Supplementary Information for

Title: Identification of novel prostate cancer genes in patients stratified by Gleason classification: role of antitumoral genes

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This PDF includes:

Supplemental Information 1

Figure S1: PCA plots regarding batch effect, Gleason score, Survival status, and vial.

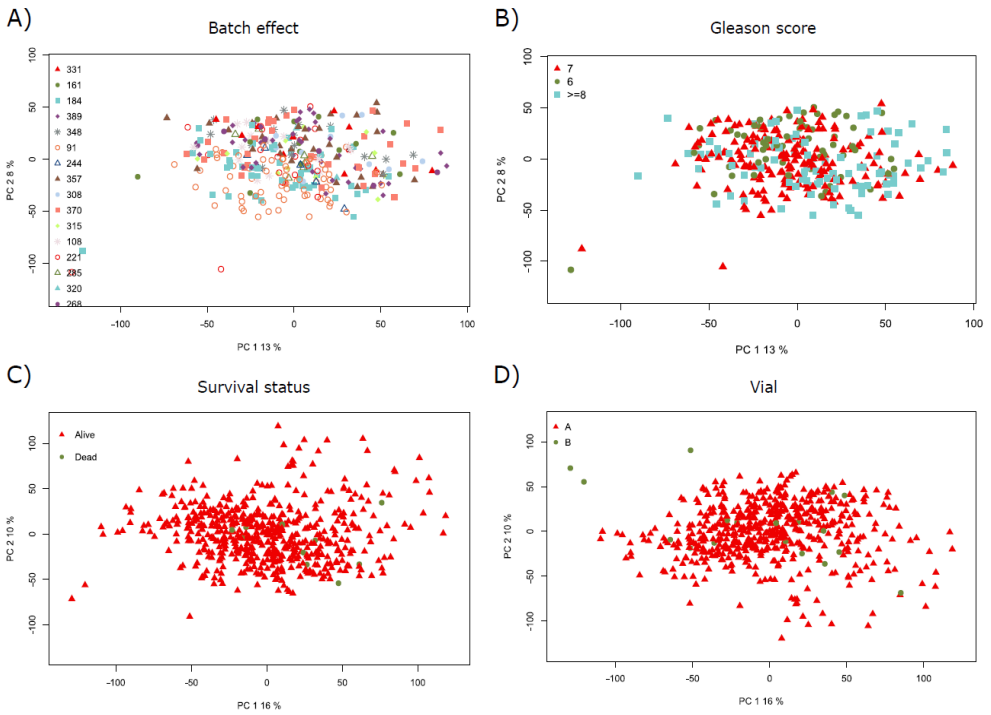

Table S1 : Number of patients and differentially expressed genes between healthy and tumoral tissue filtering by P-value <0.01 and LogFC2 found for each subset.

Subset	Nr. patients	Nr. of genes with adjusted p-value <0.01		Nr. of genes with LogFC2	
All	51	9,284	Over-expressed: 4,675	195	Over-expressed: 107
			Under-expressed: 4,609		Under-expressed: 88
Gleason 6	9	299	Over-expressed: 146	54	Over-expressed: 45
			Under-expressed: 153		Under-expressed: 9
Gleason 7	24	5,464	Over-expressed: 2,519	192	Over-expressed: 115
			Under-expressed: 2,945		Under-expressed: 77
Gleason >=8	9	0	Over-expressed: 0	0	Over-expressed: 0
			Under-expressed: 0		Under-expressed: 0

Figure S2: Expression of differentially expressed genes between healthy and tumoral tissue found in the “All'' subset. Heatmap rows represent genes and column samples. Sample annotations were considered regarding sample type, Gleason score, ethnicity, vital status, and tumor category.

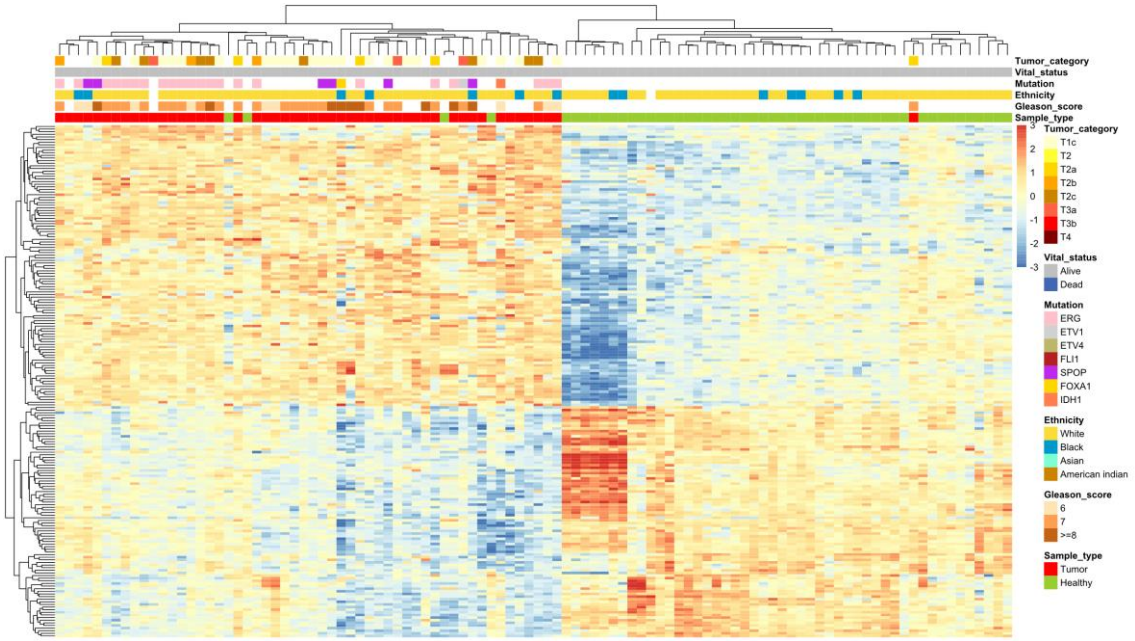

Figure S3: Expression of differentially expressed genes between healthy and tumoral tissue found in the “Gleason 6'' subset. Heatmap rows represent genes and column samples. Sample annotations were considered regarding sample type, Gleason score, ethnicity, vital status, and tumor category.

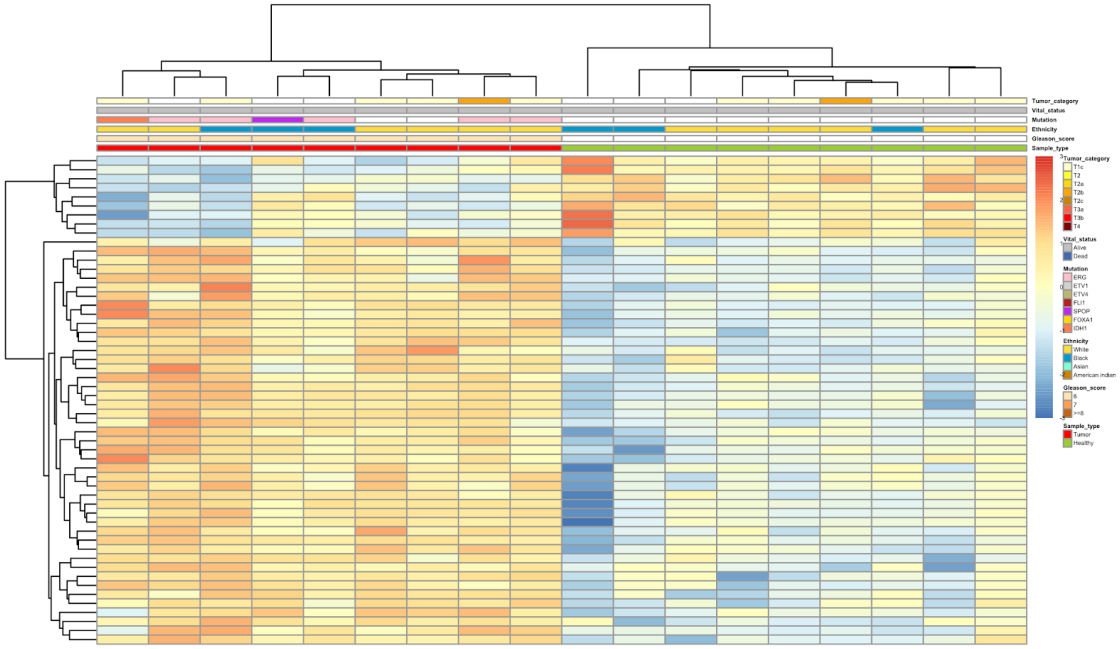

Figure S4: Expression of differentially expressed genes between healthy and tumoral tissue found in the “Gleason 7'' subset. Heatmap rows represent genes and column samples. Sample annotations were considered regarding sample type, Gleason score, ethnicity, vital status, and tumor category.

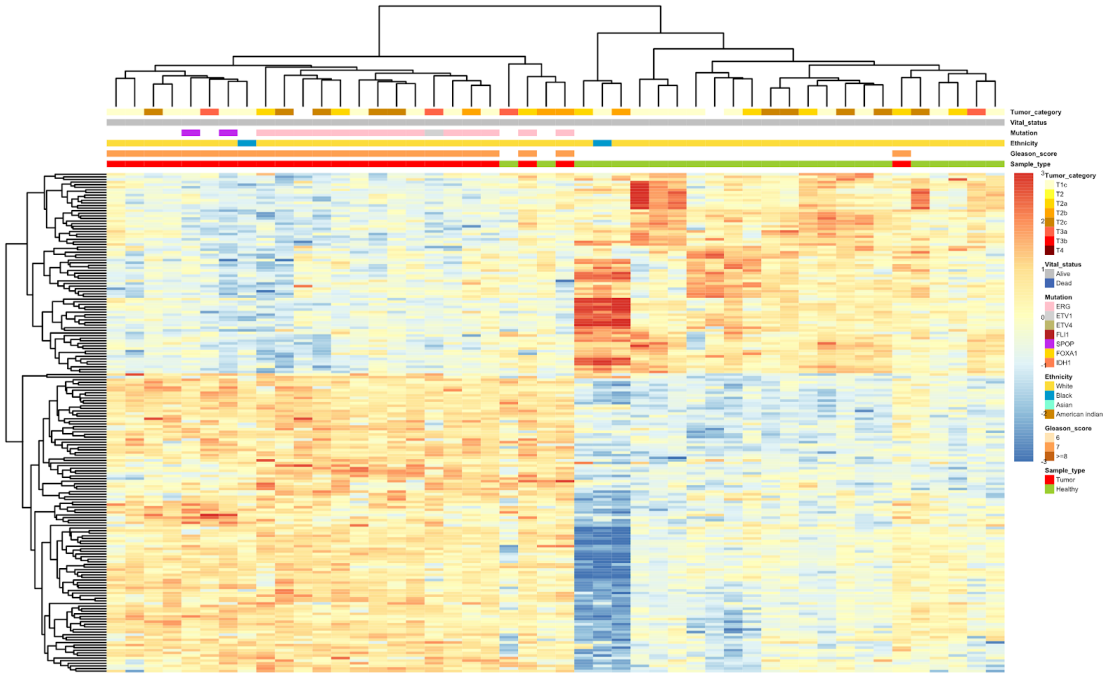

Table S2: Automatic functional annotation results.

Expression	Nr. of genes	All	Gleason 6	Gleason 7	Automatic functional annotation
Over-expressed	**35**	**X**	**X**	**X**	Calcium ion binding, regulation of the endocrine process, thyroid hormone generation and other processes related to metabolism like conjugation of carboxylic acids or aminoacids.
	16	**X**			-
	6		**X**		Cell cycle, like G2/M transition, cell cycle checkpoints, nuclear division and RhoGTPases.
	26			**X**	Lipase activity and rhodopsin-like receptors.
	3	**X**	**X**		-
	1		**X**	**X**	-
	53	**X**		**X**	Androgen receptor network in prostate cancer, skeletal system development, neuron fate commitment, anterior/posterior pattern specification, cAMP signaling pathway and DNA-binding transcription activator activity.
Under-expressed	**5**	**X**	**X**	**X**	Metabolism, especially to lipid metabolism.
	29	**X**			Multiple drugs pathways, inflammatory response, glutathione and prostaglandin synthesis and regulation.
	2		**X**		-
	20			**X**	Androgen receptor network in prostate cancer, skeletal system development, neuron fate commitment, anterior/posterior pattern specification, cAMP signaling pathway and DNA-binding transcription activator activity.
	2	**X**	**X**		-
	52	**X**		**X**	Calcium and potassium channels, GABA B receptors, mesenchyme morphogenesis, actin-based cell projection and response to alcohol.

Table S3: Type of antitumoral evidence and variability of genes previously studied in prostate cancer.

	Antitumoral Evidences			
GEN	**Genetic manipulation experiments**	**Functional**	**Effect varies with the type of cancer**	**Additional information**
PCAT14	Yes			PCa
TRPM8		Yes	Yes	PCa
DRAIC		Yes		PCa
NPY		Yes		PCa, Differential effect depending on the cell lines used
MUC2	Yes			PCa
SNCG	Yes			PCa
CCN5		Yes	Yes	PCa and breast cancer
DPT		Yes		PCa
CXCL13	Yes			PCa
AQP5	Yes			PCa
FUT3	Yes			PCa circulating cancer cells
KRT13		Yes		PCa and related to brain and bone metastasis
GPX2	Yes			PCa resistant to castration
CYP11A1		Yes		PCa resistant to castration
PTGS1	Yes			PCa neuroendocrine
MATK		Yes		PCa, breast, lung, and colorectal cancer
PIP	Yes			PCa and breast cancer

Table S4: Type of antitumoral evidence and variability of genes involved in other types of cancer.

	Antitumoral Evidences			
GEN	**Genetic manipulation experiments**	**Functional**	**Effect varies with the type of cancer**	**Additional information**
SRARP		Yes		Cancer general processes
CGREF1		Yes		Cancer general processes
UNC5A		Yes		Breast and bladder cancer
FFAR2	Yes			Colorectal cancer
TGM3	Yes		Yes	Hepatic and colorectal
TOX3	Yes		Yes	Kidney and breast cancer
C16orf74	Yes			Pancreatic and cervix cancer
P2RX6		Yes		Kidney cancer
MSLN	Yes			Lung cancer and mesothelioma
LGR6	Yes			Colorectal cancer
PDE1C	Yes			Glioblastoma
ACTC1			Yes	Glioma
EMX2OS	Yes		Yes	Ovarian and thyroid cancer
LINC00958	Yes			Pancreatic cancer and Lung adenocarcinoma
IGSF1	Yes			Thyroid cancer
SYT8	Yes			Gastric cancer with peritoneal metastasis
PGM5 AS1		Yes	Yes	Colorectal and esophageal cancer
CHP2	Yes			Breast and ovarian cancer
CRABP2	Yes		Yes	Malignant peripheral nerve sheath and breast cancer
QPRT	Yes			Cancer general processes
PON3		Yes		Cancer general processes
CA14				Cancer general processes

Table S5: : Antitumoral evidence of genes previously studied in prostate cancer.

Gene	Function	Cancer Hallmark	Ref.	PCa exp.
MATK	Potential tumor suppressor, downregulated by epigenetic modifications in multiple types of cancer and its downregulation promotes CRPC.	Met., R.C.D., C.R.	[20, 21]	OE
PCAT14	It is an AR-regulated transcript and its over-expression suppresses invasion; it is associated with favorable outcomes.	Met.	[22]	OE
TRPM8	It inhibits endothelial cell migration via a non-channel function by trapping the small GTPase Rap1.	Met.	[23]	OE
DRAIC	It is regulated by AR and FOXA1 and prevents the transformation of cuboidal epithelial cells to fibroblast-like morphology; therefore, it prevents cellular migration and invasion.	Met., R.C.D., C.R.	[24]	OE
NPY	Lower NPY expression is associated with aggressive high-grade disease and progression; it may influence the microenvironment to modulate ERG fusions.	Met.	[26]	OE
MUC2	It has been found to have tumor suppressor function, and its inhibition induced increased cell proliferation and decreased apoptosis.	Prol., R.C.D.	[27]	OE
SNCG	Interacts with AR and silencing it contributes to the inhibition of cellular proliferation and the suppression of EMT in vitro.	Met., Prol.	[28]	UE
CCN5	CCN5 affects extracellular matrix to stimulate angiogenesis and invasiveness in PCa cells.	Met., Ang.	[29]	UE
DPT	It may be involved in the pathogenesis growth, and metastasis of prostate cancer.	Met., Prol.	[30]	UE
CXCL13	It is involved in AR-induced cell migration and invasion.	Met.	[31]	UE
AQP5	It is likely to play a role in cell growth and metastasis.	Met., Prol.	[32]	UE
FUT3	siRNA treatment against FUT3 significantly reduced the cell growth rate and metastasis.	Met., Prol.	[33]	UE
KRT13	KRT13 drives metastases toward mouse bone, brain and soft tissues.	Met.	[34]	UE
GPX2	Its silencing caused significant growth inhibition and increased intracellular ROS in human (PC3) CRPC cells.	Met.	[35]	UE
CYP11A1	Its decreased expression reduced testosterone level and tumor growth in castrated mice.	C.R.	[36]	UE
PTGS1	Its increased expression is associated with cancer progression and linked to the dysregulation of the AR-SPDEF pathway.	A.R.	[37]	UE
PIP	Reduced expression inhibits the abilities of migration, adhesion and invasion in breast cancer.	Met.	[56]	UE

Table S6: Replication datasets trends compared to paired TCGA-PRAD pattern.

