AKT1 and MYC Induce Distinctive Metabolic Fingerprints in Human Prostate Cancer

Carmen Priolo\textsuperscript{1,a}, Saumyadipta Pyne\textsuperscript{1,b}, Joshua Rose\textsuperscript{1}, Erzsébet Ravasz Regan\textsuperscript{3}, Giorgia Zadra\textsuperscript{1}, Cornelia Photopoulou\textsuperscript{1}, Stefano Cacciatore\textsuperscript{1}, Denise Schultz\textsuperscript{4}, Natalia Scaglia\textsuperscript{1}, Jonathan McDunn\textsuperscript{5}, Angelo M. De Marzo\textsuperscript{4}, Massimo Loda\textsuperscript{1,2,6,7}

Departments of \textsuperscript{1}Medical Oncology, \textsuperscript{2}Pathology, Dana-Farber Cancer Institute, Brigham and Women’s Hospital, and \textsuperscript{3}Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston; \textsuperscript{4}Pathology, Johns Hopkins University, Baltimore; \textsuperscript{5}Metabolon Inc., Durham, NC, \textsuperscript{6}The Broad Institute, Cambridge, MA, \textsuperscript{7}Division of Cancer Studies, King’s College London, UK.

Current affiliations: \textsuperscript{a}Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston; and \textsuperscript{b} C.R. Rao Advanced Institute of Mathematics, Statistics and Computer Science, Hyderabad; Public Health Foundation of India, Delhi, India.

Running title: Metabolic classification of prostate cancer

Keywords: Metabolomics, mass-spectrometry, glucose and lipid metabolism, KEGG, prostate cancer.

Correspondence: Massimo Loda, Dana-Farber Cancer Institute, D1536 450 Longwood Avenue, Boston, MA 02115; massimo_loda@dfci.harvard.edu

Word count: 3168; Number of figures: 4
Abstract

Cancer cells may overcome growth factor dependence by deregulating oncogenic and/or tumor suppressor pathways that affect their metabolism, or by activating metabolic pathways de novo with targeted mutations in critical metabolic enzymes.

It is unknown whether human prostate tumors develop a similar metabolic response to different oncogenic drivers or a particular oncogenic event results in its own metabolic reprogramming.

Akt and Myc are arguably the most prevalent driving oncogenes in prostate cancer. Mass spectrometry-based metabolite profiling was performed on immortalized human prostate epithelial cells transformed by AKT1 or MYC, transgenic mice driven by the same oncogenes under the control of a prostate-specific promoter, and human prostate specimens characterized for the expression and activation of these oncoproteins. Integrative analysis of these metabolomic datasets revealed that AKT1 activation was associated with accumulation of aerobic glycolysis metabolites, whereas MYC overexpression was associated with dysregulated lipid metabolism. Selected metabolites that differentially accumulated in the MYC-high vs. AKT1-high tumors, or in normal vs. tumor prostate tissue by untargeted metabolomics, were validated using absolute quantitation assays. Importantly, the AKT1/MYC status was independent of Gleason grade and pathologic staging.

Our findings show how prostate tumors undergo a metabolic reprogramming which reflects their molecular phenotypes, with implications for the development of metabolic diagnostics and targeted therapeutics.

Précis: Findings may pave the way for a metabolic classification of prostate tumors that is complementary to genomics and signaling pathway analyses, with implications for the development of metabolic diagnostics and targeted therapeutics.
### Introduction

Metabolomics allows unbiased identification of subtle changes in metabolite profiles as affected by signaling pathways or genetic factors (1-3). Metabolic alterations may represent the integration of genetic regulation, enzyme activity, and metabolic reactions. In addition, since the known metabolome is considerably smaller than the number of genes, transcripts, or proteins, metabolomics may more clearly characterize altered cellular networks (4). Clinically, metabolic imaging technologies such as positron emission tomography, can be used to monitor disease progression and drug response (5).

