Thyroid Research

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Systems biology approach delineates critical pathways associated with papillary thyroid cancer: a multi-omics data analysis

Febby Payva[1,2*], Santhy K. S.[2*], Remya James[1,2], Amrisa Pavithra E[2] and Venketesh Sivaramakrishnan[3*]

Abstract

Background Papillary thyroid cancer (PTC) is the most prevalent follicular cell-derived subtype of thyroid cancer. A systems biology approach to PTC can elucidate the mechanism by which molecular components work and interact with one another to decipher a panoramic view of the pathophysiology.

Methodology PTC associated genes and transcriptomic data were retrieved from DisGeNET and Gene Expression Omnibus database respectively. Published proteomic and metabolomic datasets in PTC from EMBL-EBI were used. Gene Ontology and pathway analyses were performed with SNPs, differentially expressed genes (DEGs), proteins, and metabolites linked to PTC. The effect of a nucleotide substitution on a protein's function was investigated. Additionally, significant transcription factors (TFs) and kinases were identified. An integrated strategy was used to analyse the multi-omics data to determine the key deregulated pathways in PTC carcinogenesis.

Results Pathways linked to carbohydrate, protein, and lipid metabolism, along with the immune response, signaling, apoptosis, gene expression, epithelial–mesenchymal transition (EMT), and disease onset, were identified as significant for the clinical and functional aspects of PTC. Glyoxylate and dicarboxylate metabolism and citrate cycle were the most common pathways among the PTC omics datasets. Commonality analysis deciphered five TFs and fifty-seven kinases crucial for PTC genesis and progression. Core deregulated pathways, TFs, and kinases modulate critical biological processes like proliferation, angiogenesis, immune infiltration, invasion, autophagy, EMT, and metastasis in PTC.

Conclusion Identified dysregulated pathways, TFs and kinases are critical in PTC and may help in systems level understanding and device specific experiments, biomarkers, and drug targets for better management of PTC.

Keywords Papillary thyroid cancer, Systems biology, Multi-omics, DEGs, Transcription factors, Kinases

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Introduction

According to the International Agency for Research on Cancer (IARC), thyroid cancer (TC) incidence ranks seventh on the basis of global cancer statistics (https://www.wcrf.org/cancer-trends/worldwide-cancer-data/). However, it accounts for thirteenth and fifth among men and women, respectively [1]. Papillary thyroid cancer (PTC) is the most predominant type of thyroid cancer. It belongs to the well-differentiated follicular cell-derived malignant neoplasm subtype. In 2022, the World Health Organization (WHO) updated the classification of PTCs

into classical PTCs, encapsulated classic PTCs, infiltrative follicular PTCs, diffuse sclerosing PTCs, solid/trabecular PTCs, warthin like PTCs, oncocytic PTCs, clear cell PTCs, spindle cell PTCs, PTCs with fibromatosis/fasciitis-like/desmoid-type stroma, tall cell PTCs, hobnail PTCs, and columnar cell PTCs [2]. The tall cell, hobnail and columnar cell subtypes were the most aggressive types of PTC. The primary cause of PTC carcinogenesis is the deregulation of the PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways, which are essential for gene expression, cell signaling, proliferation, mitosis, cell survival, and apoptosis [3].

Diagnostic methodologies such as two-dimensional (2D) ultrasound (US), three-dimensional (3D) (US) scanning technology, and adjunct imaging techniques such as CT scanning and magnetic resonance imaging (MRI) followed by laboratory evaluation have improved the risk stratification of TC [4]. Fine needle aspiration biopsy (FNAB) is critical in PTC risk mapping via the Bethesda system of thyroid cytopathology reporting [5]. Extrathyroidal extension (ETE) in PTC can be better revealed by molecular markers [6].

The drastic progress in PTC diagnostic and treatment techniques over the past decade has improved patient outcomes and disease-free survival rates. Although total thyroidectomy with radioactive iodine (RAI) therapy as a postsurgical follow-up remains inevitable in advanced and metastatic tumors, a less extensive partial thyroidectomy and significantly reduced adjuvant RAI therapy in tumors up to 4 cm in size offer sound and adequate management in low-risk cT1N0M0 PTC patients [7, 8]. Ambulatory thyroidectomy reduces economic costs and hospitalization without compromising the safety of PTC treatment [9].

Studies have revealed the increasing incidence of unnecessary thyroidectomies in PTC patients due to the overdiagnosis and uncertainty of malignancy. Systems biology, whose roots can be traced since the early twenty-first century, can be used to address this issue. The system biology approach elaborates on the mechanism by which molecular components work and interact with one another and the environmental factors to decipher a panoramic view of the system as a whole. This highlights the intricacy of the interdependent biological networks that govern how genotype, phenotype, and environment interact [10]. Recent high-throughput analysis and multi-omics have improved our understanding of the molecular landscape of thyroid cancer, and its clinical application is expected to improve risk stratification, personalized treatment, and patient outcomes [11]. Multi-omics profiling of papillary thyroid microcarcinomas (PTMC) has revealed a unique signature of PTMC inflammation enriched with AFP mutations, elevated immune-related genes, and positive thyroglobulin and peroxidase antibodies that implies distinct biological and clinical characteristics that require different interventions [12]. Integrative multi-omics analysis of different thyroid cancers, such as BRAF-like PTC, RAS-like follicular thyroid cancer (FTC), and anaplastic thyroid cancer (ATC)-like, has been conducted to substantiate the metabolic differences among various types of thyroid cancer [13].

This paper integrated all the available significant transcriptomic, proteomic, and metabolomic datasets in PTC, comparing diseased vs. normal datasets for the first time. PTC-associated single-nucleotide polymorphisms (SNPs), differentially expressed genes, proteins, and metabolites were binned into significant pathways with potential implications in PTC pathophysiology. The functional and clinical effects of these SNPs were also determined, and the transcription factors (TFs) and kinases responsible for modifying the PTC tumor microenvironment (TME) were elucidated. The TFs, kinases, and integrated pathways from different levels of multi-omics data analysis were linked to the clinical outcomes of PTC. Therefore, an approach to target metabolism in PTC and cope with its plasticity and resistance is promising for the treatment of thyroid cancer.

Materials and methods

Single nucleotide polymorphism (SNP) analysis

Significant genes and specific SNPs associated with PTC were retrieved from DisGeNET. 83 genes and 111 SNPs were curated. SNPs were curated after the exclusion of introns and synonymous variants. DisGeNET (http://www.disgenet.org/) is a knowledge platform that collates and standardizes information on genes and their variants of clinical relevance from manifold resources. It has curated and integrated normal and abnormal traits of a wide range of human diseases [14]. The SNP analysis of the missense mutations in the exon region was performed via web-based tools, including the ClueGO plugin of Cytoscape 3.10.2, SIFT, PolyPhen-2, and SNP Nexus. The significant parent pathways and the clinical outcomes associated with PTC were analysed via the ClueGO plugin of Cytoscape 3.10.2 (https://apps.cytoscape.org/apps/cluego).

SIFT (sorting intolerance from tolerance) (https://sift.bii.a-star.edu.sg/) predicts the effect of a nucleotide substitution in the coding region on the function of a protein [15]. In the present study, the curated dbSNPs of PTC were predicted for their impact on the pathogenesis of PTC. The amino acid substitutions with a SIFT score $<=0.05$ were recorded as 'deleterious', indicating high conservation, and those with a score >0.05 were recorded as 'tolerated', indicating low conservation.

PolyPhen-2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/) is a software used to annotate the SNPs in coding sequences [16]. The impact of SNVs on the function of a protein is analysed. The PolyPhen-2 computes the score, including the sequential and structural components of the SNP, which range between 0.0 and 1.0. The SNVs that have values close to 0.0 are predicted as benign, and those close to 1.0 as probably damaging.

SNPnexus (https://www.snp-nexus.org) is an annotation tool used to predict genome sequence variation [17]. Among the various applications of SNPnexus are genome mapping, impact on protein function, phenotypic and disease connection, structural variation, pathway analysis, and clinical interpretation. Reactome pathway enrichment was also carried out, and the results were plotted.

The pathway enrichment and gene ontology of the cellular component (CC) and biological process (BP) terms were performed via Enrichr (https://maayanlab.cloud/Enrichr/) [18], whereas the molecular function (MF) terms were annotated via WebGestalt (WEB-based GEne SeT AnaLysis Toolkit) (https://www.webgestalt.org/).

Analysis of transcriptomic data

Six gene expression datasets of PTC were curated from the Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo). Datasets specifically comparing diseased to normal traits were selected from human (GSE138198 [19], GSE3678 [20], GSE9115 [21], GSE6339 [22]); transgenic mouse (GSE58689 [23], GSE118022) [24]); and cell line studies (GSE6339) via the GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array).