	TCGA-PRAD	GDS2545		GDS2546		GDS2547	
	Identical expression pattern	Present in dataset	Identical expression pattern	Present in dataset	Identical expression pattern	Present in dataset	Identical expression pattern
MATK	Yes	Yes	Yes				
NPY	Yes	Yes	Yes				
MUC2	Yes	Yes	Yes				
SNCG	Yes	Yes	Yes				
DPT	Yes	Yes	Yes				
CXCL13	Yes	Yes	Yes				
AQP5	Yes	Yes	Yes				
FUT3	Yes	Yes					
KRT13	Yes	Yes	Yes				
GPX2	Yes	Yes	Yes				
CYP11A1	Yes	Yes					
PTGS1	Yes	Yes	Yes				
PIP	Yes	Yes					
CGREF1	Yes	Yes	Yes				
UNC5A	Yes			Yes	Yes		
TGM3	Yes	Yes	Yes				
TOX3	Yes	Yes	Yes			Yes	Yes
C16orf74	Yes			Yes	Yes		
P2RX6	Yes	Yes					
MSLN	Yes	Yes					
LGR6	Yes			Yes	Yes		
PDE1C	Yes	Yes				Yes	Yes
ACTC1	Yes	Yes	Yes			Yes	
EMX2OS	Yes			Yes			
IGSF1	Yes	Yes	Yes				
SYT8						Yes	Yes
CHP2	Yes	Yes		Yes			
CRABP2	Yes	Yes	Yes				
QPRT	Yes	Yes	Yes				
PON3	Yes	Yes					
CA14	Yes			Yes	Yes	Yes	Yes

Supplemental Information 2

	Ensembl	Referencias
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4	ENSG00000166840	[4]
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Supplemental Information 3

Genes previously studied in prostate cancer.

Over-expressed in tumor with regard to healthy samples

MATK "Overexpression of CHK [=MATK] in MCF-7 breast cancer cells markedly inhibited cell growth and proliferative response to heregulin as well as decreased colony formation in soft agar. These studies indicate that CHK binds, via its SH2 domain, to Tyr1253 of the activated ErbB-2/neu and down-regulates the ErbB-2/neu-mediated activation of Src kinases, thereby inhibiting breast cancer cell growth. These data strongly suggest that CHK is a novel negative growth regulator in human breast cancer."

Zrihan-Licht, S.; Deng, B.; Yarden, Y.; McSchan, G.; Keydar, I.; Avraham, H. Csk homologous kinase, a novel signaling molecule, directly associates with the activated ErbB-2 receptor in breast cancer cells and inhibits their proliferation. J Biol Chem. 1998, 273(7), 4065-4072.

"Aberrant activation of Src-family tyrosine kinases (SFKs) directs initiation of metastasis and development of drug resistance in multiple solid tumors and hematological cancers. Oncogenic mutations in Src-family tyrosine kinases (SFKs) are rare events, aberrant activation of SFKs in cancer is likely due to dysregulation of the two major upstream inhibitors: C-terminal Src kinase (Csk) and its homolog Csk-homologous kinase (Chk/Matk). Csk and Chk/Matk inhibit SFKs by selectively phosphorylating the inhibitory tyrosine residue at their C-terminal tail. Additionally, Chk/Matk can also employ a noncatalytic inhibitory mechanism to inhibit multiple active forms of SFKs, suggesting that Chk/Matk is a versatile inhibitor capable of constraining the activity of multiple active forms of SFKs. Mounting evidence suggests that Chk/ Matk is a potential tumor suppressor downregulated by epigenetic silencing and/or missense mutations in several cancers such as colorectal and lung carcinoma."

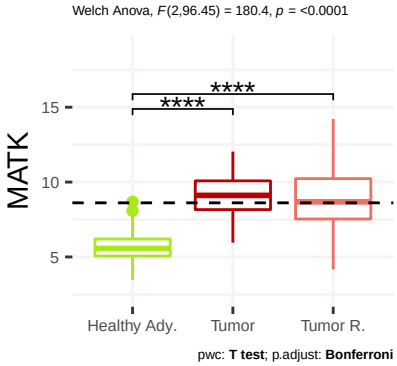
Advani, G.; Chueh,A.C.; Lim,Y.C.; Dhillon,A.; Cheng,H.C. C-homologous kinase (Chk/Matk): a molecular policeman suppressing cancer formation and progression. Frontiers in Biology 2015, 10, 195–202.

"SRC kinase is activated in castration resistant prostate cancer (CRPC), phosphorylates the androgen receptor (AR), and causes its ligand-independent activation as a transcription factor. Performing a functional genomics screen, we found that downregulation of SRC inhibitory kinase CSK [CSK is not MATK] is sufficient to overcome growth arrest induced by depriving human prostate cancer cells of androgen. CSK knockdown led to ectopic SRC activation, increased AR signaling, and resistance to anti-androgens. (...) A search in the Oncomine database revealed frequent CSK copy number losses specifically in CRPCs as compared to primary prostate cancer. A similar observation was made with an independent dataset as well as for the CSK-related tyrosine kinase MATK.

Yang,C.; Fazli,L.; Loguercio,S.; Zharkikh,i.; Aza-Blanc,P.; Gleave,M.E.; Wolf,D.A. Downregulation of c-SRC kinase CSK promotes castration resistant prostate cancer and pinpoints a novel disease subclass.Oncotarget 2015, 6, 22060–22071.

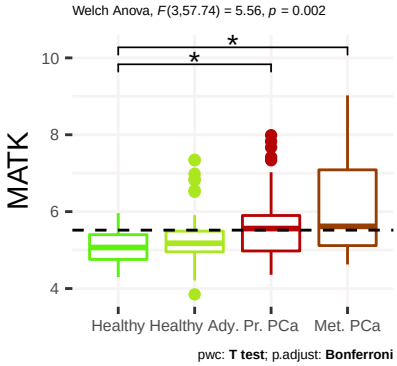
Expression of MATK

TCGA−PRAD



Healthy Ady.	51
Tumor	51
Tumor R.	427

GDS2545



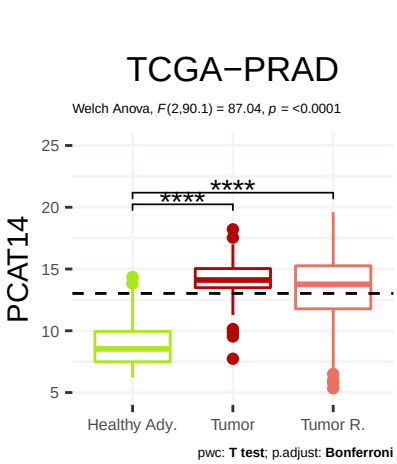
Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

PCAT14 "By performing differential expression analysis between prostate cancer with low vs high Gleason scores, we identified lncRNA PCAT14 as a prostate cancer- and lineage- specific biomarker of indolent disease. We show that PCAT14 is an AR-regulated transcript and its overexpression suppresses invasion of prostate cancer cells. Moreover, in multiple independent datasets, PCAT14 expression associates with favorable outcomes in prostate cancer and adds prognostic value to standard clinicopathologic variables."."

Shukla, S.; Zhang, X.; Niknafs, Y.S.; Xiao, L.; Mehra, R.; Cieslik, M.; Ross, A.; Schaeffer, E.; Malik, B. ;Guo, S.; Freier, S.M.; Bui, H.H.; Siddiqui, J.; Jing, X.; Cao, X.; Dhanasekaran, S.M.; Feng, F.Y.; Chinnaiyan, A.M.; Malik, R. Identification and Validation of PCAT14 as Prognostic Biomarker in Prostate Cancer. Neoplasia 2016, 18, 489–499.

"Down-regulation of PCAT-14 expression significantly associated with Gleason score and a greater probability of metastatic progression, overall survival, and prostate cancer-specific mortality across multiple independent datasets and ethnicities. Low PCAT-14 expression was implicated with genes involved in biological processes promoting aggressive disease. In-vitro analysis confirmed that low PCAT-14 expression increased migration while overexpressing PCAT-14 reduced cellular growth, migration, and invasion."

White, N.M.; Zhao, S.G.; Zhang, J.; Bozycki E.B.; Dang, H.X.; McFadden S.D.; Eteleeb, A.M.; Alshalalfa, M.; Vergara, I.A.; Erho, N.; Arbeit, J.M.; Karnes, R.J.; Den, R.B.; Davicioni, E.; Maher, C.A. Multi-institutional Analysis Shows that Low PCAT-14 Expression Associates with Poor Outcomes in Prostate Cancer. Eur Urol. 2017, 71 (2):257-266.



Healthy Ady.	51
Tumor	51
Tumor R.	427

TRPM8 [Its activity is not clear, numerous studies found referred to its antitumoral properties but there are others which talk about protumoral properties.]

"The TRPM8 channel has recently been proposed to play a protective role in prostate cancer by impairing cell motility. However, the mechanisms by which it could influence vascular behavior are unknown. Here, we reveal a novel non-channel function for TRPM8 that unexpectedly acts as a Rap1 GTPase inhibitor, thereby inhibiting endothelial cell motility, independently of pore function. TRPM8 retains Rap1 intracellularly through direct protein–protein interaction, thus preventing its cytoplasm–plasma membrane trafficking. In turn, this mechanism impairs the activation of a major inside-out signaling pathway that triggers the conformational activation of integrin and, consequently, cell adhesion, migration, in vitro endothelial tube formation, and spheroid sprouting. Our results bring to light a novel, pore-independent molecular mechanism by which endogenous TRPM8 expression inhibits Rap1 GTPase and thus plays a critical role in the behavior of vascular endothelial cells by inhibiting migration."

Genova, T.; Grolez, G.P.; Camillo, C.; Bernardini, M.; Bokhobza, A.; Richard, E.; Scianna, M.; Lemonnier, L.; Valdembri, D.; Munaron, L.; Philips, M.R.; Mattot, V.; Serini, G.; Prevarskaya, N.; Gkika, D.; Pla, A.F. TRPM8 inhibits endothelial cell migration via a non-channel function by trapping the small GTPase Rap1. J. CellBiol. 2017, 216, 2107–2130.

"Cell cycle distribution and scratch assay analysis revealed that TRPM8 induced cell cycle arrest at the G0/G1 stage ($P < 0.05$) and facilitated the cell apoptosis induced by starvation ($P < 0.05$). Furthermore, TRPM8 inhibited the migration of PC-3-TRPM8 cells ($P < 0.01$) through the inactivation of focal-adhesion kinase. It appears that TRPM8 was not essential for the survival of PC-3 cells; however, the overexpression of TRPM8 had negative effects on the proliferation and migration of PC-3 cells. Thus, TRPM8 and its agonists may serve as important targets for the treatment of prostate cancer."

Yang, Z.H.; Wang, X.H.; Wang H.P.; Hu L.Q. Effects of TRPM8 on the proliferation and motility of prostate cancer PC-3 cells. Asian J. Androl. 2009, 11(2): 157-165.

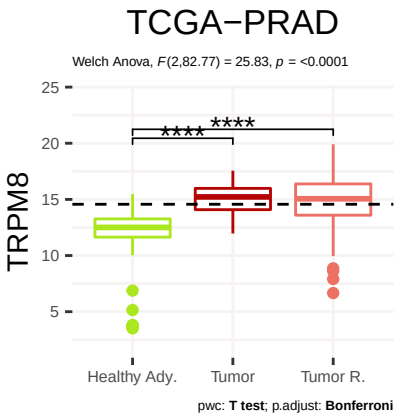
"However, recent studies have brought to light the complexity of TRPM8 isoforms in PCa. (...) Here we have studied the role of these regulatory sM8s subunits of TRPM8 in prostate cancer survival. Using a siRNA-based strategy to decipher their role as non-channel isoforms, we have demonstrated that suppression of sM8 isoforms (non-channel cytoplasmic small TRPM8 isoforms) induced the deregulation of TRPM8 and 4TM-TRPM8 (TM transmembrane domain) mRNA expression, ER and mitochondrial pathways of oxidative stress, p21 induction and apoptosis. Finally, we have demonstrated that this sM8s-mediated apoptosis in prostate cancer cells required functional 4TM-TRPM8 channels. Altogether, our results suggest that sM8 isoforms participate in resistance against pro-apoptotic signals in prostate cancer cells and consequently that targeting sM8 isoforms rather than the TRPM8 channel itself could be an appropriate and beneficial strategy against extracapsular prostate cancer."

Bidaux, G.; Borowiec, A.S.; Dubois, C.; Delcourt, P.; Schulz, C.; Abeele, F.V.; Lepage, G.; Desruelles, E.; Bokhobza, A.; Dewailly, E.; Slomianny, C.; Roudbaraki, M.; Héliot, L.; Bonnal, J.L.; Mauroy, B.; Mariot, P.; Lemonnier, L.; Prevarskaya, N. Targeting of short TRPM8 isoforms induces 4TM-TRPM8-dependent apoptosis in prostate cancer cells. Oncotarget. 2016, 7 (20): 29063-29080.

"Although TRPM8 mRNA levels increase at the early prostate cancer stages, we found that it is not proportionally translated into TRPM8 protein levels. High-throughput proteome analysis revealed that TRPM8 degradation is enhanced in human prostate cancer cells. This degradation is executed via a dual degradation mechanism with the involvement of both lysosomal and proteasomal proteolytic pathways."

Asuthkar, S.; Demirkhanyan, L.; Mueting, S.R.; Cohen, A.; Zakharian, E. High-throughput proteome analysis reveals targeted TRPM8 degradation in prostate cancer. Oncotarget 2017, 8 (8): 12877-12890.

Expression of TRPM8



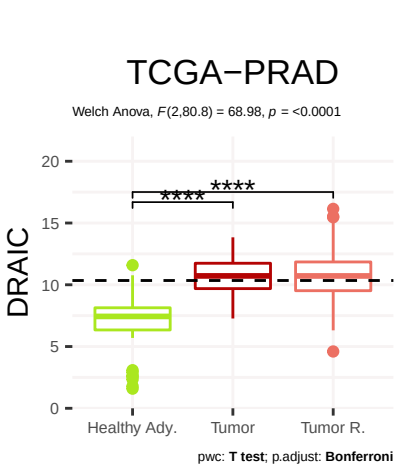
Healthy Ady.	51
Tumor	51
Tumor R.	427

DRAIC "The DRAIC lncRNA was identified from RNA-seq data and is downregulated as prostate cancer cells progress from an androgen-dependent (AD) to a castration-resistant (CR) state. Prostate cancers persisting in patients after androgen deprivation therapy (ADT) select for decreased DRAIC expression, and higher levels of DRAIC in prostate cancer are associated with longer disease-free survival (DFS). Androgen induced androgen receptor (AR) binding to the DRAIC locus and repressed DRAIC expression. In contrast, FOXA1 and NKX3-1 are recruited to the DRAIC locus to induce DRAIC, and FOXA1 specifically counters the repression of DRAIC by AR. The decrease of FOXA1 and NKX3-1, and aberrant activation of AR, thus accounts for the decrease of DRAIC during prostate cancer progression to the CR state. Consistent with DRAIC being a good prognostic marker, DRAIC prevents the transformation of cuboidal epithelial cells to fibroblast-like morphology and prevents cellular migration and invasion. (...) Finally, based on TCGA analysis, DRAIC expression predicts good prognosis in a wide range of malignancies, including bladder cancer, low-grade gliomas, lung adenocarcinoma, stomach adenocarcinoma, renal clear cell carcinoma, hepatocellular carcinoma, skin melanoma, and stomach adenocarcinoma."

Sakurai, K.; Reon, B.J.; Anaya, J.; Dutta, A. The lncRNA DRAIC/PCAT29 Locus Constitutes a Tumor-Suppressive Nexus. Mol. CancerRes. 2015, 13, 828–838.

