SUPPLEMENTAL MATERIALS AND METHODS

Reagents

All reagents and products were purchased from Merck/Sigma-Aldrich unless otherwise specified. HPLC purified Recombinant Human Lipocalin-2/NGAL (LCN2) Protein (#10222-H08H) was obtained from SinoBiological. Functional assays were performed via treatment with exogenous LCN2 at a concentration of 50 μM, as previously reported (Eilenberg et al., 2016). Each experiment was performed in triplicate with at least three independent biological replicates.

PPAT magnetic resonance imaging acquisition

Multiparametric magnetic resonance imaging (mpMRI) of the prostate and surrounding PPAT was performed via a 1.5T/3T scanner (Magnetom Aera/Vida, Siemens Healthineers) equipped with a 128-channel acquisition platform and a specific antenna dedicated to abdominal studies (30 channels). A specific prostate mpMRI protocol was used, including T2-weighted morphological sequences with high resolution in plane, diffusion sequences, and dynamic studies. The evaluation and reading of these MR images were performed by experienced radiologists, specifically those dedicated to urogenital radiology, applying version 2.1 of the PI-RADS (Prostate Imaging Reporting and Data System) guidelines.

LCN2 protein detection in plasma and urine

Biological concentrations of lipocalin-2 (LCN2/NGAL) were quantified by sandwich Enzyme-Linked Immunosorbent Assay (ELISA) using a commercial Human NGAL ELISA kit (MBS824471) according to the manufacturer's instructions. A total of 98 patient-derived samples (**Table 1, IC3/IC4**) along with conditioned media from prostate cell lines (PNT2, LNCaP, 22Rv1, PC-3, and DU145) were assayed on 96-well plates. Each plate included a seven-point standard curve [serial 2-fold dilutions from 5,000 to 78.125 pg/mL – the validated quantification range – and a zero standard (diluent)]. Samples and standards (100 μL/well) were incubated with the plate-bound capture antibody for 90 min at room temperature, followed by sequential incubations with biotinylated detection antibody and streptavidin-horseradish peroxidase (HRP, prepared 1:100), with intermediate washes. Color development was performed with TMB substrate and stopped with the supplied stop solution. Absorbance was read at 450 nm within 30 min of stopping. Finally, sample concentrations were interpolated from the respective standard curves to account for inter-plate variability. According to manufacturer's instructions, the kit's minimum detectable dose is < 40 pg/mL.

Conditioned media generation and proteomic analysis of PPAT-secretome

Conditioned media (CM) from the PPAT (secretome) was obtained from samples of **IC2**. Specifically, freshly sectioned PPAT explants, obtained during surgical intervention, were rapidly cultured to minimize tissue degradation. To eliminate weight-dependent bias, all explants derived from each patient were washed twice with cold PBS and cultured in DMEM F-12 medium (Gibco) supplemented with gentamicin (50 µg/mL) at a ratio of 7 mL per gram of tissue. The explants were then maintained in sterile flasks within a humidified incubator under standard conditions, and after 24 h, the CM was collected, filtered, and aliquoted (all processes under sterile conditions). The samples were then immediately stored at -80°C until further use in proteomic and metabolomics analyses (see below).

Total protein extraction from the PPAT-secretome was performed following previously established methods (Arenas-De Larriva et al., 2022). Briefly, 200 µL of CM was subjected to protein precipitation with cold acetone, and the resulting protein pellets were resuspended in 50 µL of 0.2% RapiGest (Waters) in 50 mM ammonium bicarbonate. The protein concentration was then determined via a Qubit Protein Assay kit (Thermo Fisher Scientific) on a Qubit fluorimeter, and 50 µg of each sample was digested with trypsin as previously described (Arenas-De Larriva et al., 2022). The protein from each sample (200 ng) was subsequently analyzed via a timsTOF Pro (Bruker) Q-TOF mass spectrometer coupled to a nanoElute (Bruker) liquid chromatography system (Arenas-De Larriva et al., 2022). Furthermore, chromatographic separation was performed on a C18 Aurora Series UHPLC emitter column (IonOpticks) using a trap-elute configuration with an Acclaim PepMap C18 trap cartridge (Thermo Fisher Scientific). The gradient and liquid chromatography (LC) parameters mirrored those reported previously (Arenas-De Larriva et al., 2022). Peptides were ionized using a Captive nano-electrospray source (Bruker) at 1500 V and analyzed via the diaPASEF acquisition method (Arenas-De Larriva et al., 2022). Data were acquired through this data-independent acquisition (DIA) approach across 96 runs, whereas quantitative analysis was conducted using a library-based approach combining FragPipe software (v15.0) and DIA-NN (Data-Independent Acquisition by Neural Networks; v1.7.16), providing a robust platform for protein quantification and DIA data analysis (Demichev et al., 2022). In this approach, all the samples were previously mixed into nine pools and analyzed via the same LC-MS platform and LC parameters as described above for the diaPASEF runs but using a DDA-PASEF acquisition method. These nine DDA runs were then used for protein identification and building the library in FragPipe software, and subsequently this library was used for extracting the quantification information from the diaPASEF runs using DIA-NN.

