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Identification of potential biomarkers in follicular thyroid carcinoma: bioinformatics and immunohistochemical analyses

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Abstract

Objectives: The prevalence of thyroid cancer has shown a progressive rise over time. This study aimed to explore the expression and underlying mechanisms of decorin (DCN) in follicular thyroid carcinoma (FTC), employing bioinformatics analysis and immunohistochemistry techniques.

Methods: The GSE27155 dataset was obtained from the Gene Expression Omnibus database. Differentially expressed genes (DEGs) and core DEGs were identified through data mining and analysis using the R language and online databases. The expression of core DEGs was validated using The Cancer Genome Atlas database. Additionally, the correlation between DCN and clinicopathological stage, tumor-infiltrating lymphocytes, and hotspot molecules in thyroid cancer was assessed using the Gene Expression Profiling Interactive Analysis and TIMER databases. Immunohistochemical (IHC) analysis was then conducted to verify the differential expression of core DCN in FTC and adjacent tissues.

Results: We confirmed the downregulation of three DEGs (DCN, GPC3, and PDGFRA). Furthermore, the analysis revealed a significant association between DCN expression and the clinical stage of patients with thyroid cancer ($p<0.0001$). DCN expression and the infiltration of several immune cells were positively correlated ($p<0.01$). A significant positive correlation was also noted between DCN and the NRAS and KRAS genes (partial cor>0, $p<0.05$). Immunohistochemical analyses revealed a significantly lower staining score (3.071 ± 2.493) for DCN protein in cancer tissues than that in adjacent tissues (8.643 ± 2.094) ($p<0.0001$).

Conclusions: DCN is underexpressed and contributes to tumor progression in FTC. Thus, DCN serves as a tumor suppressor gene in FTC and a promising therapeutic target.

Keywords: follicular thyroid carcinoma; decorin; differentially expressed genes; bioinformatics; immunohistochemical analysis

Introduction

In recent decades, there has been a significant global rise in the incidence of differentiated thyroid carcinoma (DTC). According to the GLOBOCAN 2020 data on cancer incidence and mortality, thyroid cancer ranks ninth in terms of overall incidence and fifth among malignant tumors in women [1]. Follicular thyroid carcinoma (FTC), a subtype of DTC originating from thyroid follicular cells, represents a relatively less common cancer, constituting approximately 5–15 % of all thyroid malignancies. Despite its lower prevalence, FTC exhibits greater malignancy than papillary thyroid carcinoma (PTC) and a propensity for blood dissemination, elevating the risk of distant metastasis – most frequently observed in the bone and lungs [2–4]. The prognosis of FTC is predominantly influenced by the clinical stage of cancer, and early diagnosis and intervention typically result in a more favorable outcome. Surgical resection and other therapeutic modalities can effectively extend survival and control the disease in cases with limited local and distant metastases. However, prognosis tends to be poor for advanced or recurrent cases. Therefore, the precise identification of the genes implicated in FTC and the genetic exploration of FTC have emerged as key research areas. A growing body of evidence highlights the association between aberrant gene expression and the initiation and unfavorable prognosis of FTC [5, 6]. According to the TNM staging of thyroid cancer (8th Edition) by the American Joint Committee on Cancer [7], patients aged 55 years and older are classified as stage IVB in the presence of distant metastasis (M1), regardless of tumor size (T) and lymph node infiltration (N).

With the advantages of comprehensive data and large sample sizes, gene chips have become integral to biology and medicine. Recently, the application of bioinformatics and

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microarray techniques has gained prominence in investigating tumor occurrence and development attributed to gene inactivation or mutation [8]. However, these data, while abundant, lack robust experimental foundations. Consequently, the extraction of accurate and reliable gene information is emerging as a focal point of bioinformatics research. In this study, differentially expressed genes (DEGs) in FTC and normal thyroid tissue microarrays were analyzed through bioinformatics methods and subsequently validated *via* immunohistochemical (IHC) staining of clinical samples. Furthermore, the correlation between core DEGs and immune cell infiltration in tumor tissues was explored, aiming to identify key DEGs associated with the development and progression of FTC. The findings of this research are anticipated to provide a novel theoretical foundation for the targeted therapy of FTC and related conditions.

Materials and methods

Data sources and searches

Gene expression profiles from GSE27155 were acquired and compiled from the Gene Expression Omnibus DataSets database (https://www.ncbi.nlm.nih.gov/geo/) using the keywords "follicular thyroid carcinoma, *Homo sapiens*, Expression profiling by array, and normals." The Affymetrix human genome U133A array (platform GPL96) was utilized, including 13 samples of FTC and four samples of normal thyroid tissue.

Screening of DEGs

The raw data were analyzed using the R statistical software (version 3.5.0) packages affy and limma. DEGs were identified based on the criteria of $|\log_2(\text{fold change})| > 1$ and $p < 0.05$.

Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses of DEGs

The biological functional annotation of DEGs was comprehensively analyzed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) database (https://david.ncifcrf.gov). GO functional analysis and KEGG pathway enrichment analysis were applied to the DEGs uploaded to the DAVID website, covering biological process (BP), molecular function (MF), cellular component (CC), and signaling pathway. A p-value less than 0.05 was considered statistically significant.

Protein–protein interaction (PPI) network creation and core DEG identification

The PPI network diagram was constructed using DEGs obtained from the STRING database (https://stringdb.org). Molecular complex detection and CytoHubba plugin were employed to analyze the degree of the PPIs. Significant molecular modules and core DEGs were identified by visualizing the network diagram with Cytoscape software (version 3.6.1).

Database validation of core DEG expression

RNA sequencing expression profiles (level 3) and clinical information for FTC were downloaded from The Cancer Genome Atlas (TCGA) dataset at https://portal.gdc.com. R statistical software (version 3.5.0) package ggplot2 was used to validate the results of core DEG screening.

Clinicopathological correlation analysis of decorin (DCN)

Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn) is an online website displaying analyzed tumor and normal tissue data obtained from the TCGA database [9]. The GEPIA database was used to investigate the relationship between DCN gene expression in thyroid cancer and clinicopathological staging.

Correlation analysis of DCN, immune infiltrating cells, and hotspot molecules in thyroid cancer

TIMER, a resource for systematic immune infiltrate analysis in different cancer types (https://cistrome.shinyapps.io/timer/) [10], was used to analyze the correlation between DCN expression and the abundance of immune infiltrating cells in thyroid cancer. B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages, and dendritic cells were included in the analysis. Furthermore, the gene correlation module of the TIMER database was employed to analyze the correlation between DCN and six hotspot signature genes of thyroid cancer, namely, BRAF, HRAS, NRAS, KRAS, PAX8, and peroxisome proliferator-activated receptor (PPAR)G.