"Decreased DRAIC expression predicts poor patient outcome in prostate and seven other cancers, while increased DRAIC represses growth of xenografted tumors. Here we show that cancers with decreased DRAIC expression have increased NF-KB target gene expression. DRAIC downregulation increased cell invasion and soft agar colony formation; this was dependent on NF-KB activation. DRAIC interacted with subunits of the IKB kinase (IKK) complex."

Saha, S.; Kiran, M.; Kuscu, M.; Chatrath, A.; Wotton, D.; Mayo, M.W.; Dutta, A. Long noncoding RNA DRAIC inhibits prostate cancer progression by interacting with IKK to inhibit NF-KB activation. Cancer Res. 2020, 80(5): 950-963.



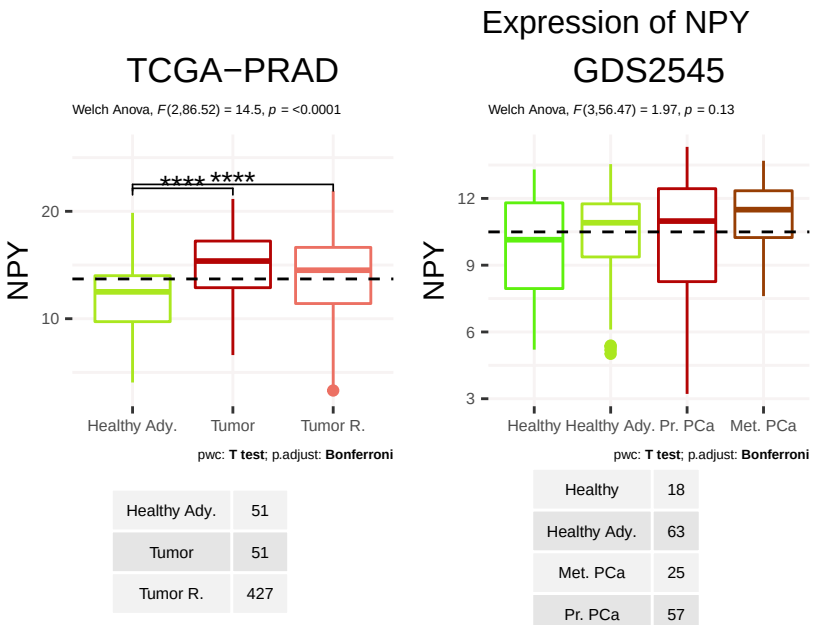
Healthy Ady.	51
Tumor	51
Tumor R.	427

NPY "[Genome-wide expression profiling of n=18818] Though NPY is highly expressed in prostate cancers relative to other cancers, low NPY expression is associated with adverse genomic and histological features, disease progression, and poor clinical outcomes. Furthermore, patients with low NPY and ERG fusions are at a high risk of developing metastasis and may be at risk of ADT resistance."

Alshalalfa, M.; Nguyen, P.L.; Beltran, H.; Chen, W.S.; Davicioni, E.; Zhao, S.G.; Rebbeck, T.R.; Schaeffer, E.M.; Lotan, T.L.; Feng, F.Y.; Mahal, B.A.Transcriptomic and Clinical Characterization of Neuropeptide Y Expression in Localized and Metastatic Prostate Cancer: Identification of Novel Prostate Cancer Subtype with Clinical Implications. Eur UrolOncol 2019, 2, 405–412.

"The role of NPY in PCa biology appears to vary in different in vitro human PCa cell systems, since it has been found to reduce the proliferation of LNCaP and DU145 cells, but to stimulate the growth of PC3 cells. These effects are mediated mainly by the NPY Y1 receptor and are associated with a clone-specific pattern of intracellular signaling activation, including a peculiar time-course of MAPK/ERK1/2 phosphorylation (long-lasting in DU145 and transient in PC3 cells)."

Ruscica, M.; Dozio, E.; Motta, M.; Magni, P. Modulatory actions of neuropeptide Y on prostate cancer growth: role of MAP kinase/ERK 1/2 activation. Adv Exp Med Biol. 2007, 604, 96-100.

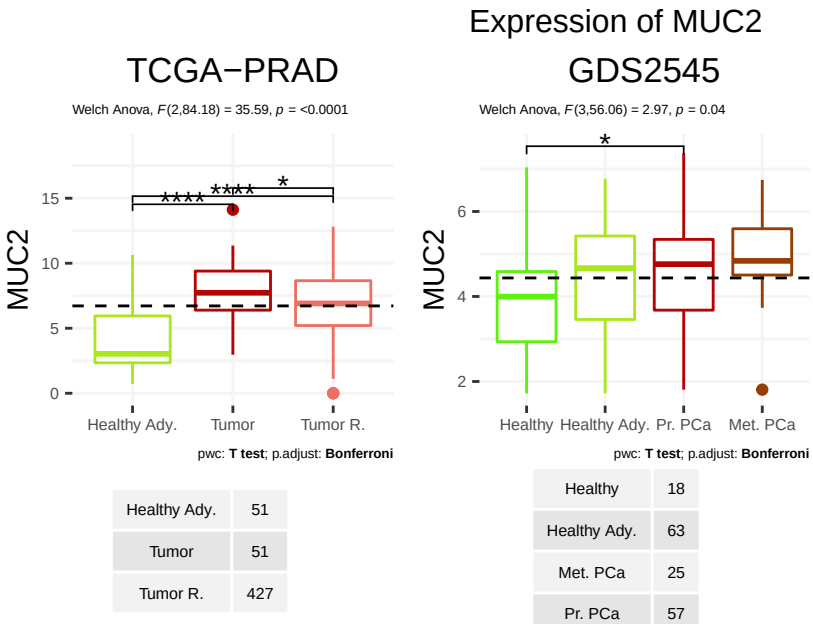


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

MUC2 "Mucinous adenocarcinoma of the prostate shows diffuse expression of MUC2, a known tumor suppressor, which is not present in either normal prostate or the majority of conventional adenocarcinomas of this organ. (...) In normal tissue, the expression of this marker is largely limited to intestinal goblet cells, hence the name 'secretory'-type mucin. (...) Absence of MUC2 induces increased cell proliferation, decreased apoptosis and increased migration of intestinal epithelial cells, ultimately leading to a spectrum of neoplastic transformation, ranging from aberrant crypt foci to adenomas to frank carcinomas."

Osunkoya, A.O.; Adsay, N.V.; Cohen, C.; Epstein, J.I.; Smith, S.L. MUC2 expression in primary mucinous and non mucinous adenocarcinoma of the prostate: ananalysis of 50 cases on radical prostatectomy. Mod. Pathol. 2008, 21, 789–794.



Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

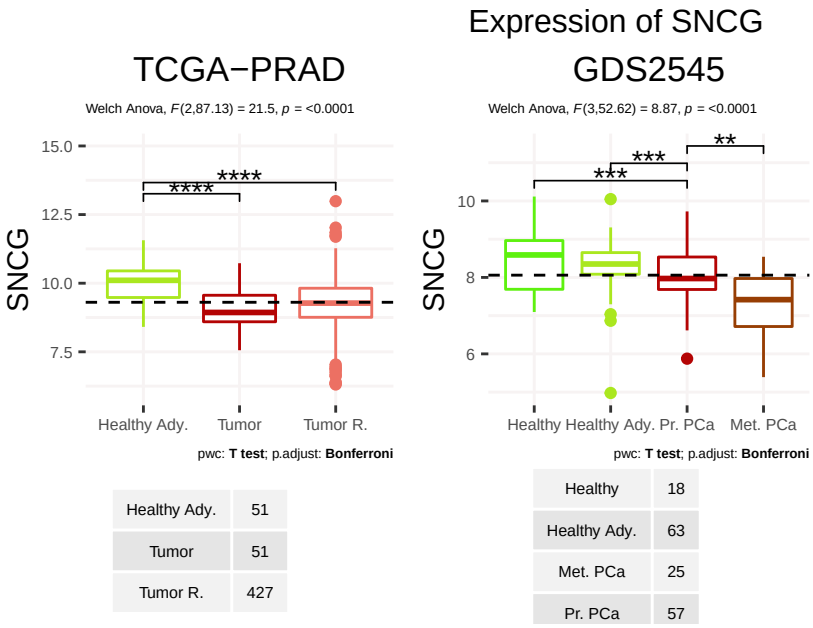
Under-expressed in tumor with regard to healthy samples

SNCG "Silencing SNCG by siRNA in LNCaP cells contributes to the inhibition of cellular proliferation, the induction of cell-cycle arrest at the G1 phase, the suppression of cellular migration and invasion in vitro, as well as the decrease of tumor growth in vivo with the notable exception of castrated mice. Subsequently, mechanistic studies indicated that SNCG is a novel androgen receptor (AR) coactivator. It interacts with AR and promotes prostate cancer cellular growth and proliferation by activating AR transcription in an androgen-dependent manner. Finally, immunohistochemical analysis revealed that SNCG was almost undetectable in benign or androgen-independent tissues prostate lesions. The high expression of SNCG is correlated with peripheral and lymph node invasion."

Chen, J.; Jiao, L.; Xu, C.; Yu, Y.; Zhang, Z.; Chang, Z.; Deng, Z.; Sun, Y. Neural protein gamma-synuclein interacting with androgen receptor promotes human prostate cancer progression. BMC Cancer 2012, 12, 593.

"DLX6-AS1 promoted PCa progression via upregulation of SNCG at a miR-497-5p dependent way".

Zhu, X.; Ma, X.; Zhao, S.; Cao, Z. DLX6-AS1 accelerates cell proliferation through regulating miR-497-5p/SNCG pathway in prostate cancer. Environmental Toxicology 2020, 1-12.



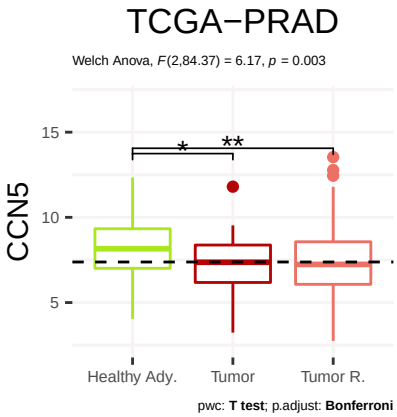
CCN5 "The Wnt-Induced Signaling Protein-2 (Wisp-2 /CCN5) is a secreted protein implicated in modification of extracellular matrix, invasion, and angiogenesis. (...) These results show that Wisp2 is down stream effector of IL-8 and is an important modulator, affecting extracellular matrix to stimulate angiogenesis and invasiveness in CaP cells. Suppression of Wisp-2 in CaP may reduce their metastatic potential."

Hashimoto, Y. Effect of Wnt signaling protein (Wisp2/CCN5) on angiogenesis and invasion in prostate cancer. J. Clin.Oncol. 2016, 30, 227.

"The studies showed that CCN5 expression is biphasic, such that in normal samples CCN5 expression is undetectable, whereas its expression is markedly increased in noninvasive breast lesions, including atypical ductal hyperplasia and ductal carcinoma in situ. Further, CCN5 mRNA and protein levels are significantly reduced as the cancer progresses from a noninvasive to invasive type. (...) CCN5 is a negative regulator of migration and invasion of breast cancer cells, and these events could be regulated by CCN5 through the modulation of the expression of genes essential for an invasive front."

Banerjee, S.; Dhar, G.; Haque, i.; Kambhampati, S.; Mehta, S.; Sengupta, K.; Tawfik, O.; Phillips, T.A.; Banerjee, S.K. CCN5/WISP-2 expression in breast adenocarcinoma is associated with less frequent progression of the disease and suppresses the invasive phenotypes of tumor cells. Cancer Res. 2008, 68(18) 7606-7612.

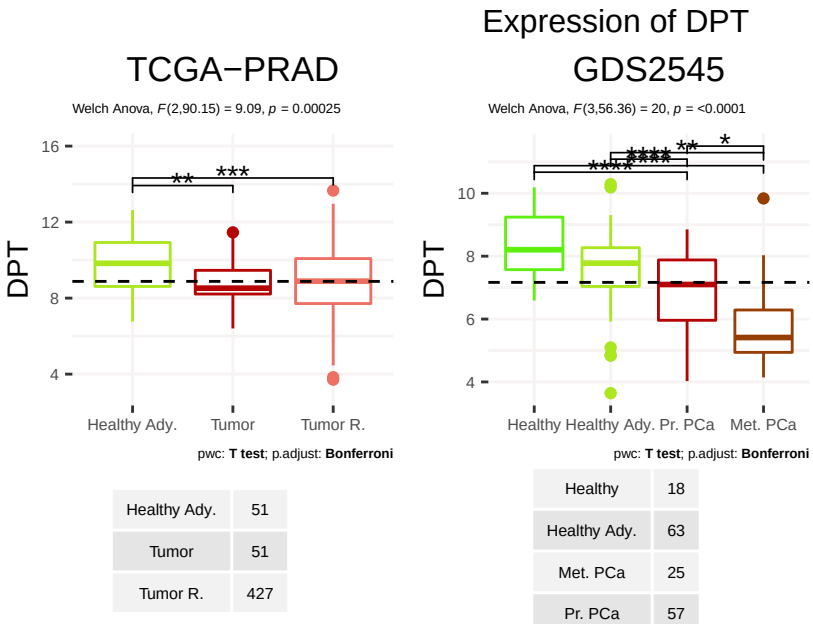
Expression of CCN5



Healthy Ady.	51
Tumor	51
Tumor R.	427

DPT "Transfectants of mouse dermatopontin cDNA into PC-3 human prostate cancer cells showed enhanced dermatopontin protein expression compared with control PC-3 cells, leading to enhanced tumor growth when mouse dermatopontin-transfected tumor cells were implanted subcutaneously in nude mice compared with the controls. There are two possibilities why dermatopontin has enhanced the PC-3 tumor growth in vivo. Dermatopontin itself is an extracellular matrix, thus increases the stroma, including collagen 1. The increased stroma may have the possibility to support the tumor growth by supplying blood and nutrition. (. . .) In conclusion, dermatopontin may be involved in the pathogenesis, growth, and metastasis of the prostate cancer"

Takeuchi, T.; Suzuki, M.; Kumagai, J.; Kamijo, T.; Sakai, M.; Kitamura, T. Extracellular matrix dermatopontin modulates prostate cell growth in vivo. J. Endocrinol. 2006, 190, 351–361.



Healthy Ady.	51
Tumor	51
Tumor R.	427

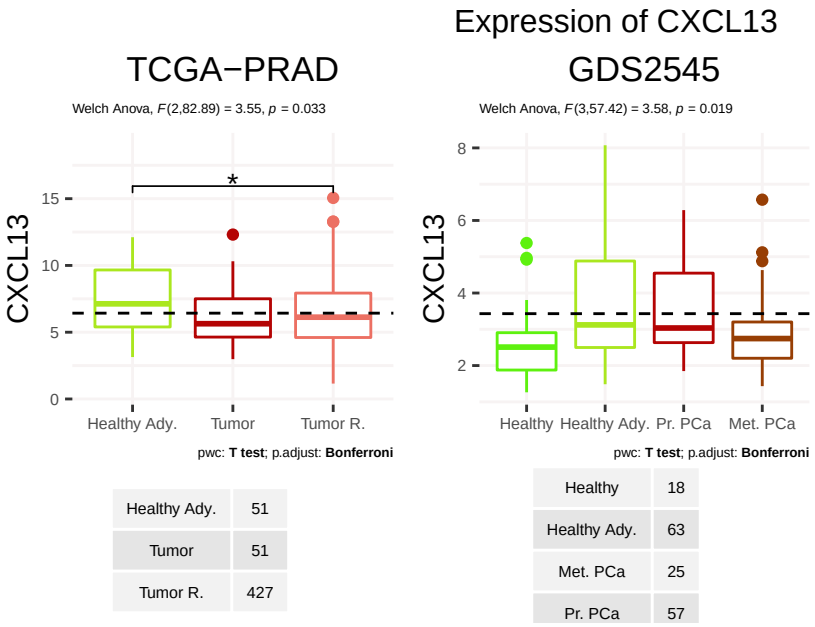
Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

CXCL13 "CXCL13, known as B cell attracting chemokine1 (BCA-1), is a member of CXC chemokine family and relevant to cancer metastasis. This study shows that CXCL13 is an androgen-responsive gene and involved in AR-induced PCa cell migration and invasion. In clinical specimens, expression of CXCL13 in PCa tissues is markedly higher than that in adjacent normal tissues. In cultures, expression of CXCL13 is up-regulated by androgen-AR axis at both mRNA and protein levels. Furthermore, Chip-Seq assay identifies canonical androgen responsive elements (ARE) at CXCL13 enhancer. (...) In addition, CXCL13 promotes G2/M phase transition by increasing Cyclin B1 levels in PCa cells. Functional studies demonstrate that reducing endogenous CXCL13 expression in LNCaP cells largely weakens androgen-AR axis induced cell migration and invasion. Taken together, our study implicates for the first time that CXCL13 is an AR target gene and involved in AR-mediated cell migration and invasion in primary PCa."

