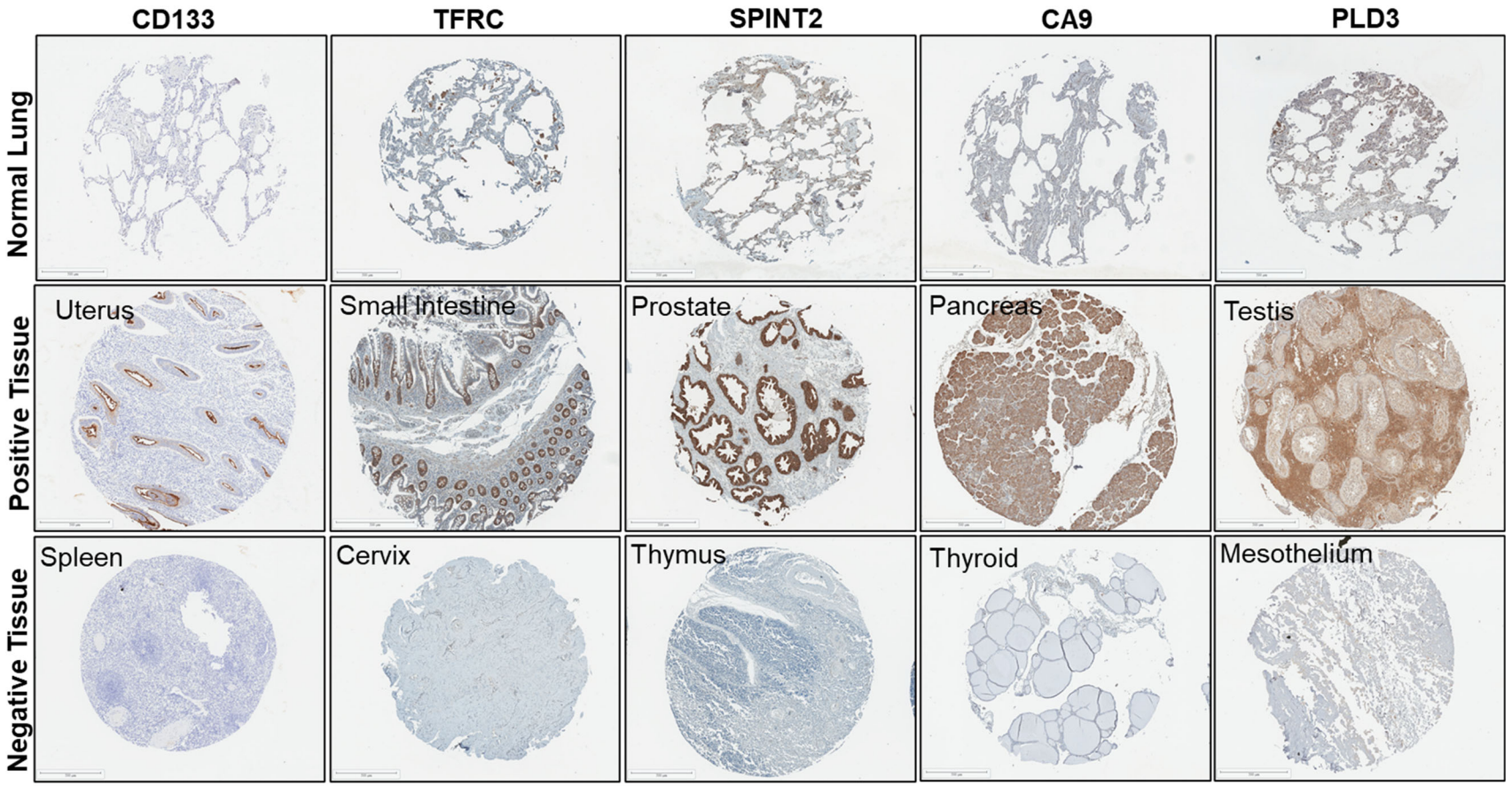

Fig. S1. Tumor associated antigens are also expressed in some normal tissues. Representative normal tissue cores that demonstrate both positive and negative expression for each immunohistochemical stain, as well as expression in normal lung cores (Scale bar is 500μM). TFRC, transferrin receptor; SPINT2, serine peptidase inhibitor, Kunitz type 2; CA9, carbonic anhydrase 9; PLD3, phospholipase D3.

