SUPPLEMENTARY MATERIAL

Prostanoid Signaling in Cancers: Expression and Regulation Patterns of Enzymes and Receptors

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Table S1. The associations of prostanoid metabolizing enzymes and prostanoid receptors with neoplastic transformation.

Prostanoids metabolizing enzymes		
TBXAS1	**Treatment with glycyrrhizin profoundly reduces expression of *TBXAS1* in human lung adenocarcinoma mice xenografts. The anti-cancer effects of glycyrrhizin are possibly attributable to the suppression of the thromboxane A_2 pathway.**	[1]
TBXAS1	NNK, a smoking carcinogen, promotes the expression of lung cancer stem cells-related β-catenin and Nanog. These effects are decreased by ozagrel, a TBXAS1 blocker, implying a role of TBXAS1 in suppression of NNK-induced lung tumorigenesis.	[2]
TBXAS1	TBXAS1 overexpression is associated with higher levels of VEGF, microvessel density, and apoptosis reduction. TBXAS1 promotes tumor growth which can be mediated through tumor angiogenesis.	[3]
TBXAS1, TBXA2R	TBXAS1 and TBXA2R are highly expressed in human breast tumors and premalignant lesions, but not in normal tissues. Thromboxane A_2 pathway is associated with HER2-positive breast cancer and lymph node metastasis.	[4]
PTGIS	*PTGIS* is frequently down-regulated in cancer and PTGIS overexpression suppressed carcinogenesis. Gene polymorphisms of PTGIS' promoter region is associated with cancer risk.	[5]
PTGIS	Prostacyclin can inhibit lung cancer progression and prostacyclin analogs may serve as novel immunomodulatory agents.	[6]
PTGIS	*PTGIS* can be considered as a candidate biomarker for advanced prostate cancer. *PTGIS* dramatically reduced in all the PCa cell lines compared with the normal prostate cell line.	[7]
PTGIS	*PTGIS* expression level in the colorectal cancer hepatic metastases was noticeably higher than in the primary cancer tissue. There is a correlation between higher *PTGIS* expression levels and shorter overall survival.	[8]
PTGIS, PTGDS	*PTGIS, PTGDS, PTGES, AKR1C3* and *TBXAS1* transcripts were elevated in benign prostatic hyperplasia, whereas in PRAD, a decrease in *PTGIS* and *PTGDS* expression is observed.	[9]
PTGDS	*PTGDS* is downregulated in the endometrial cancer compared with the atypical hyperplasia and normal endometrial. *PTGDS* expression is an independent risk factor for worse cancer prognosis.	[10]
PTGDS	*PTGDS* expression is down-regulated in lung cancer and over-expression of *PTGDS* decreases the invasiveness of lung adenocarcinoma cells.	[11]
PTGDS	High levels of *PTGDS* expression correlated with a reduction of tumor proliferation. PGD_2 treatment significantly inhibited the proliferation and migration of breast cancer cells.	[12]

PTGDS	*PTGDS* promoted tumorigenesis through MYH9-mediated regulation of Wnt-β-catenin-STAT3 signaling. PTGDS inhibition may be a novel therapeutic strategy for diffuse large B-cell lymphoma treatment.	[13]
PTGDS	Systems biology analysis showes that *PTGDS* has abnormal expression and methylation in colorectal cancer. Lowly-expressed and highly-methylated *PTGDS* had a worse prognosis.	[14]
PTGDS, PTGDR2	YAP1 inhibited the expression of lipocalin-type *PTGDS* and *PTGDR2* by gain- and loss-of-function experiments. Overexpression of *PTGDS* and *PTGDR2* suppressed the proliferation and reversed the pro-tumor effect of YAP in vivo.	[15]
AKR1C3	AKR1C3 increases androgen receptor (AR) splice variant 7 (AR-V7) expression in enzalutamide-resistant prostate cancer cells. AKR1C3 reprograms AR signaling and targeting AKR1C3 with indomethacin significantly decreases AR/AR-V7 protein expression.	[16]
AKR1C3	AKR1C3 is implicated in the production of androgens in castration-resistant prostate cancer (CRPC), polycystic ovarian syndrome, production of aromatase substrates in breast cancer and non-hormonal dependent malignancies.	[17]
PTGIS	*PTGIS* was differentially expressed and protein level was reduced in oral squamous cell carcinoma. Due to involvement in oxidative stress, PTGIS could modulate cancer development.	[18]
PTGES	PTGES protein stability is connected with complex formation PTGES / USP9X, which prevented it from ubiquitin-dependent proteasome degradation and USP9X expression was highly correlated with PTGES expression in non-small-cell lung carcinoma.	[19]
PTGES	Up-regulation of *PTGES* was associated with reduced overall and progression-free patient survival. Increased PGE2 synthesis via ADRB2–Nf-kB–PTGS2 axis drives tumor growth and metastasis.	[20]
PTGES	PTGES/PGE2 signaling links immunosuppression and metastasis in an inflammatory lung microenvironment of Gprc5a-ko mouse model.	[21]
PTGES	COX2- and mPGES1-overexpressing carcinoma cells were more efficient at forming tumors thus providing evidence for a role of PTGS2 and PTGES in colon cancer progression.	[22]
PTGES	The increase in PD-L1 expression, infiltration of T-cells and/or dendritic cells into tumors, suppression of tumor growth and response to PD-1 checkpoint inhibitors were observed in PTGES-knockout melanoma mouse model	[23]
PTGES2	miR-155 has dual-regulatory mode to reprogram the PGE_2/PGD_2 balance by up-regulating PTGES/PTGES2 and down-regulating PTGDS in breast cancer patients.	[24]
PTGES2	miR-146a, a modulator of IL-17 responses, suppresses colorectal cancer by targeting PTGES2.	[25]
PTGES2	Increased expression of *PTGES2* associates with age (P=0.0092) and the depth of myometrial invasion (P<0.0001).	[26]
PTGES3	*PTGES3* was identified as a hub gene which is closely related to cholangiocarcinoma development, progression and prognosis.	[27]
PTGES3	*PTGES3* expression was identified as a promising prognostic biomarker for primary breast cancer patients.	[28]
CBR1	Genetic inhibition of *CBR1* suppressed pancreatic cancer cell proliferation by regulating ROS generation. Gemcitabine induced *CBR1* gene expression, which could limit the anti-tumor activity of gemcitabine.	[29]
CBR1	Cell proliferation significantly decreased in *CBR1*-overexpressed cells, the number of metastatic foci was significantly higher in mice injected with *CBR1* siRNA compared to wild-type tumors.	[30]

CBR1	CBR1 plays an important role in metastasis of head and neck squamous cell carcinoma via regulation of ROS-mediated β-catenin activity. CBR1 may be a marker for metastasis progression.	[31]
CBR1	*CBR1* expression was correlated with the N classification (P<0.0001), stage (P=0.0018) and outcome (P=0.0095) as well as overall survival. Suppression of *CBR1* by *CBR1*-siRNA increased cancer cell proliferation and migration.	[32]
CBR3	CBR3-AS1 expression was significantly increased in breast cancer tissues and was closely correlated with poor prognosis. CBR3-AS1 overexpression promoted adriamycin resistance in breast cancer cells.	[33]
CBR3	CBR3-AS1 functions as an oncogene through the CBR3-AS1/miR-409-3p/SOD1 pathway, and may represent a new therapeutic target in non-small-cell lung carcinoma.	[34]
CBR3	*CBR3* 730G>A (*rs1056892*, HR = 2.57, 1.07-6.18) is a new pharmacogenomic biomarker that can be used to predict tumor recurrence in non-muscle-invasive bladder cancer patients receiving intravesical instillations pirarubicin.	[35]
	Prostanoids receptors	
PTGDR1, PTGIR, TBXA2R	*PTGDR1* methylation was most highly correlated with recurrence in patients with hypopharyngeal cancer. A similar correlation was observed for *PTGER4* in patients with laryngeal cancer. Methylation of the *PTGIR* and *TBXA2R* promoters was positively correlated with recurrence in oropharyngeal cancer.	[36]
PTGDR1, PTGDR2, PTGIR	*PTGDR1*, *PTGDR2* and *PTGIR* methylation status biomarkers for the clinical management of HPV-associated oropharyngeal cancers.	[37]
TBXA2R	TXA_2/*TBXA2R* signalling act as a neoplastic- and epigenetic-regulator, promoting chromatin remodelling and androgen receptor-mediated transcriptional activation in castration-resistant prostate cancer.	[38]
TBXA2R	Polymorphic variant *TBXA2R* (rs200445019) correlates with cancer metastasis across several cancer types. A potent and selective antagonist of TXA_2 blocks metastasis formation.	[39]
TBXA2R	*TBXA2R* enhances triple negative breast cancer (TNBC) cell migration, invasion and protects TNBC cells from DNA damage thus providing novel treatment opportunities.	[40]
TBXA2R	*TBXA2Rα* and *TBXA2Rβ* isoform expression pattern is differentially regulated via CpG methylation in the benign and the prostate cancer tissue Expression of isoforms have diagnostic significance as a predictor of prostate cancer recurrence.	[41]
PTGDR1, PTGDR2	High expression of *PTGDR2* in tumor tissue negatively correlates with overall survival. TNM stage and metastasis positively correlated with *PTGDR2* expression.	[42]
PTGDR2	*PTGDR2* is statistically associated with patient overall survival or disease-free survival in colorectal cancer.	[43]
PTGFR	$PGF_{2\alpha}$-PTGFR promotes cell proliferation; increases the abundance of cyclins, cyclin-dependent kinases, PCNA and decreases p21.	[44]
PTGFR	*PTGFR* transcripts significantly increase at the critical transition from stage T2 to T3/T4 and remain elevated in advanced prostate cancer stages.	[45]
PTGFR	The expression levels of *PTGFR* are higher in tumor than in normal endothelial cells. PTGFR protein is expressed in human tumor blood vessels.	[46]
PTGFR	Sera from ovarian cancer (OV) patients containing auto-antibodies (AAb) to PTGFR had AUC > 60% ($p < 0.01$). PTGFR is a potential biomarker for the early detection of OV.	[47]
PTGFR	High *PTGFR* transcript levels are associated with lower survival of OV patients.	[48]