Genomic loss of the PTEN locus, leading to constitutively active PI3K/AKT pathway, and 8q amplification including the MYC gene, occur in 30-70% and ~30% of prostate tumors, respectively (6), representing the most frequent genetic alterations in prostate cancer. Both activated AKT and in particular MYC overexpression faithfully reproduce the stages of human prostate carcinogenesis in genetically engineered mice (7, 8).

While MYC promotes glutaminolysis (9, 10), AKT activation is associated with enhanced aerobic glycolysis (the “Warburg effect” (11)), and/or increased expression of glycolytic enzymes in different cell types, including prostate (12). However, the impact of these oncogenes (or the genomic alterations causing their activation) on the metabolome of human prostate tumors has not yet been elucidated.

### Materials and Methods

#### Generation of AKT1-and MYC-overexpressing RWPE-1

Immortalized human prostate epithelial RWPE-1 cells were obtained from Novartis (Basel, Switzerland) and confirmed to be nontumorigenic (growth in soft agar) before performing the
experiments. RWPE-1 were authenticated by DDC Medical. Cells were infected with pBABE vector alone (RWPE-EV), myristoylated AKT1 (RWPE-AKT1) or MYC (RWPE-MYC). Briefly, cells were transduced through infection in the presence of polybrene (8 μg/mL), and retroviral supernatants were replaced with fresh media after 4 hours of incubation. Twenty-four hours later, puromycin selection (1 μg/mL) was started. Cells were grown in phenol red-free Minimum Essential Media (MEM) supplemented with 10% Fetal Bovine Serum (FBS), 0.1 mM non-essential amino acids, 1 mM sodium pyruvate and penicillin-streptomycin (Gibco, Life Technologies).

**Transgenic mice**

Ventral prostate lobes were isolated from 12-13 week-old MPAKT (FVB-Tg[Pbsn-AKT1]9Wrs/Nci) (7) and Lo-Myc (FVB-Tg[Pbsn-MYC]6Key/Nci) (8) transgenic mice and from age-matched wild-type mice (FVB/N) within 10 minutes after CO2 euthanasia. Animals’ care was in accordance with institutional guidelines (IACUC). MPAKT mice were generated and raised at the Dana-Farber Cancer Institute’s Facility (7). Lo-MYC and wild-type mice were obtained from the NCI Fredrick mouse repository and raised at the Johns Hopkins University’s Facility (13).

**Human prostate tissues**

Institutional Review Board-approved, fresh-frozen, radical prostatectomy samples were obtained from the Institutional tissue repository at the Dana-Farber Cancer Institute/Brigham and Women’s Hospital (61 tumors and 25 normals).
Percent tumor was assessed by top and bottom frozen sections. To obtain \( \geq 80\% \) tumor purity, normal tissue was trimmed and the tumor sample was re-embedded in OCT without thawing. Two-three eight-\( \mu \)m sections were cut from these tissue blocks and DNA, RNA, and proteins were purified (AllPrep DNA/RNA Micro Kit [Qiagen Inc.]). The remainder was processed for metabolite extraction (Fig. S1C).

**Metabolite profiling**

RWPE-EV, RWPE-AKT1 and RWPE-MYC cells in monolayer culture were trypsinized for 4 minutes at 37ºC. Following trypsin neutralization with 10% FBS-supplemented MEM, cells were centrifuged, cell pellets were washed twice with cold PBS before freezing. A recovery standard was added prior to the first step in the extraction process for QC purposes. Aqueous methanol extraction was used to remove the protein fraction. The resulting extract was divided into fractions for analysis by UPLC/MS/MS (positive mode), UPLC/MS/MS (negative mode), and GC/MS. Samples were placed on a TurboVap® (Zymark) to remove the organic solvent. Each sample was frozen and dried under vacuum (see also supplementary material).

