Supplementary Fig. S3

a

Higher methylation in Solid ← | → Higher methylation in Lepidic

Solid markers
Solid TRs
Lepidic markers
Lepidic TRs

promoter DNA methylation fold-change (Solid/Lepidic)

b

Lepidic-to-Solid Signature score (CHUV)

- samples from the same patient
- score increase
- score decrease

Lepidic   Papillary   Acinar   Solid

c

Lepidic-to-Solid Signature score (TCGA)

TCGA-44-7670

Normal   Lepidic   Papillary   Acinar   Solid

d

Survival by predominant pattern, TCGA − p−val = 0.414

- lepidic
- papillary
- acinar
- solid

%Survival

Time (days)

e

Dataset	(#)	HR (solid)	p-value (solid)	HR (lepidic)	p-value (lepidic)		
						● lepidic	● solid
TCGA	513	1.36	0.0014	0.775	0.011		
Chen	169	1.03	0.71	0.887	0.23		
Micke	106	1.66	0.013	0.879	0.61		
Yokota	226	1.67	0.028	0.682	0.12		
Beg	398	1.61	0.00019	0.629	0.0003		
Shedden	443	1.42	0.00044	0.798	0.0047		
Pintilie	181	1.77	0.004	0.722	0.017		
Summary	**2036**	**1.48**		**0.751**			

Hazard ratio
0.35 0.50 0.71 1.0 1.41 2.0

f

Correlation between master TF activity and Lepidic-to-Solid signature score
−0.5 0 0.5

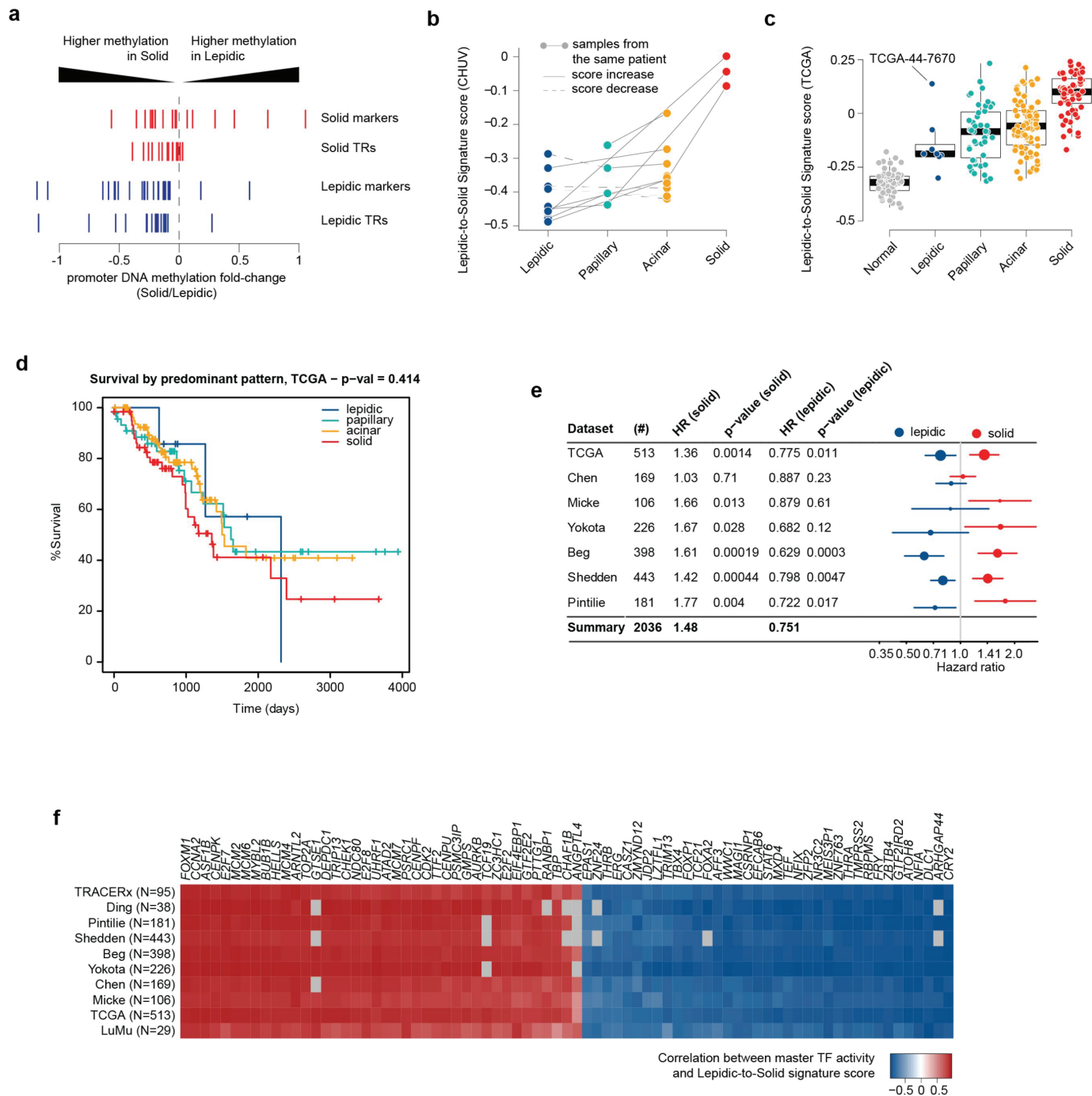**Supplementary Fig. S3**
a) Promoter DNA methylation fold-changes (solid vs. lepidic) at differentially expressed genes between lepidic and solid regions in the CHUV cohort (lepidic and solid markers) and between transcriptional regulators inferred by VIPER (solid and lepidic TR).
b,c) Lepidic-to-solid (L2S) signature scores computed with singscore for **(b)** tumor regions from the CHUV cohort and **(c)** the TCGA cohort. For the CHUV cohort, regions derived from the same patient are connected by a line (continuous: score increases, dashed: score decreases with pattern progression).
d) Kaplan-Meier curves for TCGA samples divided by predominant pattern. P-value was computed with log-rank test.
e) Hazard ratios associated with increasing values of lepidic (blue dots) and solid (red dots) markers signature scores (10% increase) in 7 independent LUAD datasets comprising >100 patients ('#' column). P-values were computed by multi-variate Cox regression inserting sex, age and stage as covariates. Dot size is proportional to the number of sample. 95% confidence intervals are reported as horizontal line segments.
f) Correlation values between inferred Transcriptional Regulator (TR) activity by VIPER and lepidic-to-solid signature scores in 10 independent datasets. All TRs are reported as column names.