Curation and enrichment analysis of Differentially expressed genes (DEGS)

DEGs were identified via the GEO2R web tool (http://www.ncbi.nlm.nih.gov/geo/geo2r) with the cut-off criteria adj. P value < 0.05. Enrichment analysis of DEGs from each dataset was performed via Enrichr. A gene ontology study was also performed on each dataset. Significant metabolites were also predicted from the DEGs. Molbiotools (https://molbiotools.com/listcompare.php) was used to find the significantly dysregulated pathways shared across the datasets.

Retrieval of transcription factors and kinases using X2K

DEGs were analysed for putative TFs and kinases linked with PTCs via eXpression2Kinases (X2K) (https://maayanlab.cloud/X2K/). It is an online tool for kinase enrichment analysis, protein–protein interaction subnetwork development, transcription factor enrichment analysis (TFEA), and TF–kinase interaction network construction [25].

Analysis of proteomic data

Proteomic studies enable an understanding of protein functions, interactions, and modifications, which is pivotal for providing holistic insight into biological systems. Five published PTC proteomics datasets, three tissue-based datasets [26–28], one plasma dataset [29], and one serum dataset [30], were analysed to elucidate the potential pathways enriched in PTC. Proteins with two-fold changes and adj. P values < 0.05 were screened for pathway enrichment analysis via Enrichr.

Analysis of metabolomic data

Metabolomic studies play a significant role in systems biology, and they integrate with other omics data to provide a comprehensive overview of the pathophysiology of a disease. Analysis of PTC tissue, serum, urine, and faecal metabolites could reveal potential biomarkers and targets for PTC. In the present study, four tissue datasets [31–34], three serum datasets [35–37], one urine dataset [35], and one faecal dataset [38] from published PTC metabolomic datasets were evaluated. Two PTC cell line works ([39, 40] were also analysed. The web-based tool MetaboAnalyst 6.0 (https://www.metaboanalyst.ca/) was used for metabolite enrichment analysis to identify the significant metabolic pathways associated with PTC.

Integration of PTC associated OMIC datasets

All the significant pathways in each of the human transcriptomics, proteomics, and metabolomics datasets were pooled. A commonality analysis of the pooled pathways between human SNPs, transcriptomics, proteomics, and metabolomics associated with PTC was conducted to identify the pathways with potential implications in PTC pathophysiology. TFs, kinases, and dysregulated pathways were linked to clinical outcomes in PTC by literature mining.

Results

SNP analysis deciphers potential mutations and critical pathways in PTC

The SNPs associated with PTC pathogenesis were curated from the DisGeNET database [41]. Eighty-three genes and 111 SNPs curated were used for the analysis. Critical PTC-related pathways were identified; these pathways were associated primarily with the immune system, signal transduction, DNA repair, programmed cell death, gene expression (transcription), haemostasis, and disease onset (Fig. 1a) and were clustered, and exhibited as Reactome pathway enrichment graph (Supplementary Fig. 1). Additionally, the SNPs were linked to clinical

a **Top 60 significant pathways of PTC associated SNPs from ClueGO Analysis**

Pathway ID	Term	Parent Pathway
R-HSA:448424	Interleukin-17 signaling	Immune system
R-HSA:139853	Elevation of cytosolic Ca2+ levels	Hemostasis
R-HSA:418346	Platelet homeostasis	Hemostasis
R-HSA:418360	Platelet calcium homeostasis	Hemostasis
R-HSA:196791	Vitamin D (calciferol) metabolism	Metabolism
R-HSA:211897	Cytochrome P450 - arranged by substrate type	Metabolism
R-HSA:211916	Vitamins	Metabolism
R-HSA:5579029	Metabolic disorders of biological oxidation enzymes	Disease
R-HSA:446652	Interleukin-1 family signaling	Immune system
R-HSA:448706	Interleukin-1 processing	Immune system
R-HSA:5218859	Regulated Necrosis	Programmed Cell Death
R-HSA:5620971	Pyroptosis	Programmed Cell Death
R-HSA:5633008	TP53 Regulates Transcription of Cell Death Genes	Gene expression (Transcription)
R-HSA:6783783	Interleukin-10 signaling	Immune system
R-HSA:6785807	Interleukin-4 and Interleukin-13 signaling	Immune system
R-HSA:9660826	Purinergic signaling in leishmaniasis infection	Disease
R-HSA:9664424	Cell recruitment (pro-inflammatory response)	Disease
R-HSA:1227986	Signaling by ERBB2	Signal Transduction
R-HSA:1227990	Signaling by ERBB2 in Cancer	Disease
R-HSA:1236394	Signaling by ERBB4	Signal Transduction
R-HSA:186763	Downstream signal transduction	Signal Transduction
R-HSA:186797	Signaling by PDGF	Signal Transduction
R-HSA:1963642	PI3K events in ERBB2 signaling	Signal Transduction
R-HSA:199418	Negative regulation of the PI3K/AKT network	Signal Transduction
R-HSA:2219528	PI3K/AKT Signaling in Cancer	Disease
R-HSA:2219530	Constitutive Signaling by Aberrant PI3K in Cancer	Disease
R-HSA:6811558	PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	Signal Transduction
R-HSA:9664565	Signaling by ERBB2 KD Mutants	Disease
R-HSA:1227986	Signaling by ERBB2	Signal Transduction
R-HSA:1227990	Signaling by ERBB2 in Cancer	Disease
R-HSA:1236382	Constitutive Signaling by Ligand-Responsive EGFR Cancer Variants	Disease
R-HSA:1236394	Signaling by ERBB4	Signal Transduction
R-HSA:1250196	SHC1 events in ERBB2 signaling	Signal Transduction
R-HSA:1643713	Signaling by EGFR in Cancer	Disease
R-HSA:177929	Signaling by EGFR	Signal Transduction
R-HSA:1963640	GRB2 events in ERBB2 signaling	Signal Transduction
R-HSA:1963642	PI3K events in ERBB2 signaling	Signal Transduction
R-HSA:199418	Negative regulation of the PI3K/AKT network	Signal Transduction
R-HSA:2219528	PI3K/AKT Signaling in Cancer	Disease
R-HSA:2219530	Constitutive Signaling by Aberrant PI3K in Cancer	Disease
R-HSA:5637810	Constitutive Signaling by EGFRvIII	Disease
R-HSA:5637812	Signaling by EGFRvIII in Cancer	Disease
R-HSA:5637815	Signaling by Ligand-Responsive EGFR Variants in Cancer	Disease
R-HSA:6811558	PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	Signal Transduction
R-HSA:8848021	Signaling by PTK6	Signal Transduction
R-HSA:9006927	Signaling by Non-Receptor Tyrosine Kinases	Signal Transduction
R-HSA:9664565	Signaling by ERBB2 KD Mutants	Disease
R-HSA:9665348	Signaling by ERBB2 ECD mutants	Disease
R-HSA:9665686	Signaling by ERBB2 TMD/JMD mutants	Disease
R-HSA:5218859	Regulated Necrosis	Programmed Cell Death
R-HSA:5633008	TP53 Regulates Transcription of Cell Death Genes	Gene expression
R-HSA:5685938	HDR through Single Strand Annealing (SSA)	DNA Repair
R-HSA:5685942	HDR through Homologous Recombination (HRR)	DNA Repair
R-HSA:5693532	DNA Double-Strand Break Repair	DNA Repair
R-HSA:5693537	Resolution of D-Loop Structures	DNA Repair
R-HSA:5693538	Homology Directed Repair	DNA Repair
R-HSA:5693554	Resolution of D-loop Structures through Synthesis-Dependent Strand Annealing (SDSA)	DNA Repair
R-HSA:5693565	Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	DNA Repair
R-HSA:5693567	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	DNA Repair
R-HSA:5693568	Resolution of D-loop Structures through Holliday Junction Intermediates	DNA Repair

b **PTC associated clinical outcome and genes involved**

Trait	
Granulocyte percentage of myeloid white cells	USF1
Eosinophil counts	HABP2
Cardiac troponin-I levels	HABP2
Plasma factor VII activating protease levels	HABP2
Blood protein levels	HABP2, CCL5, IL18R1
Eosinophil percentage of white cells	HABP2
Vitamin D levels (dietary vitamin D intake interaction)	CYP2R1
Vitamin D levels	CYP2R1
Serum 25-Hydroxyvitamin D levels	CYP2R1
Vitamin D insufficiency	CYP2R1
Nevus count or cutaneous melanoma	ATM
Cutaneous malignant melanoma	ATM
Uterine fibroids	ATM
Melanoma	ATM
Type 2 diabetes	CDKN1B
Prostate cancer	CDKN1B
Thyroid cancer	NKX2-1, MBIP
Thyroid stimulating hormone levels	MBIP
Lung Cancer (DNA repair capacity)	ERCC2, XPD
Autoimmune thyroid disease	CTLA4
Alopecia areata	CD28, CTLA4, ICOS
Breast cancer	CHEK2
Lung cancer	CHEK2
Platelet count	TERT
Glioma	TERT
Testicular germ cell tumor	TERT, hTERT
Mean corpuscular volume	TERT
Mean corpuscular hemoglobin	TERT
EGFR mutation-positive lung adenocarcinoma	TERT
Telomere length	TERT
Interstitial lung disease	TERT
Lung adenocarcinoma	TERT, CLPTM1L
Testicular germ cell cancer	TERT
Red blood cell count	TERT
Idiopathic pulmonary fibrosis	TERT

