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Exploring the Molecular and Immune Mechanisms Linking Hypothyroidism to Hepatocellular Carcinoma

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Abstract: *Background:* Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide, and endocrine, metabolic, and immune factors influence its occurrence and progression. Hypothyroidism (HT) is a common endocrine disorder that may affect cancer risk; however, its relationship with HCC remains unclear. *Objective:* This study aimed to investigate the potential molecular and immune mechanisms underlying the association between HT and HCC, with a focus on the regulatory effects of HT-related genetic variants on the hepatic tumor immune microenvironment. *Methods:* Single-nucleotide polymorphisms (SNPs) associated with HT and HCC identified through Mendelian randomization were functionally annotated using the Ensembl Genome Browser and mapped to candidate genes. Functional enrichment and pathway analyses were performed with Metascape. Differentially expressed target genes between HCC and normal liver tissues were screened using GEPIA2, and their protein expression levels were validated in the Human Protein Atlas (HPA) database. The association between target gene expression and immune cell infiltration was further evaluated using TIMER2.0. *Results:* A total of 68 candidate genes were analyzed. Enrichment analysis revealed that these genes are involved in IFN-γ–mediated immune responses, PI3K/AKT and RAC1 signaling pathways, and other immune regulatory processes. Among them, HLA-DQA1, HLA-DPB1, HLA-DQA2, and PVT1 showed significant differential expression in HCC. HLA-DQA1, HLA-DPB1, and HLA-DQA2 were positively correlated with $CD8^+$ T cells, regulatory T cells (Tregs), and M2 macrophages, suggesting that these genes may exert bidirectional effects on antitumor immunity and immunosuppression. PVT1 may influence the immune microenvironment by regulating myeloid cell recruitment and extracellular matrix remodeling. *Conclusion:* HLA-DQA1, HLA-DPB1, HLA-DQA2, and PVT1 may reduce the risk of HCC by enhancing IFN-γ–mediated antitumor immunity and modulating key signaling pathways, while also contributing to immune microenvironment remodeling. These findings provide mechanistic insights into the protective effects of HT on HCC and suggest potential targets for immunotherapeutic strategies.

Keywords: Hepatocellular carcinoma; Hypothyroidism; Immune microenvironment; HLA; PVT1

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide, with its incidence and mortality rates consistently ranking among the highest for malignant neoplasms globally [1]. Recent studies have revealed that the occurrence and progression of HCC are closely associated with multiple factors, including endocrine dysregulation, metabolic abnormalities, and immune imbalance [2]. Hypothyroidism (HT) is a common endocrine disorder in clinical practice, typically characterized by elevated serum thyroid-stimulating hormone (TSH) levels accompanied by reduced synthesis of triiodothyronine (T3) and/or thyroxine (T4). In iodine-sufficient regions, autoimmune diseases such as Hashimoto's thyroiditis are the leading causes of HT [3].

Previous studies have shown that thyroid hormones may regulate tumor initiation and progression through multiple mechanisms. For instance, thyroid hormones and TSH can directly participate in tumorigenesis by acting through cell surface receptor–mediated signaling, modulating estrogen signaling pathways, promoting angiogenesis, and regulating gene expression [4]. In addition, HT frequently coexists with chronic conditions such as diabetes and cardiovascular disease, which are closely associated with increased cancer risk [5]. Epidemiological studies have demonstrated substantial heterogeneity in the association between HT and various types of cancer. Some studies have suggested that HT is associated with increased risks of thyroid and breast cancers [6], whereas other large-scale cohort studies have not observed significant associations between HT and overall or site-specific cancer risks [7].

However, current observational studies investigating the association between HT and HCC remain controversial and are prone to confounding by factors such as age, underlying liver disease (e.g., hepatitis B or C infection), and metabolic status, making it difficult to accurately infer a causal relationship. Mendelian randomization is an epidemiological approach that uses genetic instrumental variables (IVs) to infer causal relationships between exposures and outcomes [8], thereby reducing confounding inherent in traditional observational studies. Recent studies employing Mendelian randomization have suggested an inverse causal association between HT and HCC [9]. However, thyroid hormone indices such as TSH and free thyroxine (FT4) have not shown significant causal relationships with HCC [9], indicating that the effects of HT on HCC may involve complex underlying biological mechanisms.

Based on these findings, the present study aims to further investigate the potential biological mechanisms of HT in HCC. We systematically analyze the differential expression patterns and immune infiltration characteristics of genes mapped by HT-related single-nucleotide polymorphisms (SNPs) in HCC tissues, thereby exploring the potential mechanisms through which these genes may influence HCC development by modulating the tumor immune microenvironment. Through this study, we aim to provide molecular and immunological evidence supporting the association between HT and HCC and to offer potential directions for the development of early intervention strategies and immunotherapeutic targets for HCC.

2. Materials and methods

2.1. Overall study design

This study aims to investigate the potential causal relationship between HT and HCC and to elucidate the underlying mechanisms (**Figure 1**). SNPs associated with HT and HCC were functionally annotated using the Ensembl database to identify their corresponding genes. Subsequently, the identified genes were subjected to pathway and functional enrichment analyses using the Metascape platform to uncover the potential biological processes and signaling pathways underlying the association between HT and HCC. Differential expression and prognostic significance of these genes in HCC and normal liver tissues were then analyzed using the GEPIA2 database, and protein-level validation was performed using immunohistochemistry data from The Human Protein Atlas (HPA) database. To further elucidate the immunological context, the TIMER2.0 platform was employed to systematically assess the infiltration levels of various immune cell populations, including $CD8^+$ T cells, regulatory T cells (Tregs), macrophage subtypes (M0, M1, and M2), cancer-associated fibroblasts (CAFs), neutrophils, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs).