**Absolute quantitation of metabolites**

Sufficient material was available in 56 of the human prostate tissue samples (40 tumors; 16 normals) for untargeted metabolite profiling. Oleic, arachidonic, and docosahexaenoic acids, creatine and 2-aminoadipic acid were measured using specific internal standards (see also supplementary material). Absolute values were expressed as \( \mu g/g \) tissue. Results were analyzed using the Mann-Whitney Test, and significance was defined with \( p<0.05 \).
mRNA expression analysis

Total RNA was isolated from RWPE-EV, RWPE-AKT1 and RWPE-MYC cells (RNeasy Micro Kit, Qiagen Inc., CA), prostate tumors and normal controls (AllPrep DNA/RNA Micro Kit, Qiagen Inc.). Real time PCR was performed using custom micro fluidic cards (Taqman Custom Arrays, Applied Biosystems). The list of the probes and primers is provided in Text S1. One-sample T-Test was applied using GraphPad Prism 5.0, and significance was defined with p<0.05 (see also supplementary material).

Immunohistochemistry

Immunohistochemistry for MYC, stathmin, GLUT-1, and phosphoAKT1 was performed on formalin-fixed paraffin-embedded tissue samples. Immunostaining of human tumors was scored microscopically counting the percentage of positive cells (higher or lower than 50%). The entire section was evaluated and 5 representative areas at 20x magnification were counted for an average of 500 cells per section. Fisher Test was applied using GraphPad Prism 5.0, and significance was defined with p<0.05 (see also supplementary material).

Results and Discussion

To focus on an oncogene-specific context while profiling the metabolic heterogeneity of prostate cancer, we integrated phosphorylated AKT1- or MYC–associated metabolomic signatures from prostate epithelial cells in monolayer culture, transgenic mouse prostate and primary nonmetastatic prostate tumors (Fig. 1). We aimed at identifying patterns of metabolomic changes that were different for the 2 oncogenes but common for the datasets. Human tumors were assayed for phosphorylated AKT1 and MYC expression by immunoblotting. All of these
tumors were pathological stage T2, 22 high Gleason (4+3 or 4+4) and 38 low Gleason (3+3 or 3+4). Levels of phosphoAKT1 and MYC were not associated with the Gleason grade of the tumors (Fig. S1A). K-means clustering of phosphorylated AKT1 and MYC densitometric values (Fig. 1C) was conducted to segregate 4 prostate tumor subgroups, i.e. phosphoAKT1-high/MYC-high (6/60, 10%), phosphoAKT1-high/MYC-low (21/60, 35%), phosphoAKT1-low/MYC-high (9/60, 15%) and phosphoAKT1-low/MYC-low (24/60, 40%) (Figs. 1C and S1B).

To define differential metabolic reprogramming induced by the sole activation of AKT1 or overexpression of MYC, we performed mass spectrometry-based metabolomics of prostate epithelial non-transformed RWPE-1 cells genetically engineered with constructs encoding myristoylated AKT1 or MYC, and transgenic mice expressing human myristoylated AKT1 or MYC in the prostate (Fig. 1A, B). Over 50 metabolite sets (KEGG annotation - Dataset S1) were tested using single-sample Gene Set Enrichment Analysis (GSEA). A clear clustering of phosphoAKT1-high vs. MYC-high samples was noticeable within the genetically engineered cell and mouse datasets, with phosphoAKT1-high being associated with the strongest phenotype in a distinct cluster compared to MYC-high and control samples that appeared closer together, yet recognizable as 2 subclusters (Fig. 2A, B). Human tumors fell in 3 clusters (defined by Silhouette analysis), where the phosphoAKT1-low/MYC-high tumors and the phosphoAKT1-high/MYC-low tumors differentially segregated (Fisher test, p<0.01) (Fig. 2C). Interestingly, while both RWPE-AKT1 and RWPE-MYC cells showed significant changes in intermediates of glucose metabolism and higher enrichment of the glycolysis set compared to RWPE-EV cells (Fig. 2A), only RWPE-AKT1 cells exhibited accumulation of lactate (aerobic glycolytic phenotype) (Fig. S2A). These results were even more pronounced in vivo, with exclusively the MPAKT mouse prostate samples being characterized by both high levels of lactate and
enrichment of the glycolysis set (Figs. 2B and S2A). When applied to primary non-metastatic prostate tumors stratified by the expression levels of phospho-AKT1 and MYC, the pathway enrichment analysis revealed that MYC-high tumors have a negative enrichment of glycolysis compared to nontumoral prostate tissues (Figs. 2C and S2A). Interestingly, normal prostate tissues may also be metabolically heterogeneous and exhibit a glycolytic phenotype (14), potentially attenuating the metabolic differences between normal and tumor tissue in phosphoAKT1-high tumors.