c **Molecular function analysis of the exonic SNP predicted by WebGestalt**

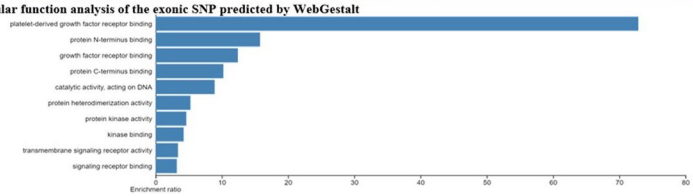


Fig. 1 SNP analysis: **a** Top 60 significant pathways of all PTC-associated SNPs from ClueGo analysis; **b** PTC-associated clinical outcomes and genes involved; **c** Molecular function analysis of the exonic SNPs predicted by WebGestalt

parameters relevant to PTC. These included blood cell counts, thyroid cancer, thyroid-stimulating hormone (TSH) levels, autoimmune thyroid disease, vitamin D levels, and deficiency, as well as other cancers (Fig. 1b). SNP analysis revealed the impact of the mutation on protein function (Supplementary Table 1). SNP enrichment analysis was performed to streamline the critical KEGG, WIKI, and Reactome pathways and decipher the CC and BP associated with these genes, as shown in Supplementary Fig. 2. The enriched BP included positive regulation of intracellular signal transduction, phosphorylation, cell population proliferation, migration, gene expression, macromolecule metabolic processes, and DNA repair. These genes were integral components of the plasma membrane, intracellular membrane, nucleus, autophagosome, and phosphatidylinositol 3-kinase complex. Molecular function includes receptor binding, protein kinase activity, and transmembrane signaling receptor activity (Fig. 1c). The significant SNPs were binned into 135 pathways with potential implications in PTC (adjusted P value < 0.05) (Supplementary Table 2).

Transcriptomic dataset analysis identifies signific DEGs, TFs, Kinases and pathways critical for PTC

Six relevant datasets—4 human datasets (GSE138198, GSE3678, GSE9115, and GSE6339), two transgenic mouse datasets (GSE58689 and GSE118022), and one cell line dataset (GSE6339)—were filtered from the whole set of 341 thyroid cancer-related series in the NCBI GEO database. Each dataset was carefully evaluated, and only those comparing PTC samples with normal controls were shortlisted for R analysis. The human datasets GSE138198, GSE3678, GSE9115, and GSE6339 yielded 4552, 1517, 787, and 468 DEGs, respectively, with adjusted p values of less than 0.05. While the cell line study (GSE6339) produced 1987 DEGs, the mouse model datasets; GSE58689 and GSE118022 produced 5571 and 9357 DEGs, respectively. The DEGs from each dataset were binned into significant pathways (adj. P value < 0.05) associated with PTC (Supplementary Table 3). Comparison of human transcriptomic datasets revealed significant common pathways associated with signaling, immune response, epithelial-mesenchymal transition (EMT), and cancer pathways as shown in Supplementary Table 3d. A comparative analysis of the human, mouse model, and cell line datasets revealed 23 shared pathways (Fig. 2 and Supplementary Table 3e).

Gene ontology analysis revealed the involvement of these DEGs in biological processes, cellular components and molecular functions (Supplementary Table 3f) associated with the pathophysiology of PTC. The GO and significant metabolites of GSE138198 (Supplementary Fig. 3), GSE3678 (Supplementary Fig. 4), GSE9115 (Supplementary Fig. 5), GSE6339 (Supplementary Fig. 6 and 7), GSE58689 (Supplementary Fig. 8), and GSE118022 (Supplementary Fig. 9) were identified. Metabolites predicted from the DEGs in various transcriptomic datasets (Supplementary Table 3 g) were found to be significantly

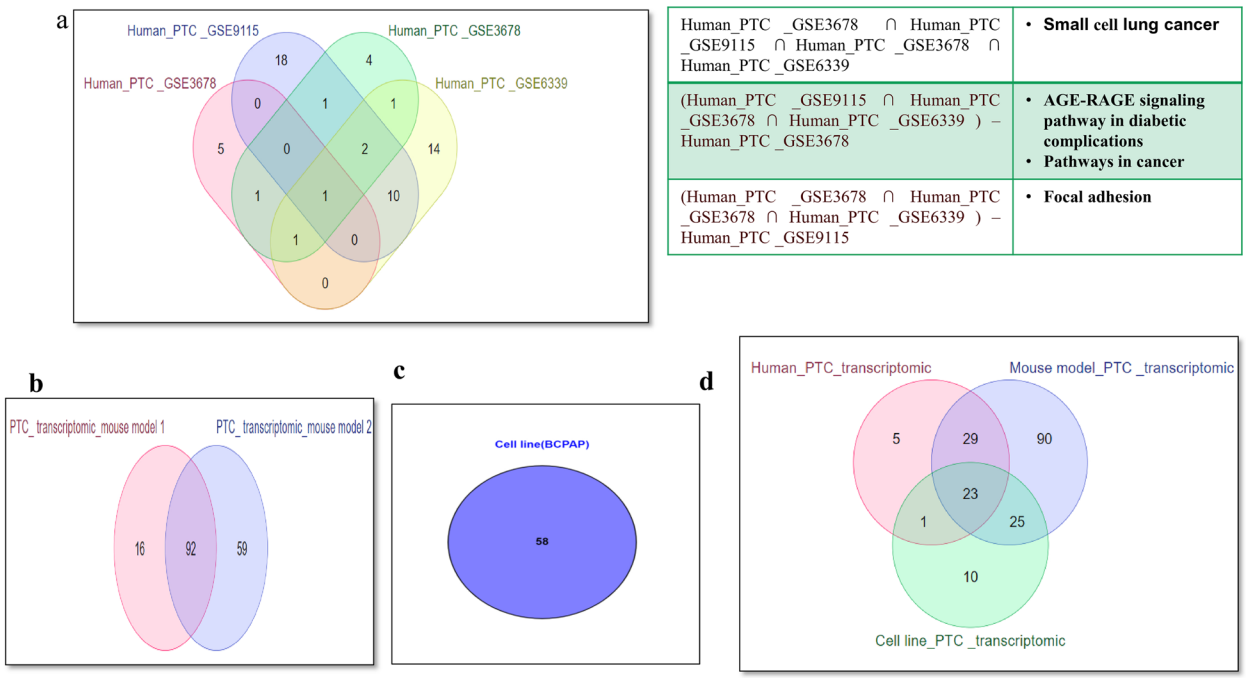


Fig. 2 Commonality analysis of significant pathways: **a** human datasets GSE138198, GSE3678, GSE9115 and GSE6339; **b** mouse model datasets GSE58689 and GSE118022; **c** cell line (BCPAP) dataset; **d** Venn diagram showing the overlap of human, mouse and cell line datasets

associated with energy metabolism, oxidative stress, electron transport chain, and signal transduction. The common metabolites predicted were exhibited in Supplementary Table 3 h.

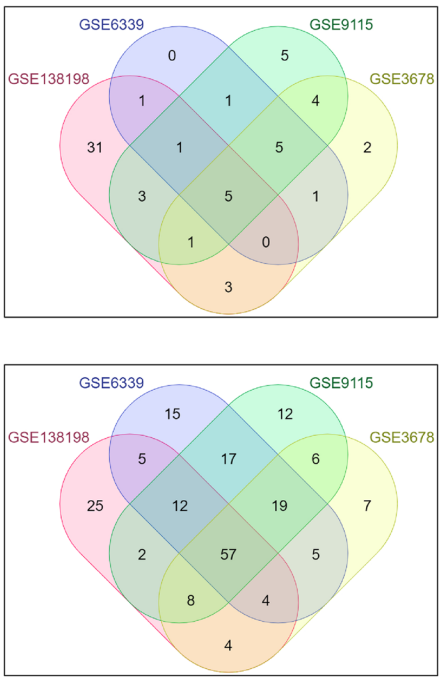
As indicated in Supplementary Table 4, potential TFs and kinases involved in the pathophysiology of PTC were shortlisted in each of the human datasets. The most important of these were then vetted by analysing the TFs and kinases shared by all or most human datasets being examined. As shown in Fig. 3, a total of five TFs and fifty-seven kinases typical of all human datasets were determined to be the most important and crucial components in PTC genesis and progression.