PTGER1	PTGER1 antagonist delayed carcinogenesis and progression of prostate cancer (PC) in knock-in mouse model. Inhibition of PTGER1 pathway may be a novel chemopreventive strategy for PC.	[49]
PTGER2	Tumor growth was reduced in *PTGER2*-knockout tumor-bearing mice. PGE_2 signaling via PTGER2 affected genes involved in tumor progression.	[50]
PTGER3	High expression of *PTGER3* in cervical cancer patients is correlated with poor prognosis.	[51]
PTGER3	*PTGER3* expression is significantly higher in clear-cell ovarian carcinoma ($p < 0.001$) compared to the other histological subtypes. *PTGER3* expression associates with mucin-1 negative OV patients overall survival.	[52]
PTGER4	PTGER4 activity promotes breast cancer cell migration, invasion, angiogenesis, lymphangiogenesis and PTGER4 antagonists may be as promising anti-cancer drugs.	[53]
PTGER4	*PTGER4* hypermethylation was more frequently observed in plasma samples of patients with lung cancer than in controls ($p = 0.0004$).	[54]
PTGER4	Blood levels of methylated *PTGER4* predict overall survival rate of patients with stage IV lung cancer as well as therapeutic efficacy.	[55]
PTGER4	*PTGER4* is upregulated after demethylation in aromatase inhibitor resistant cells and is essential for estrogen-independent growth. PTGER4 promotes resistance via ligand-independent activation of the ERα-cofactor CARM1.	[56]
PTGER4	*PTGER4* gene amplification frequency in mixed adenoneuroendocrine carcinoma is higher than in adenocarcinoma (10.5% vs 0.3%).	[57]

Table S2. Cell lines dependency on target genes' knockouts and knockdowns.

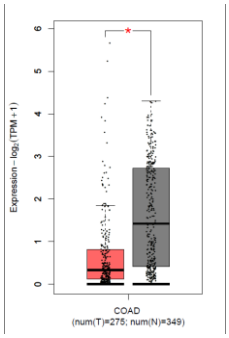
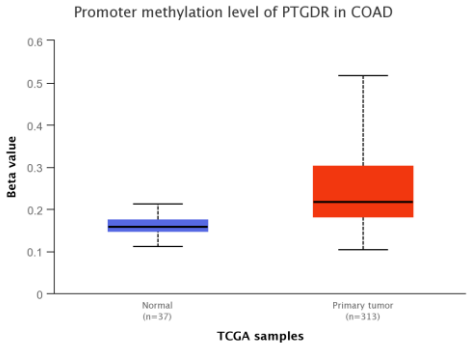
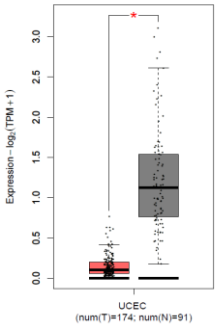
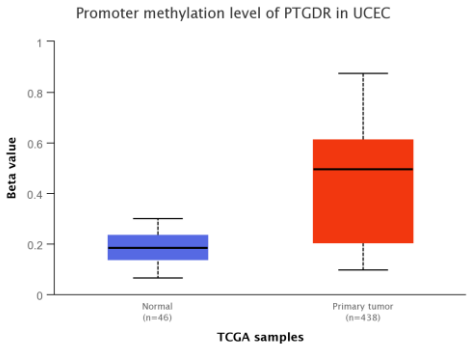
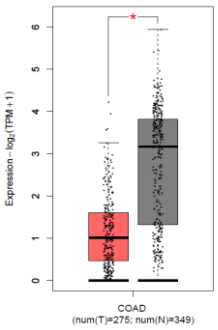
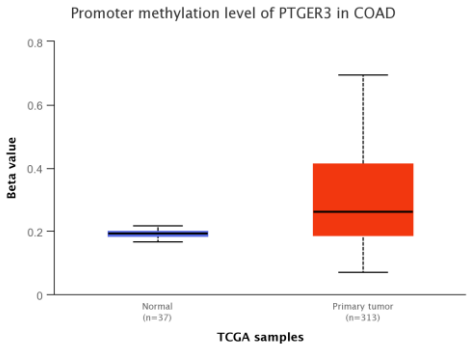
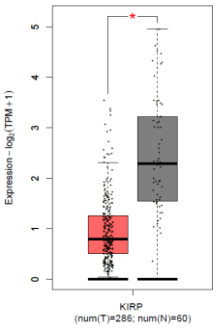
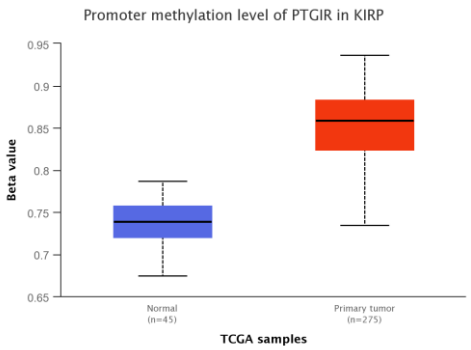
Gene name	Cancer	Cell line	Gene effect score	Gene expression log2(TPM+1)
TBXAS1	**gallbladder adenocarcinoma**	**OCUG1**	**-0.97**	**6.09**
PTGES	brain cancer	PFSK1	-0.58	3.34
	colorectal cancer	SW948	-0.51	3.17
PTGES2	sarcoma cancer	SC S214	-0.79	6.14
	head and neck cancer	SNU46	-0.67	7.3
PTGES3	**brain cancer**	**ONS76**	**-0.98**	**7.28**
	colorectal cancer	CCK81	-0.71	8.54
	gastric cancer	SCH	-0.7	no data
	kidney cancer	UMRC7	-0.69	5.57
	liver cancer	HUH7	-0.73	8.31
	lung cancer	CHAGOK1	-0.76	7.33
	lymphoma	KIJK	-0.69	7.89
	ovarian cancer	SKOV3	-0.68	8.62
	pancreatic cancer	PACADD137	-0.65	8.92
	neuroblastoma	NB69	-0.57	no data
	skin cancer	COLO679	-0.74	8.04
	thyroid cancer	SW579	-0.69	7.62
CBR3	liposarcoma	95T1000	-0.62	4.29
TBXA2R	breast cancer	SUM52PE	-0.55	0.45
	colorectal cancer	SW948	-0.58	0.06
PTGDR	**lung cancer**	**CORL279**	**-1.04**	**0.03**
PTGER3	leukemia	HEL9217	-0.76	5.24
	cervical cancer	SW954	-0.56	0
	esophageal cancer	KYSE150	-0.52	0.01
	kidney cancer	VMRCRCW	-0.72	0.01
	lymphoma	C8166	-0.56	3.38
	head and neck cancer	H413	-0.58	0
	uterine cancer	JHUEM7	-0.61	0.01
PTGER4	lung cancer	CORL279	-0.79	0.32
	lymphoma	**C8166**	**-1.37**	**5.1**

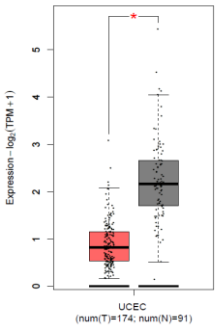
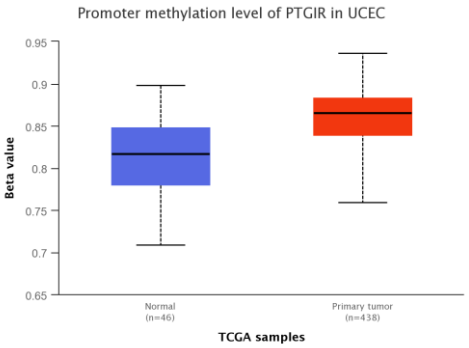
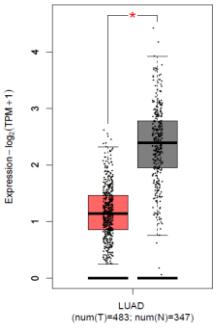
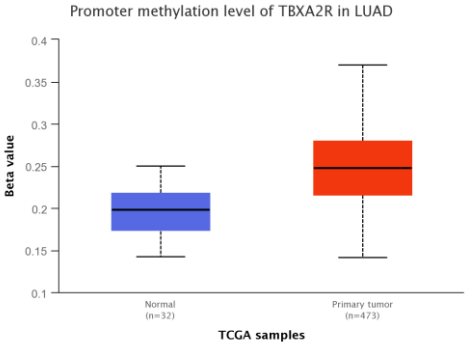
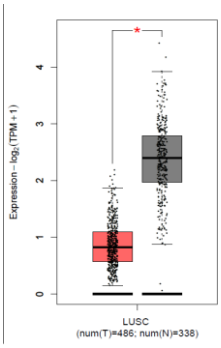
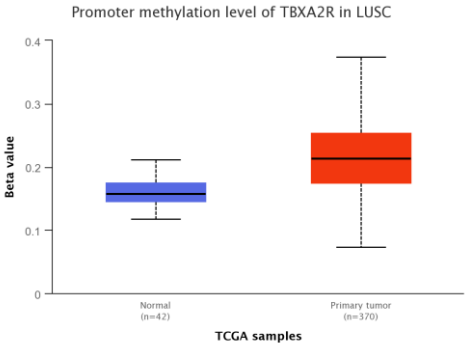
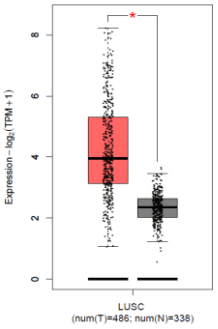
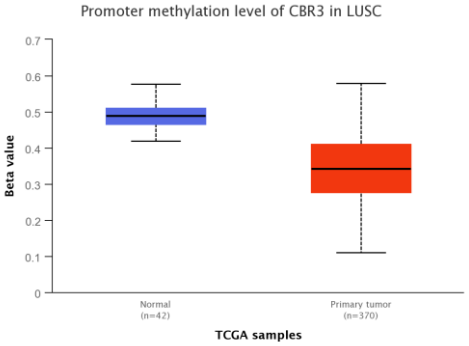
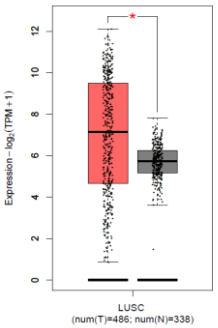
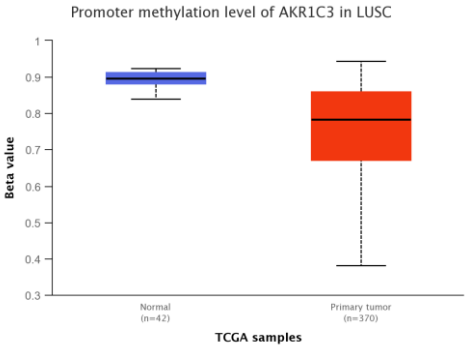
Table S3. Over-representation analysis of genes showing similar expression patterns with target genes involved in prostanoid signaling.