Next, we compared directly the AKT1 and MYC metabolic signatures (Datasets S2 and S3). Pathway enrichment analysis by GSEA was used to determine which metabolic pathways were commonly enriched across the genetically engineered models and the prostate tumor subgroups defined above, specifically comparing AKT1-high with MYC-high background. Gene set-size-normalized enrichment scores (NES) from GSEA were used to determine the extent and direction of enrichment for each pathway in the 3 data sets. Five pathways with highly positive NES and 2 pathways with highly negative NES across and common to the datasets were defined as outliers (Figs. 3A and S3A, B). These results link AKT1 activation with glycolysis and other glucose-related pathways, including the pentose phosphate shunt and fructose metabolism, and MYC overexpression with deregulated lipid metabolism (Figs. 3A and S3C). On the one hand, enrichment of the glycerophospholipid, glycerolipid and pantothenate/CoA biosynthesis metabolite sets, as well as higher levels of lipogenesis-feeding metabolites such as citrate, were distinctively associated with MYC overexpression in RWPE cells, suggesting a MYC-dependent deregulation of synthesis and/or turnover of membrane lipids. Interestingly, higher levels of both omega-3 (docosapentaenoate and docosahexaenoate) and omega-6 (arachidonate, docosadienoate and dihomo-linolenate) fatty acids were found in Lo-MYC mice and in phosphoAKT1-
low/MYC-high prostate tumors relative to MPAKT mice and phosphoAKT1-high/MYC-low
tumors (Dataset S2). Prostate cells may utilize unsaturated, exogenous essential fatty acids early
during transformation, perhaps as energy sources via oxidation (15).

As a validation of untargeted metabolomics, absolute concentrations of selected
metabolites were measured. Oleic, arachidonic and docosahexaenoic (DHA) acids were validated
in phosphoAKT1-high/MYC-low tumors (n=14) and phosphoAKT1-low/MYC-high tumors
(n=5). Oleic acid can be generated in the cell via desaturation of stearic acid by stearoyl-CoA
delta-9-desaturase (SCD1). Consistent with the semiquantitative data, all of these fatty acids
were present at a significantly higher concentration in MYC-high tumors (Fig. 3B). Additional
validation of the untargeted metabolomics included the tumor-associated 2-aminoadipic acid, an
intermediate of lysine metabolism, and creatine, which was increased in phosphoAKT1-
high/MYC-low vs. phosphoAKT1-low/MYC-high tumors (Fig. S4).

