

Figure S1. Comparisons of gene expression profiles between the human epithelial and hematopoietic stem cells, Related to Figure 1. Rank-rank hypergeometric heatmap plots of gene expression profile overlap between different cell populations. The quadrant in the lower left hand corner in each plot shows the overlap between the stem cell populations being compared. HSC1/HSC2: $n = 6$, Progenitor/Lin+: $n = 6$. Heatmap scale bars = $-\log_{10}$ p-value.

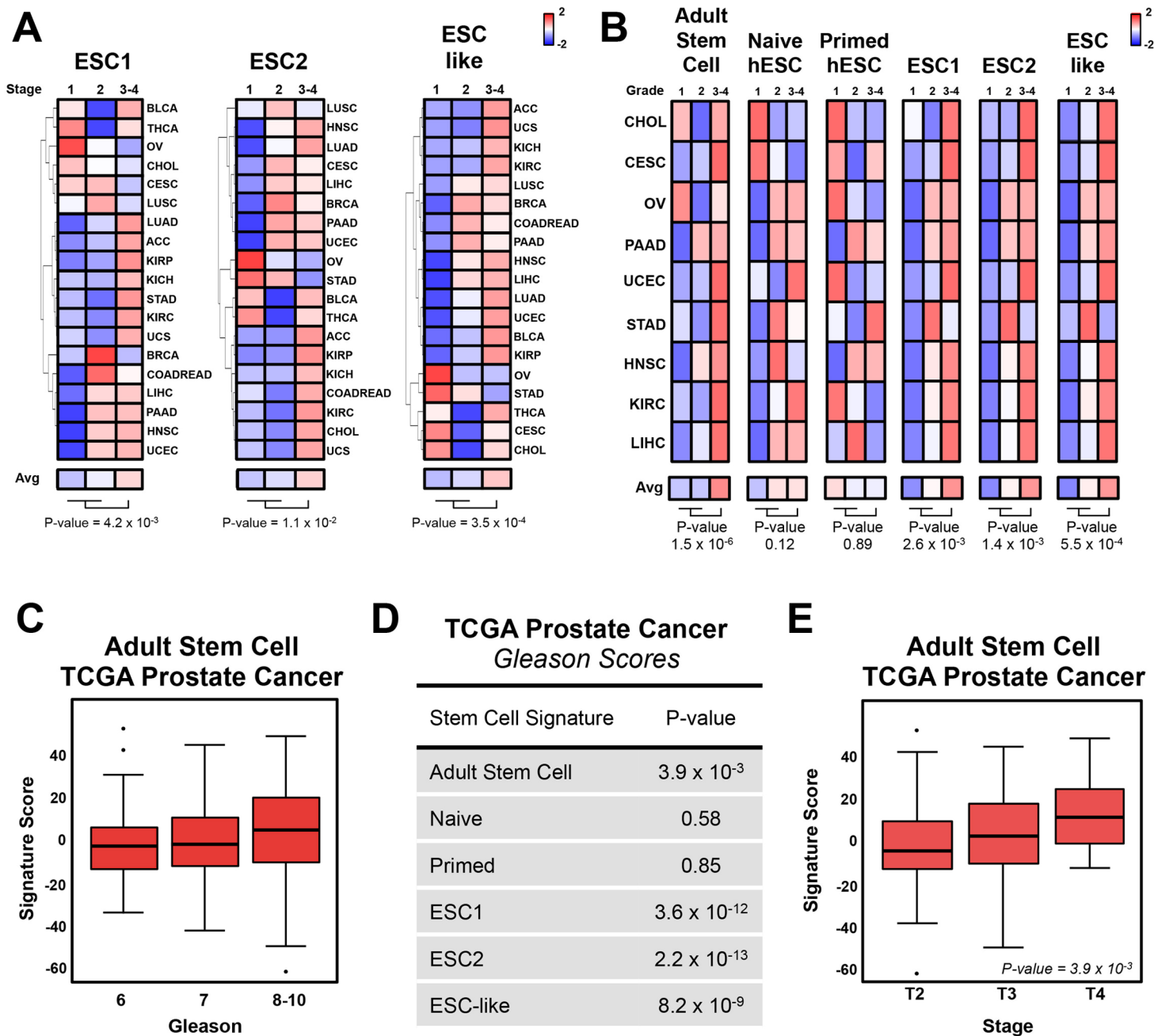


Figure S2. Comparison of stem cell signature enrichment in epithelial cancers, Related to Figure 2. (A) Unsupervised clustering of TCGA epithelial cancers according to average stem cell signature scores for each cancer stage. Scale color key is based on z-scores. (B) Heatmap of stem cell signature scores according to average stem cell signature score for each tumor grade. Scale color key is based on z-scores. (C) Box plot of the ASC signature scores for Gleason 6 ($n = 45$), Gleason 7 ($n = 246$), and Gleason 8-10 ($n = 199$) organ-confined prostate adenocarcinomas from the The Cancer Genome Atlas Research Network, 2015. Mean \pm SD. (D) P-values for stem cell signatures in TCGA prostate adenocarcinoma samples stratified according to Gleason score. P-values were calculated using ANOVA. (E) Box plot of ASC signature scores according to prostate adenocarcinoma staging from The Cancer Genome Atlas Research Network, 2015. Mean \pm SD. P-value was calculated using ANOVA.