IHC staining and evaluation

A total of 28 samples of FTC tissues, along with their corresponding 28 samples of adjacent non-cancerous tissues (paracarcinoma), were obtained from the Department of Pathology at Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences, spanning nearly a decade, for retrospective analysis. Supplementary Materials contain patient cohort information that can be referenced. Approval for the study was obtained from the hospital ethics committee (ethics number: 2021k05). The IHC staining protocol was executed as follows: tissue sections were subjected to dewaxing with xylene three times for 15 min each time, followed by rehydration with 100 % alcohol twice and subsequent rehydration with 85 and 75 % alcohol for 5 min each. The sections were thoroughly washed with distilled water. Antigen retrieval was conducted by placing the tissue sections in a repair box containing ethylenediaminetetraacetic acid antigen retrieval buffer (pH 9.0), subjected to microwave heating at medium heat for 8 min until boiling, followed by an additional 8 min at 25 °C and then medium-low heat for 7 min of antigen retrieval. After natural cooling, the slide was immersed in pH 7.4 phosphate-buffered saline (PBS) and washed three times on a decolorizing shaker for 5 min each time. Subsequently, the sections were treated with a 3 % hydrogen peroxide solution to block endogenous peroxidase activity at room temperature for 25 min away from light. This was followed by washing with PBS (pH 7.4) on a decolorizing shaker three times for 5 min each. The tissue was uniformly covered with a 3 % bovine serum albumin solution and incubated at

25 °C for 30 min before an overnight incubation at 4 °C with the primary antibody DCN obtained from Proteintech Group Inc (Wuhan, China) at a dilution ratio of 1:400. Goat Anti-Rabbit IgG H & L (Abcam, Shanghai, China) was then added and incubated at room temperature at a dilution of 1:5,000 for 50 min. This was followed by the addition of a freshly prepared 0.05 % solution of 3,3′-diaminobenzidine (DAB) for color development, and the development time was controlled using a positive fluorescence microscope (Nikon CI-S, Japan) until positive color appeared as brown or yellow after approximately 10 min. Finally, restaining with hematoxylin for 3 min, dehydration, and sealing were performed before microscopy image acquisition and analysis. Hematoxylin-stained nuclei appeared blue, whereas DAB staining indicated a positive expression with a brownish-yellow appearance. Sections were scored based on DCN-specific staining intensity and the percentage of positive tumor cells [11]. The percentage of positive cells was scored as follows: 0 (0 %), 1 (1–10 %), 2 (10–40 %), 3 (41–70 %), and 4 (71–100 %). Staining intensity was scored as 0 (no staining), 1 (light yellow), 2 (brownish yellow), and 3 (tan). The IHC staining result was determined by multiplying the staining intensity score by the percentage of positive tumor cells, yielding a range of 0–12 points. Subsequently, the scores were categorized into low- and high-expression samples on a 6-point scale. Relevant data on immunization scores can be found in the Supplementary Materials.

Statistical analyses

GraphPad Prism software Version 8.0 was employed for data processing and plotting. Quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The expression of core DEGs was verified using Wilcoxon's rank sum test along with the TCGA database. The relationship between differentially expressed genes and tumor stage was investigated using the F-test in the GEPIA database tool. The correlation between DCN expression and immune cell infiltration, as well as hotspot signature genes, was assessed using Spearman's correlation analysis. The paired samples t-test was utilized to determine differences in DCN positive expression in IHC. A significance level of $p<0.05$ was considered statistically significant.

Results

Identification of DEGs

Upon analysis of the GSE27155 dataset, a total of 298 DEGs were identified. Among these, 215 genes were upregulated, whereas 83 were downregulated. The upregulated and downregulated genes are shown in Figure 1 using cluster analysis.

GO and KEGG pathway enrichment analyses of DEGs

The DEGs were analyzed using GO enrichment analysis to evaluate their CC, MF, and BP. With regard to CC, the associated DEGs were notably enriched in components such as the extracellular matrix (ECM), extracellular exosome, membrane, and perinuclear region of the cytoplasm. In terms of MF, significant enrichments were observed in functions such as protein binding, peroxidase activity, enzyme binding, and ECM structural constituents. As for BP, DEGs were predominantly involved in processes such as

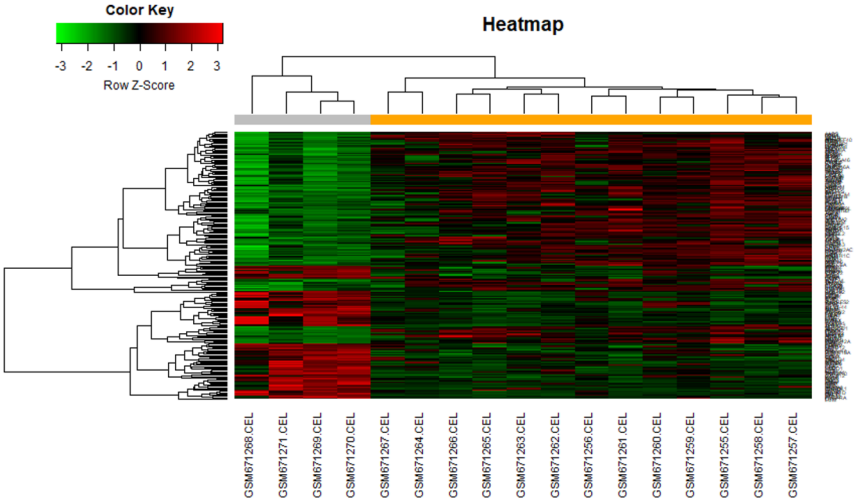


Figure 1: Heat map illustrating the DEGs between FTC and normal thyroid samples in the GSE27155 dataset. The normal thyroid tissue group is indicated by the grey module, whereas the FTC group is represented by the yellow module. Sample clustering is demonstrated in the upper branch tree, and differential gene clustering is showcased in the left branch tree. The chip sample number is annotated below, with the DEG names enumerated on the right. The color key extends from green to red, indicating the degree of expression enhancement. FTC, follicular thyroid carcinoma; DEG, differentially expressed gene.

immune response, ECM organization, cell adhesion, angiogenesis, cell migration, positive and negative regulation of cell proliferation, positive and negative regulation of the apoptotic process, positive regulation of ERK1/2 cascade, and cellular response to DNA damage stimulus. In KEGG signaling pathway analysis, the DEGs were primarily implicated in pathways including small cell lung cancer, focal adhesion, insulin signaling pathway, pathways in cancer, protein processing in the endoplasmic reticulum, phosphoinositide-3-kinase–protein kinase B (PI3K–Akt) signaling pathway, proteoglycans in cancer, mitogen-activated protein kinase signaling pathway, Rap1 signaling pathway, erythroblastic oncogene B signaling pathway, and ECM-receptor interaction. These results are illustrated in Figure 2.