Fan, L.; Zhu, Q.; Liu, L.; Zhu, C.; Huang, H.; Lu, S.; Liu, P. CXCL13 is androgen-responsive and involved in androgen induced prostate cancer cell migration and invasion. Oncotarget 2017, 8, 53244–53261.

"Mechanistic analysis revealed that PKCe overexpression and Pten loss individually and synergistically upregulate the production of the chemokine CXCL13, which involves the transcriptional activation of the CXCL13 gene via the non-canonical nuclear factor kB (NF-kB) pathway. Notably, targeted disruption of CXCL13 or its receptor, CXCR5, in prostate cancer cells impaired their migratory and tumorigenic properties."

Garg, R.; Blando, J.M.; Perez, C.J.; Abba, M.C.; Benavides, F.; Kazanietz, M.G. Protein Kinase C Epsilon Cooperates with PTEN Loss for Prostate Tumorigenesis through the CXCL13-CXCR5 Pathway. Cell Rep. 2017, 19(2), 357-388.

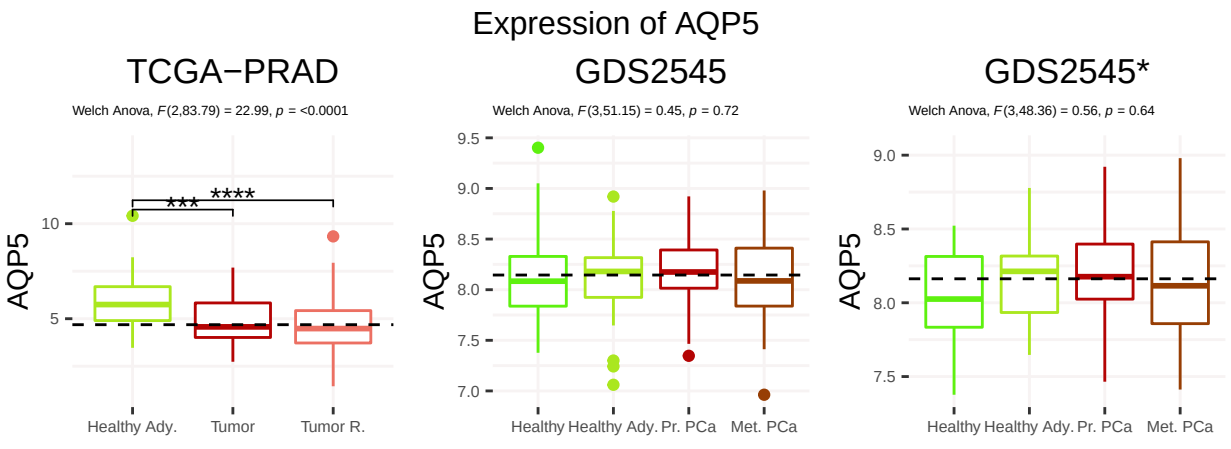


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

AQP5 "Patients who were negative for AQP5 had superior cumulative survival rate than those who were positive for it. Over-expression of AQP5 protein was also found in prostate cancer cells and cell proliferation and migration were significantly attenuated by AQP5-siRNA."

Li, J.; Wang, Z.; Chong, T.; Chen, H.; Li, H.; Li, G.; Zhai, X.; Li, Y.Over-expression of a poor prognostic marker in prostate cancer: AQP5 promotes cells growth and local invasion. WorldJSurgOncol 2014, 12, 284.



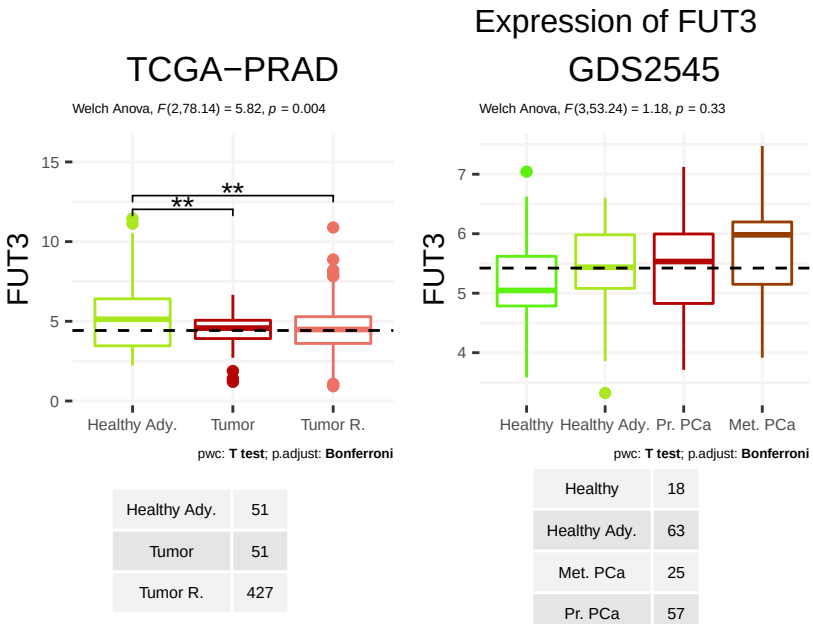
Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

Healthy	17
Healthy Ady.	59
Met. PCa	24
Pr. PCa	56

FUT3 "Our results further support the functional importance of FUT3 in E-selectin-mediated CCC (circulating cancer cells) recruitment and the feasibility of disrupting CCC metastasis using an siRNA approach. An intriguing observation from our research is the cell growth inhibition by FUT3 siRNA. Inhibition of tumor growth with reduced expression of FUT enzymes has been reported in a few references. (...) Our study provides support for using FUT3 siRNA to disrupt CCC metastasis. When delivered systemically, FUT3 siRNA will target epithelial cells without affecting leukocytes. (...) Delivery of FUT3 siRNA to epithelial cancer cells will not only block their metastasis but also slow down their proliferation, an added benefit for anti-metastasis applications."

Yin, X.; Rana, K.; Ponmudi, V.; King, M.R. Knockdown of fucosyltransferase III disrupts the adhesion of circulating cancer cells to E-selectin without affecting hematopoietic cell adhesion. Carbohydr.Res. 2010, 345, 2334–2342.



Healthy Ady.	51
Tumor	51
Tumor R.	427

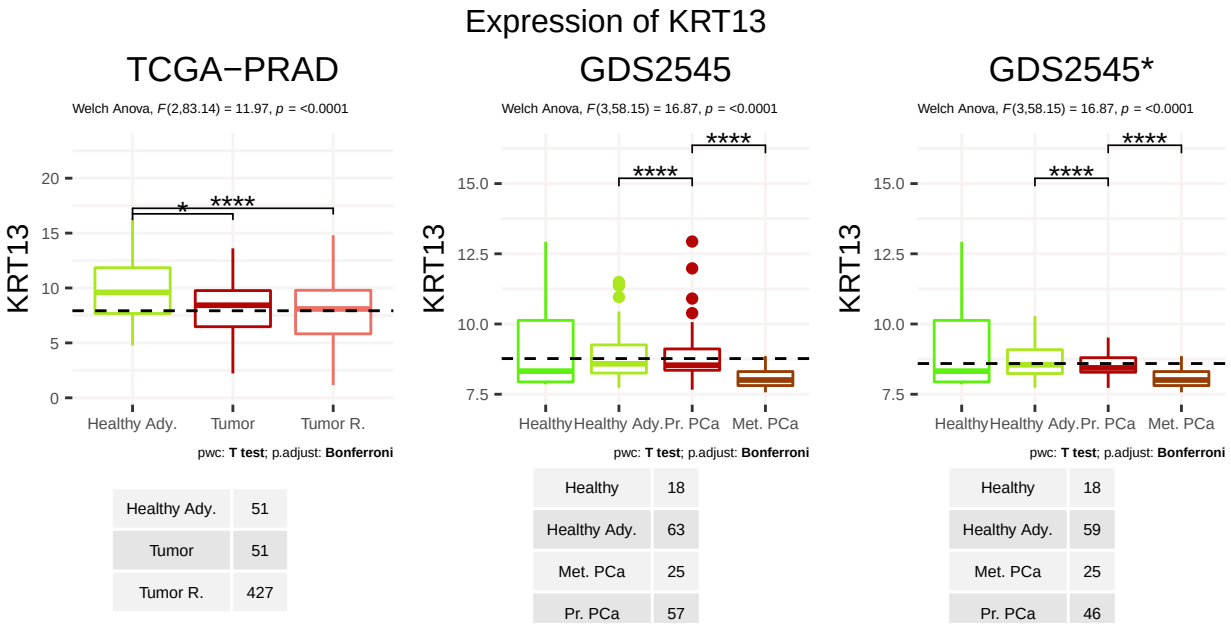
Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

KRT13 "Genetically enforced KRT13 expression in human prostate cancer cell lines drove metastases toward mouse bone, brain and soft tissues through a RANKL-independent mechanism, as KRT13 altered the expression of genes associated with EMT, stemness, neuroendocrine/neuromimicry, osteomimicry, development, and extracellular matrices, but not receptor activator NF-KB ligand (RANKL) signaling networks in prostate cancer cells."

Li, Q.; Yin, L.; Jones, L.W.; Chu, G.C.; Wu, J.B.; Huang, J.M.; Li, Q.; You, S.; Kim, J.; Lu, Y.T.; Mrdenovic, S.; Wang, R.; Freeman, M.R.; Garraway, I.; Lewis, M.S.; Chung, L.W.; Zhau, H.E. Keratin 13 expression reprograms bone and brain metastases of human prostate cancer cells. Oncotarget 2016, 7, 84645–84657.

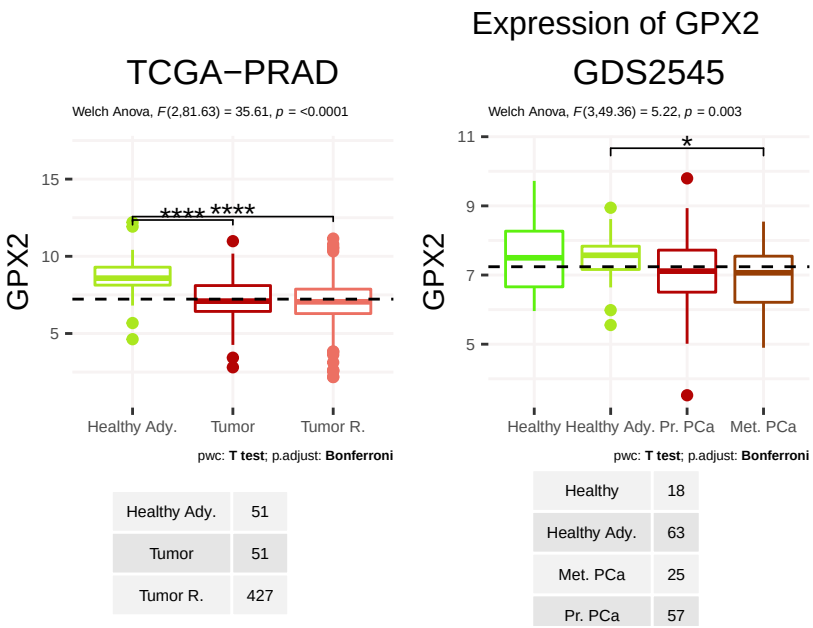
"The expression profile of KRT13 in benign fetal and adult prostate tissue and in recombinant grafts, as well as the frequency of KRT13 expression in primary and metastatic prostate cancer indicates that it may be a marker of a stem/progenitor-like cell state that is co-opted in aggressive tumor cells. KRT13 is enriched in benign stem-like cells that display androgen-resistance, apoptosis-resistance, and branching morphogenesis properties. Collectively our data demonstrate that KRT13 expression is associated with poor prognosis at multiple stages of disease progression and may represent an important biomarker of adverse outcome in patients with prostate cancer."

Liu, S.; Cadaneau R.M.; Zhang, B.; Huo, L.; Lai, K.; Li, X.; Galet, C.; Grogan, T.R.; Elashoff, D.; Freedland, S.J.; Rettig, M.; Aronson, W.J.; Knudsen, T.R.; Lewis, M.S.; Garraway, I.P. Keratin 13 Is Enriched in Prostate Tubule-Initiating Cells and May Identify Primary Prostate Tumors that Metastasize to the Bone. PLoS One. 2016, 11(10).



GPX2 "Silencing of GPX2 caused significant growth inhibition and increased intracellular ROS in both rat (PCai1) and human (PC3) CRPC cells. Flow cytometry and western blot analyses revealed that the decrease in proliferation rate of the GPX2-silenced cells was due to cyclin B1-dependent G2/M arrest. Furthermore, knockdown of Gpx2 inhibited tumor growth of PCai1 cells in castrated mice. (...) Moreover, patients with high GPX2 expression in biopsy specimen had significantly lower prostate-specific antigen recurrence-free survival and overall survival than those with no GPX2 expression."

Naiki, T.; Naiki-Ito, A.; Asamoto, M.; Kawai, N.; Tozawa, K.; Etani, T.; Sato, S.; Suzuki, S.; Shirai, T.; Kohri, K.; Takahashi, S. GPX2 overexpression is involved in cell proliferation and prognosis of castration-resistant prostate cancer. Carcinogenesis 2014, 35, 1962–1967.

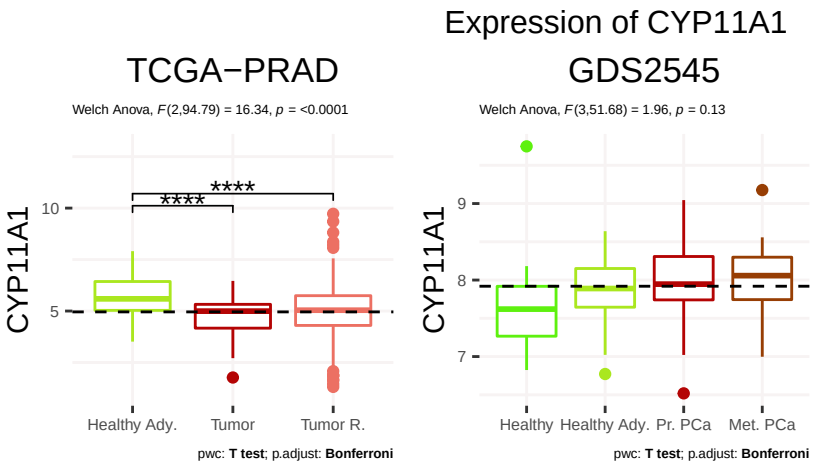


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

CYP11A1 "We uncovered that activation of the AKT-RUNX2-OCN-GPRC6A-CREB signaling axis induced expression of CYP11A1 and CYP17A1 and testosterone production in PTEN-null PCa cell lines in culture. Deletion of Runx2 in Pten homozygous knockout prostate tumors decreased CYP11A1 and Cyp17a1 expression, testosterone level and tumor growth in castrated mice."

Yang, Y.; Bai, Y.; He, Y.; Zhao, Y.; Chen, J.; Ma, L.; Pan, Y.; Hinten, M.; Zhang, J.; Karnes, R.J.; Kohli, M.; Westendorf, J.J.; Li, B.; Zhu, R.; Huang, H.; Xu, W. PTEN Loss Promotes Intratumoral Androgen Synthesis and Tumor Microenvironment Remodeling via Aberrant Activation of RUNX2 in Castration-Resistant Prostate Cancer. Clin. CancerRes. 2018, 24, 834–846.

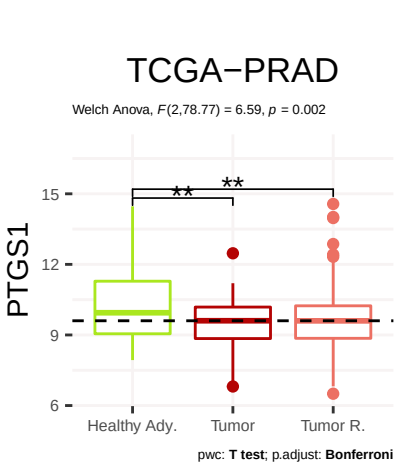


Healthy Ady.	51
Tumor	51
Tumor R.	427

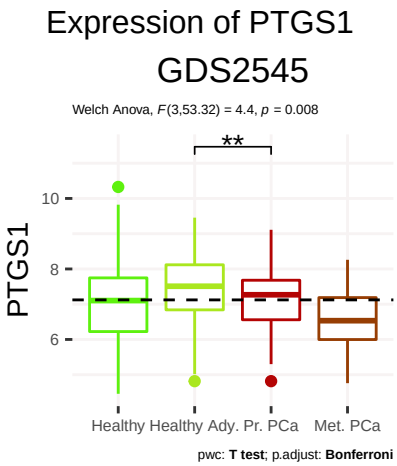
Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

PTGS1 "Prostaglandin endoperoxide synthase 1 (PTGS1), also known as cyclooxygenase 1 (COX1), was shown to regulate angiogenesis in endothelial cells. Activation of PTGS1 is involved in the inflammatory response, cell proliferation, and fatty acid metabolism during tumor progression. (...) We hypothesized that the abundance of PTGS1 may be involved in NEPC [neuroendocrine prostate cancer] differentiation following ADT. (...) Our results demonstrated that ADT induces ZBTB46 expression through the downregulation of the androgen-responsive SAM pointed domain containing ETS transcription factor (SPDEF), leading to increased expression of PTGS1 and contributing to NE differentiation of prostate cancer cells. The addition of PTGS1 inhibitor treatment can restore enzalutamide (MDV3100) sensitivity and reduce tumor growth, whereas overexpression of ZBTB46 disrupts the tumor-suppressive effect of this combination treatment and induces PTGS1- and NEPC- associated genes."