Proteomic data analysis screens PTC-associated significant differentially expressed proteins (DEPs) and deregulated pathways

Significantly differentially expressed proteins were shortlisted from published proteomic works in PTC tissue, plasma, and serum samples. Three tissue-based and one each from plasma and serum were analysed to elucidate the potential pathways enriched in PTC. A total of 1438 DEPs were pooled from the tissue datasets, whereas 121 and 18 DEPs were screened from the PTC plasma and serum datasets, respectively. Pathway enrichment analysis was conducted to identify significant pathways that were dysregulated (Supplementary Table 5). Fc gamma R-mediated phagocytosis, bacterial invasion of epithelial cells, regulation of the actin cytoskeleton, leukocyte trans endothelial migration, adherens junction, shigellosis, tight junction, pathogenic *Escherichia coli* infection, and antigen processing and presentation were the nine most essential pathways commonly observed in tissue-based PTC studies (Fig. 4). While cholesterol metabolism was prevalent in the tissue and serum PTC proteomic data, complement and coagulation cascades was the only pathway that was categorized similarly across the tissue, plasma, and serum datasets, as shown in Fig. 5.

Metabolomic data analysis screens PTC-associated significant metabolic pathways

Metabolomic data analysis plays a vital role in understanding the involvement of major metabolic pathways in disease pathophysiology. PTC-associated metabolomic studies of tissue, serum, urine, faeces, and cell lines were performed, and the significantly upregulated and downregulated metabolites were screened in each study. These metabolites were binned into significant metabolic pathways (adj. P value < 0.05 and FDR < 0.25) critical in PTC, as shown in Supplementary Table 6. Glyoxylate and dicarboxylate metabolism; alanine, aspartate, and glutamate metabolism; and aminoacyl-tRNA biosynthesis were the common metabolic pathways identified in the tissue-based studies (Fig. 6), whereas the biosynthesis of unsaturated fatty acids was the most common among the serum samples. One carbon pool associated with the folate



Transcription Factor	Common among Datasets
ESR1, GATA1, NFE2L2, SOX2, TCF3	GSE138198, GSE6339, GSE9115,GSE3678
ZBTB7A	GSE138198, GSE6339, GSE9115
PPARD	GSE138198, GSE6339, GSE3678
GATA2, SUZ12, TP53, SALL4, TRIM28	GSE6339, GSE9115,GSE3678
NELFE	GSE6339, GSE138198
UBTF, E2F1, FOXP2	GSE138198, GSE9115
CTCF, SMC3, FOXA1	GSE138198, GSE3678
RUNX1	GSE6339, GSE9115
NANOG	GSE3678, GSE6339
EZH2 AR POU5F1 SMAD4	GSE3678, GSE9115

Kinases	Common among Datasets
CDK4, CDK1, CSNK2A2, CHEK1, DNAPK, MAPK14, CDK6, JNK1, TGFBR2, AURORAA, RAF1, ERK2, MAPK8, JNK2, MAP3K7, PRKCZ, CDK5, ABL1, RPS6KA1, MAPK3, CSNK1E, CDK9, CSNK2A1, HIPK2, AKT1, PRKCB, GSK3B, CDK7, CHUK, MAPK1, CHEK2, PRKCA, GSK3BETA, PRKACA, PRKCD, GSK3ALPHA, CDK3, PRKAA1, PKBALPHA, MAPK9, CDC2, RPS6KA3, MAP2K1, EGFR, IKBKB, SRC, CK2ALPHA, CDK2, ERK1, PIM1, PRKDC, DYRK2, IKKBETA, ATM, CDK8, MAPK11, ERBB	GSE138198, GSE6339, GSE9115,GSE3678

Fig. 3 Analysis of transcription factors and kinases of the human transcriptomic datasets GSE138198, GSE6339, GSE9115 and GSE3678: Venn diagram showing the overlap of transcription factors and kinases

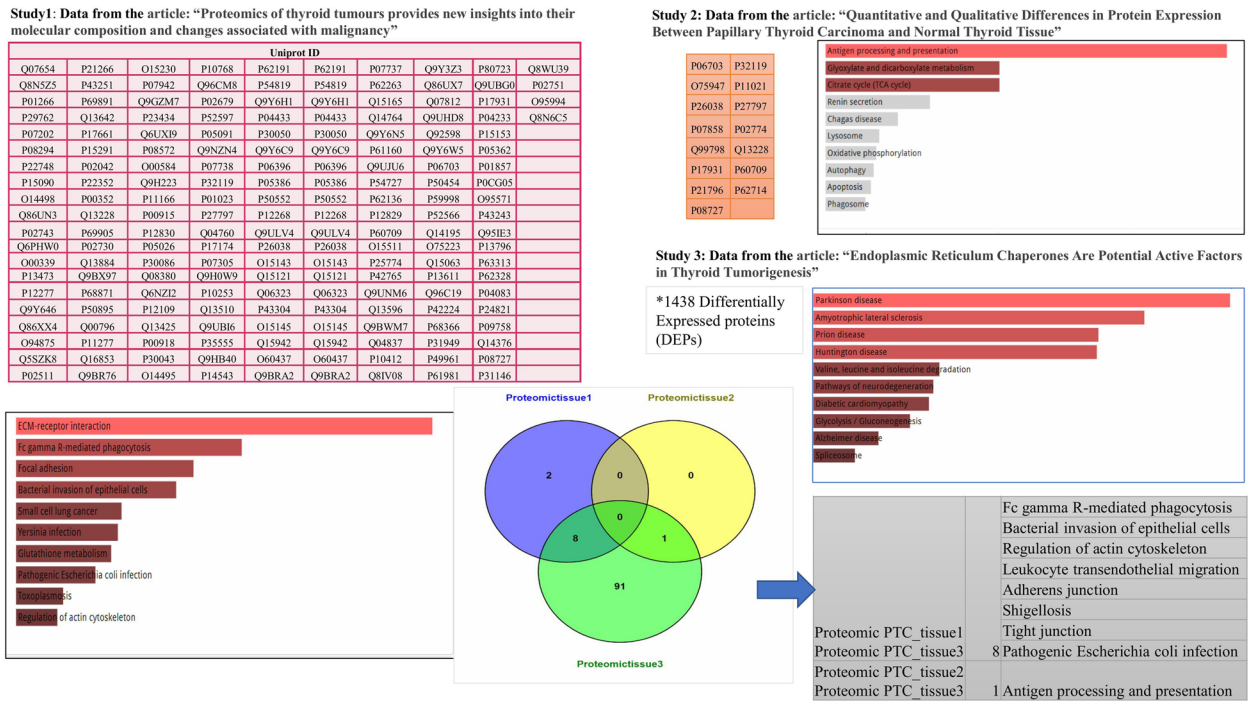


Fig. 4 Pathway analysis of differentially expressed proteins (DEPs) in tissue between PTC patients and healthy controls via Enrichr

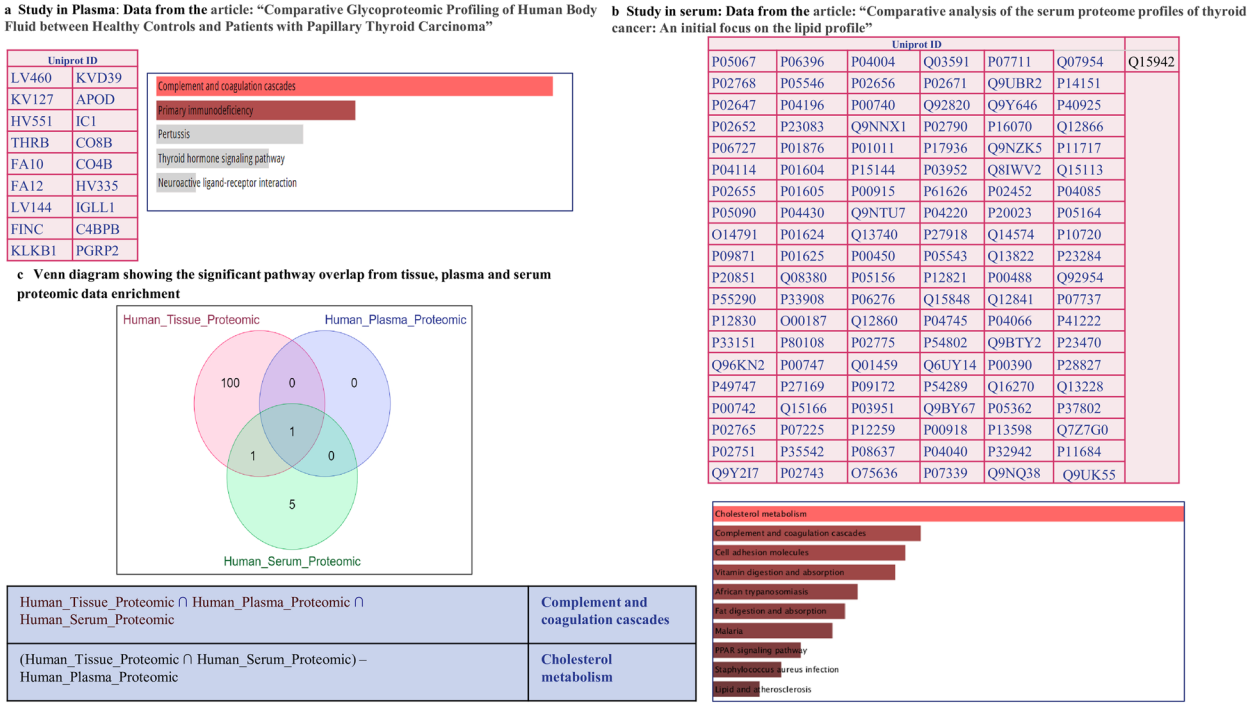


Fig. 5 Pathway analysis of differentially expressed proteins in plasma and serum between PTC patients and healthy controls via Enrichr and a commonality analysis of deregulated pathways in human proteomic samples