Next, we asked whether the metabolome changes associated with the oncogenic
transformation of prostate epithelial cells are accompanied by transcriptional changes in key
metabolic enzymes. Consistent with the metabolite profiling of RWPE-1 cells, glycolytic
components such as the glucose transporter GLUT-1 and the hexokinase 2 were increased upon
AKT1 overexpression/activation (Fig. 4A). As expected, downstream targets of AKT1 such as
HIF-1α (hypoxia-inducible factor 1) and VEGF-A (vascular endothelial growth factor A) were
induced in AKT1-overexpressing cells (Fig. S5A). RWPE-MYC cells showed increased
expression of two key enzymes of the glycerophospholipid metabolism, choline kinase alpha and
cholinephosphotransferase-1 (Fig. 4A). At the proteins level, hexokinase 2 was increased by
AKT1 activation, and choline kinase alpha was induced by MYC overexpression (Fig. 4B).
Consistent with published data (10), MYC induced the expression of glutaminase, a
glutaminolytic enzyme responsible for the conversion of glutamine into glutamate, at both the mRNA and the protein levels (Fig. 4A, B), resulting in an increased amount of glutamate relative to RWPE-EV. AKT1 activation strongly increased the expression of the neutral amino acid transporter ASCT2 (Fig. 4A, B). Interestingly, mRNA and protein expression of fatty acid synthase (FASN) was higher in RWPE-AKT1 and RWPE-MYC cells compared to RWPE-EV cells (Fig. S5A, C), as well as in prostate tumors compared to normal prostate tissue samples (Fig. S5B, C). While FASN expression can be induced downstream of AKT1 via mTORC1-mediated SREBP1 (Sterol Regulatory Element-Binding Protein 1) activation, a link between increased de novo lipogenesis and aerobic glycolysis has been proposed in various tumor types (16, 17), suggesting a multifaceted role of FASN.

Sarcosine, an intermediate of the glycine and choline metabolism previously identified as a progression marker in prostate cancer (18), was increased exclusively in the prostate of Lo-MYC mice (Fig. S2B). Associated with the sarcosine increase were a concomitant elevation of the intermediate betaine and a decrease in glycine levels (Fig. S2B). These results reflect a dysregulation of the sarcosine pathway by MYC.

To determine whether genomic alterations at the PTEN or MYC loci is predictive of active AKT1 or MYC overexpression in prostate tumors, we performed Single Nucleotide Polymorphisms (SNP) arrays using genomic DNA isolated from the same sections of each tumor or nontumoral matched control sample assayed by immunoblotting (phosphorylated AKT1 and MYC). SNP arrays revealed that 20% of these tumors harbored 10q loss and 18% harbored 8q gain including the MYC locus (Fig. S6), while co-occurrence of PTEN loss and MYC copy gain was found in 3% of tumors, consistent with published data (19). Importantly, the genomic
alterations accounted for 26% (7/27) of phosphoAKT1-high tumors and for 13% (2/15) of MYC-high tumors (Fig. S6), as expected from previous reports (20).

Finally, to identify unique mRNA expression changes in phosphoAKT1-high/MYC-low and phosphoAKT1-low/MYC-high prostate tumors, we performed a qPCR-based expression profiling analysis of 28 metabolic genes (Fig. S5D) in tumor relative to normal prostate tissues. Consistent with the MYC-dependent negative enrichment for the glycolytic pathway (Figs. 2C and S2A), high MYC expression in a phosphoAKT1-low context in human tumors was associated with decreased mRNA expression of GLUT-1 (Fig. 4C). This finding was specific to the MYC-high tumors and not generalizable to all tumors vs. normal prostate tissues (Fig. S5B). Also, no decrease in GLUT-1 expression was found in phosphoAKT1-high/MYC-high tumors (Fig. 4C). A significant association between GLUT-1 high expression and phosphoAKT1-high status was found by immunohistochemistry in a subset of this cohort (Fig. 4D and S5C). Seven of 14 phosphoAKT1-low tumors were MYC-high, and only 14% (1/7) of these showed high GLUT-1, whereas 85% (6/7) had low or no GLUT-1 expression (Fig. 4D). Altogether, these results suggest that AKT1 activation may be critical to maintain high GLUT-1 levels in prostate cancer cells, and that AKT1-independent MYC activation can potentially affect glucose uptake in prostate tumors.