Chen, W.Y.; Zeng, T.; Wen, Y.C.; Yeh, H.L.; Jiang, K.C.; Chen, W.H.; Zhang, Q.; Huang, J.; Liu, Y.N. Androgen deprivation-induced ZBTB46-PTGS1 signaling promotes neuroendocrine differentiation of prostate cancer. Cancer Lett. 2019, 440-441, 35–46.



Healthy Ady.	51
Tumor	51
Tumor R.	427



Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

PIP "Using BCa and PCa cells, we found that Runx2, a pro-metastatic transcription factor, functionally interacts with the Androgen Receptor (AR) to regulate PIP expression. Runx2 expression in C4-2B PCa cells synergized with AR to promote PIP expression. (...). PIP silencing arrested growth in cultures that were maintained with complete serum, where mitogens other than androgens likely predominated. (...) However, it is interesting to note that PIP is not always required for cell proliferation as demonstrated by the normal development of PIP knockout mice"

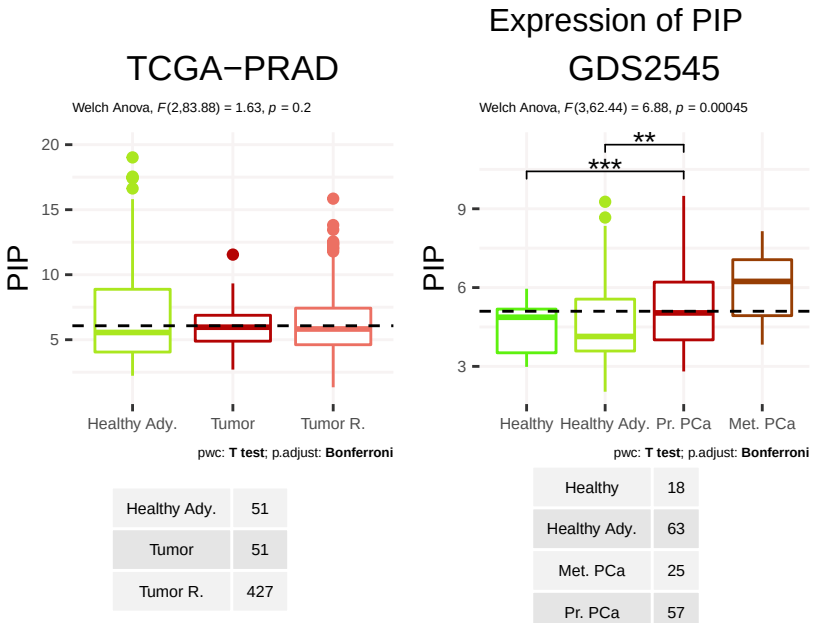
Baniwal, S.K.; Little, G.H.; Chimge, N.O.; Frenkel, B. Runx2 Controls a Feed-forward loop between Androgen and Prolactin-induced Protein (PIP) in Stimulating T47D Cell Proliferation. J Cell physiol. 2012, 227(5), 2276-2282.

[This article is not about PIPbut about RUNX2 in prostate cancer and is related to the one above] " The effects of Runx2 in C4-2B/Rx2 dox cells, as well as similar observations made by employing LNCaP, 22RV1 and PC3 cells, highlight multiple mechanisms by which Runx2 promotes the metastatic phenotype of PCa cells, including tissue invasion, homing to bone and induction of high bone turnover."

Baniwal, S.K.; Khalid, O.; Gabet, Y.; Shah, R.R.; Purcell, D.J.; Mav, D.; Kohn-Gabet, A.E.; Shi, Y.; Coetzee, G.A.; Frenkel, B. Runx2 transcriptome of prostate cancer cells: insights into invasiveness and bone metastasis. Mol Cancer. 2010, 9, 258.

"Reduced PIP expression in MDA-MB-453 cells can inhibit the abilities of migration, adhesion and invasion, which suggests that PIP plays an important role in the metastatic potency of breast cancer cells."

Zheng, Z.; Xie, X. Decreased prolactin-inducible protein expression exhibits inhibitory effects on the metastatic potency of breast cancer cells. Chin. -Ger.J.Clin.Oncol. 2013, 12, 101–105.



Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
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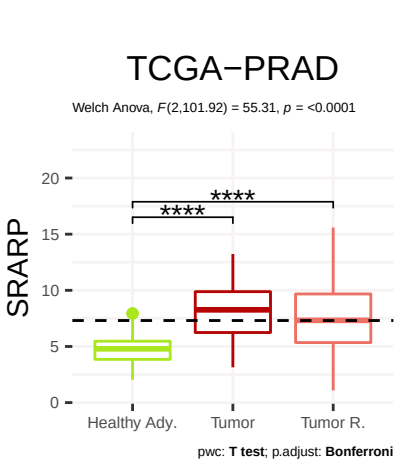
Pr. PCa	57

Genes not deeply studied in prostate cancer but in other cancer types.

Over-expressed in tumor with regard to healthy samples

SRARP "SRARP has recently been identified as a novel corepressor of the androgen receptor (AR) and is located on chromosome 1p36. Here, bioinformatics analysis of large tumor datasets was performed to study SRARP and its gene pair, HSPB7. This study demonstrated that SRARP and HSPB7 (...) are inactivated by deletions and epigenetic silencing in malignancies. Importantly, SRARP and HSPB7 have tumor suppressor functions in clonogenicity and cell viability associated with the downregulation of Akt and ERK. SRARP expression is inversely correlated with genes that promote cell proliferation and signal transduction, which supports its functions as a tumor suppressor. In addition, AR exerts dual regulatory effects on SRARP, and although an increased AR activity suppresses SRARP transcription, a minimum level of AR activity is required to maintain baseline SRARP expression in AR+ cancer cells. (...) Of note, genome- and epigenome-wide associations of SRARP and HSPB7 with survival strongly support their tumor suppressor functions. In particular, DNA hypermethylation, lower expression, somatic mutations, and lower copy numbers of SRARP are associated with worse cancer outcome. Moreover, DNA hypermethylation and lower expression of SRARP in normal adjacent tissues predict poor survival, suggesting that SRARP inactivation is an early event in carcinogenesis."

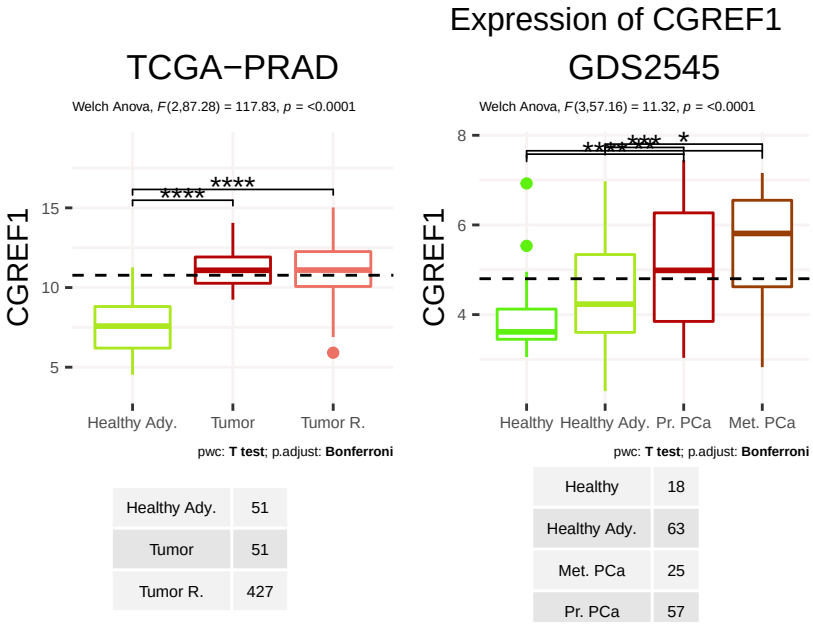
Naderi, A. SRARP and HSPB7 are epigenetically regulated gene pairs that function as tumor suppressors and predict clinical outcome in malignancies. Mol Oncol 2018, 12, 724–755.



Healthy Ady.	51
Tumor	51
Tumor R.	427

CGREF1 "Functional studies indicated that overexpression of CGREF1, or purified CGREF1 protein, can significantly inhibit the transcriptional activity of AP-1 and reduce phosphorylation of ERK (extracellular signal-regulated kinases) and p38 MAPK (mitogen-activated protein kinases), but not JNK/SAPK (c-JUN N-terminal/stress-activated protein kinase). Conversely, specific siRNAs against CGREF1 can activate the transcriptional activity of AP-1. Furthermore, overexpression of CGREF1 can repress cell proliferation, suggesting that CGREF1 might act as a repressor of the AP-1 signaling pathway and play a significant role in cell proliferation."

Deng, W.; Wang, L.; Xiong, Y.; Li, J.; Wang, Y.; Shi, T.; Ma, D. The novel secretory protein CGREF1 inhibits the activation of AP-1 transcriptional activity and cell proliferation. Int. J.Biochem.CellBiol. 2015, 65, 32–39.



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Met. PCa	25
Pr. PCa	57

UNC5A "The three mammalian receptors UNC5H1, UNC5H2, and UNC5H3 (also named UNC5A, UNC5B, and UNC5C in human) that belong to the family of the netrin-1 receptors, UNC5H, were initially proposed as mediators of the chemorepulsive effect of netrin-1 on specific axons. However, they were also recently shown to act as dependence receptors. Such receptors induce apoptosis when unbound to their ligand. We show here that the expression of the human UNC5A, UNC5B, or UNC5C is down-regulated in multiple cancers including colorectal, breast, ovary, uterus, stomach, lung, or kidney cancers. The loss/reduction of expression may be a crucial mechanism for tumorigenicity because the expression of UNC5H1, UNC5H2, or UNC5H3 inhibits tumor cell anchorage-independent growth and invasion. Moreover, these hallmarks of malignant transformation can be restored by netrin-1 addition or apoptosis inhibition. Hence, UNC5H1, UNC5H2, and UNC5H3 receptors may represent tumor suppressors that inhibit tumor extension outside the region of netrin-1 availability by inducing apoptosis."

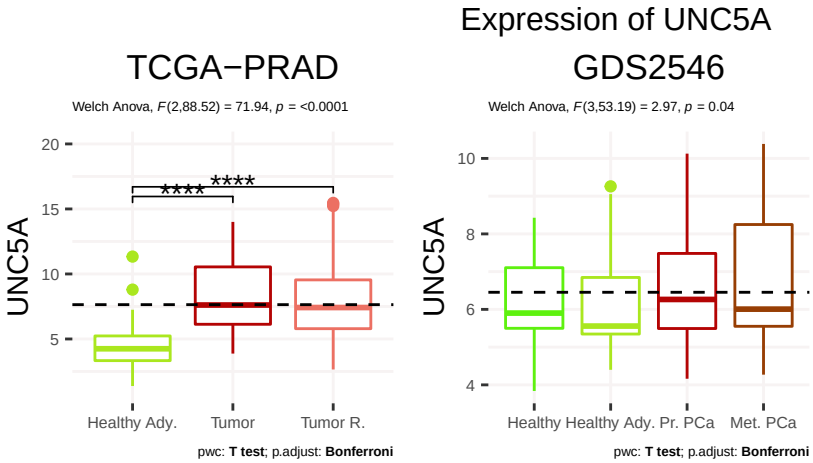
Thiebault, K.; Mazelin, L.; Pays, L.; Llambi, F.; Joly, M.O.; Scoazec, J.Y.; Saurin, J.C.; Romeo, G.; Mehlen,P.The netrin-1 receptors UNC5H are putative tumor suppressors controlling cell death commitment. Proc. Natl. Acad.Sci.U.S.A. 2003, 100, 4173–4178.

"Downregulation of UNC5A was responsible for tumorigenesis and phenotypes in BC [BLADDER CANCER]. Results from clinical samples and in vitro models provided evidence for the idea that UNC5A is a candidate tumor suppressor. Although data on a large number of patients with BC will be required in order to validate the preliminary results of our study. (. . .) Moreover, colony formation assay indicated that reexpression of UNC5A inhibited the survival of 5637 cells."

Zhu, Y.; Yu, M.; Chen, Y.; Wang, Y.; Wang, J.; Yang, C.; Bi, J. DNA damage-inducible gene, UNC5A, functions as a tumor-suppressor in bladder cancer. Tumor Biology. 2014, 35, 6887-6891.

"Consistent with in vitro results, UNC5A expression negatively correlated with EGFR expression in breast tumors, and lower expression of UNC5A, particularly in ERalpha+/PR+/HER2- tumors, was associated with poor outcome. (. . .) These studies reveal an unexpected role of the axon guidance receptor UNC5A in fine-tuning ERalpha and EGFR signaling and the luminal progenitor status of hormone-sensitive breast cancers. Furthermore, UNC5A knockdown cells provide an ideal model system to investigate metastasis of ERalpha+ breast cancers."

Padua, M.B.; Bhat-Nakshatri, P.; Anjanappa, M.; Prasad, M.S.; Hao, Y.; Rao, X.; Liu, S.; Wan, J.; Liu, Y.; McElyea, K.; Jacobsen, M.; Sandusky, G.; Althouse, S.; Perkins, S.; Nakshatri, H. Dependence receptor UNC5A restricts luminal to basal breast cancer plasticity and metastasis. Breast Cancer Res. 2018, 20,35



Healthy Ady.	51
Tumor	51
Tumor R.	427

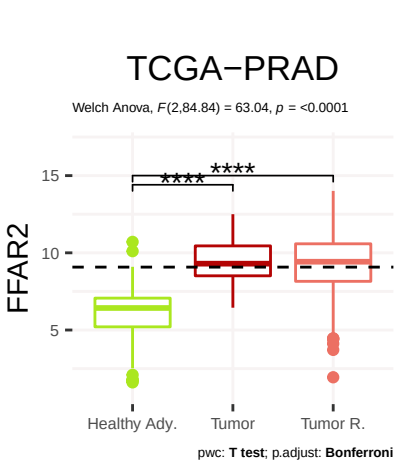
Healthy	17
Healthy Ady.	59
Met. PCa	25
Pr. PCa	66

FFAR2 "Our current study assessed whether FFAR2 deficiency drives the progression of colon cancer that is promoted by mild-inflammation. Our results suggest that FFAR2 is an important epigenetic tumor suppressor that blocks colon cancer progression (Figure 5). The downstream pathway of FFAR2, cAMP–PKA–CREB signaling, was overexpressed in the FFAR2-deficient mice, leading to overexpression of HDACs. Consequently, inflammation suppressors were hypermethylated, and their expression levels were decreased. Accordingly, our findings support the hypothesis that FFAR2 is a novel biomarker for colon cancer progression."

Pan, P.; Oshima, K.; Huang, Y.W.; Agle, K.A.; Drobyski, W.R.; Chen, X.; Zhang, J.; Yearsley, M.M.; Yu, J.; Wang, L.S. Loss of FFAR2 promotes colon cancer by epigenetic dysregulation of inflammation suppressors. Int. J.Cancer 2018, 143, 886–896.

"Restoration of GPR43 [=FFAR2] expression in HCT8 human colonic adenocarcinoma cells induced G0/G1 cell cycle arrest and activated caspases, leading to increased apoptotic cell death after propionate/butyrate treatment. (...) Our results suggest that GPR43 functions as a tumor suppressor by mediating SCFA-induced cell proliferation inhibition and apoptotic cell death in colon cancer."

Tang, Y.; Chen, Y.; Jiang, H.; Robbins, G.T.; Nie, D. G-protein-coupled receptor for short-chain fatty acids suppresses colon cancer. Int J Cancer. 2011, 128(4), 847-856.