Conditioned media mass spectrometry (metabolomic) analysis of PPAT-secretome

Metabolites for mass spectrometry analysis were extracted, derivatized, and measured as described previously (Altea-Manzano et al., 2023). Briefly, 200 µL of CM from samples of **IC2** was transferred to microtubes, 800 µL of MeOH/H_2O (5:3) (v:v) and 500 µL of -20°C cold chloroform containing heptadecanoate (10 µg/mL) were added as internal standard. The samples were subsequently vortexed at 4°C for 10 min to facilitate metabolite extraction following a centrifugation step at 4°C for 10 min at maximum speed, to generate two distinct layers: the chloroform phase (total fatty acid, FA), and the methanol phase (polar metabolites), which were further separated and dried under vacuum centrifugation (Altea-Manzano et al., 2023). The lipid fraction was then processed by esterification with 500 µL of 2% sulfuric acid in methanol at 60°C overnight, and FA were extracted by adding 600 µL of hexane and 100 µL of saturated aqueous NaCl (followed by centrifugation for 5 min) (Altea-Manzano et al., 2023). Finally, the hexane phase was separated, dried by vacuum centrifugation, and then resuspended in hexane. Analysis of FAs was performed using gas chromatography-mass spectrometry (GC-MS) on an Agilent Technologies system (8860 system coupled with a 5975C Inert MS system, Agilent Technologies, CA, USA). For the GC-MS analysis, 1 µL of each sample was injected in splitless mode with a split ratio of 1:3 or 1:9, and an inlet temperature of 270°C on a DB-FASTFAME column (30 m × 0.250 mm). Helium was used as the carrier gas (1 mL/min). While the column temperature gradient began at 50°C (1 min), ramped at 12°C/min to 180°C, then increased at 1°C/min to 200°C (held for 1 min), and finally ramped to 230°C at 5°C/min (held for 2 min) (Altea-Manzano et al., 2023). The quadrupole and source temperatures were set at 150°C and 230°C, respectively. The mass spectrometer was operated under electron impact ionization at 70 eV, scanning a mass range of 100–600 amu (Altea-Manzano et al., 2023).

Immunohistochemistry (IHC)

Formalin-fixed, paraffin-embedded tissue sections from **IC5** were processed for IHC using standard laboratory procedures, as previously described (Jiménez-Vacas et al., 2020). Briefly, 4-5 µm sections were deparaffinized in xylene, rehydrated through graded alcohols, and subjected to heat-induced antigen retrieval (citrate buffer, pH 6.0, microwave/pressure cooker). Endogenous peroxidase activity was quenched and nonspecific binding blocked prior to incubation with the primary antibodies against LCN2 (MAB1757-100, R&D System; 1:20), LRP2 (sc-515772, Santa Cruz Biotechnology; 1:500), and SLC22A17 (two different antibodies: TA810195, Origene; 1:500 / and, PA5-20543, Invitrogen; 1:400), overnight at 4 °C. After washing, slides were incubated with the appropriate HRP-conjugated secondary antibodies (anti-mouse IgG, 7076 or anti-rabbit IgG, 7074; Cell Signaling Technology), and immunoreactivity was visualized with 3,3′-diaminobenzidine (DAB). Sections were counterstained with hematoxylin, dehydrated, and

mounted. While LCN2 and LRP2 showed specific immunoreactivity, the two antibodies used for SLC22A17 (TA810195 and PA5-20543) did not yield reproducible or sufficiently specific staining patterns in these FFPE samples. Therefore, as an alternative, the analysis of SLC22A17 protein expression was primarily validated through Western Blotting in patient-derived samples (see Western Blotting section). Staining intensity and distribution for LCN2 and LRP2 were independently evaluated by board-certified pathologists who were blinded to clinical data; nuclear staining was semi-quantitatively scored as low, moderate, or high.