In summary, our data demonstrate that individual prostate tumors have distinct metabolic phenotypes resulting from their genetic complexity, and reveal a novel potential metabolic role for MYC in prostate cancer. The evidence provided links AKT1 or MYC activation with differential deregulation of glucose-related pathways as well as lipid metabolism in human prostate cancer. To our knowledge, this is the first report of oncogene-associated metabolic signatures as the result of an integrative analysis of cultured cells, mouse models and human
tumors. This opens novel avenues for the metabolic imaging and therapeutic targeting of prostate cancer patients.

**Acknowledgments:** We thank Matthew Vander Heiden for critical review of the manuscript and to William C. Hahn for providing plasmids. This work was supported by RO1CA131945, P50 CA90381, the Prostate Cancer Foundation, and philanthropic funds from Nuclea Biomarkers (Pittsfield, MA) to M.L.; the P.A.R.T. Investigatorship in Prostate Cancer Award from the Lank Center/Dana-Farber Cancer Institute and a Friends of Dana-Farber fund to C.P.; the Ramalingswami Fellowship from DBT, MoS&PI and DST (CMS Project SR/SA/MS:516/07; 21/04/2008), India, to S.P.; and the Fondazione Italiana per la Ricerca sul Cancro, Italy to S.C.. All Authors declare no competing financial interests.
References


16. Menendez JA. Fine-tuning the lipogenic/lipolytic balance to optimize the metabolic requirements of cancer cell growth: molecular mechanisms and therapeutic perspectives, *Biochim Biophys Acta* 2010; **1801**:381-391


Figure Legends

Figure 1. Integrative models of AKT or MYC-driven prostate tumorigenesis. Metabolomic profiling was performed on non-transformed prostate RWPE-1 cells (A) and mice (B) genetically engineered to overexpress myristoylated AKT1 or MYC, primary non-metastatic prostate tumors (C), and controls. AKT1 and MYC overexpression are represented by orange and green, respectively. Controls are blue. (A) PhosphoAKT1 and MYC levels in RWPE-AKT1, RWPE-MYC and control (RWPE-EV) cells are shown by immunoblots. (B) Both MPAKT and Lo-MYC transgenic mice exhibit prostate intraepithelial neoplasia at 11-13 weeks of age, as shown by Hematoxylin and Eosin (H&E) staining. Overexpression of phosphoAKT1 and MYC was confirmed by immunohistochemistry. (C) K-means clustering was used to segregate 4 prostate tumor subgroups, i.e. phosphoAKT1-high/MYC-high (dark grey dots), phosphoAKT1-high/MYC-low (orange dots), phosphoAKT1-low/MYC-high (green dots) and phosphoAKT1-low/MYC-low (light grey dots).

Figure 2. Metabolic pathway analysis in phosphoAKT1-high or MYC-high samples relative to controls. (A-C) Heatmap representation of normalized enrichment scores (p<0.05) for KEGG pathways in individual samples of the three datasets (RWPE-1 cells, MPAKT and Lo-MYC mice, and human prostate tissues). Light blue/yellow colors are used to denote high/low enrichment, as in the respective color scales. Hierarchical clustering is used for unsupervised identification of the higher-level enrichment classes. The phenotypic labels of the samples (control, phosphoAKT1-high and MYC-high) are indicated as a colored band on top of the heatmap, while the dendrogram represents the distances among them.
Figure 3. Overall differential metabolite set enrichments in phosphoAKT1-high versus MYC-high samples. (A) Simultaneous GSEA measurements in all 3 datasets (cultured cells, mouse prostate and human tumors) are shown (left panel). This information is depicted as dots in 3-dimensional space, where each dot represents a particular pathway, and each dimension a dataset. Enrichment of a pathway in phosphoAKT1-high versus MYC-high samples or vice versa is defined by a positive or negative score, respectively. The top 5 positively enriched pathways (i.e., in phosphoAKT1-high samples) and the top 2 negatively enriched pathways (i.e., in MYC-high samples) in all 3 datasets, as identified with outlier analysis (Fig. S3), are shown as orange and green dots, respectively. Normalized enrichment scores (NES) of the 7 pathways identified as outliers in the three datasets and the average of these scores are shown per each set (KEGG pathway) in the right panel. (B) Semi-quantitative (top panels) and absolute (bottom panels) measurements of arachidonic acid, docosahexaenoic acid, and oleic acid in phosphoAKT1-high/MYC-low (orange) and phosphoAKT1-low/MYC-high (green) tumor samples. Mann-Whitney Test was applied. *p<0.05, **p<0.01