Healthy Ady.	51
Tumor	51
Tumor R.	427

TGM3 "Following TGM3 inhibition and overexpression in CRC cells, it was revealed that TGM3 suppressed cell proliferation, potentially via the promotion of apoptosis and cell cycle regulation. Furthermore, TGM3 also inhibited invasion and metastasis. Finally, it was observed that TGM3 inhibited epithelial-to-mesenchymal transition and activated phosphorylated AKT serine/threonine kinase in CRC cells. The results from the present study revealed that TGM3 is a tumor suppressor in the progression of CRC, and may be used as a novel target for CRC treatment."

Feng, Y.; Ji, D. Huang, Y.; Ji, B.; Zhang, Y.; Li, J.; Peng, W.; Zhang, C.; Zhang, D.; Sun, Y.; Xu, Z. TGM3 functions as a tumor suppressor by repressing epithelial-to-mesenchymal transition and the PI3K/AKT signaling pathway in colorectal cancer. Oncol. Rep. 2020, 43, 864-876.

"We identified TGM3 to be overexpressed in HCC compared to normal tissues. Higher expression of TGM3 predicts poor prognosis in HCC patients. TGM3 knockdown led to decreased HCC cell proliferation, invasion, and xenograft tumour growth. TGM3 depletion inhibited AKT, extracellular signal–regulated kinase (ERK), p65, and glycogen synthase kinase 3beta (GSK3beta)/beta-catenin activation, but promoted levels of cleaved caspase 3. Moreover, TGM3 knockdown cells had increased E-cadherin levels and decreased vimentin levels, suggesting that TGM3 contributes to epithelial–mesenchymal transition (EMT) in HCC."

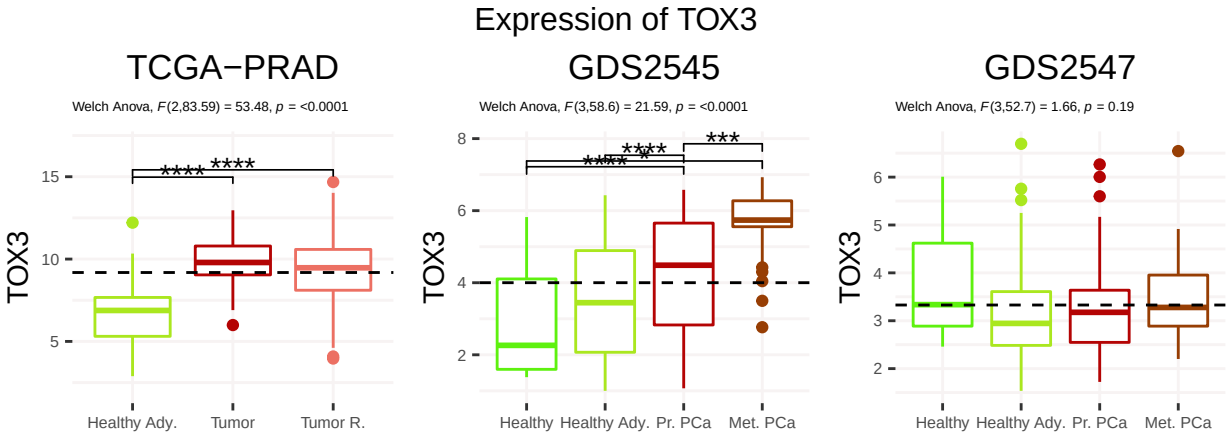
Hu, J.W.; Yang, Z.F.; Li, J.; Hu, B.; Luo, C.B.; Zhu, K.; Dai, Z.; Cai, J.B.; Zhan, H.; Hu, Z.Q.; Hu, J.; Cao, Y.; Qiu, S.J.; Zhou, J.; Fan, J.; Huang, X.W. TGM3 promotes epithelial-mesenchymal transition and hepatocellular carcinogenesis and predicts poor prognosis for patients after curative resection. Dig Liver Dis 2020, 52, 668–676.

TOX3 "TOX3 was identified as a novel cancer suppressor gene in ccRCC. Hypermethylation of CpG probes in the promoter region was associated with the functional loss of TOX3 in ccRCC cancer tissues. Downregulation of TOX3 mRNA was strongly associated with poor clinical outcomes in ccRCC. Mechanistic investigations showed that TOX3 deficiency facilitates the epithelial-mesenchymal transition due to impairment of transcriptional repression of SNAIL members SNAI1 and SNAI2 and promotes cancer cell migration and invasion. In vivo, restoring TOX3 expression reduced lung metastatic lesions and prolonged survival of mice. TOX3 combined with SNAI1 or SNAI2 predicted overall survival in ccRCC patients."

Jiang, B.; Chen, W.; Qin, H.; Diao, W.; Li, B.; Cao, W.; Zhang, Z.; Qi, W.; Gao, J.; Chen, M.; Zhao, X.; Guo ,H. TOX3 inhibits cancer cell migration and invasion via transcriptional regulation of SNAI1 and SNAI2 in clear cell renal cell carcinoma. Cancer Lett. 2019, 449, 76–86.

"High expression of this protein likely plays a crucial role in breast cancer progression. This is in sharp contrast to previous studies that indicated breast cancer susceptibility is associated with lower expression of TOX3. Together, these results suggest two different roles for TOX3, one in the initiation of breast cancer, potentially related to expression of TOX3 in mammary epithelial cell progenitors, and another role for this nuclear protein in the progression of cancer. In addition, these results can begin to shed light on the reported association of TOX3 expression and breast cancer metastasis to the bone, and point to TOX3 as a novel regulator of estrogen receptor-mediated gene expression."

Seksenyan, A.; Kadavallore, A.; Walts, A.E.; delaTorre, B.; Berel, D.; Strom, S.P.; Aliahmad, P.; Funari, V.A.; Kaye, J. TOX3 is expressed in mammary ER (+) epithelial cells and regulates ER target genes in luminal breast cancer. BMC Cancer 2015, 15, 22.



Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

Healthy	17
Healthy Ady.	58
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Pr. PCa	64

Under-expressed in tumor with regard to healthy samples

C16orf74 "Overexpression of C16orf74 protein detected by immunohistochemical analysis was an independent prognostic factor for patients with PDAC [pancreatic ductal adenocarcinoma]. The knockdown of endogenous C16orf74 expression in the PDAC cell lines KLM-1 and PK-59 by vector-based small hairpin-RNA (shRNA) drastically attenuated the growth of those cells, whereas ectopic C16orf74 overexpression in HEK293T and NIH3T3 cells promoted cell growth and invasion, respectively.

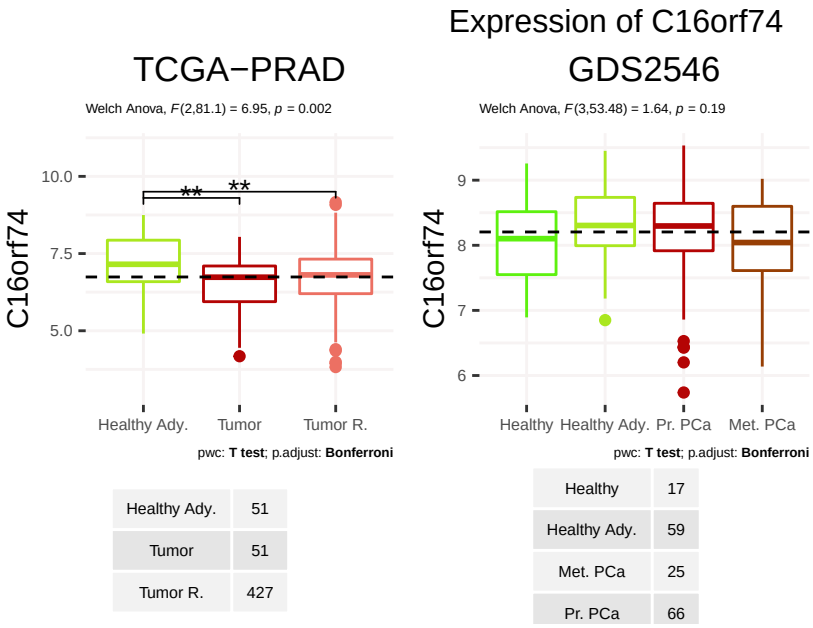
Nakamura, T.; Katagiri, T.; Sato, S.; Kushibiki, T.; Hontani, K.; Tsuchikawa, T.; Hirano, S.; Nakamura, Y. Overexpression of C16orf74 is involved in aggressive pancreatic cancers. Oncotarget 2017, 8, 50460-50475.

"Among the genes upregulated in STS [short-term survivors] (...) C16orf74 (...) are involved in NF-KB-mediated cell signaling, and (...) C16orf74 (...) in epithelial–mesenchymal transition.(...) Associated with poor OS in pancreatic cancer."

Birnbaum, D.J.; Finetti, P.; Lopresti, A.; Gilabert, M.; Poizat, F.; Raoul, J.L.; Delpero, J.R.; Moutardier, V.; Birnbaum, D.; Mamessier, E.; Bertucci, F. A 25-gene classifier predicts overall survival in resectable pancreatic cancer. BMC Med 2017, 15, 170.

"HAND2-AS1 overexpression suppressed the proliferation, colony formation, migration and invasion of cervical cancer cells. (...) This study provided evidence on the inhibitory effect of HAND2-AS1 on the development of cervical cancer through the suppression of C16orf74 expression by recruiting transcription factor E2F4."

Gong, J.; Fan, H.; Deng, J.; Zhang, Q. LncRNA HAND2-AS1 represses cervical cancer progression by interaction with transcription factor E2F4 at the promoter of C16orf74. J Cell Mol Med. 2020, 24(11), 6015-5027.



Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	17
Healthy Ady.	59
Met. PCa	25
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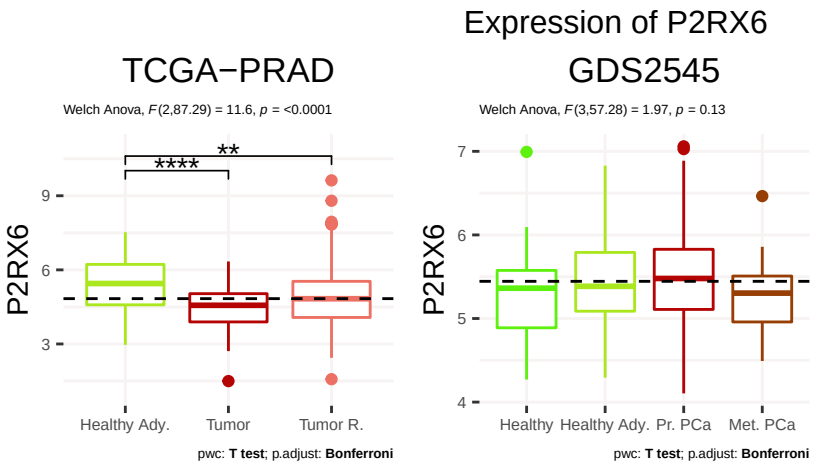
P2RX6 "Here, we found that P2RX6, a preferred receptor for ATP, contributed to the invasion and metastasis of RCC cells. (. . .) our preclinical studies using multiple in vitro cell lines and in vivo mouse models as well as human clinical studies all suggest that ATP-P2RX6-Ca2+ -p-ERK1/2-MMP9 axis facilitate RCC migration and invasion."

Gong, D.; Zhang, J.; Chen, Y.; Xu, Y.; Ma, J.; Hu, G.; Huang, Y.; Zheng, J. ;Zhai, W.; Xue, W. The m6A-suppressed P2RX6 activation promotes renal cancer cells migration and invasion through ATP-induced Ca2+ influx modulating ERK1/2phosphorylation and MMP9 signaling pathway. J. Exp. Clin. CancerRes. 2019, 38, 233.



Healthy Ady.	51
Tumor	51
Tumor R.	427

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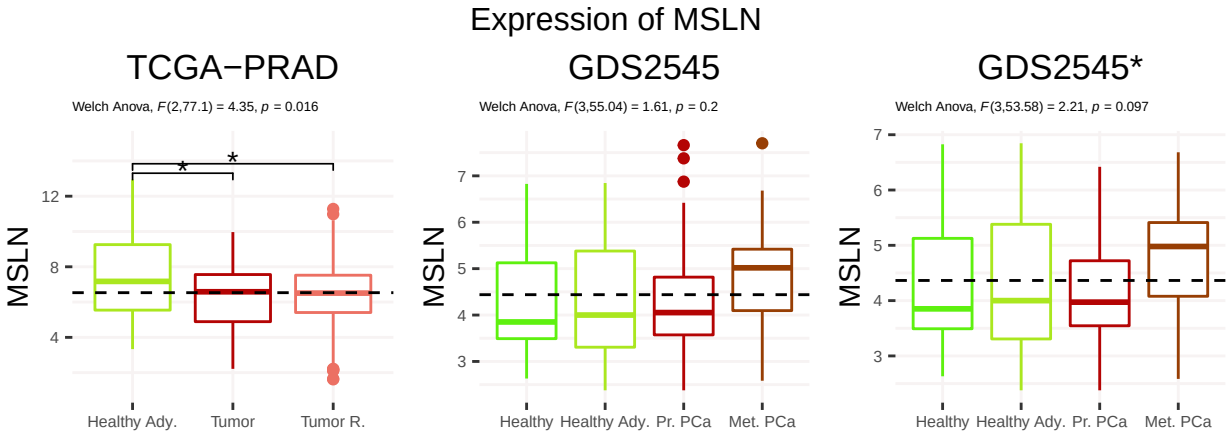
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

MSLN "Mesothelin (MSLN), a tumor-associated antigen broadly overexpressed on various malignant tumor cells, while its expression is generally limited to normal mesothelial cells, is an attractive candidate for targeted therapy. (. . .) MSLN has also been identified as a receptor of CA125 that mediates cell adhesion [6]. The interaction of CA125 and MSLN play an important role in ovarian cancer cell peritoneal implantation and increase the motility and invasion of pancreatic carcinoma cells (. . .). The overexpression of MSLN could activate the NFKB, MAPK, and PI3K pathways and subsequently induce resistance to apoptosis or promote cell proliferation, migration, and metastasis by inducing the activation and expression of MMP7 and MMP9. An increase in tumor burden and poor overall survival are associated with elevated MSLN expression according to clinical observations

Lv, J.; Li, P. Mesothelin as a biomarker for targeted therapy. Biomark Res 2019, 7, 18.

"Firstly, MSLN was found to be highly upregulated in non-small cell lung cancer (NSCLC) patient tissues and in lung carcinoma and mesothelioma cell lines. Secondly, genetic knockdown of MSLN significantly reduced anchorage-independent cell growth, tumor sphere formation, cell adhesion, migration and invasion in vitro, as well as tumor formation and metastasis in vivo. Thirdly, ectopic overexpression of MSLN induced the malignant phenotype of non-cancerous cells, supporting its role as an oncogene. Finally, mechanistic studies revealed that knockdown of MSLN reversed EMT and attenuated stem cell properties, in addition to inhibiting tumor growth and metastasis."

He, X.; Wang, L.; Riedel, H.; Wang, K.; Yang, Y.; Dinu, C.Z.; Rojanasakul, Y. Mesothelin promotes epithelial-to-mesenchymal transition and tumorigenicity of human lung cancer and mesothelioma cells. Mol Cancer. 2017, 16(1), 63.



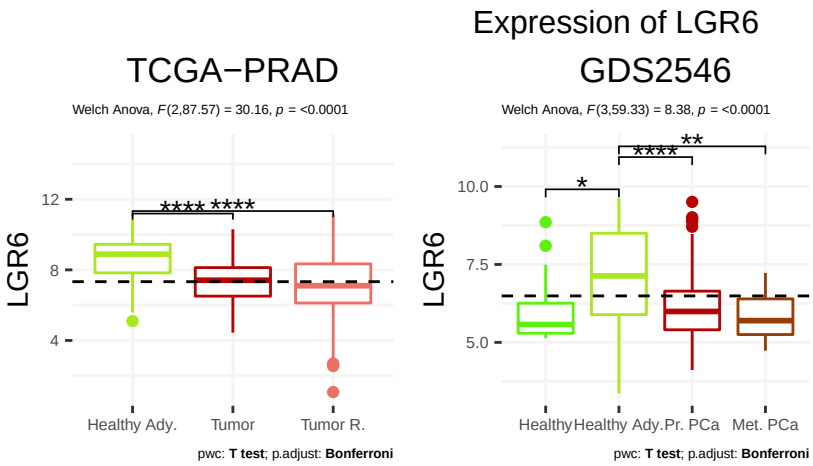
Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

Healthy	18
Healthy Ady.	63
Met. PCa	24
Pr. PCa	54

LGR6 "The results demonstrated that the level of Lgr6 was higher in CRC tissues than that in adjacent tissues, and Lgr6 overexpression increased CRC proliferation, and invasion of CRC cells in vitro. Notably, suppressing the expression of Lgr6 in CRC cells increased the expression of B-cell lymphoma-2 (Bcl-2)-associated X protein and caspase-3, but decreased the expression of Bcl-2 at the mRNA and protein levels. Lgr6 also had the ability to regulate the phosphoinositide 3-kinase/AKT signaling pathway. It was concluded that Lgr6 has a tumor-promoting role in the development of CRC"

Wang, F.; Dai, C.Q.; Zhang, L.R.; Bing, C.; Qin, J.; Liu, Y.F. Downregulation of Lgr6 inhibits proliferation and invasion and increases apoptosis in human colorectal cancer. Int. J.Mol.Med. 2018, 42, 625–632.