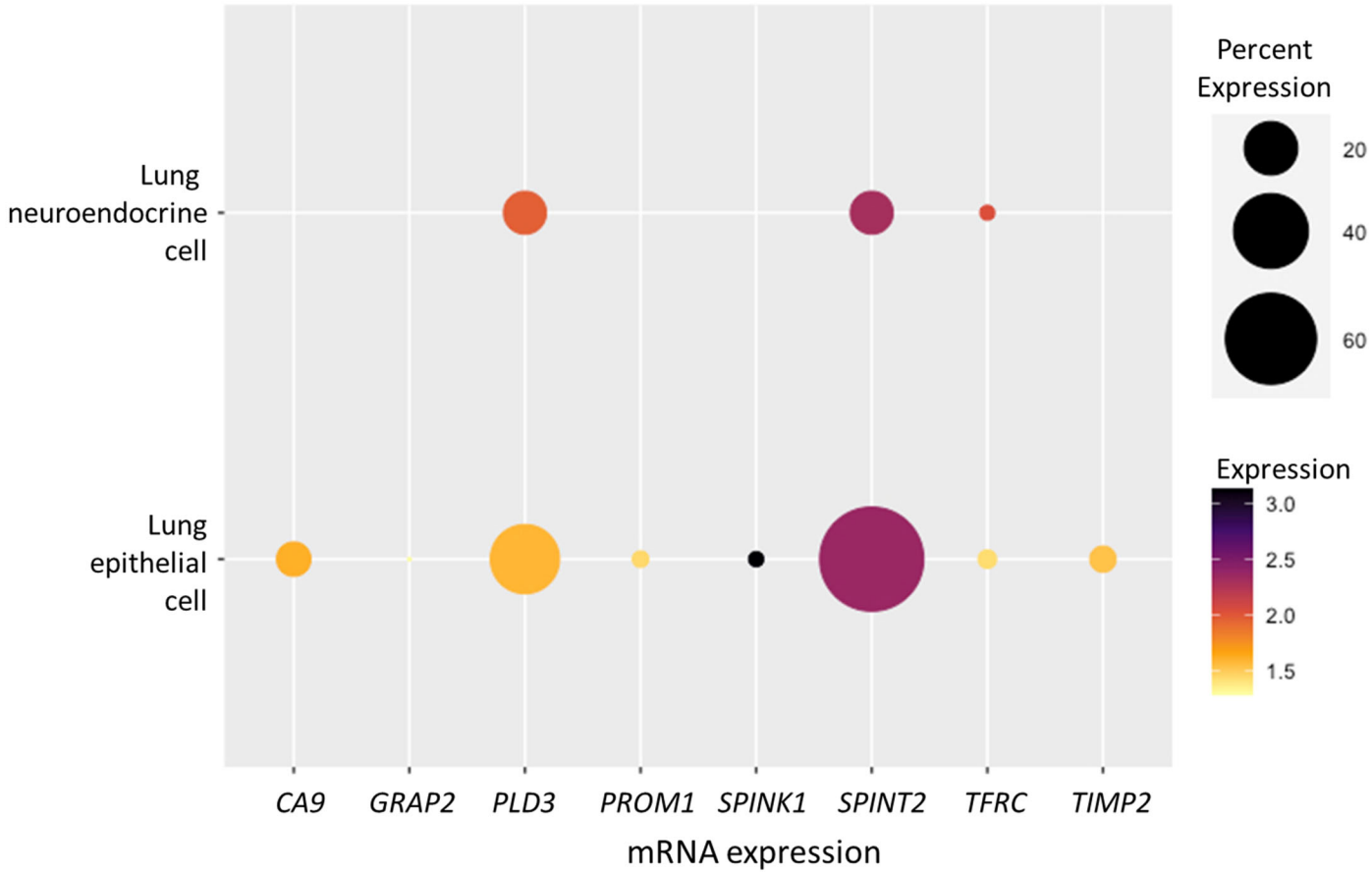

Fig. S2. **Expression of small cell lung cancer (SCLC) biomarkers in healthy lung tissue.** Single-cell RNA sequencing data for lung neuroendocrine and lung epithelial cells was analyzed using the CELLxGENE Gene Expression tool from the Chan Zuckerberg Initiative (https://cellxgene.cziscience.com/). Expression values are represented by the circle color and are based on quantile-normalized values with <2 = low expression, 2 to 4 = medium expression, and >4 = high expression. The percentage of all single cells analyzed is represented by circle size.