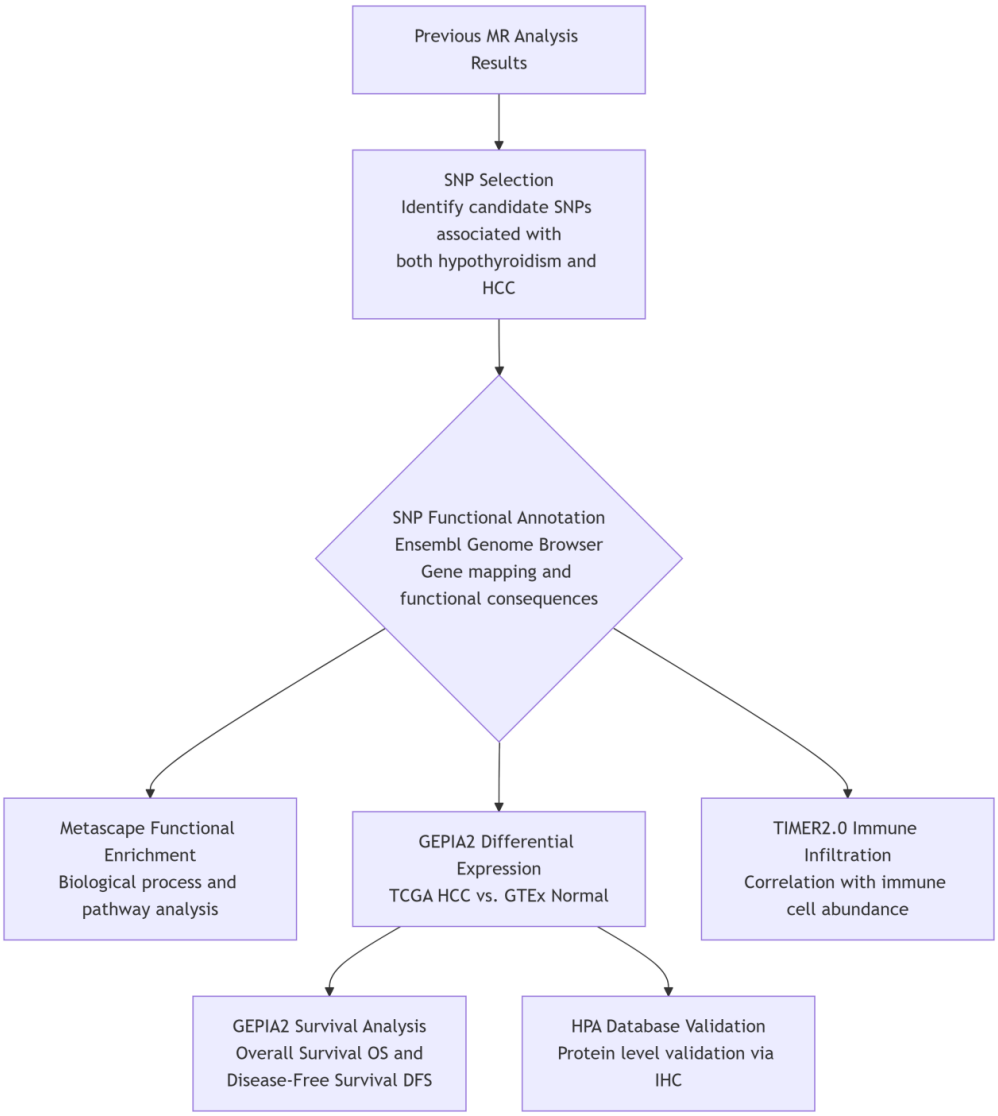

Figure 1. Experimental design flow chart.

2.2. Data sources

This study builds upon a previously published Mendelian randomization (MR) analysis [9], which indicated a significant inverse causal relationship between HT and HCC. Based on this, we further extracted the SNPs identified in the MR analysis that were associated with HT and significantly related to HCC, using these as candidate genetic variants for downstream analyses.

2.3. SNP functional annotation analysis

Functional annotation and gene mapping of the candidate SNPs were performed using the Ensembl Genome Browser (https://www.ensembl.org/) [10]. For each locus, we retrieved the chromosomal location, functional category (e.g., missense mutation, synonymous mutation, promoter region, intronic region, or regulatory region), and the corresponding target gene information.

2.4. Metascape functional enrichment analysis

Metascape (http://metascape.org/gp/index.html#/main/step1) is a comprehensive bioinformatics platform that integrates more than 40 distinct biological databases and provides various functions, including interactive analysis and gene annotation [11]. The study used Metascape to perform rapid gene expression profiling and functional enrichment analyses of the identified differentially expressed genes.

2.5. Differential expression analysis

Differential expression of candidate genes between HCC tissues (from The Cancer Genome Atlas, TCGA) and normal liver tissues (from the Genotype-Tissue Expression, GTEx, database) was analyzed using the GEPIA2 platform (http://gepia2.cancer-pku.cn/) [12]. The analysis was based on $\log_2$(TPM+1)–normalized expression values, and a univariate differential expression test was performed. Subsequently, survival analyses were conducted using the GEPIA2 platform, including overall survival (OS) and disease-free survival (DFS). Kaplan–Meier curves were generated to visualize survival outcomes, and the significance of differences was assessed using the log-rank test, with p-values < 0.05 considered statistically significant.

2.6. Protein level validation

To validate the protein-level expression of the differentially expressed genes, immunohistochemistry (IHC) results were retrieved from The Human Protein Atlas (HPA) database (https://www.proteinatlas.org/) [13] to compare protein expression between HCC and normal liver tissues. The available HPA data were used to support the validation of transcriptional results obtained from GEPIA2 analyses.

2.7. Immune infiltration analysis

To investigate the potential roles of candidate genes in the tumor immune microenvironment, correlations between candidate gene expression and the infiltration levels of various immune cells were analyzed using the TIMER2.0 database (http://timer.cistrome.org/) [14]. The immune cell types analyzed included $CD8^+$ T cells, regulatory T cells (Tregs), macrophage subtypes (M0, M1, and M2), cancer-associated fibroblasts (CAFs), neutrophils, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs). Spearman correlation analysis was used to assess the relationships between gene expression and immune cell infiltration levels, with a significance threshold set at p < 0.05.