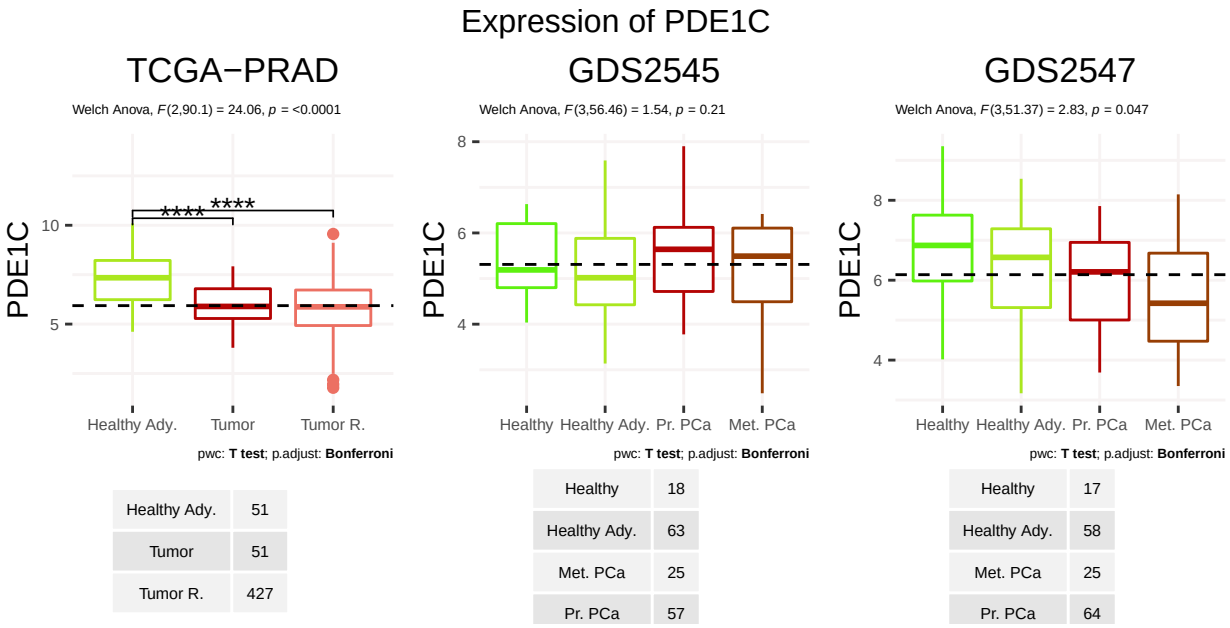


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	17
Healthy Ady.	59
Met. PCa	25
Pr. PCa	66

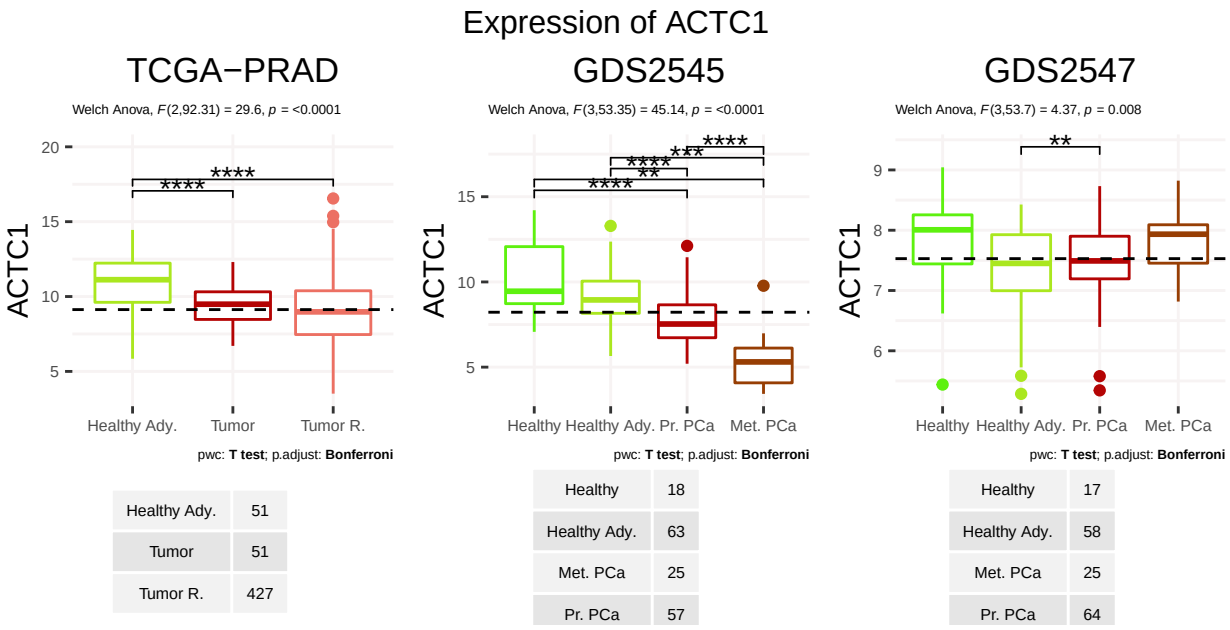
PDE1C "We demonstrate that PDE1C is essential in driving cell proliferation, migration and invasion in GBM cultures since silencing of this gene significantly mitigates these functions. We also define the mechanistic basis of this functional effect through whole genome expression analysis by identifying downstream gene effectors of PDE1C which are involved in cell cycle and cell adhesion regulation. In addition, we also demonstrate that Vinpocetine, a general PDE1 inhibitor, can also attenuate proliferation with no effect on invasion/migration."

Rowther, F.B.; Wei, W.; Dawson, T.P.; Ashton, K.; Singh, A.; Madiesse-Timchou, M.P.; Thomas, D.G.; Darling, J.L.; Warr, T. Cyclic nucleotide phosphodiesterase-1C (PDE1C) drives cell proliferation, migration and invasion in glioblastoma multiforme cells in vitro. Mol. Carcinog. 2016, 55, 268–279.



ACTC1 "ACTC1-positive GBMs indicated poorer prognosis compared with ACTC1-negative GBMs."

Ohtaki, S.; Wanibuchi, M.; Kataoka-Sasaki, Y.; Sasaki, M.; Oka, S.; Noshiro, S.; Akiyama, Y.; Mikami, T.; Mikuni, N.; Kocsis, J.D.; Honmou, O. ACTC1 as an invasion and prognosis marker in glioma. J. Neurosurg. 2017, 126, 467–475.



Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

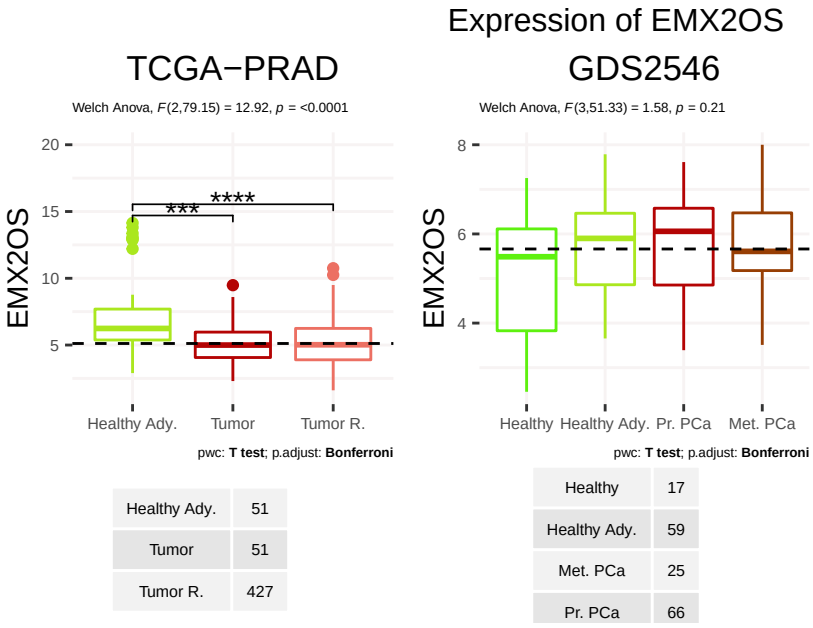
Healthy	17
Healthy Ady.	58
Met. PCa	25
Pr. PCa	64

EMX2OS "EMX2OS is overexpressed in human ovarian cancer tissues. Knockdown of EMX2OS reduced, while overexpression of EMX2OS enhanced the proliferation, invasion and sphere formation of OC cells. (. . .) We discovered that EMX2OS directly binds to miR-654 and suppresses its expression, thus leading to the upregulation of AKT3, which served as a direct target of miR-654. Moreover, miR-654 inhibited cell proliferation, invasion and sphere formation, and restoration of AKT3 reversed the effects of EMX2OS silencing or miR-654 overexpression. Furthermore, PD-L1 was identified as the key oncogenic component acting downstream of AKT3 in OC cells. Ectopic expression of PD-L1 reversed the anti-cancer functions by EMX2OS knockdown, AKT3 silencing or miR-654 upregulation in OC cells."

Duan, M.; Fang, M.; Wang, C.; Wang, H.; Li, M. LncRNA EMX2OS Induces Proliferation, Invasion and Sphere Formation of Ovarian Cancer Cells via Regulating the miR-654-3p/AKT3/PD-L1 Axis. Cancer Manag Res 2020, 12, 2141–2154.

"Based on the findings, we infer that decreased EMX2OS expression might be a valuable prognostic biomarker of unfavorable RFS [RECURRANCE FREE SURVIVAL] in classical PTC [PAPILLARY THYROID CANCER]."

Gu, Y.; Feng, C.; Liu, T.; Zhang, B.; Yang, L. The downregulation of lncRNA EMX2OS might independently predict shorter recurrence-free survival of classical papillary thyroid cancer. PLos One. 2018, 13(12).

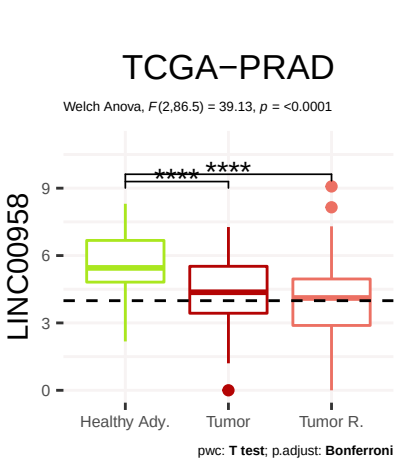


LINC00958 "LINC00958 was found notably overexpressed in LAD, which was associated with the stimulation of its promoter activity induced by SP1. LINC00958 depletion dramatically inhibited LAD cell proliferation, migration and invasion capacities by acting as a miR-625-5p sponge. MiR-625-5p curbed LAD progression via targeting CPSF7 and down-regulating its expression. Mechanically, LINC00958 was identified as a competing endogenous RNA (ceRNA) and positively regulated the expression of CPSF7 via sponging miR-625-5p."

Yang, L.; Li, L.; Zhou, Z.; Liu, Y.; Sun, J.; Zhang, X.; Pan, H.; Liu, S. SP1 induced long non-coding RNA LINC00958 overexpression facilitate cell proliferation, migration and invasion in lung adenocarcinoma via mediating miR-625-5p/CPSF7axis. Cancer CellInt. 2020, 20, 24.

"LINC00958 knockdown represses EMT, invasion, and metastasis of PC [PANCREATIC CANCER] cells via the down-regulation of miR-330-5p/PAX8 axis (Fig. 7). Therefore, the identification of LINC00958 via miR-330-5p/PAX8 in PC cells may aid in facilitating the existing understanding of the mechanisms of PC, with potential of serving as a prognostic marker for the treatment of PC in the future."

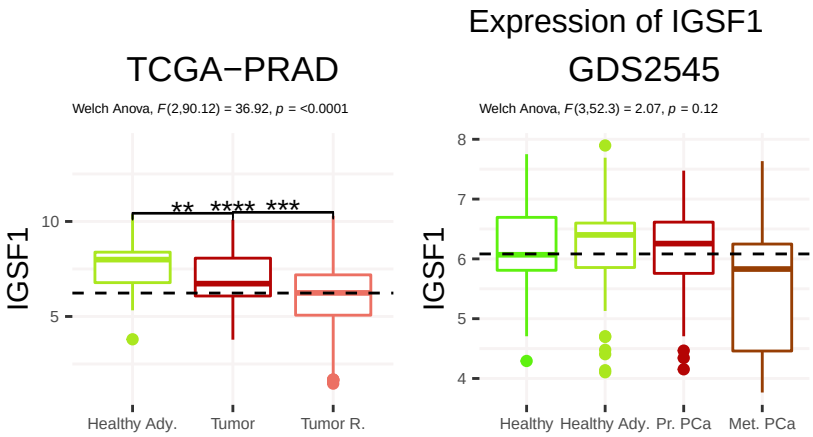
Chen, S.; Chen, J.Z.; Zhang, J.Q.; Chen, H.X.; Qui, F.N.; Yan, M.L.; Tian, Y.F.; Peng, C.H.; Shen, B.Y.; Chen, Y.L.; Wang, Y.D. Silencing of long noncoding RNA LINC00958 prevents tumor initiation of pancreatic cancer by acting as a sponge of microRNA-330-5p to down-regulate PAX8. Cancer Lett. 2019, 1, 446-449.



Healthy Ady.	51
Tumor	51
Tumor R.	427

IGSF1 "Loss-of-function analysis showed that IGSF1 knockdown could inhibit the cell proliferation and significantly impair the migration and invasion in vitro. Wnt signalling is frequently activated in a variety of tumours and be essential for tumourigenic properties. Our results demonstrated that silencing of IGSF1 would inhibit the expression of N-cadherin, EZH2, and vimentin. Results of our study shared downregulated IGSF1 expression in thyroid cancer cell line can inhibit cell metastasis by EMT."

Guan, Y.; Wang, Y.; Bhandari, A.; Xia, E.; Wang, O. IGSF1: A novel oncogene regulates the thyroid cancer progression. Cell Biochem.Funct. 2019, 37, 516–524.



Healthy Ady.	51
Tumor	51
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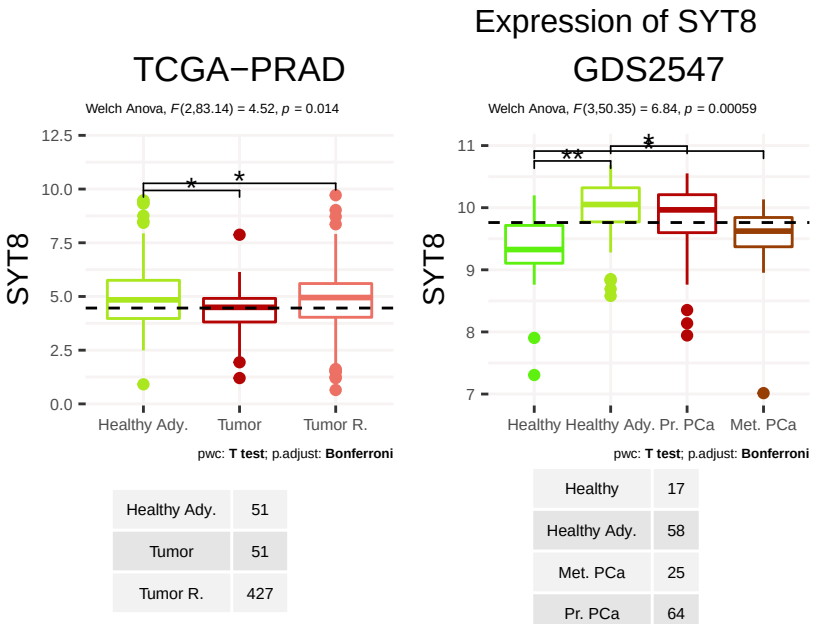
Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

SYT8 "SYT8 levels above the cut-off value were significantly and specifically associated with peritoneal metastasis, and served as an independent prognostic marker for peritoneal recurrence-free survival of patients with stage II/III GC. The survival difference between patients with SYT8 levels above and below the cut-off was associated with patients who received adjuvant chemotherapy. Inhibition of SYT8 expression by GC cells correlated with decreased invasion, migration, and fluorouracil resistance. Intraperitoneal administration of SYT8-siRNA inhibited the growth of peritoneal nodules and prolonged survival of mice engrafted with GC cells."