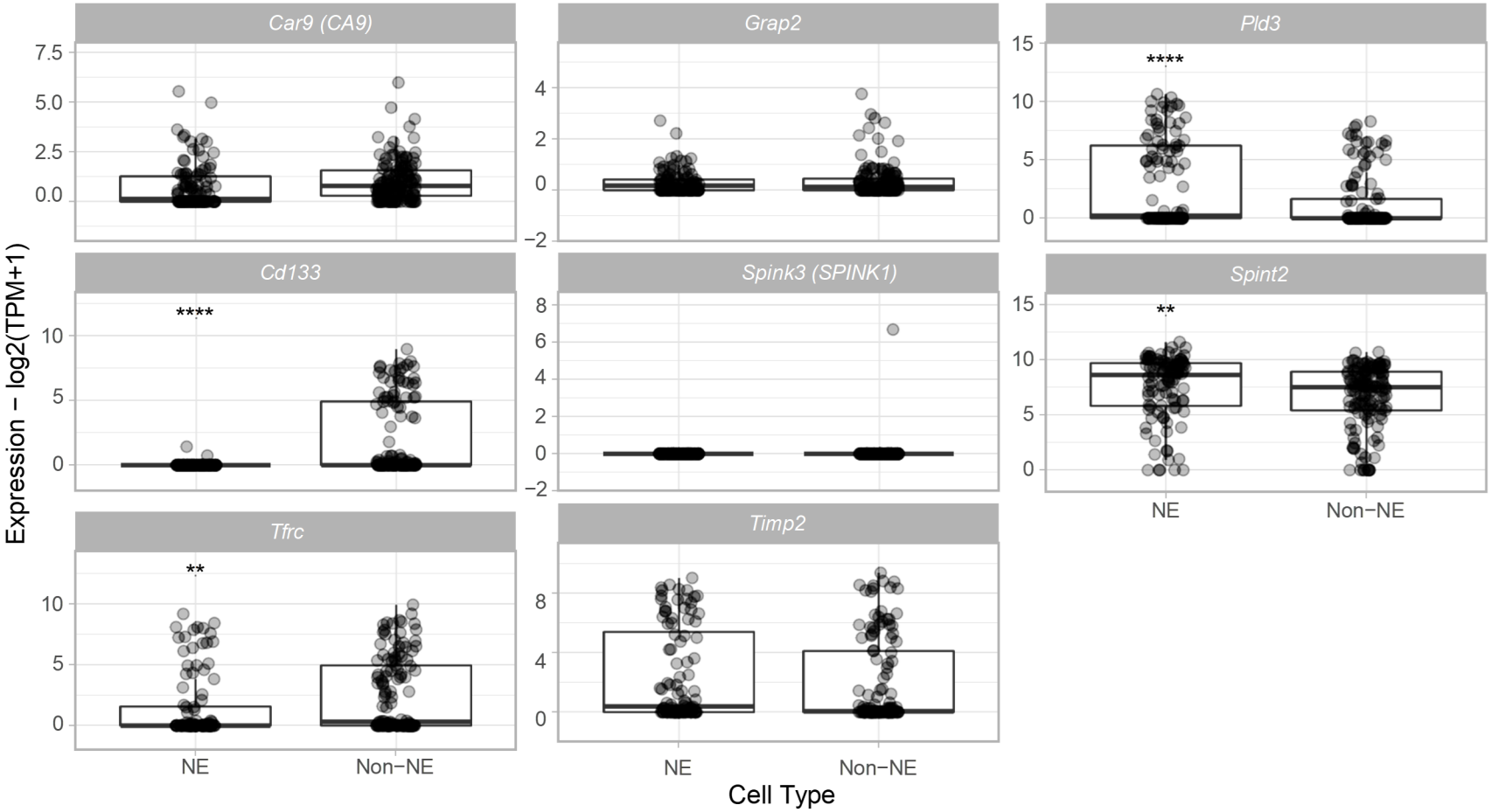

Fig. S3. **Expression of SCLC biomarkers in non-transformed lung tissue from mice**. Single-cell RNA sequencing data for pulmonary neuroendocrine (PNE) and non-neuroendocrine (NE) cells in the lung were analyzed from the GSE136580. *Car9* and *Spink3* are the mouse homologues for human *CA9* and *SPINK1*. Expression values are compared with two-way analysis of variance (ANOVA) with post-hoc Bonferroni adjustment. **p<0.01, ****p<0.0001. TPM, transcripts per million. Box and whisker plots indicate the median and upper and lower quartiles.