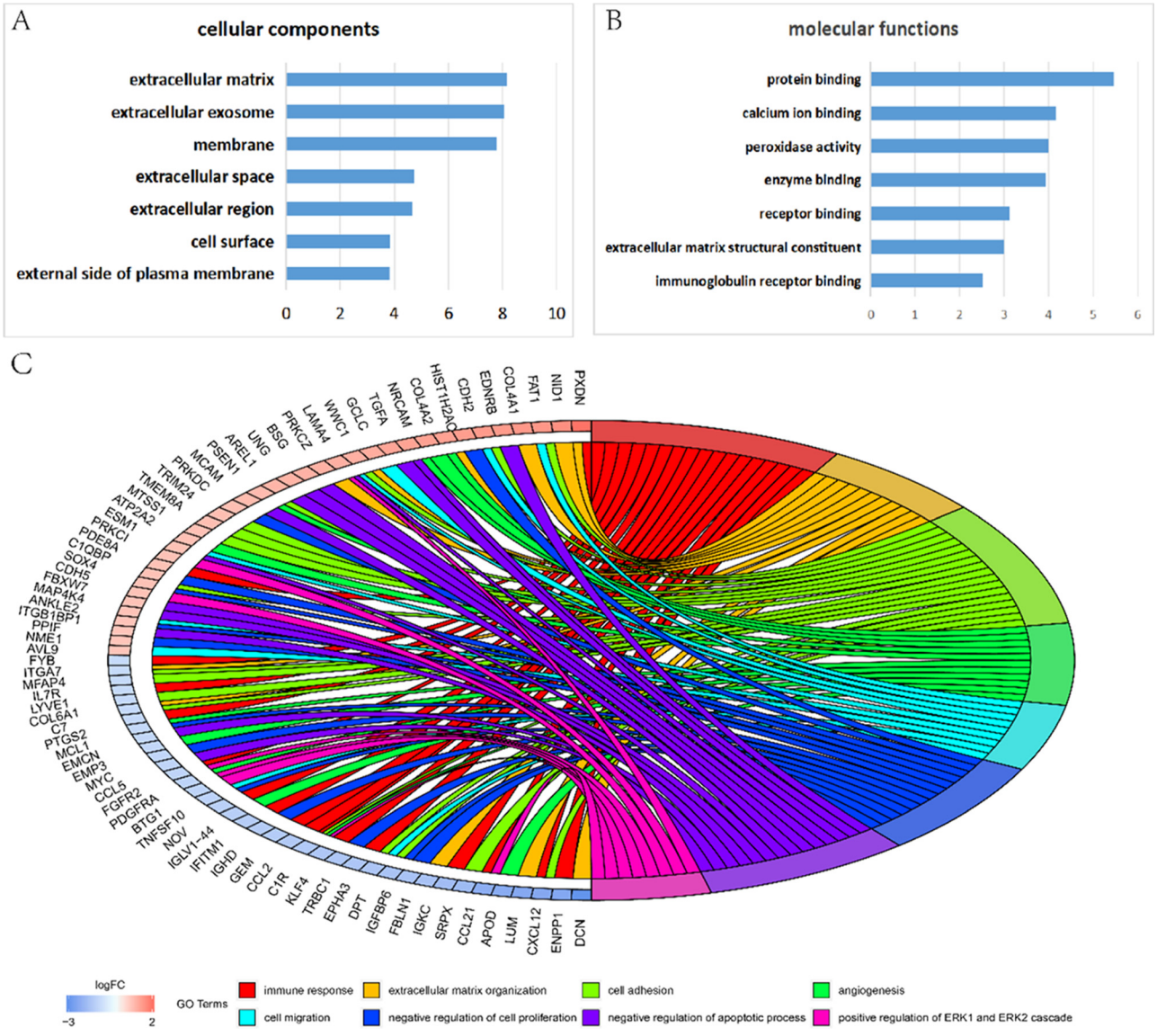


Figure 2: GO and KEGG pathway enrichment analyses of DEGs. (A) Cellular components; (B) molecular functions; (C) distribution of DEGs enriched in various biological processes in FTC; (D) KEGG signaling pathway. The dot sizes represent the count of the enriched DEGs, and the dot color represents the p-value. DEG, differentially expressed gene; GO, gene ontology; KEGG, Kyoto encyclopedia of genes and genomes; FTC, follicular thyroid carcinoma.

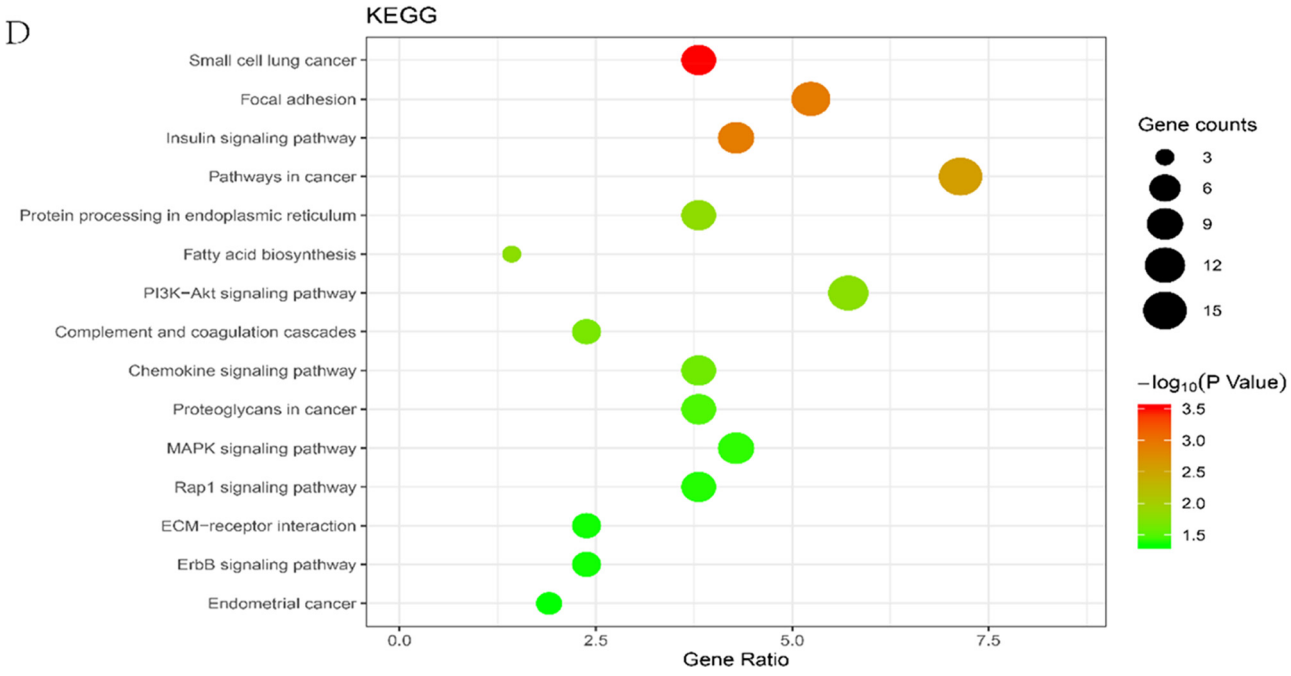


Figure 2: Continued.