3. Results

3.1. SNP functional annotation analysis

To further investigate the potential functions and biological significance of the SNPs identified in the Mendelian randomization analysis of HT and HCC, we performed a systematic functional annotation of these SNPs. The 71 highly associated SNPs selected from the results were first deduplicated and then functionally annotated using the Variant Effect Predictor (VEP) tool provided by the Ensembl database, identifying the genomic location, potential functional effects, and associations with diseases or phenotypes for each SNP. After deduplication, 68 target genes were ultimately selected for subsequent analyses.

3.2. Functional enrichment analysis

3.2.1. Pathway and process enrichment analysis

Enrichment analysis of genes corresponding to the SNPs identified in the MR analysis revealed that these genes were primarily involved in immune regulation and cell signaling pathways (**Figure 2**). The most significant enrichment was observed in the autoimmune thyroid disease pathway (hsa05320, $Log_{10}P = –7.16$), suggesting a close association between HT-related genetic variants and immune function. Further analysis showed that the gene set was significantly enriched in the positive regulation of immune response (GO:0050778) and positive regulation of type II interferon production (GO:0032729), indicating that these genes may participate in antitumor processes by enhancing interferon signaling pathways. In addition, the RAC1 regulatory pathway (PID RAC1 REG PATHWAY) and PI3K/AKT signaling pathway (GO:0051896) were also significantly enriched, both of which are key drivers of cell proliferation and survival. Moreover, the gene set showed enrichment trends in the negative regulation of myeloid cell differentiation (GO:0045638), inflammatory response (GO:0006954), and macrophage efferocytosis (hsa04148), suggesting that these genes may play roles in modulating the inflammatory environment and immune cell functions.

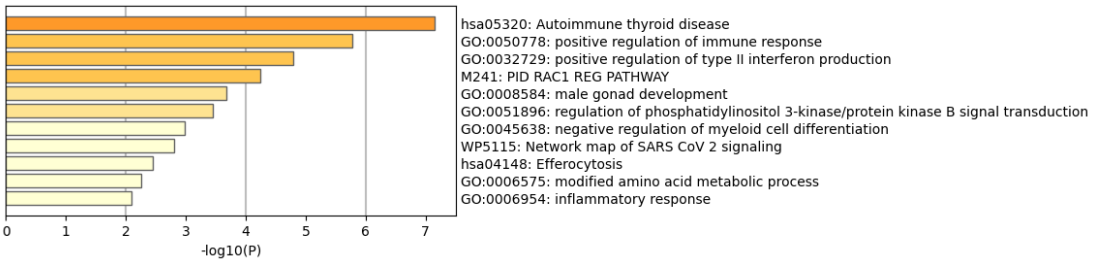

Figure 2. Pathway and process enrichment analysis.

3.2.2. DisGeNET11 disease association analysis

DisGeNET[11] analysis revealed that HT-related genes were significantly enriched in multiple autoimmune diseases (**Figure.** 3), including hypothyroidism (35 genes, 59%, $Log_{10}P = –44.00$, $Log_{10}q = –40.00$), Hashimoto's disease (13 genes, 22%, $Log_{10}P = –13.00$, $Log_{10}q = –9.50$), Graves' disease (18 genes, 31%, $Log_{10}P = –16.00$, $Log_{10}q = –13.00$), celiac disease (18 genes, 31%), and autoimmune chronic hepatitis (10 genes, 17%). Additionally, enrichment was observed for blood thyroid-stimulating hormone analysis (4 genes, 6.8%) and autoimmune hepatitis with central lobular necrosis (4 genes, 6.8%). These findings indicate that HT-related genes are highly associated with various autoimmune diseases and may participate in the negative regulation of HCC development by modulating the hepatic microenvironment through systemic immune regulation.

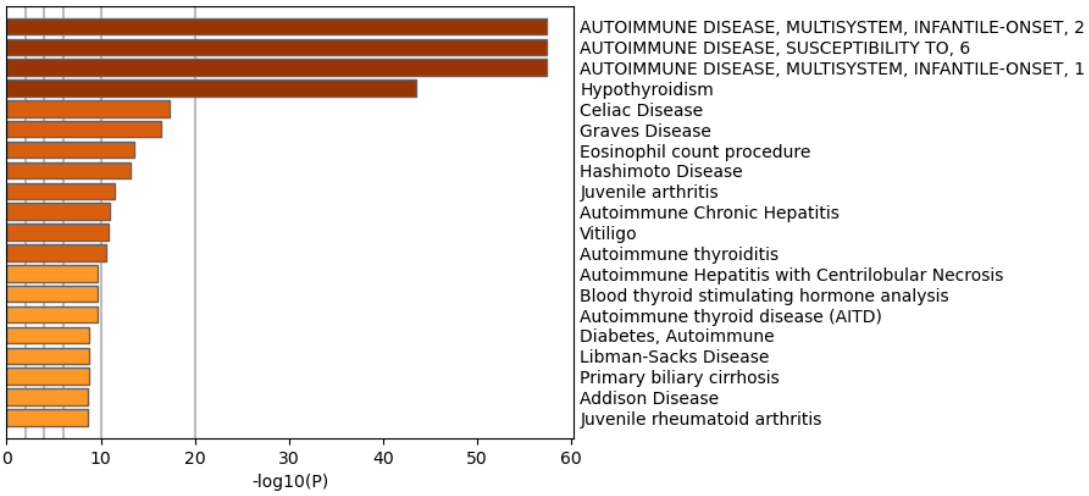

Figure 3. DisGeNET11 disease association analysis.