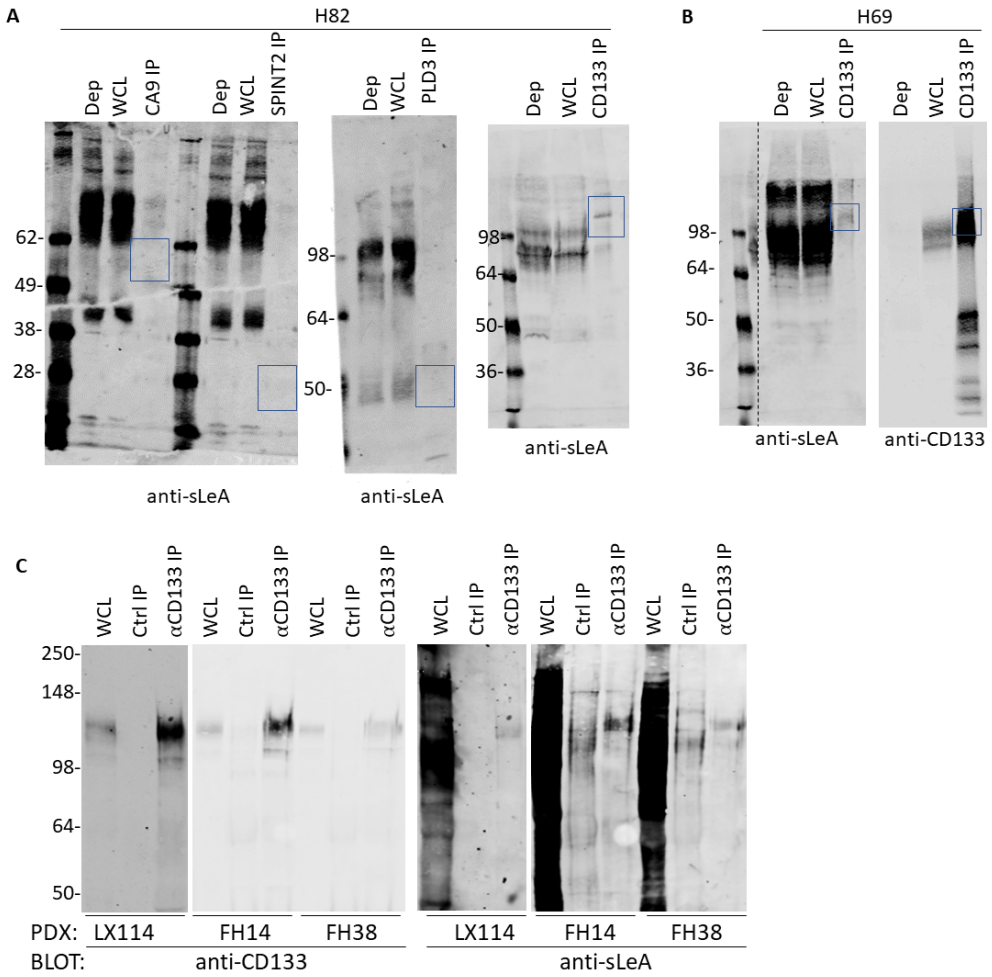

Fig. S4. CD133 has cancer-specific glycosylation of sLeA SCLC cell lines and patient-derived xenografts (PDXs). (**A**). Shown are immunoblots from H82 lysates immunoprecipitated (IP) with CA9, SPINT2, PLD3, or CD133 antibody and probed with anti-SleA antibody. Depleted (Dep), whole cell lysates (WCL) and target-specific IP are shown. Ctrl, control antibody. Blue boxes indicate expected target protein size. (**B**) Shown are immunoblots from H69 SCLC cell line lysates immunoprecipitated with CD133 antibody and probed with anti-CD133 or anti-sLeA antibodies. (**C**) Shown are immunoblots from 3 SCLC PDX lysates (LX114, FH14, FH38) immunoprecipitated with CD133 antibody and probed with anti-CD133 and anti-sLeA antibodies.