PPI construction and molecular module analysis

The PPI network was constructed, comprising 159 network nodes and 367 edges (Figure 3A). Four key modules (subnetworks) were identified from the PPI network (Figure 3B–E). Notably, Module A was enriched in ECM organization, participating in ECM receptor interaction, protein digestion and absorption, PI3K-Akt signaling, and focal adhesion pathways. Seven key network nodes (NID1, COL4A1, COL4A2, COL6A1, FBLN1, LUM, and DCN) were identified in Module A. Module B, located in the mitochondrial outer membrane, contributing to fatty acid biosynthesis, degradation, metabolism, and adipocyte signaling pathways. ACACB, ACSL1, ACSL3, and ACADVL are four vital network nodes that are involved in these processes. Module C engaged in adhesion, leukocyte migration, chemokine signaling, and other pathways. This module primarily consists of 14 key network nodes, including SOX4, CDC42, CCL2, KLF4, and CDH5. Module D was primarily enriched in BP involving the active regulation of cell migration and cell proliferation, participating in Rap1 signaling, EGFR tyrosine kinase inhibitor resistance, actin cytoskeleton regulation, and Ras signaling pathways. This process primarily involves eight key network nodes: TGFA, PRKCZ, MCAM, PRKCI, PIK3R3, FGFR2, PDGFRA, and CXCL12.

Screening of core DEGs

Centrality analysis of the PPI network, employing 12 algorithms from the cytoHubba plugin, including MCC, DMNC, and Degree, combined with the four module significant genes, identified the top three most significant core DEGs. The downregulated genes, namely, DCN, PDGFRA, and GPC3, emerged as the most significant core DEGs in this analysis.

Validation of core DEG expression using the TCGA database

The findings revealed a significant reduction in the expression of three key DEGs (DCN, GPC3, and PDGFRA) in FTC tissues compared with normal tissues ($p<0.0001$) (Figure 4).

Correlation analysis between DCN and tumor pathological stage

The GEPIA database was utilized to analyze the tumor pathological stages in the three core DEGs, revealing a more significant correlation between DCN expression and thyroid cancer stage compared to PDGFRA ($p<0.0001$) (Figure 5). No significant difference was observed in thyroid cancer stage between GPC3 ($p>0.05$).