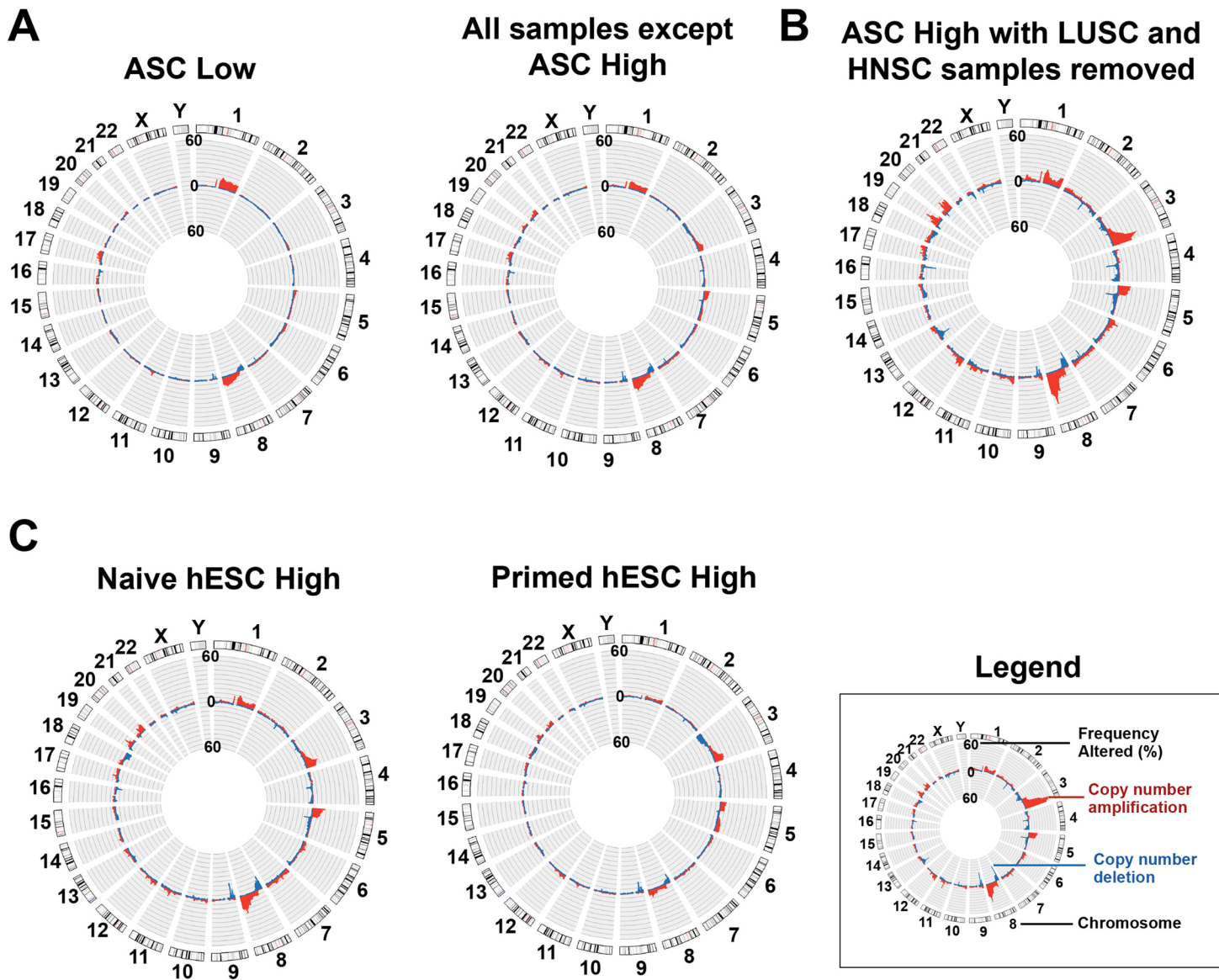
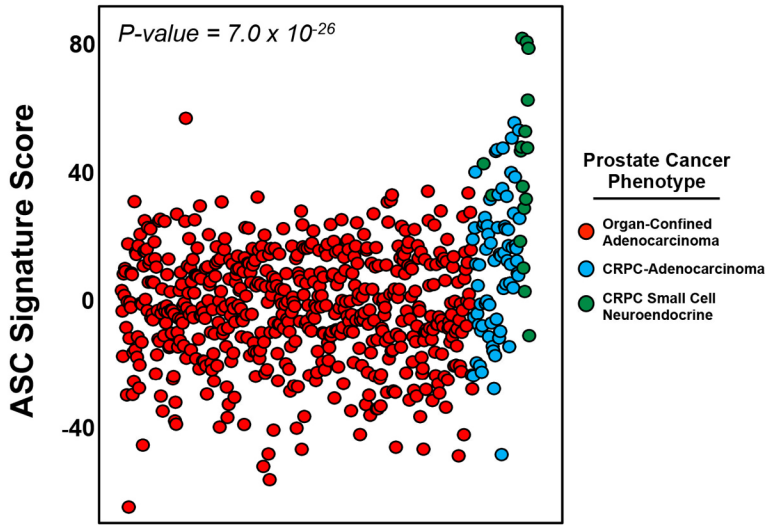