Figure 4. Relative mRNA expression of metabolic genes. (A) Relative qPCR analysis of mRNA levels of genes of glucose, glycerophospholipid and glutamine metabolism in RWPE-AKT1 (orange bars) and RWPE-MYC (green bars) cells normalized to RWPE-EV (blue bars) cells. (B) Immunoblotting of hexokinase 2 (HK2), the glutamine transporter ASCT2, glutaminase (GLS), and choline kinase alpha (CHKα) in RWPE-AKT1, RWPE-MYC, and RWPE-EV cells. (C) Relative qPCR analysis of mRNA levels of the glucose transporter GLUT-1 in phosphoAKT1-high/MYC-low (orange bar; n=13), phosphoAKT1-low/MYC-high (green bar; n=5), and phosphoAKT1-high/MYC-high (dark grey bar; n=3) prostate tumors versus
normal prostate samples (blue bar; n=9). (D) Hematoxylin and eosin (H&E) and immunohistochemical staining for MYC, stathmin (an AKT downstream target used as a surrogate of AKT activity) and GLUT-1 in representative cases of phosphoAKT1-low/MYC-high and phosphoAKT1-high/MYC-low prostate tumors. Red cells (arrow head) represent a positive control for GLUT-1 staining. One-sample T-Test was performed using average fold change of at least 3 experiments (A) or samples (C). *p<0.05, **p<0.01, ***p<0.001.
Fig. 1

A

RWPE-AKT1 cells

EV AKT1

PhosphoAKT1

β-actin

EV MYC

MYC

β-actin

B

MPAKT

Transgenic mice

Lo-Myc

H&E

PhosphoAKT1

H&E

MYC

C

Human prostate tumors

PhosphoAKT1
Fig. 3

A

B

Pathway | Cell  | Mouse | Human | Mean |
--------|-------|-------|-------|------|
Glycolysis Gluconeogenesis | 1.36  | 1.28  | 1.59  | 1.41 |
Fructose and Mannose Metabolism | 1.46  | 1.22  | 1.31  | 1.33 |
Pentose Phosphate Pathway | 1.46  | 0.99  | 1.42  | 1.29 |
Propanoate Metabolism | 0.97  | 1.42  | 1.18  | 1.19 |
Amino Sugar and Nucleotide Sugar Metabolism | 1.29  | 0.66  | 1.53  | 1.16 |
Glycerolipid Metabolism | -1.04 | -0.99 | -0.85 | -0.96 |
Fatty Acid Biosynthesis | -0.95 | -0.87 | -1.34 | -1.05 |

Arachidonic acid

Docosahexaenoic acid

Oleic acid

Arachidonic acid

Docosahexaenoic acid

Oleic acid

PhosphoAKT1-high MYC-high

PhosphoAKT1-high MYC-high

PhosphoAKT1-high MYC-high

PhosphoAKT1-high MYC-high

PhosphoAKT1-high MYC-high

PhosphoAKT1-high MYC-high
AKT1 and MYC Induce Distinctive Metabolic Fingerprints in Human Prostate Cancer

Carmen Priolo, Saumyadipta Pyne, Joshua Rose, et al.

Cancer Res  Published OnlineFirst October 16, 2014.

Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-14-1490

Supplementary Material
Access the most recent supplemental material at:
http://cancerres.aacrjournals.org/content/suppl/2014/10/16/0008-5472.CAN-14-1490.DC1

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.