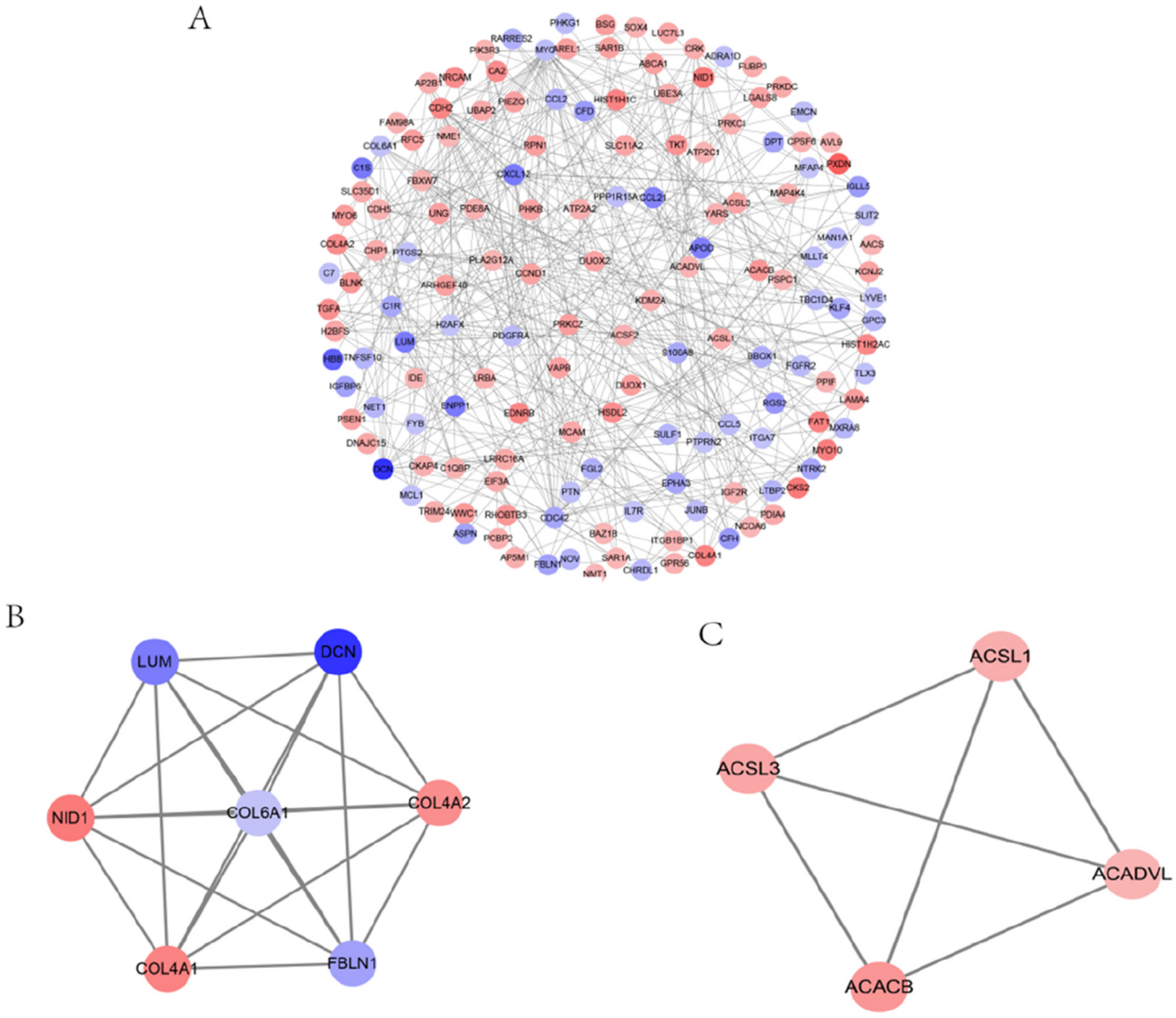


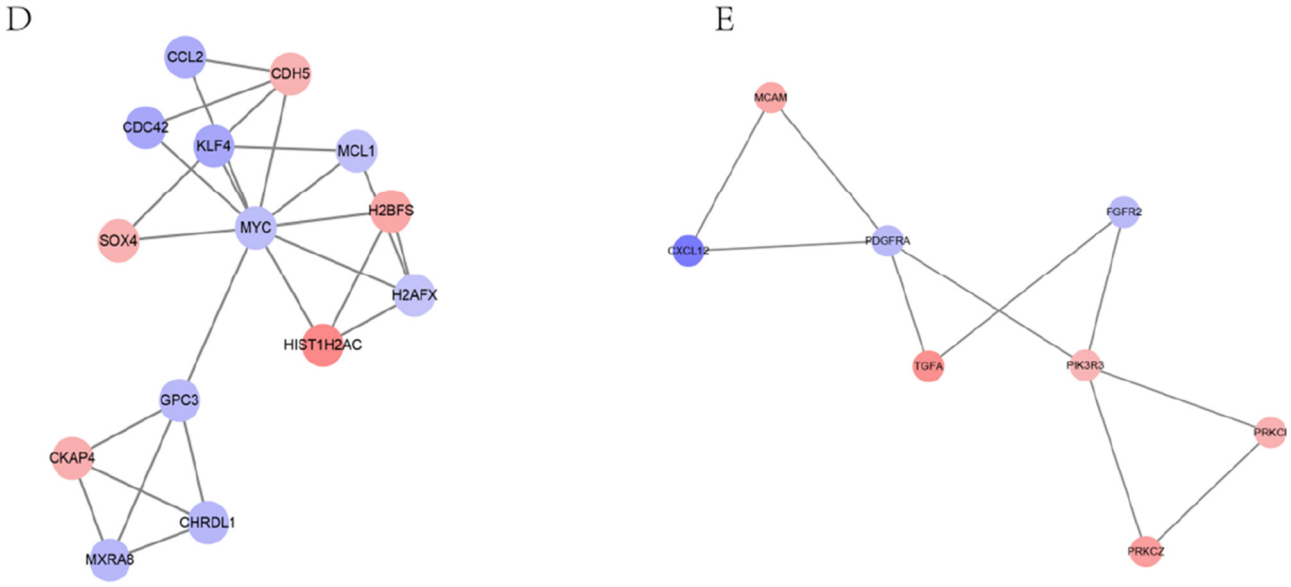
Figure 3: DEGs encode the PPI network and four key modules. (A) The PPI network of DEGs. (B–E) Key modules 1, 2, 3, and 4, respectively. In these figures, circles represent genes and lines indicate the protein interactions among them. In particular, red circles denote upregulated genes, blue circles indicate downregulated genes, and the colors indicate fluctuations in gene expression. DEG, differentially expressed gene; PPI, protein–protein interaction.

Correlation analysis between DCN and immune infiltrating cells

Results from TIMER database analysis indicated a negative correlation (partial cor<0, p<0.01) between DCN expression and tumor purity in thyroid cancer. Moreover, DCN gene expression exhibited significant correlations (partial cor>0, p<0.01) with B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells (Figure 6A). The "survival module" analysis of the TIMER database revealed a significant association between low levels of infiltrating $CD8^+$ T cells in thyroid cancer and poor overall survival (p<0.05) (Figure 6B).

Correlation analysis between DCN and hotspot signature genes in thyroid cancer

Using TIMER database analysis, DCN was found to be positively correlated with NRAS and KRAS genes with statistical significance (partial. cor>0, p<0.05). Furthermore, DCN exhibited a negative correlation with HRAS and PAX8 genes with statistical significance (partial. cor<0, p<0.05). However, no significant correlations were observed between DCN and BRAF and PPARG or PPAR-γ genes (p>0.05) (Figure 7). These findings provide valuable insights into the relationship between DCN and characteristic hotspot genes in thyroid cancer.



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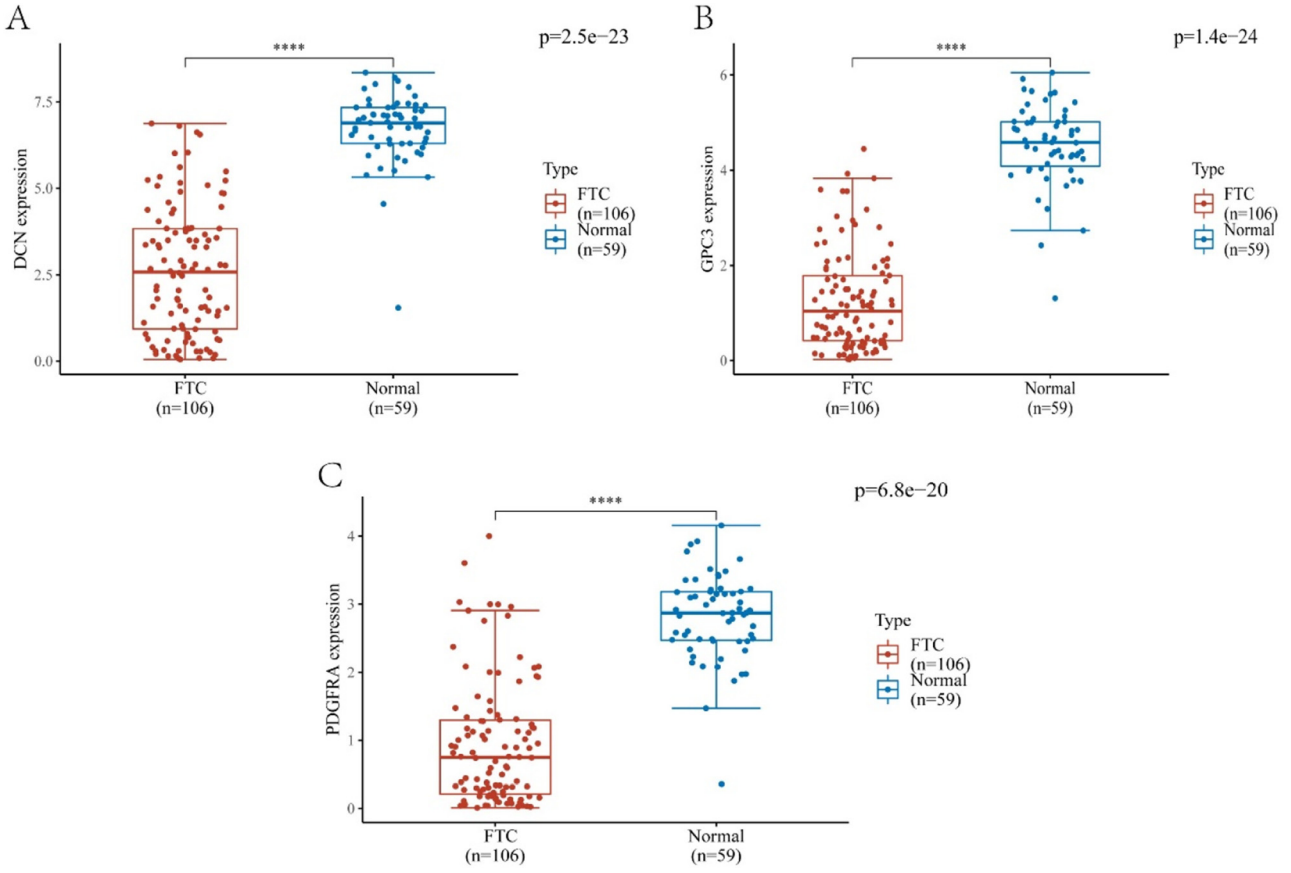

Figure 4: Expression of the three core genes: DCN, GPC3, and PDGFRA (****p<0.0001). DEG, differentially expressed gene; DCN, decorin; GPC3, glypican-3; PDGFRA, platelet-derived growth factor receptor alpha.