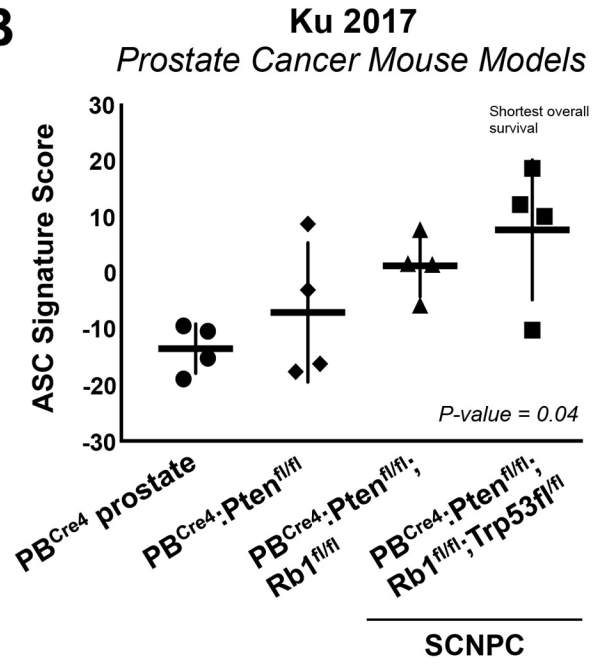
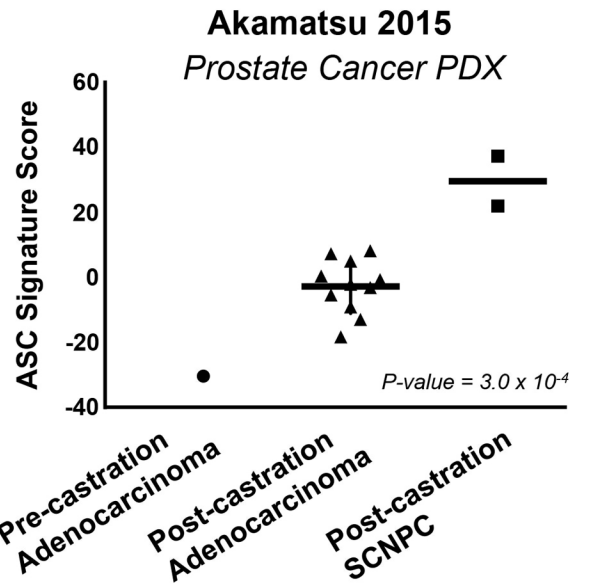