Kanda, M.; Shimizu, D.;Tanaka,H.; Tanaka, C.; Kobayashi, D.; Hayashi, M.; Iwata, N.; Niwa, Y.; Yamada, S.; Fujii, T.; Sugimoto, H.; Murotani, K.; Fujiwara, M.; Kodera, Y. Significance of SYT8 For the Detection, Prediction, and Treatment of Peritoneal Metastasis From Gastric Cancer. Ann. Surg. 2018, 267, 495–503.



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Tumor	51
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Healthy	17
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Met. PCa	25
Pr. PCa	64

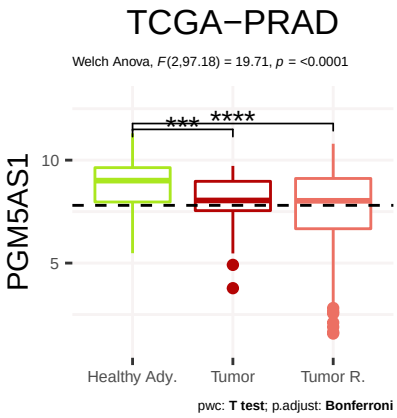
PGM5AS1 "PGM5-AS1 was upregulated in CRC tissues and cell lines; however, its downregulation contributed to the decreasing of cell viability, growth, migration, and invasion of SW480 and HCT116 cells. (. . .) The loss of miR-484 expression in CRC might be involved in the promotion and metastasis of CRC, which may be caused by the overexpression of PGM5-AS1. Hence, the downregulation of PGM5-AS1 could be a therapeutic target in the prevention or intervention of CRC."

Shen, Y.; Qi, L.; Li, Y.; Zhang, Y.; Gao, X.; Zhu, Y.; Wang, K. The Downregulation of lncRNA PGM5-AS1 Inhibits the Proliferation and Metastasis Via Increasing miR-484 Expression in Colorectal Cancer. Cancer Biother.Radiopharm. 2020.

"“Functional experiments revealed that exogenous expression of PGM5-AS1 significantly suppressed the proliferation, migration, and invasion of ESCC cells in vitro as well as tumor growth in vivo. Mechanistically, PGM5-AS1 was transcriptionally activated by p53 and it could directly interact with and sequester miR-466 to elevate PTEN expression, thereby inhibiting ESCC progression."

Zhihua, Z.; Weiwei, W.; Lihua, N.; Jianying, Z.; Jiang, G. p53-induced long non-coding RNA PGM5-AS1 inhibits the progression of esophageal squamous cell carcinoma through regulating miR-466/PTENaxis. IUBMB Life 2019, 71, 1492–1502.

Expression of PGM5AS1



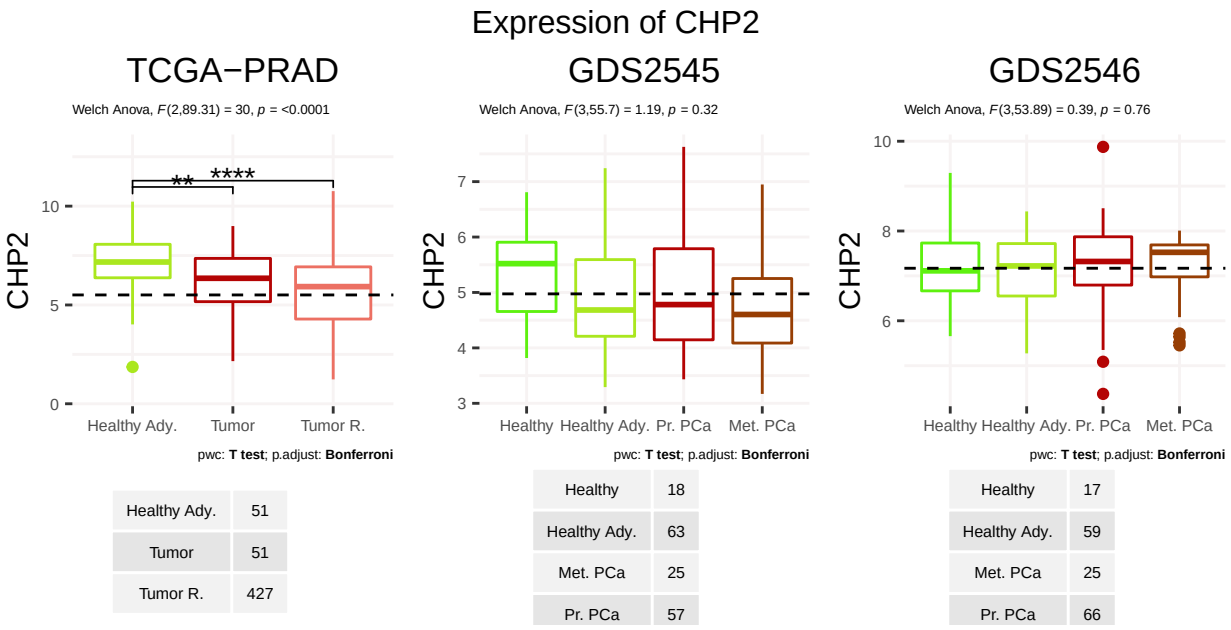
Healthy Ady.	51
Tumor	51
Tumor R.	427

CHP2 "Moreover, it was demonstrated that overexpressing CHP2 significantly enhanced, whereas silencing endogenous CHP2 inhibited, the proliferation and tumorigenicity of breast cancer cells in vitro and in vivo. In addition, overexpression of CHP2 accelerated, whereas inhibition of CHP2 retarded, G1–S phase cell-cycle transition in breast cancer cells. Mechanistically, overexpression of CHP2 activated AKT signaling and suppressed the transactivation of the forkhead box O3 (FOXO3/FOXO3a) transcription factor."

Zhao, X.; Xie, T.; Dai, T.; Zhao, W.; Li, J.; Xu, R.; Jiang, C.; Li, P.; Deng, J.; Su, X.; Ma, N. CHP2 Promotes Cell Proliferation in Breast Cancer via Suppression of FOXO3a. Mol. CancerRes. 2018, 16, 1512–1522.

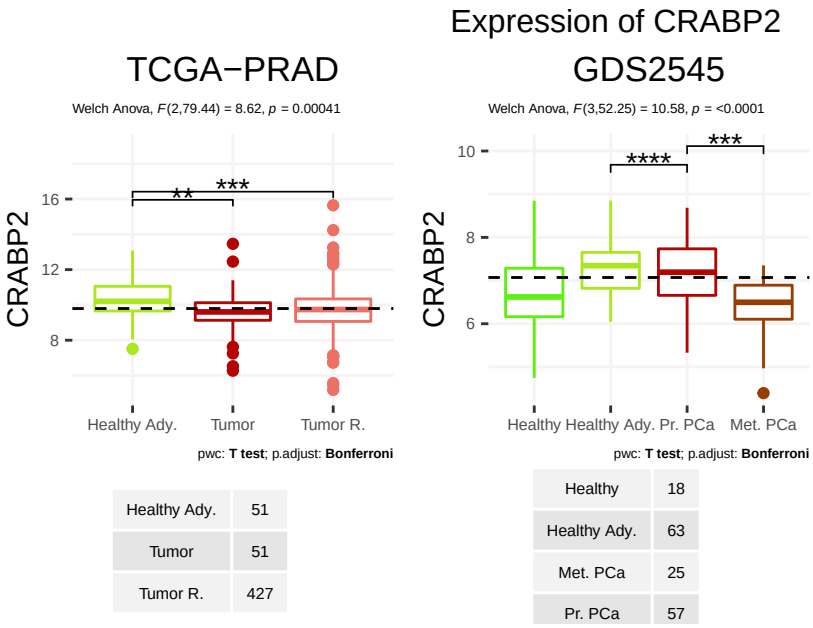
"CHP2-transfected OVCAR3/CHP2 cells showed increased proliferation rates and exhibited increased activities of cell adhesion, migration and invasion. The current study provides the first evidence that overexpression of the CHP2 gene affects the biological behavior of ovarian cancer cell line OVCAR3 and is one of key mechanisms for ovarian carcinoma progression, suggesting that CHP2 may be an attractive target for biological anticancer therapy."

Jin, Q.; Kong, B.; Yang, X.; Cui, B.; Wei, Y.; Yang, Q. Overexpression of CHP2 enhances tumor cell growth, invasion and metastasis in ovarian cancer. In VIvo, 2007, 21(4), 593-598.



CRABP2 "Although overexpression of CRABP2 is described in several cancers, it has not yet been studied in MPNSTs. (. . .) Knockdown of CRABP2 in MPNSTs that resulted in reduced viability and proliferation. Its loss reduces viability and proliferation and induces apoptosis, cytotoxicity and interferon-signaling in malignant peripheral nerves heath tumors. (. . .) We found expression of CRABP2 in human tumor Schwann cells and that loss of CRABP2 in MPNSTs reduces viability and proliferation but induces apoptosis, cytotoxicity, and interferon-alpha signaling. This study suggests that CRABP2 may be mandatory for cell survival."

Fischer-Huchzermeyer, S.; Dombrowski, A.; Hagel, C.; Mautner, V.F.; Schittenhelm, J.; Harder, A. The Cellular Retinoic Acid Binding Protein 2 Promotes Survival of Malignant Peripheral Nerve Sheath Tumor Cells. Am. J.Pathol. 2017, 187, 1623–1632.

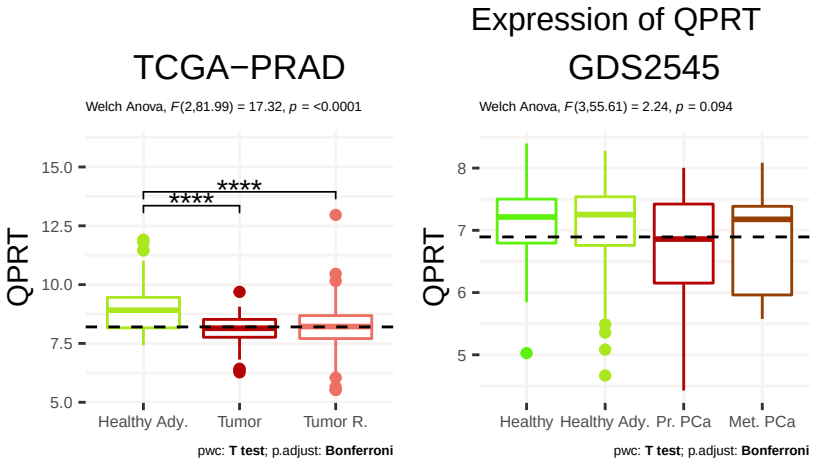


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

QPRT "QPRT was identified as a caspase-3 binding protein using double layer fluorescent zymography, but was not a substrate for caspase-3. (. . .) Depletion of QPRT resulted in increases in active-caspase-3 with a resultant increase in spontaneous cell death. Such a role poses an alternative function for QPRT protein in addition to its key role in de novo NAD+ synthesis."

Ishidoh, K.; Kamemura, N.; Imagawa, T.; Oda, M.; Sakurai, J.; Katunuma, N. Quinolinate phosphoribosyl transferase, a key enzyme in de novo NAD(+) synthesis, suppresses spontaneous cell death by inhibiting over production of active-caspase-3. Biochim. Biophys.Acta 2010, 1803, 527–533.

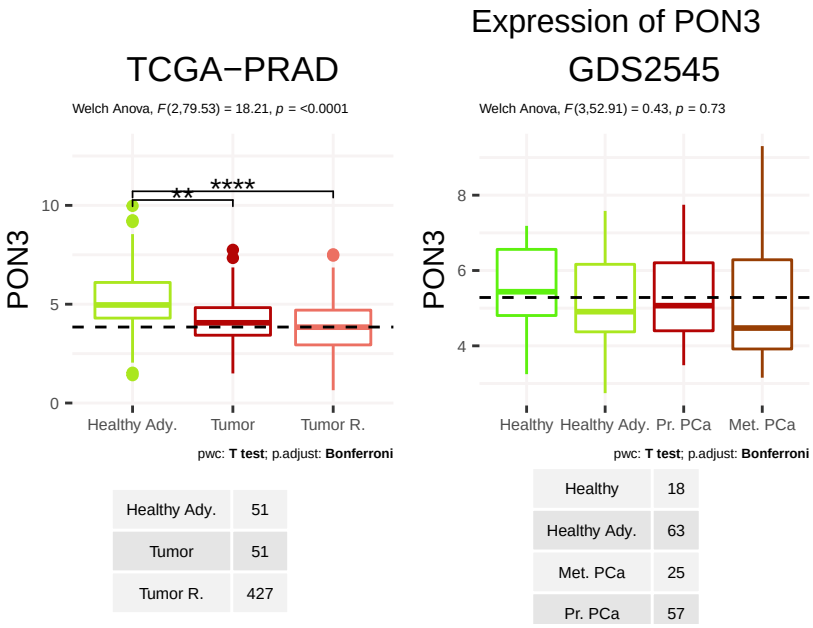


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

PON3 "PON3 is found overexpressed in various human tumors and diminishes mitochondrial superoxide formation. It directly interacts with coenzyme Q10 and presumably acts by sequestering ubisemiquinone, leading to enhanced cell death resistance. Localized to the endoplasmic reticulum (ER) and mitochondria, PON3 abrogates apoptosis in response to DNA damage or intrinsic but not extrinsic stimulation. (...) In concordance with the effect of PON3 on JNK/CHOP, and CHOP's role in cell death, PON3 also abrogated tunicamycin-induced cell death, that is, caspase-3 activation."

Schweikert, E.M.; Devarajan, A.; Witte, I.; Wilgenbus, P.; Amort, J.; Förstermann, U.; Shabazian,A.; Grijalva, V.; Shih, D.M.; Farias-Eisner, R.; Teiber, J.F.; Reddy, S.T.; Horke, S. PON3 is upregulated in cancer tissues and protects against mitochondrial superoxide-mediated cell death. Cell DeathDiffer. 2012, 19, 1549-1560.

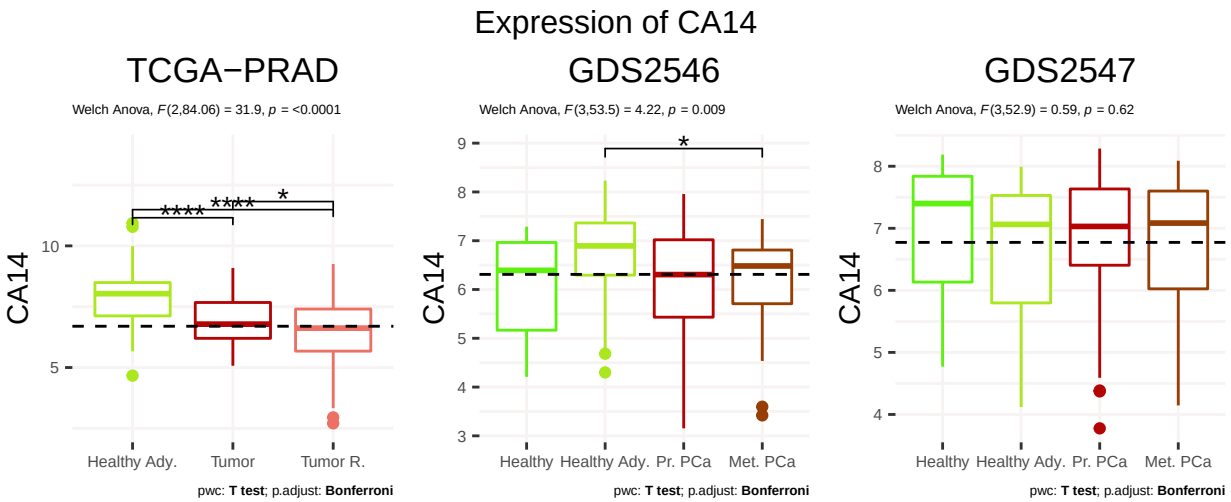


Healthy Ady.	51
Tumor	51
Tumor R.	427

Healthy	18
Healthy Ady.	63
Met. PCa	25
Pr. PCa	57

CA14 It is usually upregulated in cancer and linked with deacidification.

Xu, K.; Mao, X.; Mehta, M.; Cui, J.; Zhang, C.; Mao, F.; Xu, Y. Elucidation of how cancer cells avoid acidosis through comparative transcriptomic data analysis. PLoS ONE 2013, 8, e71177.



Healthy Ady.	51
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Healthy	17
Healthy Ady.	59
Met. PCa	25
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Healthy	17
Healthy Ady.	58
Met. PCa	25
Pr. PCa	64