insight into the molecular pathology of PTC. To enhance the understanding of the disease, future studies should include the analysis of eQTL and qQTL data from tumor tissues, which could provide a more comprehensive view of the genetic landscape associated with PTC. Furthermore, our study sample was primarily composed of participants of European ancestry, which may limit the generalizability of our findings to other ethnic groups or populations. The genetic diversity and potential differences in disease manifestation across various populations necessitate the validation of our findings in a more diverse set of populations to ensure broader applicability. In summary, while our study establishes a robust foundation for the development of novel PTC drugs and lays the groundwork for future research and clinical trials, the absence of experimental validation and the limitations of the TCGA dataset underscore areas that necessitate further investigation. Addressing these limitations is crucial for advancing our understanding of PTC and for the development of effective therapeutic approaches.

5 Conclusion

In conclusion, our analysis linked low S100 A12 and high LY75 expression to papillary thyroid carcinoma (PTC) development and progression. These findings suggest that enhancing S100 A12 activity or suppressing LY75 could represent novel therapeutic strategies to counteract immune evasion in PTC. While preclinical validation remains essential to validate efficacy and safety, targeting these molecules may complement existing treatments to improve clinical outcomes. Further research should prioritize testing these approaches in biologically relevant models to advance translation.

Author contributions CHEN GAO wrote the main manuscript text;CHEN GAO prepared Figs. 1, 2, 3, 4,Tables 1, 2, 3 and Tables S1–S5,Jianxiong Xu prepared Figs. 1; All authors reviewed the manuscript.

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Data availability The analytical approach was ethically sound, as all data utilized in this study had received prior approval and consent in their original studies. 1. Proteome data were sourced from the deCODE database (https://www.decode.com/summarydata/) for the Icelandic population [Ferkingstad E,Sulem P,Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53 (12):1712–1721. https://doi.org/10.1038/s41588-021-00978-w], as well as from the UK Biobank Pharmaceutical Proteomics Project (UKB-PPP) (https://www.synapse.org/Synapse:syn51364943/wiki/622119) 2. Blood cis-eQTL data within 1 Mb of the central location of each gene were obtained from the eQTLGen Consortium. 3. 731 immunological features (accession numbers: GCST0001391-GCST0002121) from the GWAS catalog database (https://www.ebi.ac.uk/gwas/) 4. Papillary thyroid carcinoma GWAS statistics were obtained from the Finnish Database Consortium 5. Differential expression data for papillary thyroid carcinoma (PTC) were obtained from the TCGA and GETx databases using the GEPIA2 tool (http://gepia2.cancer-pku.cn/#index).

Declarations

Competing interests The authors declare no competing interests.

References

1. Boucai L, Zafereo M, Cabanillas ME. Thyroid cancer: a review. JAMA. 2024;331(5):425–35. https://doi.org/10.1001/jama.2023.26348.
2. Desai TA, Hedman ÅK, Dimitriou M, et al. Identifying proteomic risk factors for overall, aggressive, and early onset prostate cancer using Mendelian Randomisation and tumour spatial transcriptomics. EBioMedicine. 2024;105: 105168. https://doi.org/10.1016/j.ebiom.2024.105168.
3. Wang K, Yi H, Wang Y, et al. Proteome-wide multicenter Mendelian randomization analysis to identify novel therapeutic targets for lung cancer. Arch Bronconeumol. 2024;60(9):553–8. https://doi.org/10.1016/j.arbres.2024.05.007.
4. Ferkingstad E, Sulem P, Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53(12):1712–21. https://doi.org/10.1038/s41588-021-00978-w.
5. Sun BB, Chiou J, Traylor M, et al. Plasma proteomic associations with genetics and health in the UK Biobank. Nature. 2023;622(7982):329–38. https://doi.org/10.1038/s41586-023-06592-6.
6. Võsa U, Claringbould A, Westra HJ, 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(9):1300–10. https://doi.org/10.1038/s41588-021-00913-z.
7. Orrù V, Steri M, Sidore C, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. Nat Genet. 2020;52(10):1036–45. https://doi.org/10.1038/s41588-020-0684-4.
8. Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362: k601. https://doi.org/10.1136/bmj.k601.
9. Gkatzionis A, Burgess S, Newcombe PJ. Statistical methods for cis-Mendelian randomization with two-sample summary-level data. Genet Epidemiol. 2023;47(1):3–25. https://doi.org/10.1002/gepi.22506.
10. Chen Z, Wang X, Teng Z, et al. Modifiable lifestyle factors influencing psychiatric disorders mediated by plasma proteins: a systemic Mendelian randomization study. J Affect Disord. 2024;350:582–9. https://doi.org/10.1016/j.jad.2024.01.169.

11. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol. 2013;178(7):1177–84. https://doi.org/10.1093/aje/kwt084.
12. Cohen JF, Chalumeau M, Cohen R, et al. Cochran's Q test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. J Clin Epidemiol. 2015;68(3):299–306. https://doi.org/10.1016/j.jclinepi.2014.09.005.
13. Hemani G, Bowden J, Davey SG. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet. 2018;27(R2):R195–208. https://doi.org/10.1093/hmg/ddy163.
14. Verbanck M, Chen CY, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8. https://doi.org/10.1038/s41588-018-0099-7.
15. Sanderson E. Multivariable Mendelian randomization and mediation. Cold Spring Harb Perspect Med. 2021;11(2): a038984. https://doi.org/10.1101/cshperspect.a038984.
16. Carter AR, Sanderson E, Hammerton G, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur J Epidemiol. 2021;36(5):465–78. https://doi.org/10.1007/s10654-021-00757-1.
17. Cai H, Ye BG, Ao JY, et al. High expression of S100A12 on intratumoral stroma cells indicates poor prognosis following surgical resection of hepatocellular carcinoma. Oncol Lett. 2018;16(4):5398–404. https://doi.org/10.3892/ol.2018.9270.
18. Karl J, Wild N, Tacke M, et al. Improved diagnosis of colorectal cancer using a combination of fecal occult blood and novel fecal protein markers. Clin Gastroenterol Hepatol. 2008;6(10):1122–8. https://doi.org/10.1016/j.cgh.2008.04.021.
19. Åberg AM, Bergström SH, Thysell E, et al. High monocyte count and expression of S100A9 and S100A12 in peripheral blood mononuclear cells are associated with poor outcome in patients with metastatic prostate cancer. Cancers (Basel). 2021;13(10):2424. https://doi.org/10.3390/cancers13102424.
20. Mandarino A, Thiyagarajan S, Martins ACF, et al. S100s and HMGB1 crosstalk in pancreatic cancer tumors. Biomolecules. 2023;13(8):1175. https://doi.org/10.3390/biom13081175.
21. Karihtala P, Leivonen SK, Puistola U, et al. Serum protein profiling reveals an inflammation signature as a predictor of early breast cancer survival. Breast Cancer Res. 2024;26(1):61. https://doi.org/10.1186/s13058-024-01812-x.
22. Ning X, Sun S, Hong L, et al. Calcyclin-binding protein inhibits proliferation, tumorigenicity, and invasion of gastric cancer. Mol Cancer Res. 2007;5(12):1254–62. https://doi.org/10.1158/1541-7786.MCR-06-0426.
23. Xia P, Ji X, Yan L, et al. Roles of S100A8, S100A9 and S100A12 in infection, inflammation and immunity. Immunology. 2024;171(3):365–76. https://doi.org/10.1111/imm.13722.
24. Horackova K, Zemankova P, Nehasil P, et al. A comprehensive analysis of germline predisposition to early-onset ovarian cancer. Sci Rep. 2024;14(1):16183. https://doi.org/10.1038/s41598-024-66324-2.
25. Kessler MD, Damask A, O'Keeffe S, et al. Common and rare variant associations with clonal haematopoiesis phenotypes. Nature. 2022;612(7939):301–9. https://doi.org/10.1038/s41586-022-05448-9.