Western Blotting

Protein levels of GAPDH, LCN2, SLC22A17, and LRP2 were determined by Western blot in a subset of samples from IC6 (n=6 BPH and n=8 PCa; see Table 1). Briefly, total proteins were isolated using radioimmunoprecipitation assay (RIPA) buffer (Thermo Fisher Scientific) supplemented with Pierce Protease and Phosphatase inhibitors (Thermo Fisher Scientific). Protein concentration was quantified using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific). For each sample, 20 µg of protein was resuspended in SDS-DTT loading buffer, sonicated, and boiled at 95°C for 5 minutes. Due to the different molecular weights of the target proteins, two different electrophoresis and transfer protocols were employed. For LCN2 and SLC22A17, proteins were separated by SDS–polyacrylamide gel electrophoresis using any kD Mini-Protean TGX gels (Bio-Rad) and transferred to Immun-Blot PVDF Membranes (Bio-Rad). In contrast, for the high-molecular-weight protein LRP2 (~520 kDa), samples were resolved on 5% polyacrylamide gels and transferred to 0.45 µm PVDF membranes using a wet transfer system for 2 hours at 90V. Membranes were blocked with 5% non-fat dry milk in tris-buffered saline/0.05% tween 20 (Sigma-Aldrich) and incubated overnight at 4 °C with the specific primary antibodies for LCN2 (MAB1757-100, R&D System), SLC22A17 (PA5-20543 Invitrogen), LRP2 (sc-515772, Santa Cruz Biotechnology), or GAPDH (sc-32233, Santa Cruz Biotechnology) at 1:1000. Subsequently, membranes were incubated with appropriate secondary antibodies HRP–conjugated anti-rabbit immunoglobulin G (IgG; 7074, Cell Signaling Technology) or anti-mouse IgG (7076, Cell Signaling Technology) at 1:2000. Proteins were detected using an enhanced chemiluminescence detection system (Bio-Rad). Densitometric analysis was carried out with ImageJ software, and GAPDH protein levels were used to normalize LCN2, SLC22A17, and LRP2 expressions.

Total RNA isolation and reverse transcription

Total RNA was extracted from PPAT samples via TRIzol® Reagent (Thermo Fisher Scientific) from 100 mg of tissue, as previously described (Pérez-Gómez et al., 2023). Following extraction, RNA samples were subjected to DNase treatment using the Qiagen RNase-Free DNase Kit to eliminate any contaminating genomic DNA. RNA concentration and purity were subsequently assessed using the Nanodrop One Microvolume UV-Vis Spectrophotometer (Thermo Fisher Scientific). Subsequently, 1 μg of RNA per sample was reverse transcribed using random hexamer primers and the RevertAid RT Reverse Transcription Kit (Thermo Fisher Scientific). The resulting cDNA was stored at -20 °C until further use.

Real-time qPCR and transcriptomic arrays

A comprehensive selection of 72 adipokine related genes was implemented according to bibliographic criteria focused on their functional relevance. Additionally, specific human primers for transcripts belonging to the inflammasome (37 genes) and internal reference genes (*RPLP0*, *LRP10*, and *PGK1*) were used, as previously reported (Herrero-Aguayo et al., 2021). Primers were designed (using *Primer3 software v.0.4.0*), purchased (Metabion), and validated for use in real-time qPCR and in a customized qPCR 96.96 dynamic array based on microfluidic technology following methods previously described by our laboratory (Fuentes-Fayos et al., 2020). The sequences of all the primers used in this study are provided in **Supplementary Table S1**. Absolute mRNA copy numbers were determined using 12.5 ng of cDNA per PPAT sample. The thermal profiling and qPCR analysis procedures used for primer validation are detailed elsewhere (Luque et al., 2015). A normalization factor was calculated to adjust the mRNA expression levels and control for variations in reverse transcription efficiency using three previously validated internal reference genes (*LRP10*, *PGK1,* and *RPLP0*) (Pérez-Gómez et al., 2023) and the GeNorm 3.3 software (Pérez-Gómez et al., 2023; Vandesompele et al., 2002). A custom microfluidic-based qPCR array (Fluidigm) was employed to simultaneously assess the expression of the target genes used in this study (adipokines / inflammasome components) in PPATs from **IC1** via the Biomark System and Fluidigm® Real-Time PCR Analysis Software v.3.0.2 and Data Collection Software v.3.1.2 (Standard Biotools). Additionally, transcriptomic profiling of **IC6** samples was carried out using the Human Transcriptome Array 2.0 (HTA 2.0, Thermo Fisher Scientific, #902162), which offers broad coverage of coding and non-coding transcripts at single-exon resolution. RNA from PCa and control samples was processed following the manufacturer's protocol, including array hybridization, washing, and scanning.