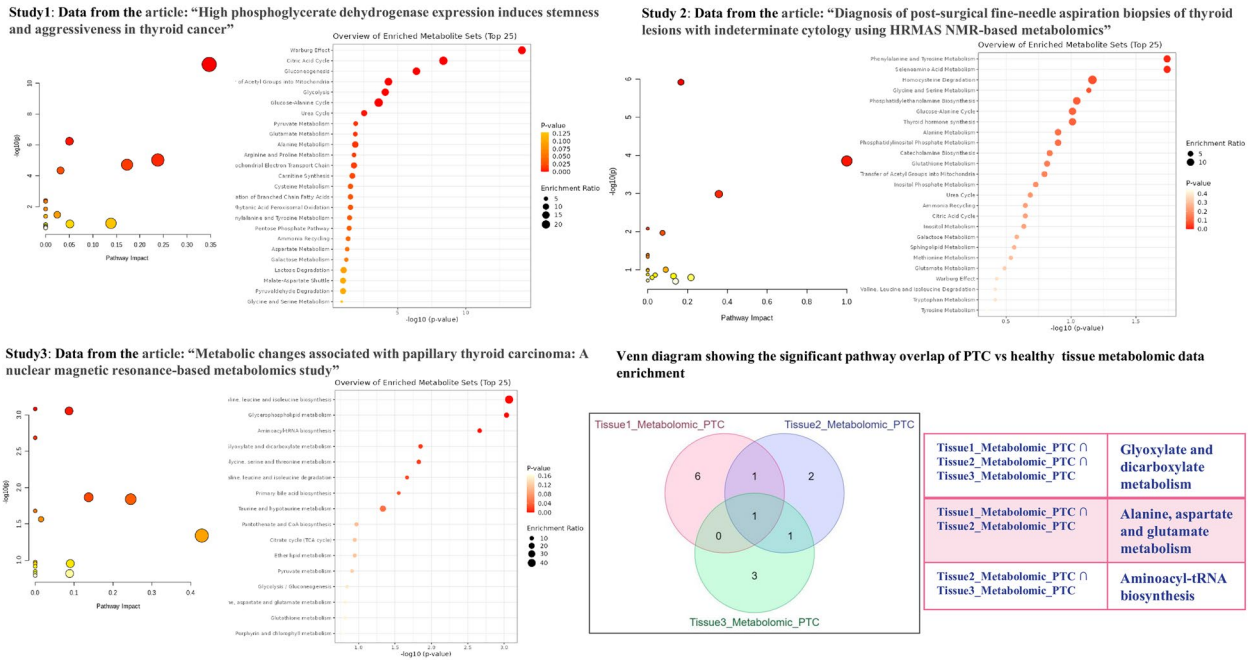


Fig. 6 Enrichment analysis of human tissue metabolomic studies of PTC patients compared with healthy controls

pathway was enriched in the urine samples, whereas glycerophospholipid metabolism and glycerolipid metabolism were substantially enriched in the faecal analysis (Fig. 7). Alanine, aspartate and glutamate metabolism; the citrate cycle (TCA cycle); and glycolysis/gluconeogenesis were prominent in the PTC cell line studies.

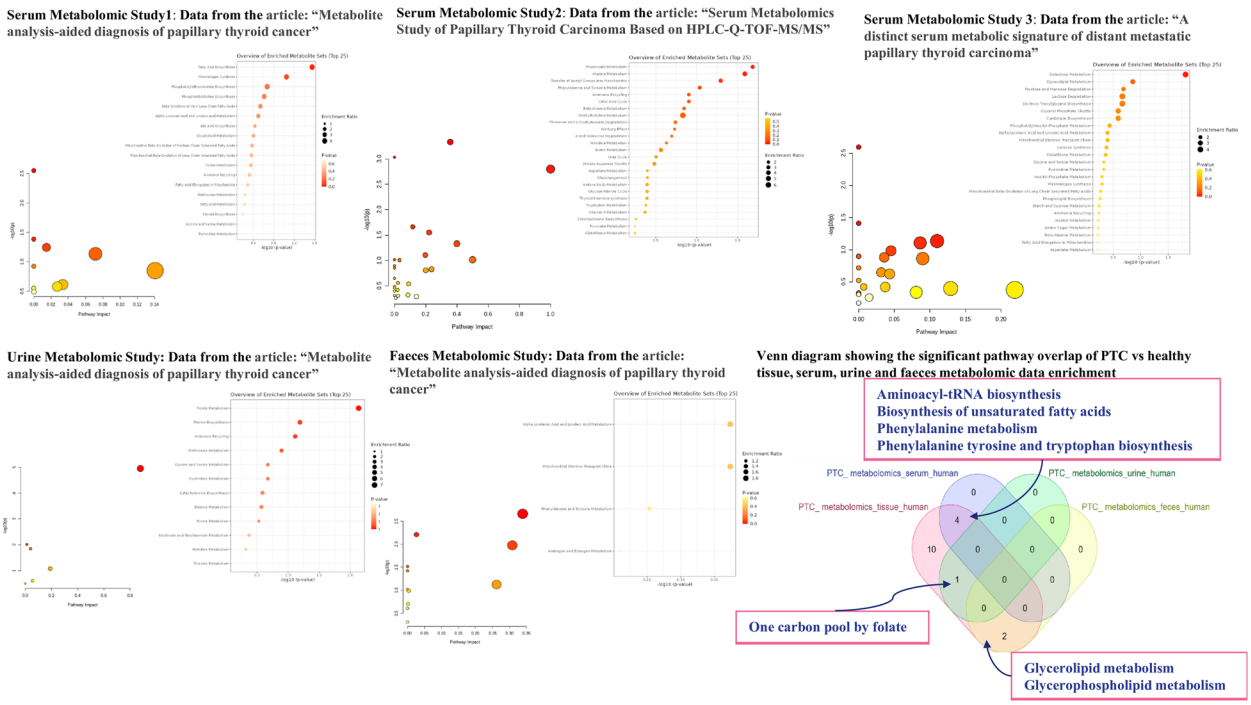


Fig. 7 Enrichment analysis of human metabolomic studies (serum, urine, and faeces) of PTC patients compared with healthy controls and a commonality analysis of deregulated pathways in human metabolomic samples

Human and cell line metabolomic datasets associated with PTC were compared, and approximately nine crucial metabolic pathways were found to be similar, while eight and ten unique pathways were observed in humans and cell lines, respectively, as shown in Supplementary Table 6d. Commonality analysis of the human metabolomic data is shown in Fig. 7.

PTC multi-omics dataset integration highlights crucial pathways in PTC tumorigenesis

Integration of significant pathways of human SNPs, transcriptomics, proteomics, and metabolomic data analysis is substantial in identifying the pathways with the most potential implication in the pathophysiology of PTC. TCA cycle and glyoxylate and dicarboxylate metabolism were found to be shared among the PTC-transcriptomic, proteomic, and metabolomic dataset analysis, while many protein, carbohydrate, and nucleic acid metabolic pathways, signaling pathways, EMT pathways, and disease pathways were identified as altered in the process of PTC progression as shown in Table 1 and Fig. 8 a. The integration of the combined disrupted pathways of human, mice and cell line datasets at different levels of OMICs were also done and is exhibited in Fig. 8 b. The significant dysregulated metabolic pathways, and TFs were linked to PTC's clinical outcomes, as shown in Fig. 9 and Supplementary Table 7 a and b while potential kinases were linked to PTC as depicted in Supplementary Table 7 c.