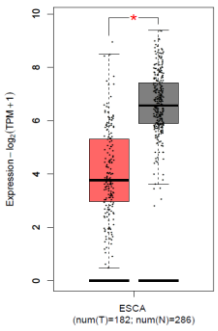
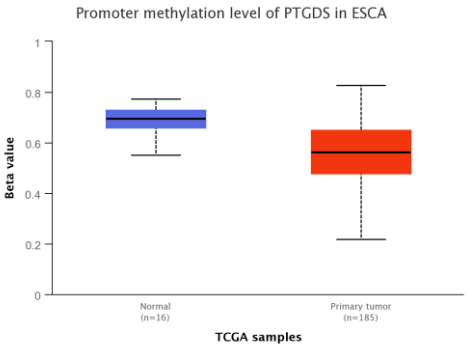
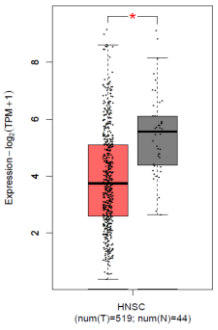
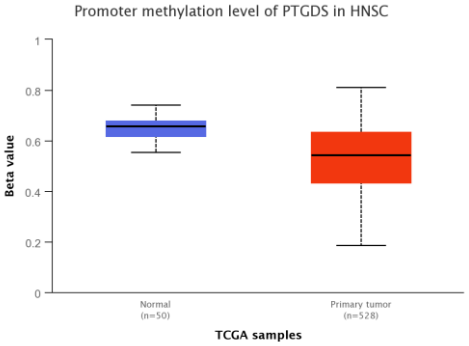
Target genes (cluster)	Tumor	Co-expressed genes	Enrichment with Reactome pathway terms
TBXAS1 (I)	KIRC	71	Fc-gamma receptor (FCGR) dependent phagocytosis Classical antibody-mediated complement activation Toll-like receptor cascades
	LIHC	73	Classical antibody-mediated complement activation Immunoregulatory interactions between a lymphoid and a non-lymphoid cell
	GBM	138	Cross-presentation of particulate exogenous antigens (phagosomes) Classical antibody-mediated complement activation MyD88 deficiency (TLR2/4)
	PCPG	139	Initial triggering of complement Fc-gamma receptor (FCGR) dependent phagocytosis
	OV	134	Fc-gamma receptor (FCGR) dependent phagocytosis Immunoregulatory interactions between a lymphoid and a non-lymphoid cell MyD88 deficiency (TLR2/4)
	ACC	149	Cross-presentation of particulate exogenous antigens (phagosomes) Fcgamma receptor (FCGR) dependent phagocytosis Regulation of complement cascade
	LGG	191	Cross-presentation of particulate exogenous antigens (phagosomes) Classical antibody-mediated complement activation Antigen activates B cell receptor (BCR) leading to generation of second messengers DAP12 signaling
	UVM	229	FCERI mediated MAPK activation Classical antibody-mediated complement activation Endosomal/vacuolar pathway Translocation of ZAP-70 to immunological synapse RHO GTPases activate NADPH oxidases Antigen processing-cross presentation
PTGIS (I)	BLCA	54	Smooth muscle contraction RHO GTPases activate CIT
	CHOL	63	Extracellular matrix organization
	COAD	71	Molecules associated with elastic fibres
	READ	70	Muscle contraction
	PRAD	157	Smooth muscle contraction Cell-extracellular matrix interactions
	TGCT	391	Extracellular matrix organization Collagen chain trimerization MET activates PTK2 signaling Elastic fibre formation
PTGDS (I)	ESCA	115	Phosphorylation of CD3 and TCR zeta chains Signaling by Rho GTPases Immune system
	CHOL	320	Antigen activates B cell receptor (BCR) leading to generation of second messengers Fc-gamma receptor (FCGR) dependent phagocytosis DAP12 signaling Interleukin receptor SHC signaling

	KICH	374	PD-1 signaling Extracellular matrix organization
PTGES3 (I)	THCA	183	Processing of capped intron-containing pre-mRNA mRNA splicing - major pathway
	SKCM	432	rRNA modification in the nucleus and cytosol mRNA splicing - major pathway Nucleotide excision repair
PTGES (II)	ACC	111	Extracellular matrix organization Collagen degradation Collagen formation
TBXA2R (III)	COAD	274	Defective B3GALTL causes Peters-plus syndrome (PpS) Regulation of insulin-like growth factor (IGF) transport and uptake by insulin-like growth factor binding proteins (IGFBPs) Rho GTPase cycle
PTGFR (III)	COAD	148	Collagen formation (degradation) Extracellular matrix organization Cell surface interactions at the vascular wall
	TGCT	69	Extracellular matrix organization ECM proteoglycans Elastic fibre formation
PTGER3 (III)	COAD	118	Collagen chain trimerization Molecules associated with elastic fibres
	LIHC	26	Collagen formation (degradation) NCAM1 interactions
	PAAD	30	Molecules associated with elastic fibres
	READ	50	Elastic fibre formation
	TGCT	85	Smooth muscle contraction ECM proteoglycans Platelet activation, signaling and aggregation
PTGER4 (III)	ACC	134	RHO GTPases activate CIT RHO GTPases Activate ROCKs Collagen formation (degradation) Signaling by Interleukins Immunoregulatory interactions between a lymphoid and a non-lymphoid cell Binding and uptake of ligands by scavenger receptors Innate immune system Integrin cell surface interactions
	GBM	26	Assembly of collagen fibrils and other multimeric structures MET activates PTK2 signaling Anchoring fibril formation
	KIRP	63	Innate immune system Trafficking and processing of endosomal TLR
	MESO	50	Generation of second messenger molecules Immune system Translocation of ZAP-70 to immunological synapse

Table S4. Concordance between changes of gene expression and promoter methylation patterns.

Gene	Tumor	Differential gene expression	Differential gene promoter methylation*
Down-regulated genes and an increase in promoter methylation in tumors			
PTGDR	COAD		
PTGDR	UCES		
PTGER3	COAD		
PTGIR	KIRP		

PTGIR	UCES		
TBXA2R	LUAD		
TBXA2R	LUSC		
Up-regulated genes and a decrease in promoter methylation in tumors			
CBR3	LUSC		
AKR1C3	LUSC		
Down-regulated genes and a decrease in promoter methylation in tumors			

PTGDS	ESCA		
PTGDS	HNSC		

*p-value < 0.05.

Table S5. Over-representation analysis of master regulators using KEGG database as a data source.