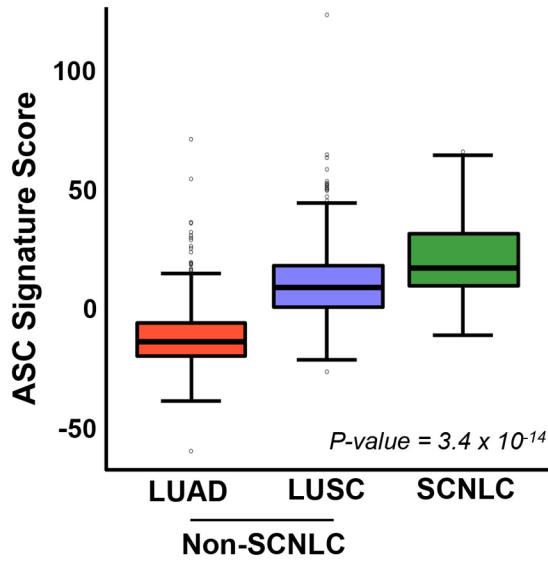
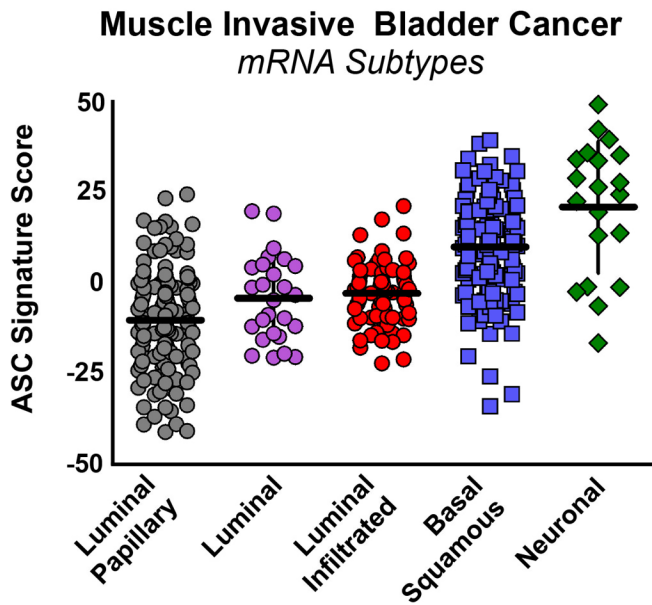