26. Mehdi S, Macdonald E, Galpin K, et al. LY75 suppression in mesenchymal epithelial ovarian cancer cells generates a stable hybrid EOC cellular phenotype, associated with enhanced tumor initiation, spreading and resistance to treatment in orthotopic xenograft mouse model. Int J Mol Sci. 2020;21(14):4992. https://doi.org/10.3390/ijms21144992.
27. Mehdi S, Bachvarova M, Scott-Boyer MP, et al. LY75 ablation mediates mesenchymal-epithelial transition (MET) in epithelial ovarian cancer (EOC) cells associated with DNA methylation alterations and suppression of the Wnt/β-catenin pathway. Int J Mol Sci. 2020;21(5):1848. https://doi.org/10.3390/ijms21051848.
28. Mengos AE, Gastineau DA, Gustafson MP. The CD14 + HLA-DR lo/neg monocyte: an immunosuppressive phenotype that restrains responses to cancer immunotherapy. Front Immunol. 2019;10:1147. https://doi.org/10.3389/fimmu.2019.01147.
29. Heeren AM, Koster BD, Samuels S, et al. High and interrelated rates of PD-L1+CD14+ antigen-presenting cells and regulatory T cells mark the microenvironment of metastatic lymph nodes from patients with cervical cancer. Cancer Immunol Res. 2015;3(1):48–58. https://doi.org/10.1158/2326-6066.CIR-14-0149.
30. Hicks KC, Chariou PL, Ozawa Y, et al. Tumour-targeted interleukin-12 and entinostat combination therapy improves cancer survival by reprogramming the tumour immune cell landscape. Nat Commun. 2021;12(1):5151. https://doi.org/10.1038/s41467-021-25393-x.
31. Fang P, Li X, Dai J, et al. Immune cell subset differentiation and tissue inflammation. J Hematol Oncol. 2018;11(1):97. https://doi.org/10.1186/s13045-018-0637-x.
32. Liu Z, He S, Huang Z, et al. Regulation of ferroptosis-related genes in CD8+ NKT cells and classical monocytes may affect the immunotherapy response after combined treatment in triple negative breast cancer. Thorac Cancer. 2023;14(34):3369–80. https://doi.org/10.1111/1759-7714.15128.
33. Willimsky G, Blankenstein T. Sporadic immunogenic tumours avoid destruction by inducing T-cell tolerance. Nature. 2005;437(7055):141–6. https://doi.org/10.1038/nature03954.
34. Galdiero MR, Varricchi G, Marone G. The immune network in thyroid cancer. Oncoimmunology. 2016;5(6): e1168556. https://doi.org/10.1080/2162402X.2016.1168556.
35. Kang JH, Zappasodi R. Modulating Treg stability to improve cancer immunotherapy. Trends Cancer. 2023;9(11):911–27. https://doi.org/10.1016/j.trecan.2023.07.015.
36. Zhou W, Brumpton B, Kabil O, et al. GWAS of thyroid stimulating hormone highlights pleiotropic effects and inverse association with thyroid cancer. Nat Commun. 2020;11(1):3981. https://doi.org/10.1038/s41467-020-17718-z.
37. Shen J, Zhang H, Jiang H, et al. The effect of micronutrient on thyroid cancer risk: a Mendelian randomization study. Front Nutr. 2024;11:1331172. https://doi.org/10.3389/fnut.2024.1331172.
38. Chen B, Yan Y, Wang H, et al. Association between genetically determined telomere length and health-related outcomes: a systematic review and meta-analysis of Mendelian randomization studies. Aging Cell. 2023;22(7): e13874. https://doi.org/10.1111/acel.13874.