Description	Size	Overlap	P-value	Genes
Pathways in cancer	524	6	2.22e-5	*AR; EP300; MAX; RELA; SP1; SPI1*
Transcriptional misregulation in cancer	186	4	7.71e-5	*MAX; RELA; SP1; SPI1*
Prostate cancer	97	3	2.58e-4	*AR; EP300; RELA*
Maturity onset diabetes of the young	26	2	5.43e-4	*FOXA2; HNF4A*
Herpes simplex infection	185	3	0.0017	*EP300; POLR2A; RELA*
Huntington disease	193	3	0.0019	*EP300; POLR2A; SP1*
Mitophagy	65	2	0.0033	*RELA; SP1*
Acute myeloid leukemia	66	2	0.0034	*RELA; SPI1*
Human T-cell leukemia virus 1 infection	255	3	0.0042	*EP300; RELA; SPI1*
TGF-beta signaling pathway	84	2	0.0055	*EP300; SP1*

Table S6. A list of predicted regulatory oncomiRs for target genes involved in prostanoid signalling.

miR name	Score	Gene name
hsa-miR-34b-3p	0.461	*TBXAS1*
hsa-miR-502-5p	0.484	*TBXAS1*
hsa-miR-496	0.539	*PTGIS*
hsa-miR-34a-5p	0.547	*PTGIS*
hsa-miR-449a	0.542	*PTGIS*
hsa-miR-449b-5p	0.542	*PTGIS*
hsa-miR-34c-5p	0.541	*PTGIS*
hsa-miR-888-3p	0.763	*PTGES3*
hsa-let-7a-2-3p	0.706	*PTGES3*
hsa-let-7g-3p	0.655	*PTGES3*
hsa-miR-422a	0.586	*PTGES3*
hsa-miR-378a-3p	0.568	*PTGES3*
hsa-miR-223-5p	0.549	*PTGES3*
hsa-miR-510-5p	0.532	*PTGES3*
hsa-miR-377-3p	0.522	*PTGES3*
hsa-miR-522-3p	0.506	*PTGES3*
hsa-miR-224-3p	0.5	*PTGES3*
hsa-miR-495-3p	0.498	*PTGES3*
hsa-miR-19a-3p	0.491	*PTGES3*
hsa-miR-421	0.482	*PTGES3*
hsa-miR-136-5p	0.474	*PTGES3*
hsa-miR-376c-3p	0.454	*PTGES3*
hsa-miR-338-5p	0.444	*PTGES3*
hsa-miR-605-5p	0.414	*PTGES3*
hsa-miR-519d-3p	0.414	*PTGES3*
hsa-miR-767-3p	0.78	*PRXL2B*
hsa-miR-486-3p	0.52	*PRXL2B*
hsa-miR-211-3p	0.485	*PRXL2B*
hsa-miR-423-5p	0.463	*PRXL2B*
hsa-miR-149-3p	0.411	*PRXL2B*
hsa-miR-149-3p	0.516	*PTGES*
hsa-miR-377-3p	0.474	*PTGES*
hsa-miR-508-5p	0.458	*PTGES*
hsa-miR-296-5p	0.453	*PTGES*
hsa-miR-329-3p	0.424	*PTGES*
hsa-miR-362-3p	0.42	*PTGES*
hsa-miR-335-3p	0.757	*CBR1*
hsa-miR-511-5p	0.563	*AKR1C3*
hsa-miR-184	0.562	*AKR1C3*
hsa-miR-149-5p	0.641	*PTGIR*
hsa-miR-589-5p	0.488	*PTGIR*
hsa-miR-326	0.483	*PTGIR*
hsa-miR-608	0.402	*PTGIR*
hsa-miR-135a-5p	0.641	*PTGER1*
hsa-miR-135b-5p	0.554	*PTGER1*
hsa-miR-31-5p	0.855	*TBXA2R*

hsa-miR-182-5p	0.732	*TBXA2R*
hsa-miR-520a-5p	0.553	*TBXA2R*
hsa-miR-149-3p	0.539	*TBXA2R*
hsa-miR-525-5p	0.537	*TBXA2R*
hsa-miR-485-5p	0.509	*TBXA2R*
hsa-miR-425-5p	0.5	*TBXA2R*
hsa-miR-340-3p	0.467	*TBXA2R*
hsa-miR-657	0.447	*TBXA2R*
hsa-miR-30b-3p	0.433	*TBXA2R*
hsa-miR-508-5p	0.41	*TBXA2R*
hsa-miR-185-5p	0.766	*PTGDR2*
hsa-miR-519e-5p	0.708	*PTGDR2*
hsa-miR-625-5p	0.583	*PTGDR2*
hsa-miR-515-5p	0.581	*PTGDR2*
hsa-miR-661	0.523	*PTGDR2*
hsa-miR-550a-5p	0.497	*PTGDR2*
hsa-miR-499a-5p	0.629	*PTGDR*
hsa-miR-200a-3p	0.564	*PTGDR*
hsa-miR-27a-3p	0.559	*PTGDR*
hsa-miR-27b-3p	0.554	*PTGDR*
hsa-miR-141-3p	0.54	*PTGDR*
hsa-miR-20a-5p	0.539	*PTGDR*
hsa-miR-106b-5p	0.538	*PTGDR*
hsa-miR-140-3p	0.526	*PTGDR*
hsa-miR-511-5p	0.524	*PTGDR*
hsa-miR-362-3p	0.522	*PTGDR*
hsa-miR-106a-5p	0.512	*PTGDR*
hsa-miR-338-5p	0.488	*PTGDR*
hsa-miR-329-3p	0.488	*PTGDR*
hsa-miR-487a-3p	0.435	*PTGDR*
hsa-miR-513a-3p	0.43	*PTGDR*
hsa-miR-130b-3p	0.677	*PTGER2*
hsa-miR-130a-3p	0.629	*PTGER2*
hsa-miR-361-3p	0.598	*PTGER2*
hsa-miR-497-3p	0.566	*PTGER2*
hsa-miR-301a-3p	0.56	*PTGER2*
hsa-miR-454-3p	0.552	*PTGER2*
hsa-miR-515-5p	0.544	*PTGER2*
hsa-miR-19a-3p	0.509	*PTGER2*
hsa-miR-19b-3p	0.509	*PTGER2*
hsa-miR-141-5p	0.471	*PTGER2*
hsa-miR-532-3p	0.471	*PTGER2*
hsa-miR-421	0.439	*PTGER2*
hsa-miR-205-3p	0.436	*PTGER2*
hsa-miR-410-3p	0.436	*PTGER2*
hsa-miR-188-3p	0.433	*PTGER2*
hsa-miR-148b-3p	0.424	*PTGER2*
hsa-miR-452-5p	0.406	*PTGER2*
hsa-let-7f-2-3p	0.821	*PTGFR*
hsa-miR-330-3p	0.669	*PTGFR*
hsa-miR-423-5p	0.624	*PTGFR*

hsa-miR-513a-3p	0.567	*PTGFR*
hsa-miR-590-3p	0.511	*PTGFR*
hsa-miR-145-5p	0.466	*PTGFR*
hsa-miR-150-5p	0.458	*PTGFR*
hsa-miR-520f-3p	0.443	*PTGFR*
hsa-miR-34c-3p	0.435	*PTGFR*
hsa-miR-621	0.405	*PTGFR*
hsa-miR-96-5p	0.714	*PTGER3*
hsa-miR-142-5p	0.622	*PTGER3*
hsa-miR-27b-3p	0.566	*PTGER3*
hsa-miR-27a-3p	0.536	*PTGER3*
hsa-miR-380-3p	0.523	*PTGER3*
hsa-miR-151a-3p	0.49	*PTGER3*
hsa-miR-106a-5p	0.454	*PTGER3*
hsa-miR-106b-5p	0.444	*PTGER3*
hsa-miR-590-3p	0.443	*PTGER3*
hsa-miR-152-3p	0.435	*PTGER3*
hsa-miR-561-3p	0.428	*PTGER3*
hsa-miR-148a-3p	0.424	*PTGER3*
hsa-miR-28-5p	0.422	*PTGER3*
hsa-miR-181b-5p	0.421	*PTGER3*
hsa-miR-148b-3p	0.416	*PTGER3*
hsa-miR-20a-5p	0.413	*PTGER3*
hsa-miR-181d-5p	0.407	*PTGER3*
hsa-miR-708-5p	0.402	*PTGER3*
hsa-miR-484	0.804	*PTGER4*
hsa-miR-590-3p	0.657	*PTGER4*
hsa-miR-515-5p	0.634	*PTGER4*
hsa-miR-92a-3p	0.632	*PTGER4*
hsa-miR-32-5p	0.632	*PTGER4*
hsa-miR-92b-3p	0.632	*PTGER4*
hsa-miR-367-3p	0.605	*PTGER4*
hsa-miR-130a-5p	0.601	*PTGER4*
hsa-miR-25-3p	0.593	*PTGER4*
hsa-miR-1226-3p	0.592	*PTGER4*
hsa-miR-24-3p	0.586	*PTGER4*
hsa-miR-372-3p	0.557	*PTGER4*
hsa-miR-520c-3p	0.546	*PTGER4*
hsa-miR-520b	0.543	*PTGER4*
hsa-miR-520e	0.543	*PTGER4*
hsa-miR-34c-3p	0.541	*PTGER4*
hsa-miR-23a-3p	0.531	*PTGER4*
hsa-miR-23b-3p	0.531	*PTGER4*
hsa-miR-302c-3p	0.518	*PTGER4*
hsa-miR-302d-3p	0.518	*PTGER4*
hsa-miR-363-3p	0.516	*PTGER4*
hsa-miR-302a-3p	0.515	*PTGER4*
hsa-miR-302b-3p	0.515	*PTGER4*
hsa-miR-373-3p	0.482	*PTGER4*
hsa-miR-129-2-3p	0.452	*PTGER4*
hsa-miR-520a-3p	0.438	*PTGER4*
hsa-miR-20b-5p	0.435	*PTGER4*

hsa-miR-20a-5p	0.426	*PTGER4*
hsa-miR-520d-3p	0.425	*PTGER4*
hsa-miR-17-5p	0.423	*PTGER4*
hsa-miR-93-5p	0.407	*PTGER4*
hsa-miR-106b-5p	0.401	*PTGER4*

Table S7. Expression ratio (tumor/normal) of predicted master oncomiRs that can regulate mRNAs of genes involved in prostanoid signaling.