Discussion

SNPs have various implications for PTC tumorigenesis and progression [42]. Our study revealed the connection of the PTC-linked SNPs to the parent pathways associated with the immune system, signal transduction, DNA repair, programmed cell death, gene expression (transcription), haemostasis, and disease onset. Previous studies have investigated the role of molecular signaling cascades [43] and the importance of immune-related genes and cells in modifying the PTC microenvironment [44].

PTC transcriptome research has revealed increased immune signaling involving cytokines or T cells and an upregulated CD8 + T-cell and Th1 cell biomarkers. The recurrent and dedifferentiated advanced PTCs demonstrated an overexpression of genes associated with immune escape signaling pathways in addition to the PI3K and MAPK signaling pathways [45]. The integration of all the dysregulated pathways of the various transcriptomic datasets in the present study substantiated the idea that cytokine immune pathways (Th17 cell differentiation and chemokine signaling), molecular signaling pathways (AGE-RAGE, PI3K-Akt, P53, and MAPK

Table 1 Integrated dysregulated pathways from PTC-associated human multi-OMICs data

Human_PTC_transcriptomic ∩ Human_PTC _proteomic ∩ Human_PTC _metabolomic	Citrate cycle (TCA cycle) Glyoxylate and dicarboxylate metabolism
Human_PTC _proteomic ∩ Human_PTC _metabolomic	Alanine aspartate and glutamate metabolism Aminoacyl-tRNA biosynthesis Arginine and proline metabolism Butanoate metabolism Fructose and mannose metabolism Glycine serine and threonine metabolism Glycolysis/Gluconeogenesis Pentose phosphate pathway Phenylalanine metabolism Propanoate metabolism Pyruvate metabolism Synthesis and degradation of ketone bodies Tyrosine metabolism Valine leucine and isoleucine degradation
Human_PTC_transcriptomic ∩ Human_PTC_metabolomic	Glycerolipid metabolism
Human_PTC _metabolomic ∩ Human_PTC_SNPs	Inositol phosphate metabolism
Human_PTC_transcriptomic ∩ Human_PTC _proteomic ∩ Human_PTC_SNPs	Bacterial invasion of epithelial cells Focal adhesion Human papillomavirus infection Necroptosis Nonalcoholic fatty liver disease PI3K-Akt signaling pathway Pathogenic *Escherichia coli* infection Pathways of neurodegeneration Prion disease Proteoglycans in cancer Small cell lung cancer Yersinia infection
Human_PTC_transcriptomic ∩ Human_PTC _proteomic	Arrhythmogenic right ventricular cardiomyopathy Diabetic cardiomyopathy ECM-receptor interaction Fc gamma R-mediated phagocytosis Glutathione metabolism Platelet activation Tight junction Viral myocarditis
Human_PTC_proteomic ∩ Human_PTC_SNPs	Adherens junction African trypanosomiasis Alzheimer disease Amoebiasis Apoptosis Central carbon metabolism in cancer Complement and coagulation cascades Coronavirus disease Estrogen signaling pathway Ferroptosis Fluid shear stress and atherosclerosis HIF-1 signaling pathway Malaria Regulation of actin cytoskeleton Salmonella infection Shigellosis Thermogenesis Thyroid hormone synthesis Viral carcinogenesis

signaling pathways), as well as pathways related to cancer, infection, metabolism, and EMT, are key factors in the tumorigenesis of PTC. Our analysis revealed enrichment of focal adhesion, ECM-receptor interaction, and proteoglycans in cancer pathways, all of which contribute significantly to the EMT process and cause inflammation, invasion, and metastasis [46, 47] in PTC [48].

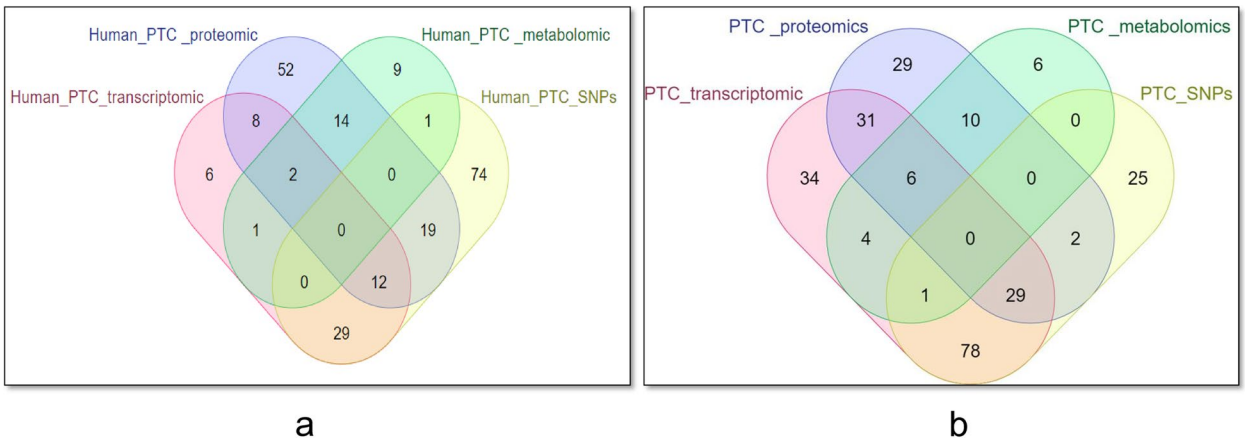


Fig. 8 Comparative analysis of dysregulated pathways of a) human-PTC SNP, transcriptomic, proteomic and metabolomic datasets b) combined human, mouse model and cell line PTC datasets at different OMICs level

Metabolic features differ relative to the molecular framework determined by the nature of the mutation. This paper's combined transcriptomic, proteomic, and metabolomic PTC data analysis revealed dysregulation of the TCA cycle, and glyoxylate and dicarboxylate metabolism. Metabolic reprogramming, which is crucial in PTC pathogenesis, involves increased dependence on glycolysis and changes in the TCA cycle and biosynthesis of fatty acids and amino acid metabolism. The TCA cycle is the primary source of energy (ATP), and intermediates like citrate for fatty acid biosynthesis. TCA cycle dysregulation also resists targeted therapy in PTC [49]. Upregulation of glutaminolysis leads to an increase in glutamine breakdown into α-ketoglutarate, which is an intermediate of the TCA cycle and helps to maintain energy in tumor cells for proliferation and metastasis [50, 51]. Glyoxylate and dicarboxylate metabolism was another significant pathway dysregulated in the analysis, which was validated in serum amino acid profiling in PTC0 patients in previous works on the basis of differential expression of glycine, glutamine, and glutamic acid [52] This pathway is also linked to other cancers, such as prostate cancer [53], and gastric cancer [54]. Glyoxylate and dicarboxylate metabolism are closely interconnected to the TCA cycle by shared intermediates, such as malate. These dysregulated pathways help cancer cells cope with nutrient stress.

Fourteen pathways were found common between proteomic and metabolomic PTC data. The carbohydrate, amino acid, and fatty acid metabolism pathways were influential. Glycolysis/gluconeogenesis and the pentose phosphate pathway (PPP) were the most significant pathways. The upregulation of glycolysis/gluconeogenesis pathways in tumors indicates glucose reprogramming. The gluconeogenic enzymes phosphoenolpyruvate carboxykinase 1 (PCK 1) and phosphoenolpyruvate carboxykinase 2 (PCK 2) play key roles in cancer metabolism [55]. According to the Warburg effect, the cancer cell may rely on aerobic glycolysis to satisfy the increased energy demand. The upregulation of glycolysis via HIF-1α signaling initiated by the PI3/Akt/mTOR pathway may lead to a decrease in glucose and an increase in AMP levels. This activates AMP-activated protein kinase (AMPK), which may promote catabolic pathways to increase the ATP production required for cancer proliferation and metastasis [56]. HIF-1α signaling and the PI3K/Akt/mTOR pathway were also found significant and upregulated in our PTC omics data analysis. Next significant pathway is PPP, which is important in the synthesis of ribonucleotide precursors and NADPH. Cancer cells spare glucose for the PPP to manage energy demand and oxidative stress. Targeting the PPP increases reactive oxygen species (ROS) levels and induces apoptosis in thyroid cancer [57]. Glycolysis and the PPP acidify the TME, which promotes invasion and metastasis by destroying the extracellular matrix (ECM), and promoting EMT and angiogenesis [58].