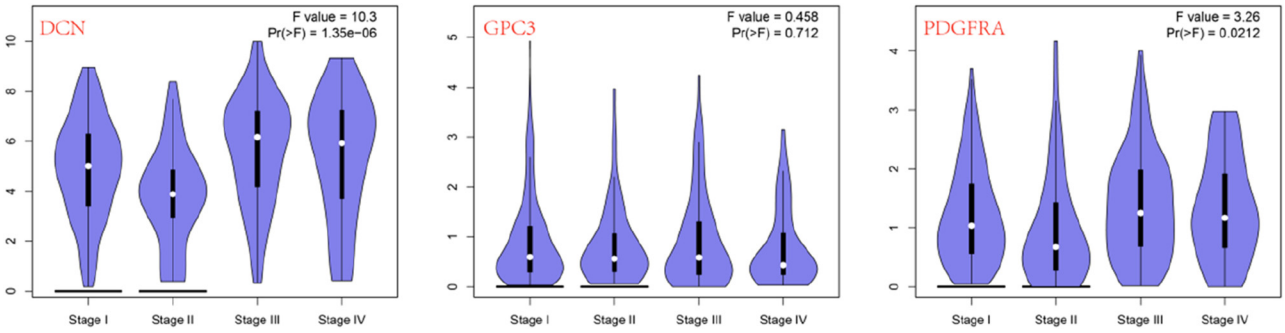

Figure 5: Association between the three core DEGs expression and tumor stage in thyroid cancer.

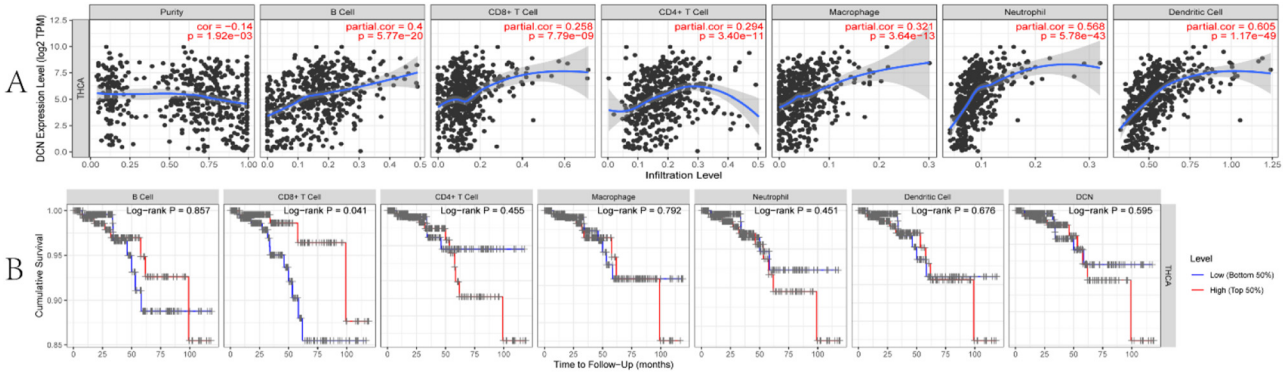

Figure 6: Correlation analysis between DCN expression and infiltrating immune cells in thyroid cancer. (A) The relationship between DCN expression and proportions of infiltrating immune cells in THCA. (B) Cumulative survival of infiltrating immune cells in THCA. THCA, thyroid cancer; DCN, decorin.

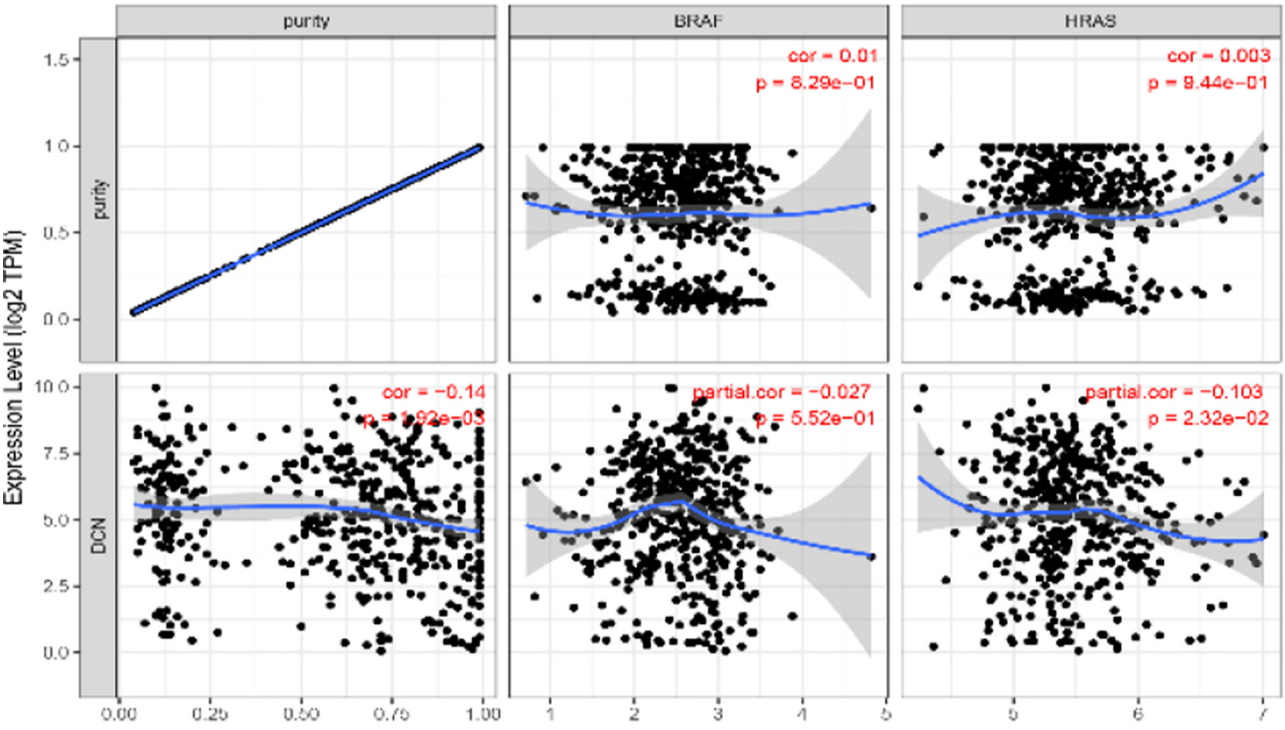

Figure 7: Correlation analysis between DCN and hotspot signature genes in thyroid cancer.