Tumors	BRCA	COAD	ESCA	KIRP	LIHC	LUAD	PAAD	PRAD	SKCM	STAD	UCEC
oncomiRs*											
hsa-miR-148b-3p	2.23										3.37
hsa-miR-149-3p		0.05									
hsa-miR-19a-3p						3.71	0.34	2.68		3.97	3.51
hsa-miR-20a-5p			2.71			3.16		4.2		4.24	3.38
hsa-miR-27a-3p		3.48	2.36								2.54
hsa-miR-27b-3p											
hsa-miR-338-5p				0.36							
hsa-miR-34c-3p										2.63	
hsa-miR-377-3p	0.48	0.39									
hsa-miR-421	2.03									3.5	5.16
hsa-miR-423-5p						0.43		2.49			
hsa-miR-508-5p											0.13
hsa-miR-511-5p											
hsa-miR-513a-3p											
hsa-miR-515-5p											
hsa-miR-590-3p	2.14					3.3	0.39				2.82

*molecular targets of human oncomiRs were predicted using CSmiRTar web-based tool (http://cosbi4.ee.ncku.edu.tw/CSmiRTar/) and average normalized score (ANS) above 0.4 was considered significant: miR-106a-5p (PTGDR 0.512, PTGER3 0.454); miR-106b-5p (PTGDR 0.538, PTGER3 0.444, PTGER4 0.401); miR-148b-3p (PTGER2 0.424, PTGER3 0.416); miR-149-3p (PRXL2B 0.411, PTGES 0.516, TBXA2R 0.539); miR-19a-3p (PTGES3 0.491, PTGER2 0.509); miR-20a-5p (PTGDR 0.539, PTGER3 0.413, PTGER4 0.426); miR-27a-3p (PTGDR 0.559, PTGER3 0.536); miR-27b-3p (PTGDR 0.554, PTGER3 0.506); miR-338-5p (PTGES3 0.444, PTGDR 0.488); miR-34c-3p (PTGFR 0.435, PTGER4 0.541); miR-377-3p (PTGES3 0.522, PTGES 0.474); miR-421 (PTGES3 0.482, PTGER2 0.439); miR-423-5p (PRXL2B 0.463, PTGFR 0.624); miR-508-5p (PTGES 0.458, TBXA2R 0.41); miR-511-5p (AKR1C3, 0.563, PTGDR 0.524); miR-513a-3p (PTGDR 0.43, PTGFR 0.567); miR-515-5p (PTGDR2 0.581, PTGER2 0.544, PTGER4 0.634); miR-590-3p (PTGFR 0.511, PTGER3 0.443, PTGER4 0.657).

Table S8. Antibody staining of proteins involved in prostanoid signaling according to the Human Proteome Atlas portal.

Legend

	High antibody staning
	Medium antibody staining
	Low antibody staining
	Not detected
	No data

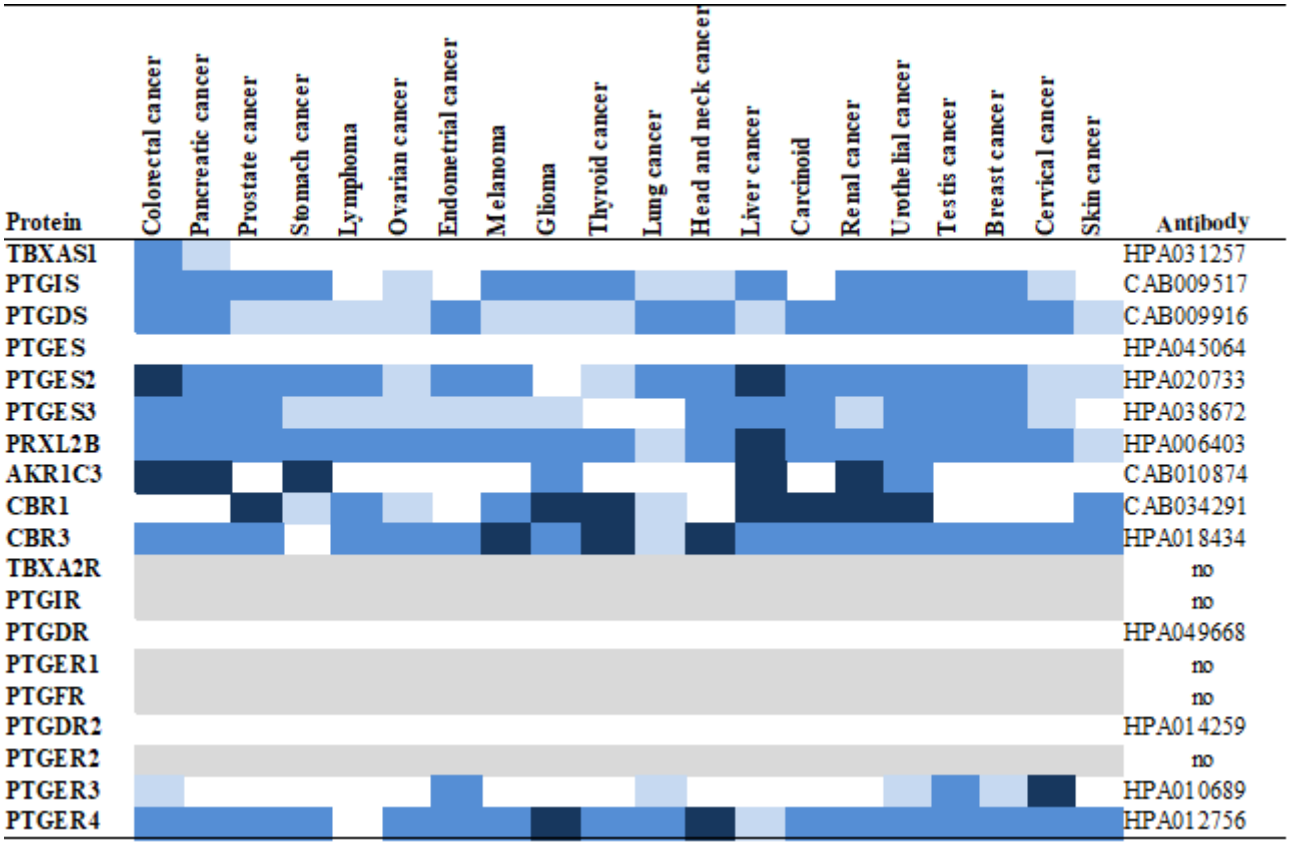


Table S9. Prediction of genes, which expression patterns can be associated with genetic polymorphism in target genes in melanoma tumors.

Gene Expression	Mean mutant (*n*=45)	Mean wild (*n*=420)	FC (mutant/wild)	Direction	*p*-value	Group #
Group #1 (TBXAS1, PTGIS, AKR1C3)						
NYNRIN	295.62	600.46	2.04	down	6.40e-04	1
SVEP1	120.02	244.67	2.04	down	5.30e-03	1
RAPGEF4	156.36	319.1	2.04	down	6.80e-03	1
STUM	105.47	214.06	2.04	down	1.77e-02	1
MAOB	318.89	650.08	2.04	down	2.64e-02	1
H2AFY2	104.91	217.34	2.08	down	2.45e-02	1
FAM19A5	248.42	529.88	2.13	down	1.37e-02	1
SPON1	271.09	585.87	2.17	down	2.53e-02	1
PP7080	234.67	522.83	2.22	down	1.75e-02	1
CNTN4	110.93	251.88	2.27	down	6.62e-03	1
SORL1	740.89	1739.45	2.33	down	9.71e-04	1
ELN	256.58	590.5	2.33	down	4.57e-03	1
LPAR1	185.09	428.7	2.33	down	5.03e-03	1
EYA1	265.31	620.51	2.33	down	1.82e-02	1
GPX3	1495.11	3494.13	2.33	down	2.83e-02	1
SORCS2	179.58	421.82	2.33	down	2.90e-02	1
SLC26A4	109.31	260.83	2.38	down	9.35e-03	1
MYO5B	231.2	551.79	2.38	down	1.67e-02	1
FGFBP2	163.29	397.78	2.44	down	2.82e-02	1
PCSK6	125.11	313.13	2.5	down	5.37e-03	1
DGKI	198.69	492.13	2.5	down	1.69e-02	1
TKTL1	127.73	322.78	2.5	down	4.30e-02	1
FRZB	182.00	463.27	2.56	down	1.68e-02	1
SDK2	128.78	328.1	2.56	down	1.81e-02	1
BCAN	2972.58	7976.38	2.7	down	2.75e-02	1
XIST	257.44	712.28	2.78	down	8.21e-04	1
BMP7	236.89	654.16	2.78	down	2.05e-02	1
SYNPO2	216.67	594.82	2.78	down	2.70e-02	1
SFRP4	261.6	729.68	2.78	down	4.34e-02	1
HOXB13	106.13	335.41	3.12	down	1.72e-04	1
PI15	510.27	1713.52	3.33	down	1.65e-03	1
SCUBE3	167.89	572.22	3.45	down	4.11e-02	1
FMOD	730.64	2705.39	3.7	down	4.09e-03	1
CHRDL1	124.73	647.37	5.26	down	4.36e-03	1
THBS4	187.42	997.69	5.26	down	1.41e-02	1
F5	133.82	704.83	5.26	down	2.96e-02	1
RELN	110.00	620.7	5.56	down	3.83e-02	1
PROM1	42.36	243.96	5.88	down	1.77e-02	1
ADAMTS14	314.00	158.76	1.98	up	4.78e-02	1
RN7SK	266.42	112.7	2.36	up	4.91e-02	1
RGS5	11231.76	2918.47	3.85	up	2.98e-02	1
Group #2 (PTGDR, PTGFR, PTGER3)						
SFN	232.94	3647.73	16.67	down	4.79e-02	2
ROBO2	120.28	249.21	2.08	down	2.15e-02	2
ATP1B2	438.06	925.65	2.13	down	1.20e-02	2
LRRC61	125.21	270.09	2.17	down	1.41e-02	2

SDC1	1104.57	2440.85	2.22	down	1.49e-02	2
GLB1L2	162.74	374.09	2.27	down	9.10e-03	2
FGFBP2	171.96	401.22	2.33	down	1.38e-02	2
LINC00504	187.49	462.6	2.44	down	2.76e-02	2
TTYH1	216.75	568.64	2.63	down	7.99e-03	2
LYNX1	188.13	576.44	3.03	down	1.84e-05	2
FLG	334.04	1101.29	3.33	down	5.14e-03	2
RHCG	120.83	414.58	3.45	down	3.10e-02	2
PKP1	237.62	1770.05	7.69	down	8.43e-03	2
ILDR2	202.45	100.3	2.02	up	2.91e-02	2
CDH2	1731.6	844.24	2.05	up	3.66e-02	2
RNF128	513.87	248.71	2.07	up	6.90e-03	2
GBP1	5171.89	2471.26	2.09	up	7.98e-04	2
PDCD1LG2	248.79	106.21	2.34	up	9.06e-03	2
ALDH1A2	439.96	113.84	3.86	up	4.04e-02	2

Table S10. Cancer-specific expression and regulation patterns of prostanoid-metabolizing enzymes and receptors.