3.2.3. PaGenBase tissue/cell specificity analysis

PaGenBase analysis revealed that HT-related genes exhibited tissue- or cell-specific expression, including thyroid tissue (5 genes, 8.5%, $Log_{10}P = –4$, $Log_{10}q = –1.50$) and HL60 cells (3 genes, 5.1%, $Log_{10}P = –3$, $Log_{10}q = –0.68$). This suggests that some of the identified genes may participate in systemic or local immune and metabolic regulation through thyroid- or blood cell-specific functions.

3.2.4. TRRUST Transcription factor regulation analysis

TRRUST analysis indicated that RFX family transcription factors (RFXANK, RFXAP, RFX5) each regulated three genes (5.1%, $Log_{10}P = –5.40$ to $–5.20$, $Log_{10}q = –2.60$ to $–2.40$). This suggests that the RFX family may play a critical role in regulating the expression of HT-related genes and modulating immune functions.

3.2.5. Transcription factor target analysis

Transcription factor target analysis revealed significant enrichment of PRDM5 target genes (3 genes, 5.1%, $Log_{10}P = –2.80$, $Log_{10}q = –0.46$), STAT4 01 (4 genes, 6.8%, $Log_{10}P = –2.70$), STAT5A 03 (4 genes, 6.8%, $Log_{10}P = –2.70$), and STAT6 01 (4 genes, 6.8%, $Log_{10}P = –2.70$); TERF2 and ZNF507 target genes included 3 and 5 genes, accounting for 5.1% and 8.5%, respectively. These results suggest that transcription factors such as STATs and PRDM5 may participate in cell signaling, immune regulation, and maintenance of cellular homeostasis by regulating HT-related genes.

3.3. Differentially expressed genes and protein level verification

Differential expression analysis of 68 selected genes between liver hepatocellular carcinoma (LIHC) and normal tissues was performed using GEPIA2 (**Figures 4**–**6**), which identified four significantly differentially expressed genes: HLA-DQA1, HLA-DPB1, PVT1, and HLA-DQA2. Subsequent analysis of OS and DFS revealed no significant association between these four genes and patient survival. Protein-level validation using The Human Protein Atlas indicated that HLA-DQA1 and HLA-DPB1 were markedly overexpressed in HCC tissues compared with normal liver tissues, consistent with the differential expression results obtained from GEPIA2. IHC images for PVT1 and HLA-DQA2 were unavailable.

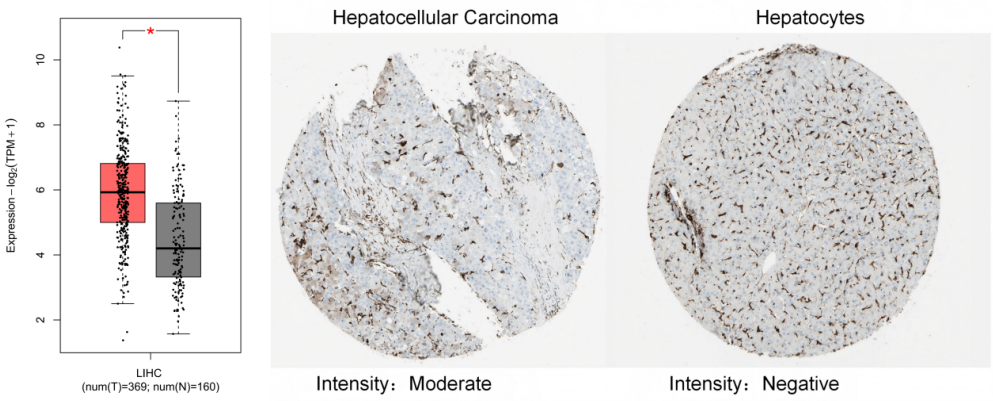

Figure 4. HLA-DPB1 differential expression analysis.

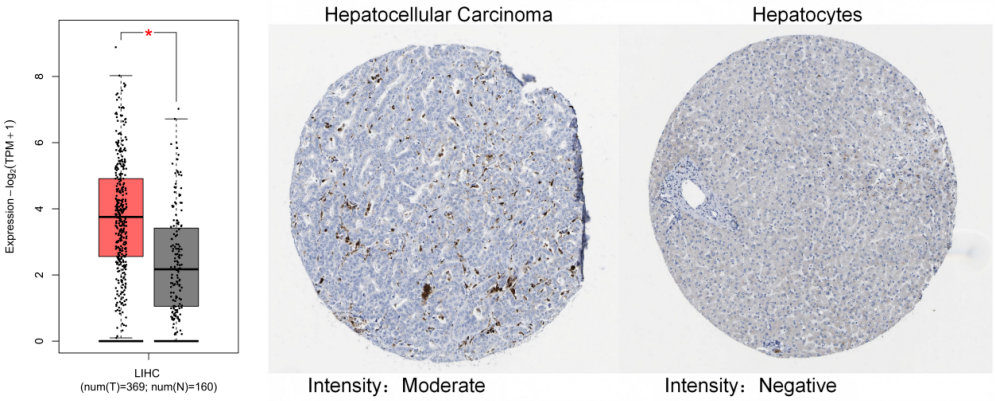

Figure 5. HLA-DQA1 differential expression analysis.