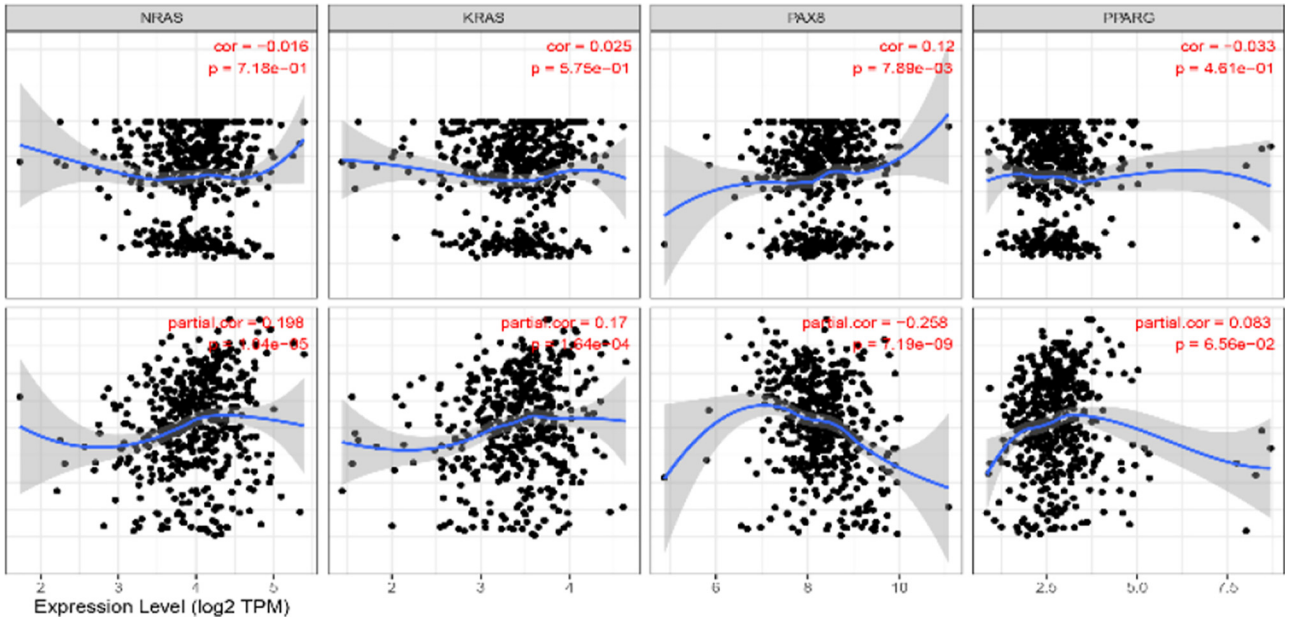

Figure 7: Continued.

IHC validation

IHC staining experiments were conducted to select the most differentially expressed DCN among the core DEGs. The staining score of DCN in tumor tissues (3.071 ± 2.493) was significantly lower ($p<0.0001$) than that in adjacent normal tissues (8.643 ± 2.094), confirming the underexpression of DCN in FTC (Figures 8 and 9). The immunohistochemical images of 28 patients with follicular thyroid carcinoma (FTC) and their corresponding adjacent non-cancerous tissues can be found in the Supplementary Materials.

Discussion

The incidence of thyroid carcinoma, particularly DTC, has seen a notable rise in recent years. While surgical intervention has generally proven effective, cases of advanced FTC or recurrence may lead to poor prognoses [12]. In this study, the integration of data mining from FTC and normal thyroid microarrays, utilizing bioinformatics and high-throughput sequencing, identified three significant core DEGs: DCN, GPC3, and PDGFRA, all of which were underexpressed in FTC tumor tissues. Among these genes, DCN,

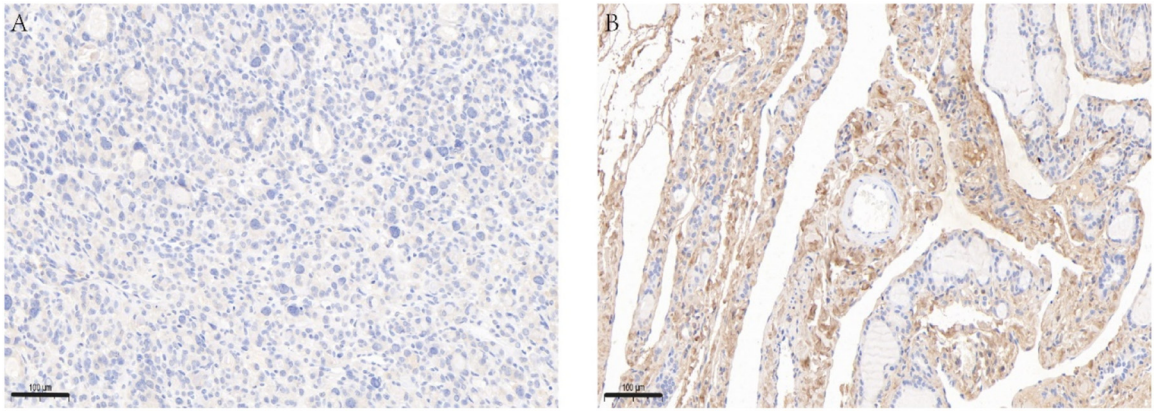

Figure 8: Immunohistochemical images of DCN expression in FTC tissues and paired adjacent noncancerous tissues (×200). Scale bar: 100 μm. (A) Negative DCN staining in the FTC tissue. (B) Positive DCN staining in the adjacent noncancerous tissues. FTC, follicular thyroid carcinoma; DCN, decorin.

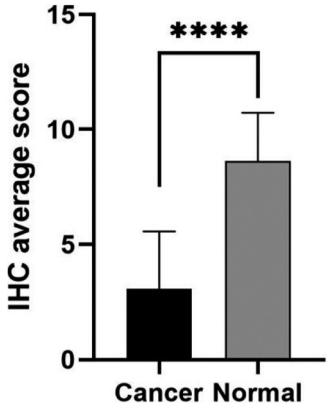

Figure 9: Immunohistochemical scoring plots of FTC (28 samples) and adjacent noncancerous tissues (28 samples) (****p<0.0001).

identified as a leucine-rich low-protein proteoglycan primarily found in the mammalian connective tissue within the ECM [13], has multifaceted biological activities. These include the inhibition of collagen fiber formation and the regulation of cell proliferation, migration, and adhesion [13]. While previous studies, such as Arnaldi et al. [14], reported a high percentage of DCN underexpression in various thyroid conditions, its specific role in FTC has not been extensively explored. Therefore, investigating the protein expression profile and developmental roles of DCN in FTC tissues becomes crucial.