Genes	**Gene expression tumor/normal**	Gene copy number variations frequency, %	Differential expression tumor/normal		
			Promoter methylation status	miR expression	Master regulators expression
Co-expressed genes in lung squamous cell carcinoma (LUSC)					
AKR1C3	↑	3.78 (del)	Hypermethylation ↓	miR-511 ↓ ; miR-184 ↔	FOXA2 ↓ ; LMNB1 ↑ ; MAX ↔; POLR2A ↔; SPI1 ↓
CBR1	↑	< cut-off	Unmethylated	miR-335 ↔	
CBR3	↑	< cut-off	Hypomethylation ↓	n/d	
Co-expressed genes in esophageal carcinoma (ESCA)					
CBR1	↓	< cut-off	Unmethylated	miR-335 ↑	KDM4C ↔
CBR3	↓	< cut-off	Hypomethylation ↓	n/d	
Signature of eight up-regulated genes in pancreatic adenocarcinoma					
TBXAS1	↑	< cut-off	Unmethylated	n/d	POLR2A ↔; CTCF ↑ ; IRF1 ↑ ; KLF4 ↑ ; STAG1 ↔
PTGIS	↑	6.42 (ampl)	Hypomethylation	n/d	
PTGDS	↑	13.76 (ampl)	Hypermethylation	n/d	
PTGES	↑	5.5 (ampl)	Unmethylated	n/d	
PTGES2	↑	9.17 (ampl)	Hypomethylation	n/d	
PTGES3	↑	4.59 (ampl)	Unmethylated	miR-223 ↓ ; miR-19a ↓ ; miR-605 ↓	
PRXL2B	↑	8.26 (ampl) 8.26 (del)	n/d	miR-486 ↓ ; miR-211 ↓ ; miR-423 ↓	
AKR1C3	↑	< cut-off	Hypermethylation	n/d	
CBR1	↑	< cut-off	Unmethylated	n/d	
CBR3	↑	< cut-off	Hypermethylation	n/d	
Down-regulation of *PTGIS* and *PTGIR* genes in seven tumors					
KICH					
PTGIS	↓	< cut-off	n/d	n/d	RNF2 ↔; SPI1 ↔; ZNF263 ↔
PTGIR	↓	< cut-off	n/d	miR-149 ↓ ; miR-326 ↓	
KIRP					
PTGIS	↓	< cut-off	Hypomethylation	miR-496 ↓ ; miR-34a ↑	AR ↑ ; RNF2 ↔; SPI1 ↑ ; ZNF263 ↔
PTGIR	↓	< cut-off	Hypermethylation ↑	miR-589 ↑	
LUAD					
PTGIS	↓	< cut-off	Hypomethylation	miR-34a ↑	SPI1 ↓ ; RELA ↔; RCOR1 ↔; MAZ ↔; CEBPB ↓ ; FOXA2 ↔ LMNB1 ↑
PTGIR	↓	< cut-off	Hypermethylation ↑	miR-326 ↓	
LUSC					
PTGIS	↓	< cut-off	Hypomethylation	miR-34c ↓	SPI1 ↓ ; RELA ↔; RCOR1 ↔; MAZ ↑ ;

					CEBPB ↓ ; FOXA2 ↓ ; LMNB1 ↑
PTGIR	↓	< cut-off	Hypermethylation ↑	miR-326 ↓ ; miR-149 ↑	
			THCA		
PTGIS	↓	< cut-off	Hypomethylation	miR-34a ↑	n/d
PTGIR	↓	< cut-off	Hypermethylation ↑	n/d	n/d
			UCEC		
PTGIS	↓	< cut-off	Hypomethylation	miR-449a ↑ ; miR-449b ↑ ; miR-34a ↑	ZBTB7A ↓
PTGIR	↓	< cut-off	Hypermethylation ↑	miR-326 ↑ ; miR-589 ↑ ; miR-149 ↑	

Notes: ↑ or ↓ - statistical significant increase or decrease of gene expression or methylation status, respectively; ↔ no statistical significant changes (tumor/normal). Gene expression cut-off level |log2FoldChange| tumor/normal = 1, *p*-value < 0.01. Comparative analysis of gene expression was performed using TCGA datasets.

Cancer-specific copy number variations frequency (%) values of aimed genes were retrieved from cBioPortal database at cut-off values = 3%. Gene alterations are amplification (ampl) and deletion (del). Copy number variations in pancreatic cancer were evaluated with UTSW Nat Commun 2015 cBioPortal dataset. n/d – not determined.

Table S11. Gene expression changes of modifying proteins retrieved from the Biogrid database and physically interacting with the proteins involved in prostanoid signaling.

Target proteins	**Post-translational modifications**			
	Ubiquitination / deubiquitination	**Phosphorylation / dephosphorylation**	Glycosylation	Neddylation
Gene expression in lung squamous cell carcinoma (LUSC)				
AKR1C3	UBE2W ↔, SIAH2 ↑	CDK9 ↔ , CSK ↔	n/d	n/d
CBR1	MARCH2 ↔, MARCH3 ↔, MARCH4 ↔, OTUB1 ↔, VHL ↔, WWP2 ↔	MAPK13↔ , PINK1 ↔ PRKAB1 ↔	B3GNT2 ↔ , OGT ↓	UBE2M ↔
CBR3	ARIH2 ↔	NEK4 ↔, PINK1 ↔ , RIOK1 ↔	n/d	n/d
Gene expression in esophageal carcinoma (ESCA)				
CBR1	MARCH3 ↑ , MARCH2 ↔ , OTUB1 ↔ ,VHL ↔, WWP2 ↔	MAPK13 ↔ PINK1 ↔ , PRKAB1 ↔	B3GNT2 ↔ , OGT ↔	UBE2M ↔
CBR3	ARIH2 ↔	NEK4 ↔, PINK1 ↔ , RIOK1 ↔	n/d	n/d
Signature of eight up-regulated genes in pancreatic adenocarcinoma				
TBXAS1	n/d	n/d	n/d	n/d
PTGIS	n/d	n/d	n/d	n/d
PTGDS	n/d	n/d	n/d	n/d
PTGES	n/d	n/d	n/d	n/d
PTGES2	n/d	STK24 ↑	n/d	n/d
PTGES3	n/d	MAP4K1 ↑ , MAP4K4 ↑ , PRKCD ↑ , PRKAA2 ↔	n/d	UBE2M ↑
PRXL2B	n/d	PDPK1 ↔	n/d	n/d
AKR1C3	UBE2W ↑ , SIAH2 ↔	CDK9 ↔, CSK ↑	n/d	n/d
CBR1	MARCH2 ↑ , MARCH3 ↑ , MARCH4 ↔, OTUB1 ↑ , VHL ↑ , WWP2 ↔	MAPK13 ↔, PINK1 ↑ , PRKAB1 ↑	B3GNT2 ↑ , OGT ↓	UBE2M ↑
CBR3	ARIH2 ↔	NEK4 ↔, PINK1 ↑ , RIOK1 ↔	n/d	n/d
Down-regulation of *PTGIS* and *PTGIR* genes in seven tumors				
KICH				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1 ↔	MAP2K7 ↔, PRKCA↔, STK39 ↑	n/d	n/d
KIRP				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1 ↓	MAP2K7 ↔, PRKCA ↔, STK39 ↔	n/d	n/d
LUAD				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1↔	MAP2K7↔, PRKCA↔, STK39 ↑	n/d	n/d
LUSC				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1↔	MAP2K7↔, PRKCA↔, STK39 ↔	n/d	n/d
THCA				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1↔	MAP2K7↔, PRKCA↔, STK39 ↔	n/d	n/d
UCEC				
PTGIS	n/d	n/d	n/d	n/d
PTGIR	LNX1↔	MAP2K7 ↓ , PRKCA ↓ , STK39 ↔	n/d	n/d

Notes: ↑ or ↓ - statistical significant increase or decrease of gene expression, respectively; ↔ no statistical significant changes (tumor/normal); n/d – not determined.