Many amino acid metabolic pathways, such as alanine, aspartate, and glutamate metabolism; arginine and proline metabolism; glycine serine and threonine metabolism; phenylalanine metabolism; and valine, leucine, and isoleucine degradation, were found dysregulated in the present study. Altered amino acid metabolism is a hallmark of cancer origin. Amino acids act as donors of carbon and nitrogen under nutrient-deprived conditions and fuel tumor cells, and they are the source for the de novo biosynthesis of lipids, purines, and pyrimidines, which are crucial for tumor survival and progression. Amino acids are also involved in cell signaling, cancer immunity, angiogenesis, transcription

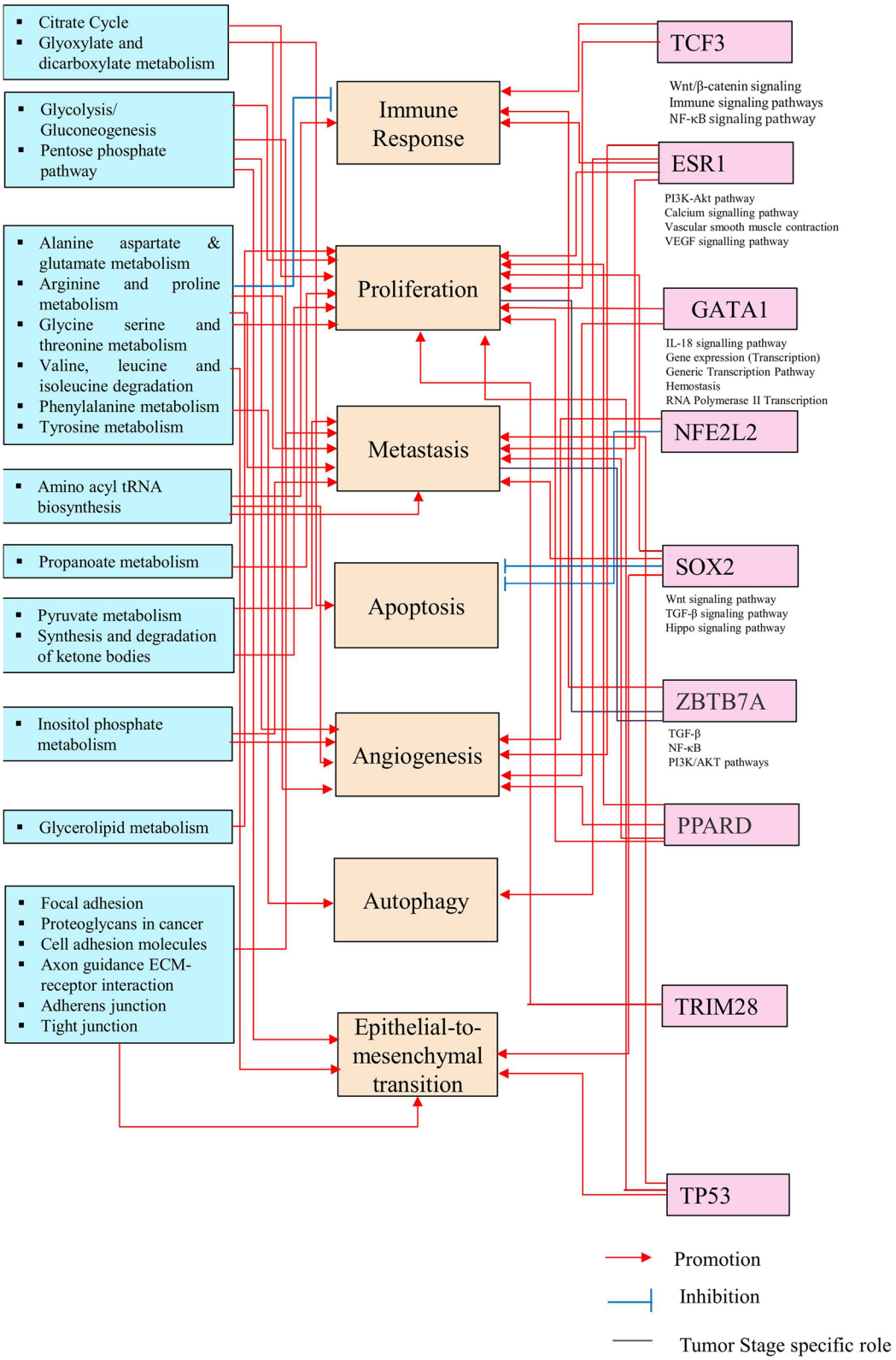


Fig. 9 Summary of multi-omics studies exhibiting the deregulated pathways, and transcription factors and their influence on the biological processes associated with PTC

regulation, epigenetic modification, and metabolic regulation [59]. Amino acid metabolomics in saliva can be used as a non-invasive diagnostic method for thyroid cancer detection [60].

The amino acids glutamine, arginine, and aspartate play significant roles in tumor maintenance. Glutamine is converted to glutamate, which, in turn, upon transamination or deamination, is converted to α-ketoglutarate, an intermediate of the TCA cycle, which plays a vital role in cancer energetics and epigenetic modification. Purine and pyrimidine biosynthesis from glutamine is a source for DNA biogenesis and repair in the TME. Glutamate is also responsible for maintaining oxidative balance. Glutamine-derived phosphoenolpyruvate (PEP) generates acetyl Co-A in the nutrient-deficient TME and feeds the TCA cycle to sustain the energy demands of a cancer cell [61]. Arginine enters via cationic amino acid transporters (CAT) or can be synthesized from aspartate and citrulline in the urea cycle. Nitric oxide (NO) produced from arginine in the presence of nitric oxide synthase-2 (NOS-2) increases angiogenesis and suppresses the immune response. In PTC, NO induces vascular endothelial growth factor (VEGF-D) and is associated with lymph node metastasis [62]. Aspartate, which is interconvertible with asparagine, is a limiting metabolite in cancer progression under hypoxia [63]. This amino acid plays a significant role in the biosynthesis of proteins and nucleotides that are essential for tumor progression and EMT.

Oncometabolite-like branched-chain amino acids (BCAAs) valine, leucine, and isoleucine are elevated in thyroid cancers [64]. Since essential, the transporter for these amino acids, L-type amino acid transporter 1 (LAT1), are crucial for tumor survival and are upregulated in thyroid cancer cells, making them potential therapeutic targets for PTC treatment [65]. The valine, leucine, and isoleucine degradation pathways are significant in PTC, as they produce succinyl-CoA and acetyl-CoA, which enter the TCA cycle for excess ATP generation. The addition of acetyl-CoA to the TME can lead to protein acetylation and epigenetic modification. Leucine stimulates the mTOR pathway, which is critical in PTC [66, 67].

Serine/glycine plays a critical role in cancer cells. They are the primary carbon donors for the folate cycle, which is important for the biosynthesis of proteins, lipids, and nucleic acids; cellular homeostasis; and methylation reactions [68]. One carbon enters one-carbon metabolism from serine in the presence of serine hydroxy methyltransferase (SHMT 2) in mitochondria. SHMT2 is involved in PTC metastasis by activating the Akt signaling pathway [69].

Lipid metabolic pathways like glycerolipid metabolism, propanoate metabolism, pyruvate metabolism, and synthesis and degradation of ketone bodies were found significant in PTC and is discussed in Supplementary Table 7a.

Focal adhesion, proteoglycans in cancer, cell adhesion molecules, axon guidance ECM-receptor interactions, adherens junctions, and tight junctions were the EMT pathways dysregulated in the PTC omics analysis. All these pathways are crucial in the transition from E-cadherin-expressing differentiated epithelial cells to mesenchymal cells, which are the least differentiated and express vimentin, N-cadherin, and fibronectin. EMT associated immunohistochemical markers Ki-67 is highly expressed in advanced PTC [70].

Transcription factors are proteins that bind to particular DNA and control its expression, and are essential for cellular activities such as growth, proliferation, differentiation, and death. In many malignancies, reprogramming and dysregulation of these TFs may fuel carcinogenesis. The development of practical approaches to directly and indirectly target TFs in cancer treatment is difficult; these approaches include focusing on protein–protein interactions, the DNA-binding domain, and proteasomal degradation [71]. Previous studies have examined the important roles that the thyroid-specific TFs NKX2-1, FOXE1, and PAX8 play in the development and spread of thyroid cancer [72]. All the human datasets we examined showed shared dysregulation of ESR1, GATA1, NFE2L2, SOX2, and TCF3. The nuclear membrane estrogen receptor 1 (ERα) protein, which controls cell development and metabolism when it binds to estrogen, is expressed by the transcription factor ESR1. ESR1 was linked to central lymph node metastasis in PTC patients with positive BRAF protein expression, and it was elevated in males, young patients, and multifocal patients. PTC patients with BRAF mutations had lower overall survival rates when ESR1 expression was higher [73]. ERα overexpression induces proliferation, autophagy, and metastasis in PTC, whereas ERβ is proapoptotic [74]. ERα, HIF1α (hypoxia), and nuclear factor-κB (NFκB) (inflammation) are linked in the processes of PTC origin, metastasis, and cancer immunity [75]. GATA binding protein 1 (GATA1) is a transcription factor that binds to particular DNA locations and promotes the proliferation, maturation, and differentiation of RBCs and megakaryocytes [76]. GATA1 binds histone deacetylase 2 (HDAC2) to the promotor of nuclear receptor binding protein 2 (NRBP2), a tumor suppressor, and causes histone deacetylation, which inhibits its expression and increases angiogenesis and TME markers in PTC [77]. In ovarian, breast, and colorectal cancers, among other cancers, GATA1 has crucial regulatory functions in angiogenesis, invasion, metastasis, and proliferation [78–80]. The transcription factor NFE2L2/NRF2 (Nuclear factor erythroid-derived