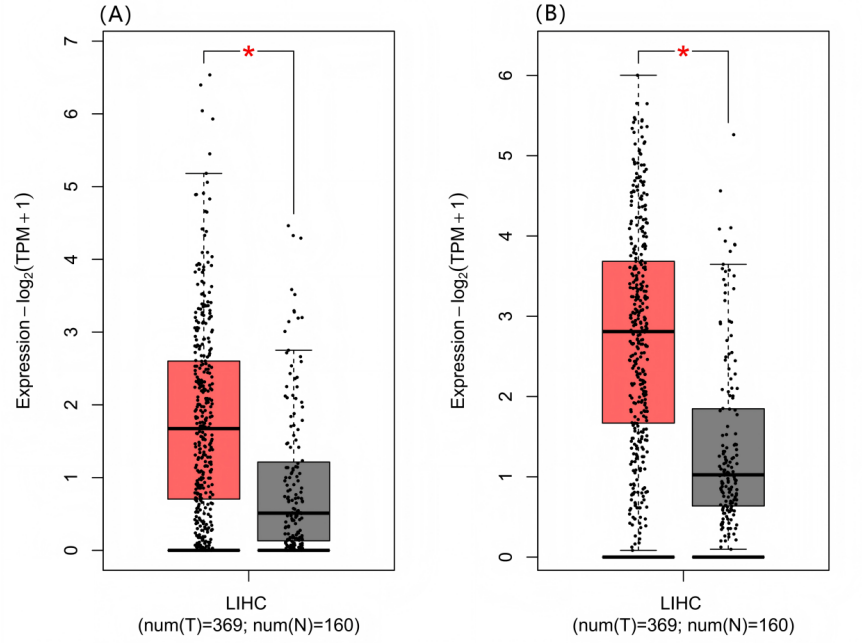

Figure 6. Differential expression of (A)HLA-DQA2 and (B)PVT1 in LHCC.

3.4. Immune infiltration analysis

Using the TIMER2.0 platform, correlations between the differentially expressed genes HLA-DQA1, HLA-DPB1, PVT1, and HLA-DQA2 and the infiltration levels of various immune cell types were analyzed (**Figures 7–10**). In HCC tissues, HLA-DQA1 expression was significantly positively correlated with Tregs (Rho = 0.674, $P = 5.64 \times 10^{-47}$), $CD8^+$ T cells (Rho = 0.637, $P = 1.28 \times 10^{-40}$), M2 macrophages (Rho = 0.612, $P = 6.90 \times 10^{-37}$), and activated NK cells (Rho = 0.510, $P = 2.93 \times 10^{-24}$), while showing a significant negative correlation with tumor purity (Rho = –0.476, $P = 5.91 \times 10^{-21}$), suggesting higher expression in immune-infiltrated tumor microenvironments. HLA-DPB1 was significantly positively correlated with Tregs (Rho = 0.708, $P = 9.39 \times 10^{-54}$), M2 macrophages (Rho = 0.674, $P = 5.85 \times 10^{-47}$), and $CD8^+$ T cells (Rho = 0.463, $P = 9.26 \times 10^{-20}$), and negatively correlated with tumor purity (Rho = –0.478, $P = 3.59 \times 10^{-21}$), indicating potential involvement in both immunosuppressive and immunoactive cellular processes. HLA-DQA2 was significantly positively correlated with Tregs (Rho = 0.462, $P = 1.27 \times 10^{-19}$), M1 macrophages (Rho = 0.331, $P = 2.97 \times 10^{-10}$), M2 macrophages (Rho = 0.479, $P = 3.35 \times 10^{-21}$), $CD8^+$ T cells (Rho = 0.386, $P = 1.02 \times 10^{-13}$), and MDSCs (Rho = 0.237, $P = 8.28 \times 10^{-6}$), while negatively correlating with tumor purity (Rho = –0.243, $P = 4.90 \times 10^{-6}$). Overall, PVT1 exhibited weaker correlations with immune cell infiltration compared to HLA genes, showing positive associations with M0 macrophages (Rho = 0.261, $P = 8.8 \times 10^{-7}$), cancer-associated fibroblasts (Rho = 0.187, $P = 4.77 \times 10^{-4}$), and neutrophils (Rho = 0.143, $P = 7.62 \times 10^{-3}$), but no significant correlation with $CD8^+$ T cells (Rho = –0.033, $P > 0.05$).

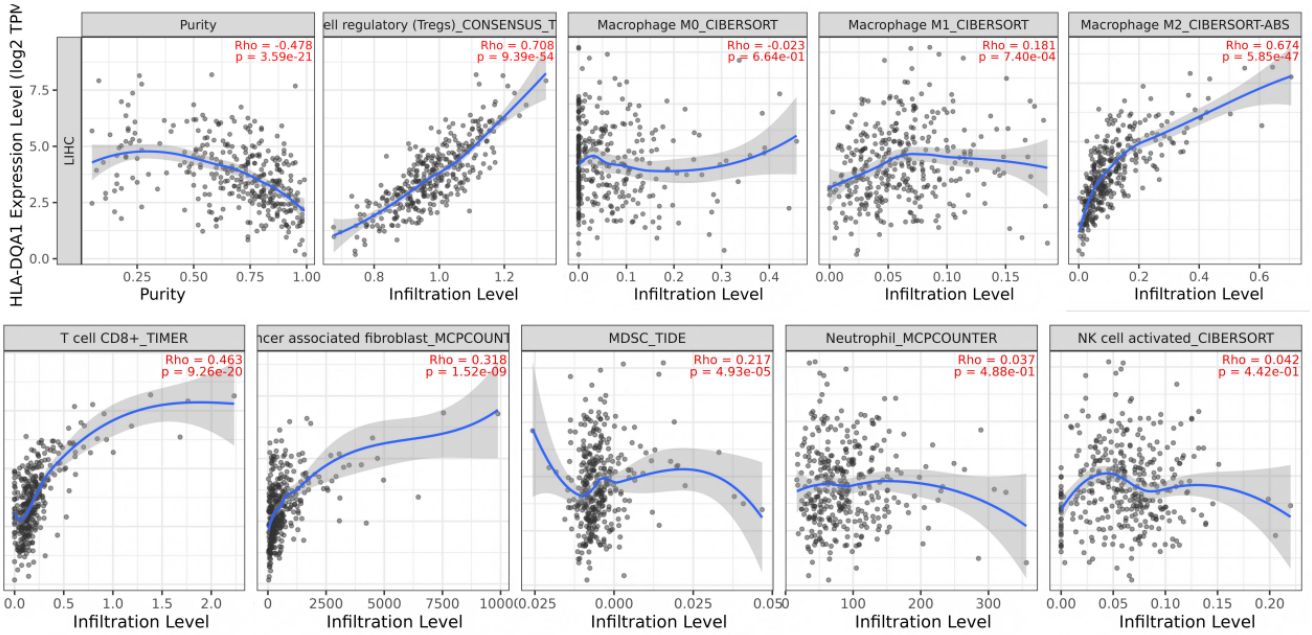

Figure 7. HLA-DQA1 Immune infiltration analysis.