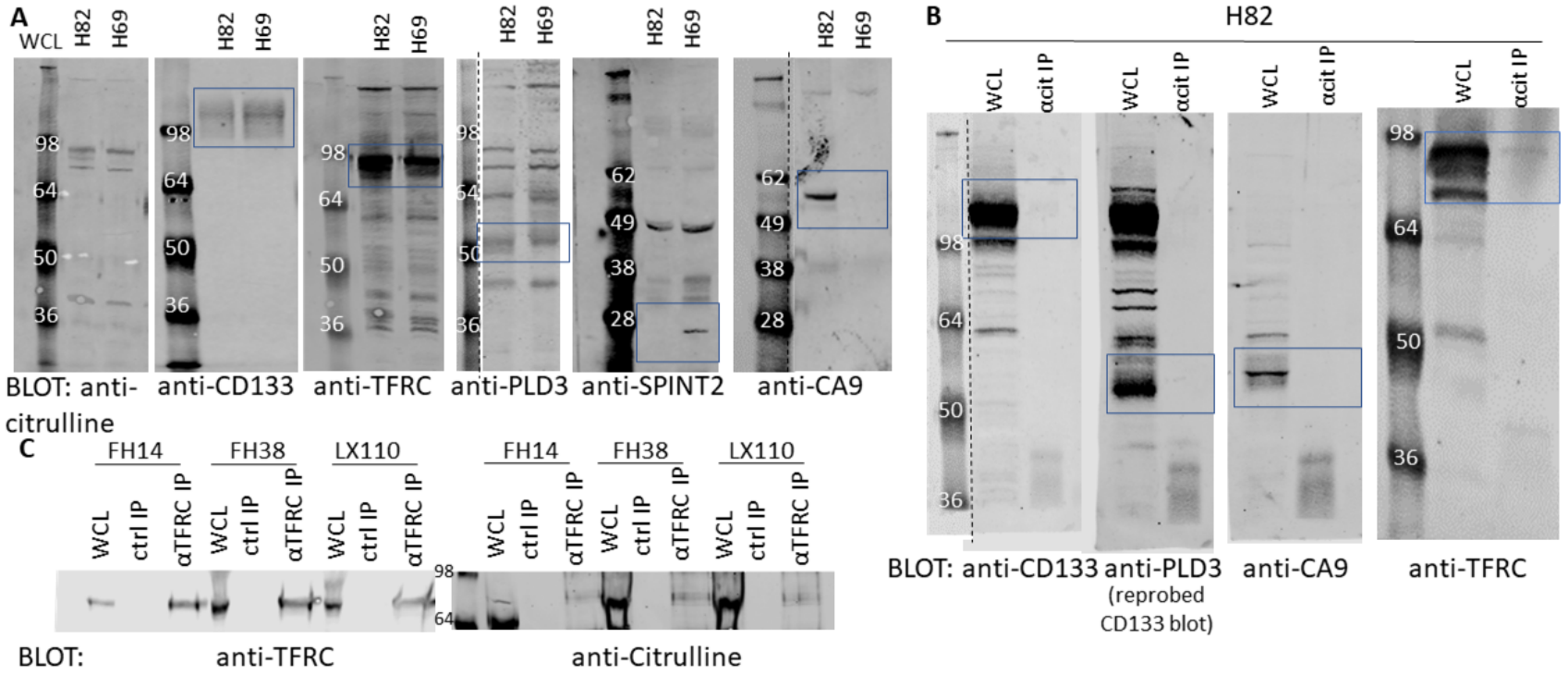

Fig. S5. TFRC is citrullinated. (**A**) Shown are immunoblots from H82 and H69 WCL probed with antibodies to citrulline, CD133, TFRC, PLD3, SPINT2, and CA9. Blue boxes indicate expected target protein size. Cropped versions of anti-Citrulline and anti-TFRC blots are shown in Fig. 5A but the full blots are also shown here for comparison with other target proteins. (**B**) Immunoblots from H82 lysates immunoprecipitated with citrulline antibody and probed with anti-CD133, PLD3, CA9, or TFRC antibody. CD133 and then PLD3 were used to sequentially probe the same blot. (**C**) Shown are immunoblots from 3 SCLC PDX lysates immunoprecipitated with TFRC antibody and probed with anti-TFRC and anti-citrulline antibody.