Figure S3. Cancer related genomic alterations associated with stem cell signature status, Related to Figure 3. (A) Circos plot of copy number variations associated with adult stem cell signature LOW (ASC Low) epithelial cancer specimens or all epithelial cancer samples that are not ASC High. (B) Circos plot of ASC High associated alterations after removal of lung squamous and head and neck squamous carcinoma samples that were designated as ASC High. (C) Circos plot of naive hESC or primed hESC High associated copy number variations.

A**B****C****D****E**

Muscle Invasive Bladder Cancer mRNA Subtypes

Comparison	Q-value
Neuronal vs. Basal Squamous	1.6×10^{-2}
Neuronal vs Luminal Infiltrated	1.6×10^{-7}
Neuronal vs Luminal	1.5×10^{-5}
Neuronal vs Luminal Papillary	8.6×10^{-7}

Figure S4. Adult stem cell signature scores in small cell neuroendocrine cancers, Related to Figure 4. (A) Adult stem cell signature scores in organ-confined prostate adenocarcinoma (red circles), castration-resistant metastatic prostate adenocarcinoma (blue circles), and castration-resistant metastatic small cell neuroendocrine prostate cancer (green circles) specimens. Samples are from Beltran et al., 2016; Robinson et al., 2015; and The Cancer Genome Atlas Research Network, 2015. P-value was calculated using ANOVA. (B) Adult stem cell signature scores in prostate cancer mouse models (top; Ku et al., 2017) and a prostate cancer patient derived xenograft that converts from an adenocarcinoma to a SCN phenotype following castration (bottom; Akamatsu et al., 2015). (C) Adult stem cell signature scores in small cell neuroendocrine lung cancer (n = 56) and non-small cell neuroendocrine lung adenocarcinoma (LUAD, n = 573) and lung squamous cell carcinoma (LUSC, n = 548) clinical samples. Mean +/- SD. P-value was calculated using student's t-test between SCNLC and Non-SCNLC samples. (D) Adult stem cell signature scores for muscle invasive bladder cancer mRNA subtypes described in Robertson et al., 2017. Mean +/- SD. (E) Q-values for muscle invasive bladder cancer mRNA subtype comparisons to the neuronal mRNA subtype.