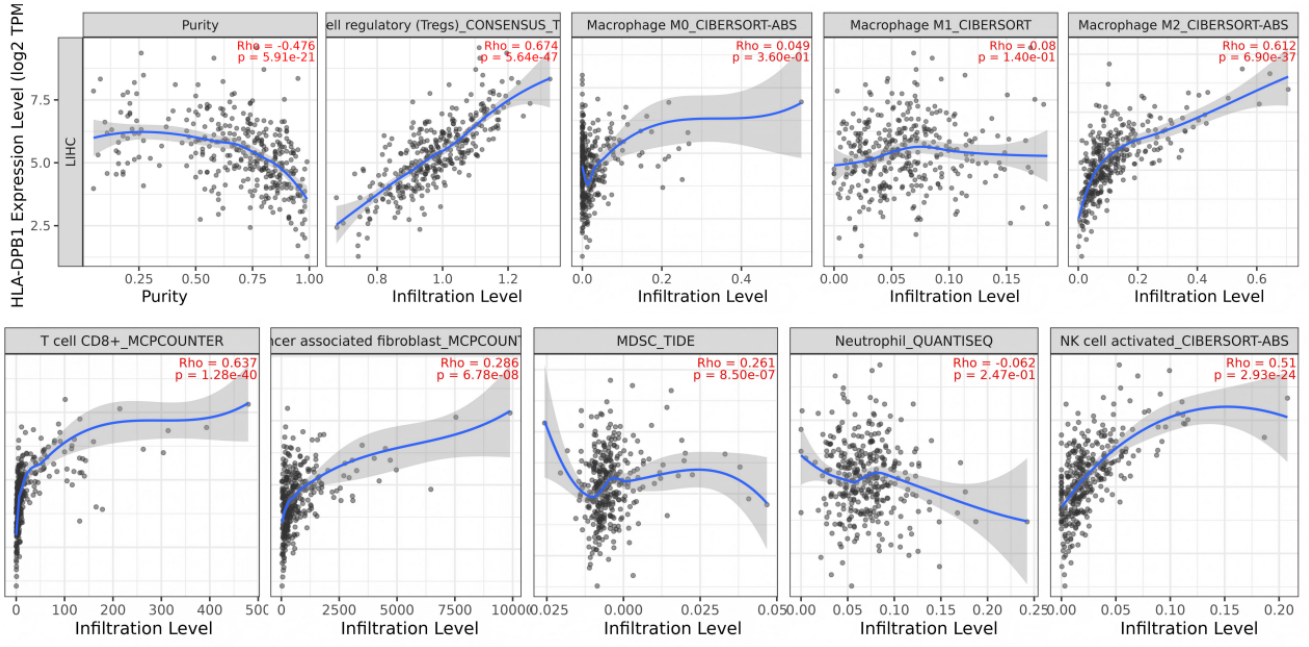

Figure 8. HLA-DPB1 Immune infiltration analysis.

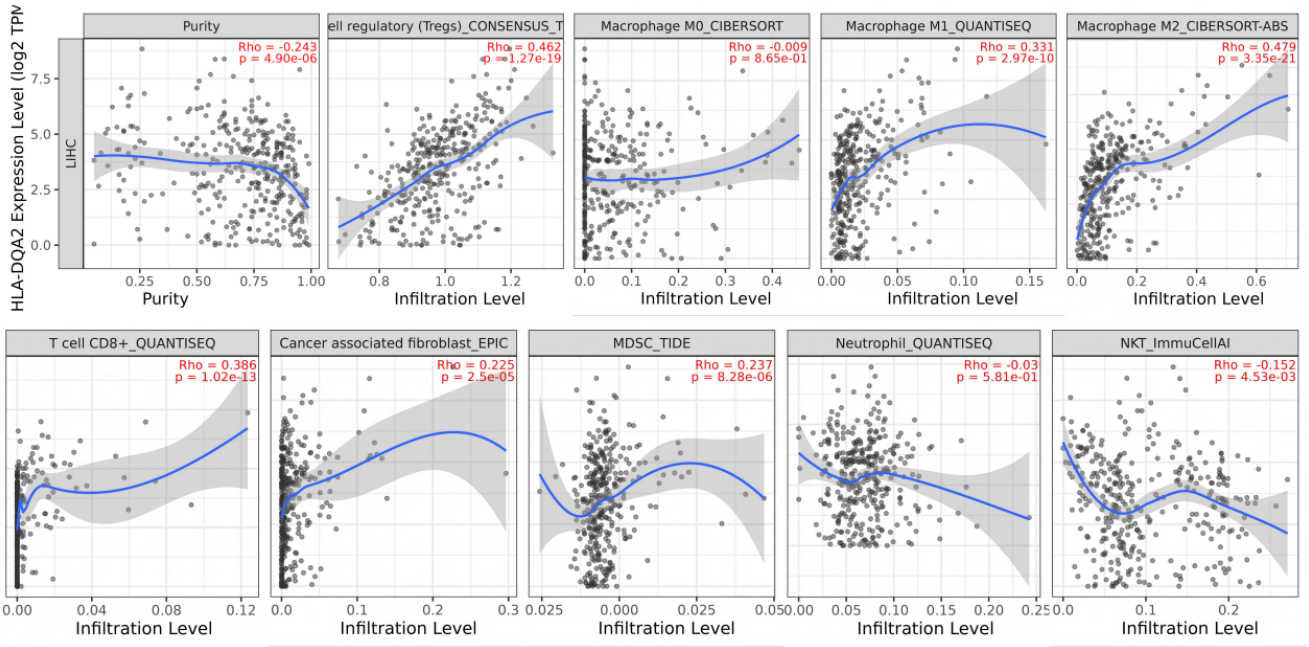

Figure 9. HLA-DQA2 Immune infiltration analysis.