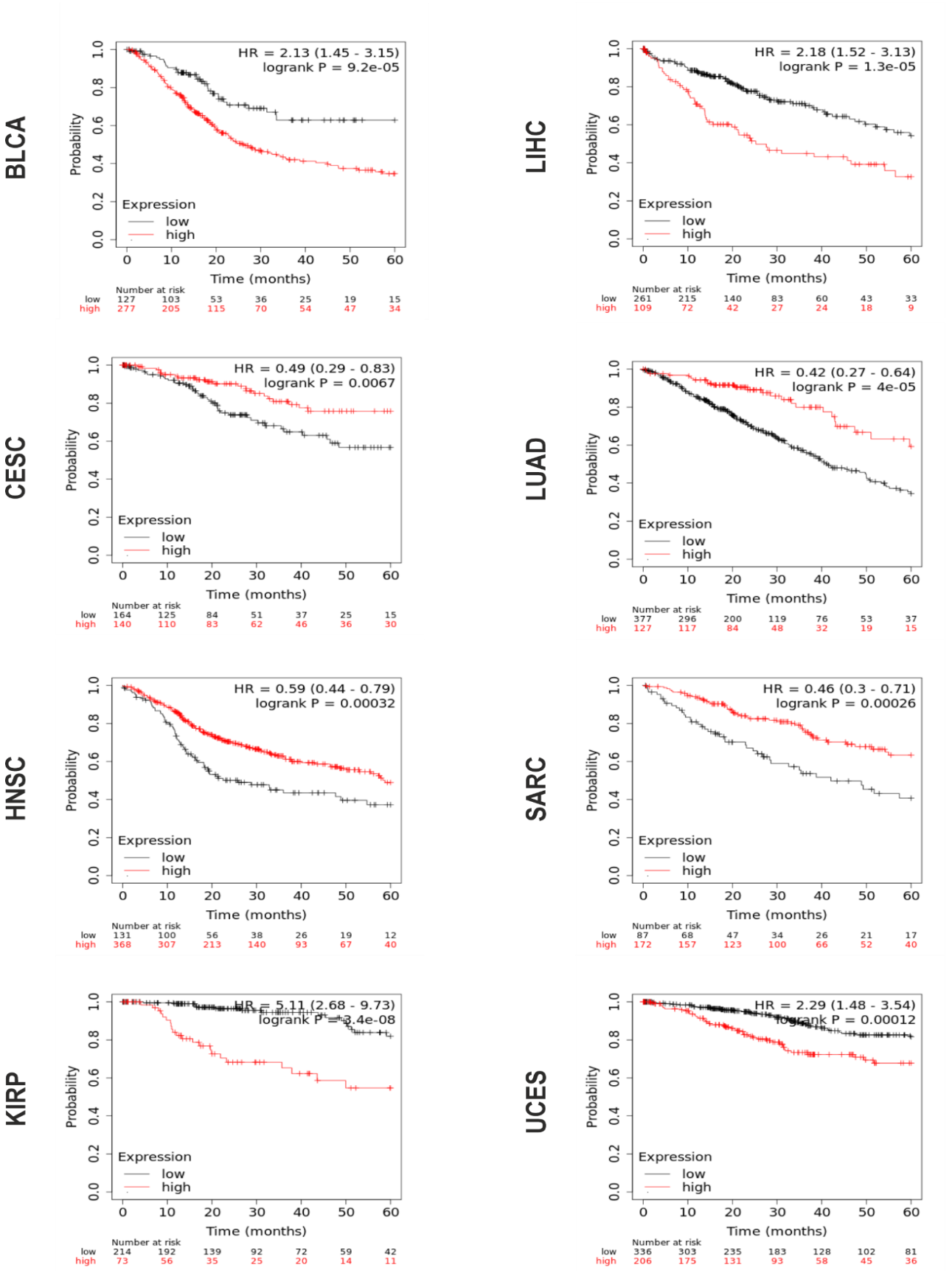


Figure S1. Kaplan-Meier plots: overall survival vs expression levels of target genes in several tumors.

Tumors abbreviations and gene expression signatures are presented below:

BLCA - Bladder Urothelial Carcinoma (*PTGIS, PTGDS, PTGFR* and *PTGER3*);

CESC - Cervical squamous cell carcinoma and endocervical adenocarcinoma (*PTGDS, AKR1C3, CBR1, CBR3, PTGDR, PTGDR2, PTGER2* and *PTGER4*);

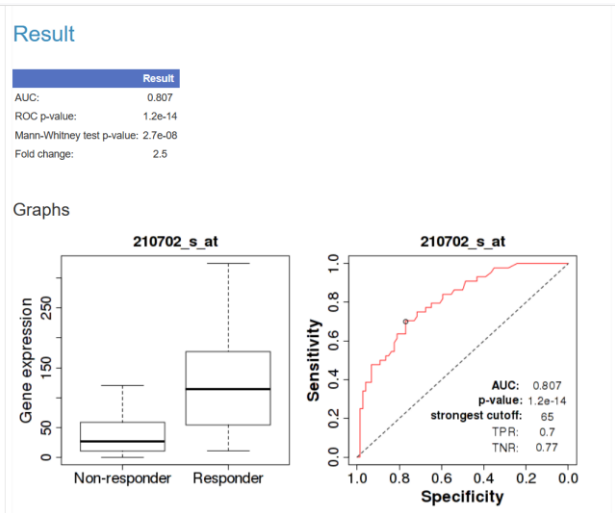
HNSC - Head and Neck squamous cell carcinoma (*PTGDS, CBR3, PTGIR, PTGFR, PTGDR2* and *PTGER3*);

KIRP - Kidney renal papillary cell carcinoma (PTGIS, PTGDS, PTGES3, AKR1C3, CBR3, TBXA2R, PTGDR, PTGER1, PTGFR and PTGER3);

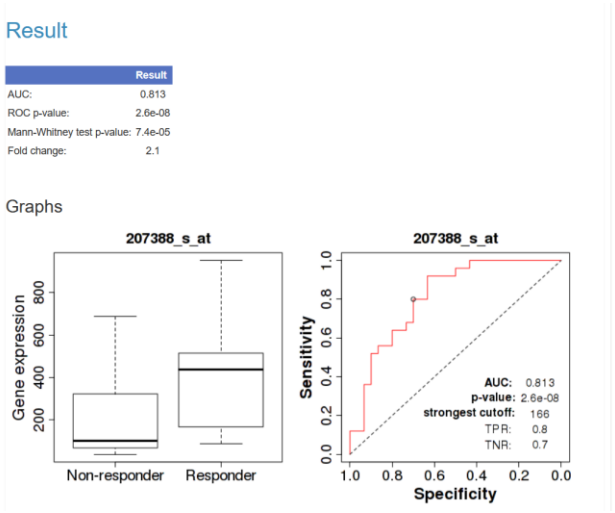
LIHC - Liver hepatocellular carcinoma (*PTGES2, PTGES3, PRXL2B, AKR1C3* and *PTGES*); LUAD - Lung adenocarcinoma (*PTGDS* and *PTGDR2*);

SARC - Sarcoma (TBXAS1, PTGDS, AKR1C3, PTGIS, CBR3, TBXA2R, PTGDR, PTGFR, PTGER3 and PTGER4);

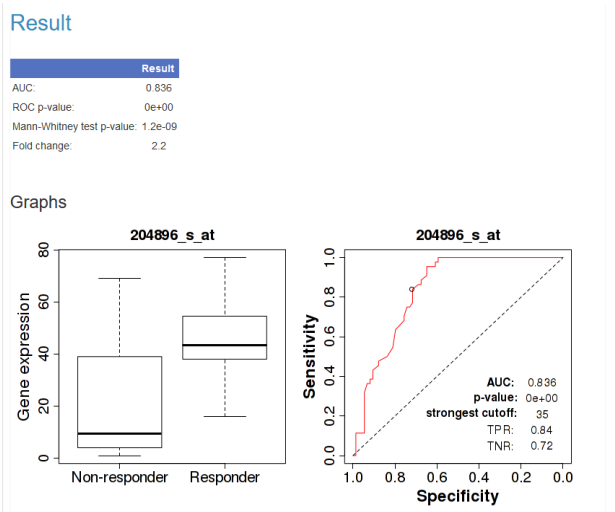
UCES - Uterine Corpus Endometrial Carcinoma (*PTGER1, PTGER3* and *PTGER4*).



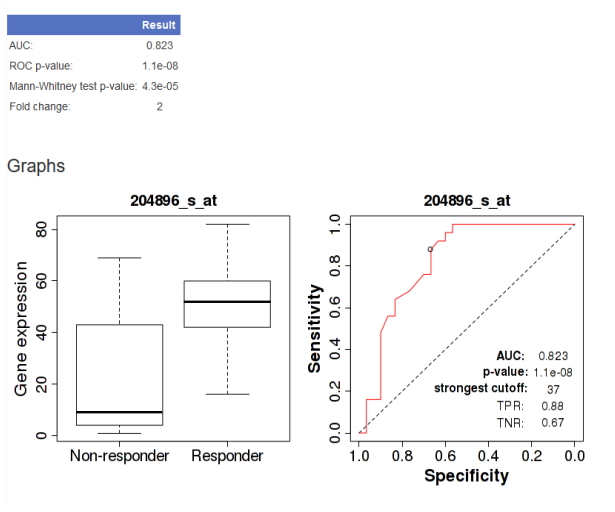
Settings: PTGIS (210702_s_at); pathological complete response sample; fluorouracil, epirubicin and cyclophosphamide treatment; histology: HER2+; AUC = 0.81; fold change = 2.5. 74 non-responders and 44 responders



Settings: PTGES (207399_s_at); pathological complete response sample; fluorouracil, epirubicin and cyclophosphamide treatment; histology: HER2+ and ER-; AUC = 0.81; fold change = 2.1. 30 non-responders and 25 responders.



Settings: PTGER4 (204896_s_at); pathological complete response sample; fluorouracil, epirubicin and cyclophosphamide treatment; histology: HER2+;



Settings: PTGER4 (204896_s_at); pathological complete response sample; fluorouracil, epirubicin and cyclophosphamide treatment; histology: HER2+;

AUC = 0.84; fold change = 2.2. 74 non-responders and 44 responders	AUC = 0.82; fold change = 2.0. 30 non-responders and 25 responders.