Plasmid and siRNA Mediated genetic modulation in LCN2/SLC22A17 axis

To induce high levels of the target proteins, cells were transfected with either an empty pcDNA3.1 vector (mock control; GenScript) or pcDNA3.1 encoding either human LCN2 (OHu27037, GenScript) or SLC22A17 (OHu07298, GenScript; 1 μg per well) using Lipofectamine 3000 (L3000015, Invitrogen) according to the manufacturer's instructions. Specifically, LCN2 overexpression was performed in PNT2, 22Rv1, and DU145, while SLC22A17 was overexpressed in PNT2, 22Rv1, and PC-3 lines. Transfections were performed in biological triplicate, and cells were maintained under standard culture conditions. Transfection efficiency and protein overexpression levels were validated 48 h post-transfection by quantitative RT-qPCR and immunoblotting.

For loss of function studies, PNT2, DU145 and PC-3 cell lines (seeded at 200,000 cells/well) were transfected with a validated siRNA targeting SLC22A17 (L-007451-01-0020, Dharmacon) or with a non-targeting scramble control siRNA (Thermo Fisher Scientific) at 25nM using Lipofectamine RNAiMAX (Thermo Fisher Scientific) following the manufacturer's protocol. For all *in vitro* models, reagent volumes, incubation times, and cell densities were optimized to minimize transfection-related cytotoxicity. Furthermore, all functional experiments included technical and biological replicates and were repeated independently at least three times. Pellets were collected at a defined post transfection interval (in both approaches) and stored at −20 °C for further downstream inflammatory-related proteomic analysis (see below).

Functional approaches (proliferation, migration, apoptosis, invasion, tumorspheres, and colony formation)

A group of experiments was conducted to determine the functional impact of LCN2 treatment on different PCa cell models, as previously described in our laboratory (Hormaechea-Agulla et al., 2017; Montero-Hidalgo et al., 2024; Sáez-Martínez et al., 2024). Briefly, proliferation was assessed with the resazurin cell viability assay (CANVAX) using 4,000 cells seeded per well in 96-well plates and incubated in accordance with the manufacturer's instructions.

A migration assay was conducted using 96-well gridded plates, with 40,000 PC-3, DU145 and PNT2 cells seeded into each well. The LNCaP and 22Rv1 cell lines were excluded from this assay because of their propensity to form cell clusters, which prevents the formation of a uniform monolayer required for accurate wound closure quantification. After 24 h of incubation, the cells were serum-starved by replacing the medium with serum-free medium for 16 h. Subsequently, wounds were created in each well using the Incucyte Cell Migration Kit (Sartorius) following a pre-wash with water for 5 min and 70% ethanol for additional 5 min. Image acquisition was performed at 0-, 6, and 24 h post-wounding, with three random images taken per well for subsequent data acquisition and analysis.

Cell migration and invasion assays were further evaluated using Millicell Cell Culture Inserts (Ref: PI8P01250, Sigma-Aldrich) following the manufacturer's instructions. For the migration assay, LNCaP and 22Rv1 cells were seeded into non-coated inserts, while for the invasion assay, inserts were pre-coated by incubating them overnight at 4 °C with 300 µL of Human Collagen IV at 0.25 mg/mL (Ref: C5533, Sigma-Aldrich). For both functional assays, 300,000 cells were resuspended in 300 µL of serum-free RPMI 1640 medium and seeded into the pre-coated inserts. These inserts were then placed in the wells of a 24-well plate containing 300 µL of complete medium supplemented with 20% FBS, which acted as a chemoattractant. A negative control using serum-free medium in the lower chamber was included in each experiment. Migration and invasion were assessed after 24 h and 48 h of incubation at 37 °C, respectively. Subsequently, the cells that had moved to the lower surface were fixed and stained with a solution of 0.05% crystal violet and 6% glutaraldehyde. For quantification, the crystal violet was solubilized from the cells using 10% acetic acid, and absorbance at 560 nm was measured using the VANTAstar device (BMG Labtech). The apoptosis induction capability was assessed via the Caspase-Glo® 3/7 Assay System (Promega) following the manufacturer's protocol. Briefly, 10,000 transfected cells were seeded per well in a 96-well white-enhanced contrast microplate. After 72h, an equal volume of Caspase-Glo® reagent was added to each well, and the plates were incubated for 1 hour at room temperature. Luminescence was measured using a microplate reader to quantify caspase-3/7 activity as an indicator of apoptosis.