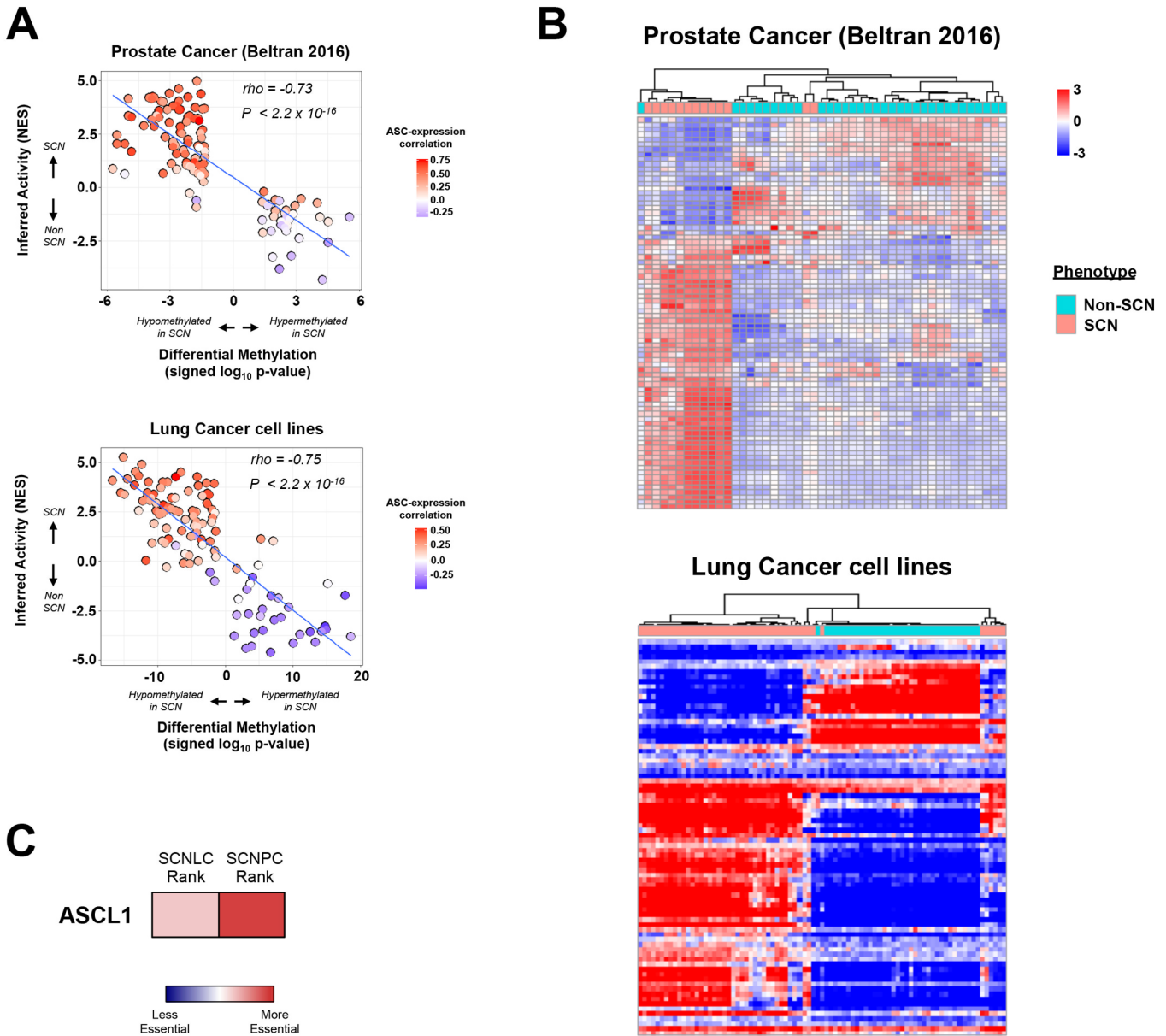


Figure S5. Common methylation events in small cell neuroendocrine prostate and lung cancers, Related to Figure 7. (A) Correlation plots of gene activation and signed log p-values for common negatively correlated and differentially methylated genes in the human prostate cancer (top) and lung cancer cell line (bottom) datasets. Inferred protein activation was calculated using VIPER. Inset heatmap represents the rho correlation value of each gene's expression with the adult stem cell signature score. (B) Unsupervised clustering of human prostate cancer (top) and lung cancer cell lines (bottom) using the activation scores of the common negatively correlated and differentially methylated genes. Scale Bar represents the z-score. (C) ASCL1 gene essentiality in lung and prostate small cell neuroendocrine cancers. Heatmap reflects ASCL1's essentiality ranking relative to approximately 17,000 total genes (scale bar).

Table S1. Gene signatures for normal human adult stem cells, naive embryonic stem cells and primed embryonic stem cells, Related to Figure1.