Figure S2. A. Predictive value of gene expression of prostanoid-metabolizing enzymes and prostanoid receptor in breast cancer.

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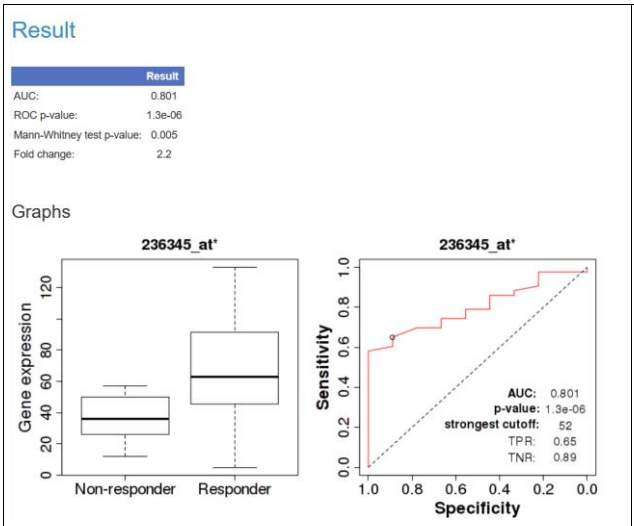
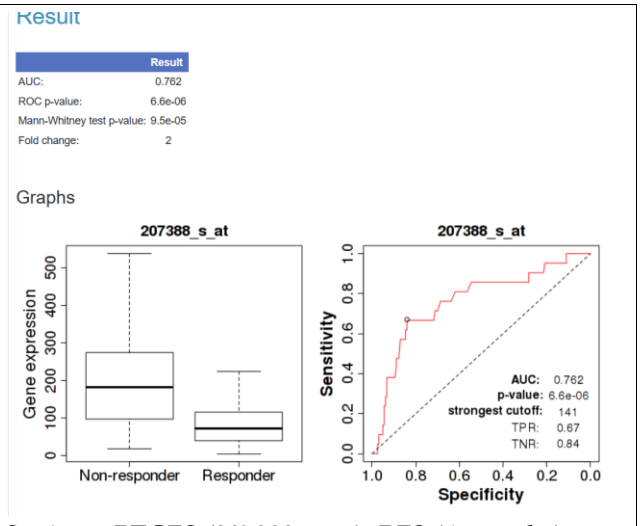
<td> 

Settings: TBXAS1 (236345_at), pathological response sample; taxane treatment; histology: serous; grade: G3; debulk optimal; AUC=0.80; fold change = 2.2. 268 responders, 35 non-responders.</td>
<td> 

Settings: PTGES (207388_s_at), RFS (6 months) sample; taxane treatment; histology: serous; grade: G3; debulk suboptimal; AUC=0.76; fold change = 2.0. 163 responders, 21 non-responders.</td>
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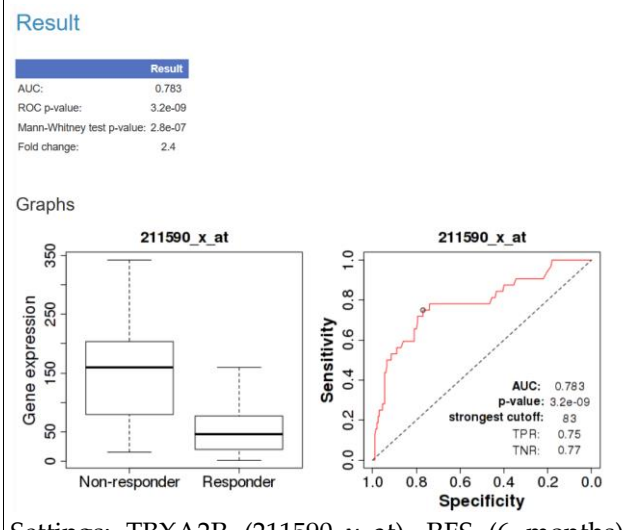
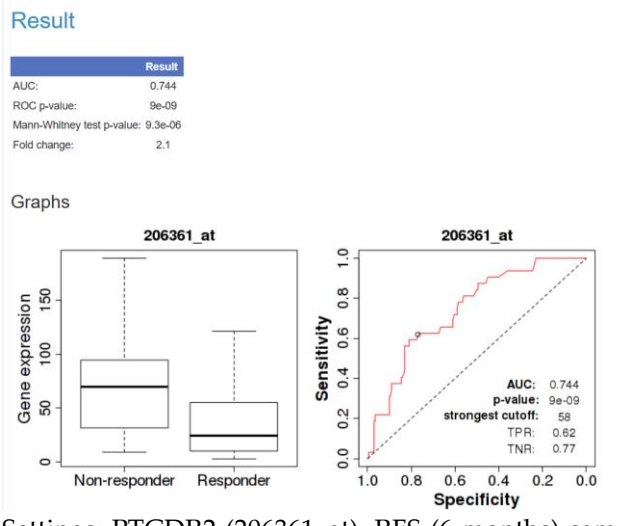
<td> 

Settings: TBXA2R (211590_x_at), RFS (6 months) sample; platin treatment; histology: serous; grade: G3; debulk suboptimal; AUC=0.78; fold change = 2.4. 200 responders, 32 non-responders.</td>
<td> 

Settings: PTGDR2 (206361_at), RFS (6 months) sample; platin treatment; histology: serous; grade: G3; debulk suboptimal; AUC=0.74; fold change = 2.1. 200 responders, 32 non-responders.</td>
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Figure S2. B. Predictive value of gene expression of prostanoid-metabolizing enzymes and prostanoid receptor in ovarian cancer.

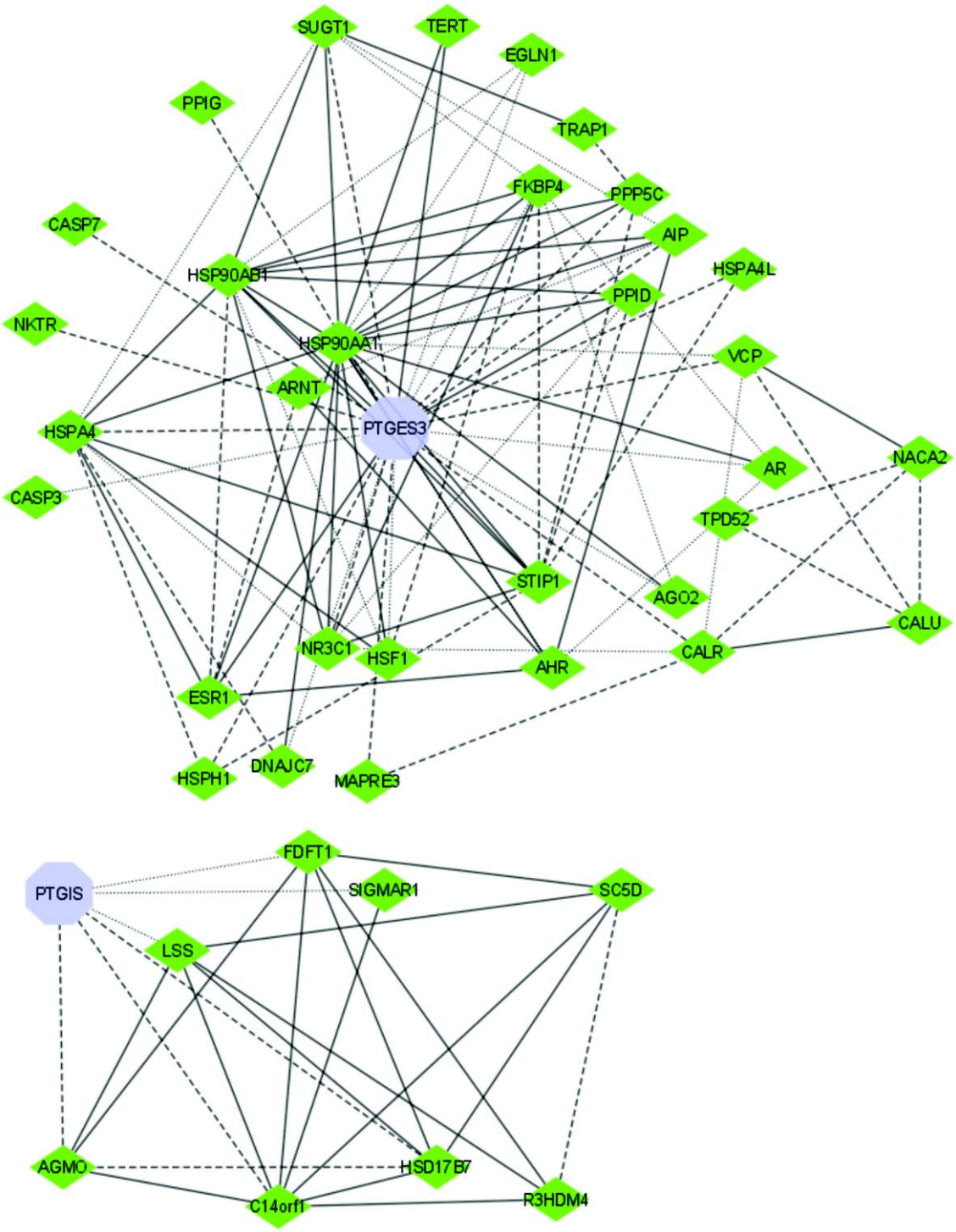

Figure S3. Protein-protein interaction subnetworks with PTGIS and PTGES3 and their physically interacting protein partners, sharing similar subcellular localization pattern with target proteins. Edges, selected with dotted, dashed and solid lines, indicate 0.4-0.5, 0.5-0.7 and 0.7-0.99 STRINGdb combined scores (experimentally_determined_interactions), respectively.

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