The tumorspheres formation was evaluated in ultra-low attachment 24 well plates (Corning Costar). Cells were seeded at 2,000 cells/well in DMEM/F 12 supplemented with EGF 20 ng/mL (Ref: E9644-.2MG, Sigma-Aldrich), FGF 10 ng/mL (Ref: 100-18B, Peprotech), and B27 (Ref: 12587010, Thermo Fisher Scientific) and maintained for 10 days. After incubation, spheres were imaged with a digital camara coupled to a microscope and number of spheres was quantified using ImageJ software.

Finally, to evaluate clonogenic capacity, 6-well plates were seeded with 4,000 cells/well and incubated for 10 days at 37°C and 5% CO_2. Colonies (corresponding to accumulations of more than 50 cells) were fixed and stained with crystal violet solution (6% glutaraldehyde, 0.5% Violet Crystal) for 30 min, and a picture was taken for further analysis.

Human Phosphorylation Pathway Profiling Array

To determine the differential phosphorylation levels of 55 proteins involved in 5 key oncogenic pathways (MAPK, AKT, JAK/STAT, NF-κB, and TGF-β), the Human Phosphorylation Pathway Profiling Array C55 Kit (Raybiotech, Inc., #AAH-PPP-1-4) was used in DU145 cells in response to LCN2 treatment (24 h), according to the manufacturer's guidelines and as previously described

(León-González et al., 2021; Porcel-Pastrana et al., 2025). Briefly, the cells were lysed in specific buffer supplemented with phosphatase inhibitors (Raybiotech), and the protein concentration was determined. Then, the membranes were incubated with blocking buffer at 25°C for 30 minutes, followed by overnight incubation at 4°C with 1 mL of cell lysate [2.5-fold dilution; 100,000 cells/well; $n = 4$ (pooled), untreated controls and LCN2-treated cells]. The membranes were then incubated with a detection antibody cocktail for 2 hours at RT, followed by a 2-hour incubation with an HRP-labeled anti-rabbit secondary antibody. Chemiluminescent signals were detected using an enhanced chemiluminescence (ECL) reagent system (GE Healthcare). Densitometric analysis of the array spots was performed with ImageJ software (v1.8.0_172), and positive control spots were used for normalization. Positive control spots were used as a normalizing factor. The results are expressed as the log2 of the fold change in the signal of each protein compared with the signal of the control.