Adult Stem Cell signature	Naive hESC signature	Primed hESC signature
VSNL1	DNMT3L	SALL2
AKR1B1	ALPPL2	DUSP6
NOTCH4	NLRP7	LRRN1
TMEM237	SLC25A16	P3H2
SAMD5	DPPA5	CDH2
PKD2	ATAD3B	VRTN
NAP1L1	OLAH	UCHL1
PTTG1	SAMHD1	STC1
CDK6	PYGB	FGFBP3
CDCA7	TFCP2L1	NELL2
ACSL4	LCP1	ANOS1
HELLS	NEFH	FZD7
IKBIP	RAB15	THY1
PLTP	SUSD2	PHLDA1
TMEM201	VSIG10	USP44
CACHD1	PRSS12	NAP1L3
ILF3	PTPRU	SPRY4
DNMT1	ASRGL1	PTPRZ1
USP31	A4GALT	EDNRB
FAM216A	DNAJC15	ADAMTS19
SLC41A1	CBFA2T2	FREM2
PFKM	KHDC1L	PCYT1B
KANK1	SLC8B1	TAGLN
SUPT16H	SLC35F6	CAV1
ADCY3	AARS2	COL7A1
FGD1	CDHR1	CYP26A1
PTPN14	SLC25A44	MAP7
C20orf27	SLC7A7	PODXL
LGR6	REEP1	GRPR
SLC16A7	PINK1	NTS
JAM3	GAS7	PLCH1
FBL	KLHL18	COL18A1
NASP	HYAL4	PCDH18
RANBP1	DCAF4	CRABP1
PRNP	TGFBR3	EPHA2
DSE	SLC23A2	VIM
GPX7	TUBB4A	NECTIN3
KDELC1	VAV2	GLI2
FCHSD2	SLC16A10	FAM13A
SLCO3A1	IL6R	DPYSL2
CCNB1IP1	ARPC1B	ATP8A1
LOC284023	MYBL2	PMEL
NOL9	TNS3	ZIC2
NKRF	CACNA2D2	GPC6
NUP107	ITGAM	FKBP10
RCC2	GALNT6	SEMA3A
ARHGAP25	NDUFAB1	SALL1
DDX46	KLF5	ROR1
TCOF1	UPP1	HEPH
GMPS	DACT2	MEX3A

Table S4. Mutations associated with human stem cell signatures (q-value < 0.05), Related to Figure 3.

Gene	Q-value	Frequency Altered
<i>Adult Stem Cell</i>		
TP53	3.0×10^{-52}	69.5 %
FBXW7	3.0×10^{-4}	10.4 %
NOTCH1	2.1×10^{-3}	7.9 %
<i>Naive hESC</i>		
TP53	3.0×10^{-7}	54.2 %
OR4A5	4.8×10^{-3}	4.2 %
NOTCH1	7.1×10^{-3}	7.9 %
PRDM9	7.1×10^{-3}	7.7 %
<i>Primed hESC</i>		
VHL	4.8×10^{-17}	13.1 %

Table S6. Epithelial cancers included in the pan-epithelial cancer dataset, Related to STAR methods.

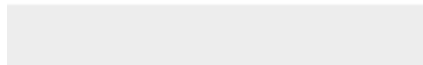
Cancer type	TCGA abbreviation	Number of Samples
Adrenocortical Carcinoma	ACC	77
Bladder Urothelial Carcinoma	BLCA	358
Breast Invasive Carcinoma	BRCA	921
Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma	CESC	218
Cholangiocarcinoma	CHOL	33
Colorectal Adenocarcinoma	COADREAD	260
Head and Neck Squamous Cell Carcinoma	HNSC	434
Kidney Chromophobe	KICH	65
Kidney Renal Clear Cell Carcinoma	KIRC	494
Kidney Renal Papillary Cell Carcinoma	KIRP	261
Liver Hepatocellular Carcinoma	LIHC	353
Lung Adenocarcinoma	LUAD	491
Lung Squamous Cell Carcinoma	LUSC	401
Ovarian Serous Cystadenocarcinoma	OV	296
Pancreatic Adenocarcinoma	PAAD	174
Stomach Adenocarcinoma	STAD	372
Thyroid Carcinoma	THCA	502
Uterine Corpus Endometrial Carcinoma	UCEC	369
Uterine Carcinosarcoma	UCS	57



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Supplemental Videos and Spreadsheets

Table S2_ASC Copy Number Amplifications.xlsx

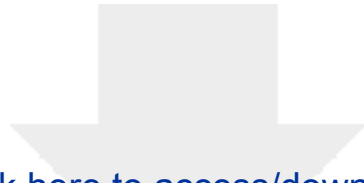




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Supplemental Videos and Spreadsheets
Table S3_ASC Copy Number Deletions.xlsx





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Supplemental Videos and Spreadsheets
Table S5_Common methylated genes.xlsx