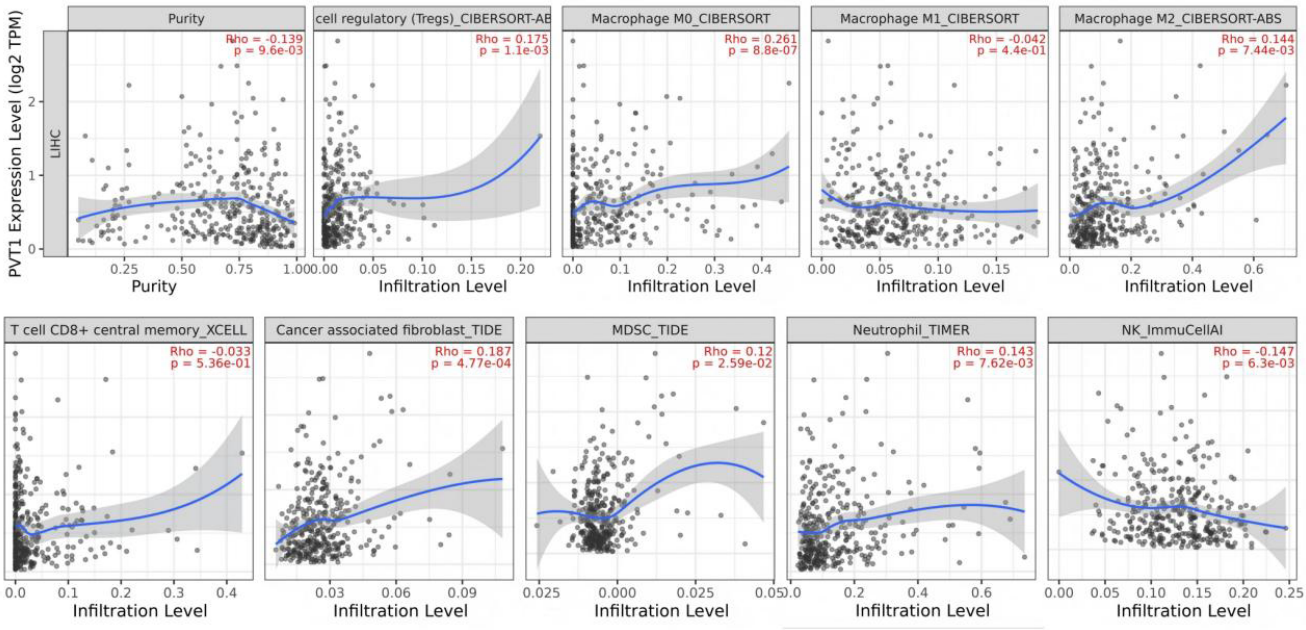

Figure 10. PVT1 Immune infiltration analysis.

4. Discussion

This study systematically explored the potential molecular mechanisms linking hypothyroidism (HT) and hepatocellular carcinoma (HCC) by integrating Mendelian randomization results with multi-level bioinformatic analyses. Initially, pathway enrichment analysis was performed to characterize the signaling features of HT-associated genes, followed by differential expression and immune infiltration analyses, which further identified HLA-DQA1, HLA-DPB1, HLA-DQA2, and PVT1 as key genes potentially involved in modulating the immune microenvironment of HCC.

4.1.The potential molecular mechanism of HT and HCC negative correlation

Pathway enrichment analysis indicated that HT-associated genes were primarily enriched in type II interferon (IFN-γ) signaling and positive regulation of immune response pathways. IFN-γ, a key cytokine in antitumor immunity, enhances antigen presentation, promotes cytotoxic T lymphocyte (CTL) activation, and induces tumor cell apoptosis [15]. Thus, the genetic background associated with HT may enhance IFN-γ-mediated immune surveillance, improving the clearance of abnormal hepatocytes and thereby exerting a protective effect.

Additionally, enrichment of PI3K/AKT and RAC1 signaling pathways suggests that HT may suppress key axes promoting cell proliferation and migration, thereby attenuating HCC initiation and progression. This is consistent with previous studies indicating the role of thyroid hormones in PI3K/AKT regulation [16], further supporting a molecular explanation for the inverse association between HT and HCC.

Disease association analysis using DisGeNET revealed that HT-associated genes are closely linked to multiple autoimmune diseases, particularly thyroid autoimmune disorders and autoimmune hepatitis. This suggests that HT may indirectly improve the hepatic microenvironment through heightened immune responses, thereby inhibiting HCC development. Tissue- and cell-specific analyses demonstrated that HT-associated genes exhibit specific expression in thyroid tissue and blood cells (HL60), further suggesting that they may mediate hepatoprotective

effects via systemic immune and metabolic regulation.

Transcription factor analysis indicated that RFX, STAT, and PRDM5 families play crucial roles in regulating HT-associated genes. The STAT family is involved in cell proliferation, apoptosis, and inflammation regulation, whereas the RFX family serves as a key regulator of MHC gene expression. These findings suggest that the genetic background associated with HT may modulate immune homeostasis and inflammatory responses through transcriptional regulatory networks, thereby exerting systemic inhibitory effects on HCC.

HT-associated genes were significantly enriched in inflammatory responses, negative regulation of myeloid cell differentiation, and macrophage efferocytosis. These processes are crucial for alleviating chronic inflammation, facilitating clearance of necrotic cells, and mitigating liver fibrosis, suggesting that HT may indirectly reduce HCC risk by improving the hepatic immune microenvironment.