In FTC, DCN genes were found to be primarily involved in BPs such as ECM composition, cell aging, negative regulation of protein kinase activity, positive regulation of phosphatidylinositol 3-kinase signaling, and negative regulation of angiogenesis and primarily enriched in proteoglycan signaling pathways in cancer (Table 1). These processes and pathways are closely linked to the development and progression of various malignancies, suggesting that DCN regulates FTC progression by influencing these pathways. Notably, DCN expression is considered crucial for tumor initiation and progression, possibly acting as a tumor suppressor [15]. Goldoni et al. [16] revealed that DCN can effectively inhibit the growth and metastasis of breast cancer cells, proposing it as a drug candidate for targeted therapy. Horvath et al. [17] reported that hepatocarcinoma tissues exhibited low DCN expression, suggesting that DCN inhibits liver cancer growth via cell proliferation inhibition, cell cycle arrest, and increased caspase-3 enzyme activity. Bi et al. [18] reported low DCN expression in colorectal cancer tissues, and increased DCN expression was found to inhibit the growth and metastasis of colorectal cancer cells. These findings align with our observations, highlighting the importance of DCN in patients with FTC.

As the understanding of tumor biology and immunology deepens, researchers increasingly acknowledge the close relationship between tumorigenesis and the tumor microenvironment (TME). The TME, consisting of the ECM, cancer-associated fibroblasts, vascular epithelial cells, and infiltrating immune cells, plays a critical role in cancer development [19]. Immune cell infiltration within solid tumors is recognized as a key factor in TME-associated carcinogenesis [20]. Morana et al. [21] reported that changes in the TME affect apoptosis in tumor cells, promoting tumor cell occurrence and development. In this study, a positive correlation was found between the expression of DCN and the infiltrating abundance of tumor-infiltrating lymphocytes (TILs), including B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells, in cancer tissues from patients with thyroid cancer. Thus, low DCN expression in thyroid cancer tissues is associated with reduced TIL infiltration, potentially altering the TME and promoting tumorigenesis and progression. Moreover, DCN may affect the survival time of patients with thyroid cancer *via* the regulation of $CD8^+$ T cell infiltration, indicating its potential role as an immune regulator in thyroid cancer.

FTC poses challenges in clinical diagnosis as accurate identification via fine needle aspiration biopsy or

Table 1: Involvement of DCN in various biological processes in FTC and pathway enrichment analysis.

Category	Term	Function	Count	p-Value	Genes
BP	GO:0030198	Extracellular matrix organization	11	1.18E-04	COL4A2, COL4A1, LUM, LAMA4, BSG, COL6A1, PXDN, ITGA7, FBLN1, NID1, **DCN**
BP	GO:0007568	Aging	6	0.046785231	GCLC, EDNRB, AMFR, CCL2, APOD, **DCN**
BP	GO:0006469	Negative regulation of protein kinase activity	5	0.03014537	INPP5K, CHP1, ITGB1BP1, **DCN**, ASPN
BP	GO:0014068	Positive regulation of phosphatidylinositol 3-kinase signaling	5	0.00737823	NTRK2, PDGFRA, CCL5, UBE3A, **DCN**
BP	GO:0016525	Negative regulation of angiogenesis	5	0.006248128	COL4A2, CCL2, PTN, SULF1, **DCN**
KEGG_PATHWAY	hsa05205	Proteoglycans in cancer	8	0.034279618	CDC42, CCND1, LUM, MYC, GPC3, PIK3R3, ELK1, **DCN**

intraoperative frozen section pathology is elusive. Confirmation typically relies on postoperative paraffin section pathology. Consequently, the implementation of molecular diagnostic technologies before clinical intervention has become a central focus in FTC research. Currently, genes such as BRAF, RAS, and PAX8-PPARG, recognized as characteristic hotspot genes for thyroid cancer, are widely employed in clinical molecular testing to differentiate between benign and malignant thyroid nodules. BRAF, extensively studied in thyroid fine needle aspiration cytopathology, is frequently mutated in PTC (in up to 80 % of cases) but less frequently mutated in FTC [22]. This study corroborates previous findings by revealing no correlation between DCN and BRAF, consistent with the results reported by Mayson et al. [22]. The RAS family genes are a class of proto-oncogenes that are very conservative during biological evolution, including KRAS, HRAS, and NRAS. They are closely related in function and structure, and both encode G proteins [23]. The mutation rates of RAS are second only to BRAF and are most common in FTC, followed by follicular type PTC, and less frequently in classical type PTC [24]. This study reveals a positive correlation between the DCN gene and NRAS and KRAS genes, as well as a negative correlation with HRA, indicating the involvement of DCN in the BP of RAS mutation in FTC. Rearrangements of the PPARG gene, particularly PAX8-PPARG, are common in follicular lesions, including FTC [25]. This study reveals an inverse correlation between DCN and PAX8 but no correlation with PPARG, suggesting a correlation between DCN expression and PAX8--PPARG rearrangements.

We retrospectively validated DCN expression in FTC tumor tissues and paracarcinoma tissues using IHC analysis, confirming its low expression in cancer tissues, consistent with DCN mRNA expression findings from Arnaldi et al. [14]. This validation enhances the reliability of the low expression data of DCN in FTC obtained through mining. Furthermore, they verified the authenticity and accuracy of the bioinformatics analysis results, highlighting the significant role of the DCN gene in FTC progression. A significant association between DCN and thyroid cancer stage was identified, suggesting its potential as a tumor suppressor gene in FTC pathogenesis. These findings align with existing literature reports [14–18].

Altogether, the downregulation of DCN expression may be associated with the development, progression, and immune infiltration of FTC. The study findings establish a theoretical basis for understanding the molecular mechanisms underlying FTC pathogenesis and the translational application of immunotherapy. Additionally, the DCN gene emerges as a potential biomarker and therapeutic target for FTC in clinical practice. Nevertheless, the study acknowledges limitations in not elucidating the specific mechanism and related signaling pathways of DCN in FTC, calling for further in-depth investigation.

Research ethics: Approval was obtained from the Institutional Review Board (IRB) of Jiading District Central Hospital Affiliated Shang hai University of Medicine & Health Sciences for the publication of this literature review (ethics number: 2021k05).

Informed consent: Informed consent was obtained from all individuals included in this study.

Author contributions: Qianhuang L was responsible for experimental design, experimental analysis, and thesis writing. Ye M collected and screened the data and wrote the manuscript. Pengcheng C was responsible for research guidance and thesis review. All authors contributed to the article and approved the submitted version.

Competing interests: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Data availability: Publicly available datasets were analyzed in this study. This data can be found here: https://www.ncbi.nlm.nih.gov/geo/, https://portal.gdc.com,http://gepia.cancer-pku.cn, https://cistrome.shinyapps.io/timer/, accessed on 21 April 2023. The immunohistochemical images, , and patient cohort information of the 28 cancer cases and their corresponding adjacent tissues mentioned in this study can be found in the **Supplementary Materials**. For any further inquiries, please contact the corresponding author.

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