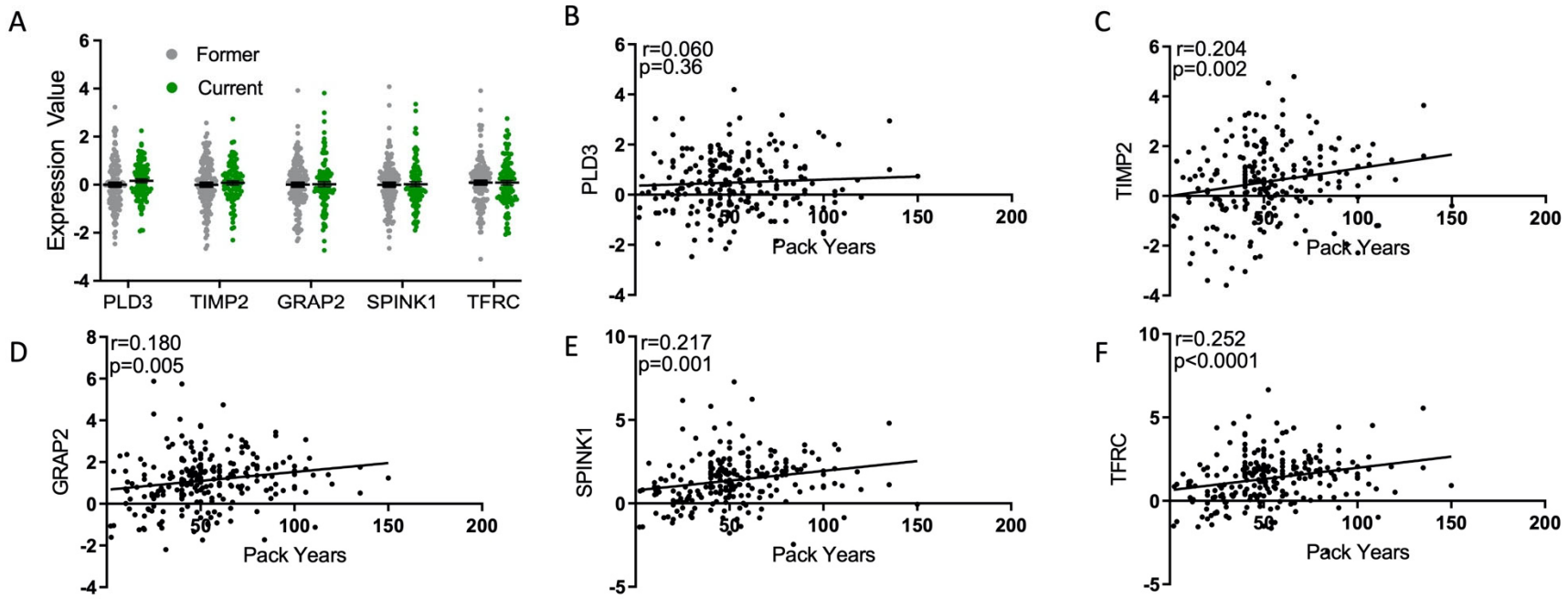

Fig. S6. Panel autoantibodies are weakly associated with smoking pack years. (**A**) Panel autoantibodies are not differentially expressed in current versus former smokers (current n=100, former n=140). Data are presented as mean±SEM. (**B to F**) Panel autoantibodies including PLD3 (B), TIMP2 (C), GRAP2 (D), SPINK1 (E), and TFRC (F) are loosely correlated with number of smoking pack years. Data were analyzed by Pearson correlation, n=240. TIMP2, tissue inhibitor of metalloproteinases 2; GRAP2, growth factor receptor-bound protein 2-related adaptor protein 2; SPINK1, serine peptidase inhibitor Kazal type 1.