Olink-targeted high-throughput inflammatory proteomic profiling

Targeted proteomic profiling was performed on whole-cell lysates obtained from LCN2-overexpressing and SLC22A17-silenced prostate cell models. Total proteins were extracted using radioimmunoprecipitation assay (RIPA) buffer (Thermo Fisher Scientific) supplemented with Pierce Protease and Phosphatase inhibitors (Thermo Fisher Scientific). Following lysis, samples were clarified by centrifugation to remove cellular debris. Protein quantification was conducted using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, #23227). To comply with the proximity extension assay (PEA) requirements, all samples were standardized and normalized to a final protein concentration of 1 mg/mL (within the 0.5–1 mg/mL range) using the same RIPA lysis buffer. Once normalized, the proteomic analysis was carried out using the Olink® Target 96 Inflammation (COBIOMIC-95302; 92 protein targets) according to the manufacturer's protocol. Aliquots were stored at −80 °C until analysis. The complete list of the 92 targets measured in the inflammatory panel is provided in **Supplementary Table S2**. After oligonucleotide-conjugated antibodies were incubated with each sample, reporter sequences were quantified by real time PCR and converted to Normalized Protein eXpression (NPX) values on a log2 scale for relative quantification. Raw NPX data were subjected to standard quality control and normalization procedures including inspection of internal controls and inter plate normalization. All downstream statistical analyses were performed on the normalized NPX matrix.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software Inc., San Diego, USA), RStudio v1.4.1717 (R version 2024.09.0+375), MetaboAnalyst v6.0 (https://www.metaboanalyst.ca/), and SPSS v25.0 (IBM, Armonk, NY, USA). Post-processing and quantitative analyses of the prostate area and PPAT morphological characteristics were conducted using the Picture Archiving Communication System (PACS) System v.12 (Carestream/Philips). Metabolite abundances were calculated from raw chromatograms using an in-house MATLAB script. Metabolomic data were normalized to the initial extract volume of each sample. Relative abundances were normalized to the internal standard, heptadecanoate, and a standard curve for each metabolite was generated and analyzed in parallel. Proportional Venn diagrams were created using DeepVenn web application (https://arxiv.org/abs/2210.04597). The STRING platform (https://string-db.org/) was used to construct functional protein association networks and perform GO enrichment analyses. The node-edges map, as well as the KEGG-based enrichment analysis, was performed on NetworkAalyst3.0 (https://www.networkanalyst.ca/NetworkAnalyst/home.xhtml). Imaging analyses were performed via ImageJ v1.8.0_172 software (Schneider et al., 2012). Gene Ontology (GO) enrichment analysis was performed on up-regulated genes between groups T1 and T2 using the R package clusterProfiler (Wu et al., 2021). Gene identifiers were mapped to Entrez IDs using the human genome annotation package org.Hs.eg.db (10.18129/B9.bioc.org.Hs.eg.db). Dot plot visualizations of enriched GO biological processes were generated with the enrichplot package (Wang et al., 2022) and further customized using ggplot. Only GO terms with adjusted p-values < 0.05 were displayed, and the top 15 categories were plotted to summarize the most significant biological processes. To further explore the downstream biological pathways associated with the studied genes, Gene Set Enrichment Analysis (GSEA) was performed. Patients from both the external public cohort (TCGA) and the internal cohort (HTA) were stratified based on their expression profiles using k-means clustering via the Morpheus web tool. Specifically, samples were divided into three clusters, and only the two extreme groups (clusters 1 and 3, representing high and low expression, respectively) were selected for comparison. GSEA was then conducted comparing these two groups against the Hallmark reference database. Processing of the raw HTA data (including quality assessment, background adjustment, normalization, and probe-level filtering) was carried out using the Transcriptome Analysis Console (TAC) software v4.1 (Thermo Fisher Scientific). Statistical differences between two groups were evaluated via parametric (t-test) or nonparametric (Mann–Whitney U) tests based on normality assessments via the Kolmogorov–Smirnov test. Clinical descriptive characteristics were compared using chi-square tests and one way-ANOVA followed by Bonferroni post hoc analysis. Bivariate correlations were assessed using Spearman's or Pearson's correlation coefficients as appropriate. Fisher's z-test was employed to determine significant differences between correlation coefficients across conditions. Hierarchical clustering was performed using Ward's method. Statistical significance was

considered when $p < 0.05$. A trend for significance was indicated when P values ranged between ≥ 0.05 and <0.1.

Data availability

The microfluidic, proteomic and metabolomic datasets, along with other data generated in this study, are available upon request from the corresponding author. Human PCa transcriptomics cohorts (i.e., TCGA ("The Molecular Taxonomy of Primary Prostate Cancer," 2015); Grasso (Grasso et al., 2012)) were accessed through CANCERTOOLS: http://genomics.cicbiogune.es/CANCERTOOL/index.html, cBioPortal - https://www.cbioportal.org/, and GEPIA2 - http://gepia2.cancer-pku.cn/). The proteomic data used for the longitudinal progression analysis were obtained from the study by Zhang et al. (2025) (Zhang et al., 2025) and accessed through the Prostate Cancer Atlas portal (https://www.prostatecanceratlas.org/). Cancer cell line expression data were accessed through Cancer Cell Line Encyclopedia web application (https://www.ebi.ac.uk/gxa/home) (Barretina et al., 2012; Ghandi et al., 2019). The data from PPAT conditioned media available from an independent external cohort were obtained from the study of Sacca and collaborators (Sacca et al., 2019). Additionally, a detailed report describing the bioinformatic pipeline, quality control procedures, and integrative analyses performed across transcriptomic, metabolomic, and proteomic datasets has been made publicly available as Supplementary Report 1 in Figshare (DOI: 10.6084/m9.figshare.31916142).

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