2-like 2) is essential for angiogenesis, immunological infiltration, and the body's reaction to oxidative stress. It attaches itself to the antioxidant response elements (AREs) found in the promoters of genes that express antioxidant proteins. In PTC, NRF2 is significantly active and controls angiogenesis, antioxidant transcriptional responses, and cell survival [81, 82]. Another putative TF that binds to lncRNA LINC01510 promoter and increases LINC01510 expression in PTC is SRY-box transcription factor 2 (SOX2), which has antiapoptotic and functional implications for invasion, migration, and proliferation [83]. The sonic Hedgehog pathway regulates SOX2 at the transcriptional level and promotes thyroid cancer stem cell-driven PTC [84]. By promoting EMT transition through the modulation of the WNT/β-catenin signaling network, SOX2 facilitates lymph node and distant metastasis [85–87]. Transcription factor 3 (TCF3) is the next important TF in PTC. It helps reduce the disease-free lifespan in PTC by regulating the overexpression of the oncogene HOXD9, which impacts immunological signaling pathways, in conjunction with EZH2. Oncogenesis, recurrence, and treatment resistance are caused by the correlation of HOXD9 with the NF-κB signaling pathway, which in turn triggers the MAPK signaling pathway [88].

Transcription factors ZBTB7A, PARD, TP53, TRIM28, GATA2, SUZ12, and SALL4 were found common to three of the human transcriptomic datasets under study, which were also considered significant in PTC. Zinc finger and BTB domain-containing 7A (ZBTB7A/FBI-1/Pokemon) play significant roles in tumorigenesis and metastasis across various cancer types [89]. ZBTB7A/Pokemon expression is linked to PTC carcinogenesis, and because it negatively regulates aerobic glycolysis, ZBTB7A/Pokemon expression inversely correlates with PTC tumor size [90]. The next significant TF, PARD (peroxisome proliferator-activated receptor delta), mediates nuclear receptor signaling and transcriptional suppression. In thyroid cancer, PPARD stimulates cell proliferation via a mechanism dependent on cyclin E1 [91]. Cell division, angiogenesis, apoptosis, metastasis, tumor metabolism, and the immunological response are all impacted by PPARD [92]. The transcription factor p53 (TP53) responds to cellular stress (such as hypoxia, DNA damage, and spindle damage) by altering its protein level and post-translational modification state. ATM, ATR, Chk1, and MAPK phosphorylation are among the mechanisms that activate p53 [93]. More than 80% of ATCs have p53 gene mutations, which are crucial in the development of thyroid tumors from well-differentiated (papillary and follicular) to poorly differentiated (anaplastic) TCs [94]. In addition to causing the p53 protein to lose its tumor suppressor function, p53 mutations, especially those that occur in "hot spots", such as R175H and R273H, also confer protein oncogenic properties that promote angiogenesis, metastasis, and cell proliferation [95]. Transcription intermediary factor-β (TIF1β), also known as TRIM28 (tripartite motif containing 28), contributes to the development of tumors by poly-ubiquitinating and degrading substrates such as AMPK, RLIM (RING finger LIM-domain-interacting protein), and SUMOylating PD-L1 (programmed cell death ligand 1). TRIM28 is far more prevalent in thyroid cancer patients than in healthy controls [96].

In this study, GATA2, SUZ12, and SALL4 were also identified as significant in PTC. Although previous researches have shown that these TFs were linked to several malignancies, there hasn't been any direct link found in the literature between PTC and these TFs. GATA binding protein 2 (GATA2) is a transcription factor linked to the immunological response and hematopoiesis. GATA2 has been investigated in relation to the invasion, cell motility, and metastasis of many malignancies, including prostate, colorectal, and breast cancer [97–99]. SUZ12 (SUZ12 polycomb repressive complex 2 subunit) is a critical element of the polycomb repressive complex 2 (PRC2), which methylates histone H3 and causes transcriptional suppression of the impacted target gene. In numerous malignancies, including colorectal, gastric, and small-cell lung cancer, SUZ12 has been connected to invasion, metastasis, and proliferation [100–102]. SUZ12 regulation is essential for the epigenetic process of BRAF(V600E)-driven thyroid cancer carcinogenesis, both transcriptionally and post-transcriptionally [103]. SALL4 is a stem cell regulator that, when overexpressed, promotes cancer, proliferation, and metastasis by regulating mitochondrial oxidative phosphorylation genes and the Wnt/β-catenin, PI3K/AKT, and Notch signaling pathways. It inhibits the apoptotic pathway of Bcl-2 family proteins. It is linked to the immune response in the development of tumors and affects hematopoiesis through an epigenetic mechanism [104].

Protein kinases play a role in PTC by regulating signaling pathways that affect cell survival, transformation, and antiapoptotic effects. The present work identified typical kinases from all the human PTC GEO datasets under study. The significant kinases involved in PTC pathophysiology belongs to CDK, CHEK, MAPK, CSNK, JNK, CDC, ERK, PRK, GSK, RPS6KA, DNAPK, and TGFBR2 families. The implications of these significant kinases in PTC tumorigenesis are discussed in Supplementary Table 7c.

The present in-silico multi-omics data analysis was able to identify deregulated pathways, TFs, and kinases in PTC that were prevalent across datasets, taxa, methodologies, populations, and study setting confirming their significance. The functional implication of the identified

pathways was validated using literature mining and were found to modulate the biological processes associated with PTC. However, the data obtained need to be experimentally validated in larger cohorts. Despite the limitation, these core pathways, TFs, and kinases identified may act as critical drug targets and biomarkers, and could be employed in future research to precisely identify non-invasive diagnostic methods and individualized PTC treatment plans. Pre-clinical and clinical research should follow in order to apply these significant in-silico insights to clinical practice.

Conclusion

PTC is the most prevalent endocrine cancer affecting the follicular cells of the thyroid gland. The present work analysed the SNP, transcriptomic, proteomic, and metabolomic data of PTC via an integrative approach. The study identifies TFs and kinases, as well as significant deregulated pathways at varying OMIC levels associated with PTC and further based on literature it helps to validate the potential role of these in PTC progression and prognosis. Glyoxylate and dicarboxylate metabolism and the citrate cycle were the most common pathways across the PTC omics datasets. The commonality analysis deciphered five TFs and fifty-seven kinases crucial for PTC genesis and progression. Further, the data also help to show that the core pathways are conserved across datasets, taxa, methodologies, populations, and study settings. Though, the findings are not validated in a larger cohort, we believe that the present study helps to provide a systems level understanding and might help to device specific experiments to comprehend the role of deregulated pathways as potential biomarker and therapeutic targets in PTC. The deregulated pathways, TFs, and kinases modulate critical biological processes like proliferation, angiogenesis, immune infiltration, invasion, autophagy, EMT, and metastasis in PTC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13044-025-00230-1.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.
Supplementary Material 9.
Supplementary Material 10.
Supplementary Material 11.
Supplementary Material 12.
Supplementary Material 13.
Supplementary Material 14.
Supplementary Material 15.
Supplementary Material 16.

Acknowledgements

We are grateful to the Principal, Dr. Usha A.A. and Dr. Rita Latha D'couto (Rtd. Principal), St. Joseph's College for Women, Alappuzha, Kerala, India, for providing all assistance and inspiration for the work. Thanks to Dr. K. Manimegalai and all other staff of the Department of Zoology, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, Tamil Nadu, India, for their encouragement and support.

Authors' contributions

FP – Febby Payva, SKS – Santhy KS, RJ – Remya James, APE -Amrisa Pavithra E, VS- Venketesh Sivaramakrishnan. FP, SKS & VS designed the research framework and defined the objectives of the study. FP & VS contributed to the development of the study's conceptual framework. FP & RJ collected and curated the genomic data used in the study. FP, SKS & VS performed the statistical analysis and interpretation of the genomic data. VS, RJ & SKS assisted in analysing the data and interpreting the results. FP, APE and VS refined the methodology and ensured its alignment with the study objectives. SKS and VS supervised the overall research project and guided the team. SKS ensured the availability of tools and software required for data analysis. FP, RJ & APE created visual representations of the data and results. FP, RJ & APE designed the figures and tables for the manuscript. FP wrote the original draft. APE & RJ contributed sections to the draft and provided critical input. All the authors reviewed and edited the manuscript for clarity and scientific rigor.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Received: 25 November 2024 Accepted: 10 February 2025
Published online: 11 April 2025

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