4.2.The significance of differentially expressed genes and immune infiltration

4.2.1.The roles of the HLA-DQA1, HLA-DPB1, and HLA-DQA2 genes

HLA-DQA1, HLA-DPB1, and HLA-DQA2 are MHC class II molecules primarily responsible for presenting exogenous antigens and regulating $CD4^+$ T cell activation [17]. In this study, these genes were found to be differentially overexpressed in HCC. Although no significant associations were observed in OS or DFS analyses, immune infiltration analysis revealed strong correlations with $CD8^+$ T cells, Tregs, and M2 macrophages, suggesting the presence of both immune-activating and immunosuppressive signals within the tumor microenvironment. On one hand, high expression of MHC II molecules may enhance antigen presentation efficiency, thereby activating $CD4^+$ T cells and indirectly stimulating $CD8^+$ T cell-mediated antitumor responses, potentially inhibiting tumor growth in early stages or under specific conditions. On the other hand, aberrant or sustained high expression of HLA molecules may promote Treg recruitment or activate myeloid-derived suppressor cells, indirectly facilitating tumor immune tolerance and immune evasion. Previous studies have also indicated that abnormal expression of HLA II genes in cancers can impact antigen presentation pathways and T cell function [18]. Collectively, these findings suggest that HLA-DQA1, HLA-DPB1, and HLA-DQA2 may exert bidirectional regulation within the HCC immune microenvironment, simultaneously participating in antitumor immune activation and promoting immunosuppression and tumor escape. This dual role provides a potential mechanistic explanation for the inverse association between hypothyroidism and HCC and indicates that these genes may contribute to hypothyroidism-associated susceptibility to HCC via modulation of the tumor immune microenvironment.

4.2.2. The roles of PVT1 of the gene

PVT1, located on human chromosome 8q24.21, is a prototypical oncogenic long non-coding RNA (lncRNA) that promotes tumor progression through multiple mechanisms in various cancers [19], including acting as a miRNA sponge, stabilizing oncogenic proteins such as MYC, modulating epigenetic regulatory complexes, and mediating intercellular communication via exosomes to influence immune cell behavior. In this study, PVT1 was found to be significantly overexpressed in HCC, suggesting its potential involvement in hepatocarcinogenesis. Although no significant associations were observed in overall survival (OS) or disease-free survival (DFS) analyses, immune infiltration analysis using TIMER2.0 suggests that PVT1 may modulate the tumor immune microenvironment. Potential mechanisms include PVT1 promoting the recruitment of myeloid cells and their polarization toward immunosuppressive M2 macrophages via upregulation of chemokines or TGF-β signaling, or indirectly

modulating immune cell infiltration and function by activating cancer-associated fibroblasts (CAFs) to remodel the extracellular matrix and cytokine network. This effect likely occurs primarily at the stage of macrophage precursor recruitment, followed by polarization toward immunosuppressive phenotypes under tumor microenvironmental signals, suggesting that PVT1 may facilitate immune evasion in HCC through microenvironmental remodeling. Previous studies have demonstrated that PVT1 can competitively bind miRNAs, such as miR-143-3p and miR-214, to regulate downstream target gene expression [20], thereby promoting HCC cell proliferation, migration, and invasion, and stabilizing NOP2 to enhance tumor stem-like properties. Functional studies further indicate that PVT1 knockdown suppresses tumor cell proliferation and induces apoptosis [21], highlighting its potential as a therapeutic target for HCC.

4.3. Limitations

This study primarily relied on publicly available databases and bioinformatic analyses to systematically investigate the expression patterns and potential immunoregulatory roles of HT-related SNP-targeted genes in HCC. However, several limitations should be noted. First, the analyses were based solely on in silico approaches, lacking experimental validation; therefore, the observed gene expression differences and correlations with immune infiltration require confirmation through in vitro or in vivo experiments. Second, the molecular mechanisms underlying the causal relationship between HT and HCC remain incompletely elucidated. Although Mendelian randomization analyses suggest a negative association, prior literature indicates that HT-related hormonal indices (e.g., TSH, FT4) have not been shown to exert direct causal effects on HCC. Thus, further studies combining clinical samples and functional experiments are needed to clarify how HT may influence HCC development. Third, the immune microenvironment analysis was limited to gene expression correlations and cannot fully reflect the functional state or spatial distribution of immune cells within tumors.

Future research could be expanded in several directions. On one hand, functional experiments using clinical cohorts or in vitro/in vivo models should validate the roles of PVT1, HLA-DQA1, HLA-DPB1, and HLA-DQA2 in the HCC immune microenvironment, including their effects on macrophage polarization, Treg modulation, and antigen-presenting capacity. On the other hand, investigating the dynamic relationship between HT-related hormone levels and immune regulatory pathways may reveal the molecular mechanisms by which HT reshapes the HCC immune landscape. Multi-omics integrative analyses, such as transcriptomics, single-cell sequencing, and spatial omics, could further elucidate the complex interactions among tumor, immunity, and metabolism, providing theoretical foundations for early risk assessment and precision interventions in HT-associated HCC.

5. Conclusion

This study, based on Mendelian randomization results and bioinformatic analyses, systematically explored the potential mechanisms linking HT and HCC. HT-related genes may reduce HCC risk by enhancing IFN-γ-mediated antitumor immunity and suppressing the PI3K/AKT and RAC1 signaling axes. Key genes, including HLA-DQA1, HLA-DPB1, HLA-DQA2, and PVT1, potentially modulate the tumor immune microenvironment, influence myeloid cell polarization, and remodel the extracellular matrix, thereby exerting bidirectional regulation of both immune activation and immunosuppression. This study provides mechanistic insights into the protective effects of HT on HCC and identifies potential targets for immune-based interventions.

Disclosure statement

The authors declare no conflict of interest.

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