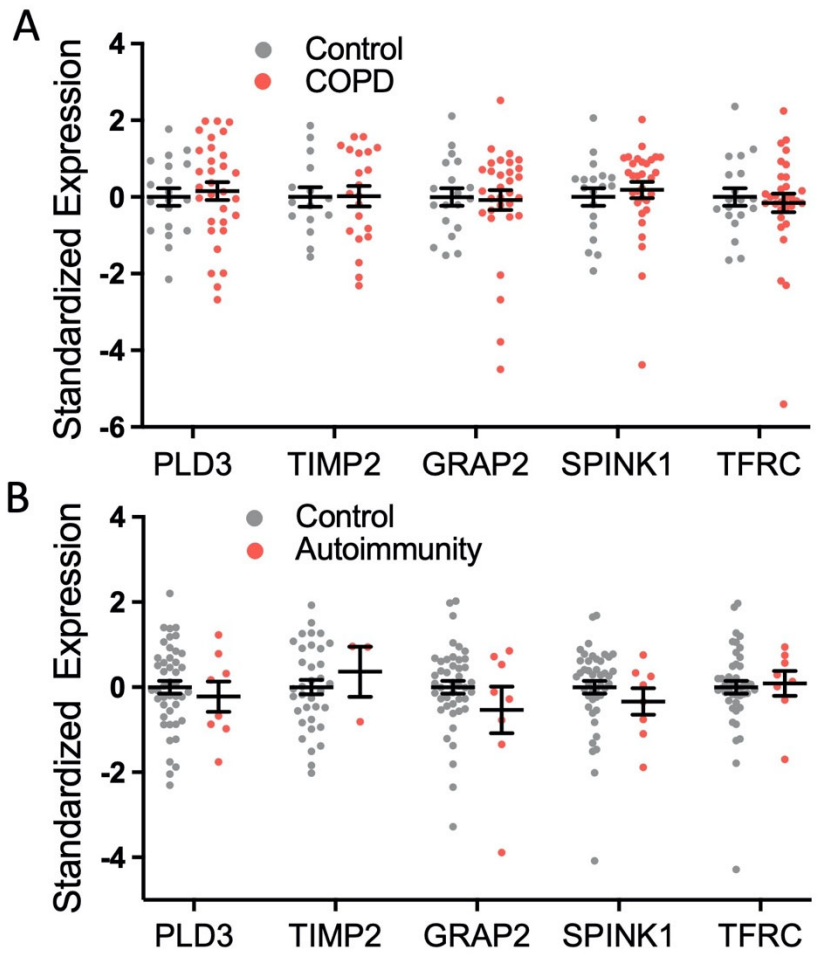

Fig. S7. Panel autoantibodies are not associated chronic obstructive pulmonary disease (COPD) or autoimmunity. Expression of panel autoantibodies are not associated with (**A**) COPD (n=19 controls and 31 cases) or (**B**) autoimmunity [type 1 diabetes (n=3), rheumatoid arthritis (n=2), hypothyroidism (n=2) or myasthenia gravis (n=2)]. One individual had both type 1 diabetes and myasthenia gravis diagnoses (total n=44 controls and 8 cases). Data are presented as mean±SEM.

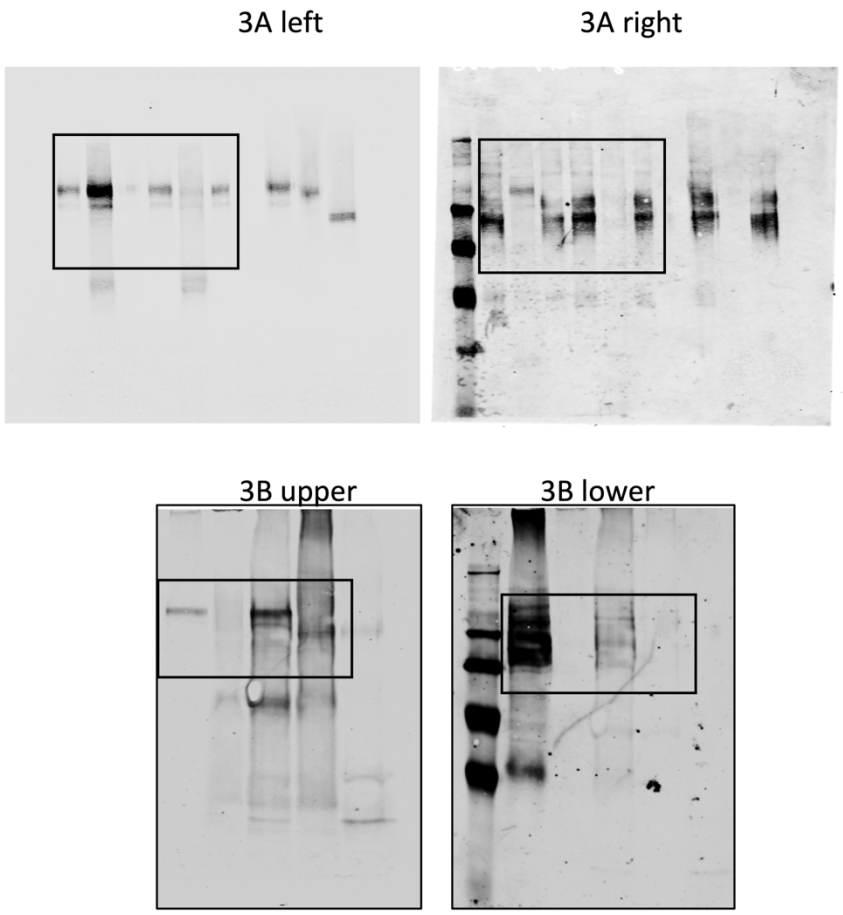

Fig. S8. Uncropped western blots for Fig. 3.

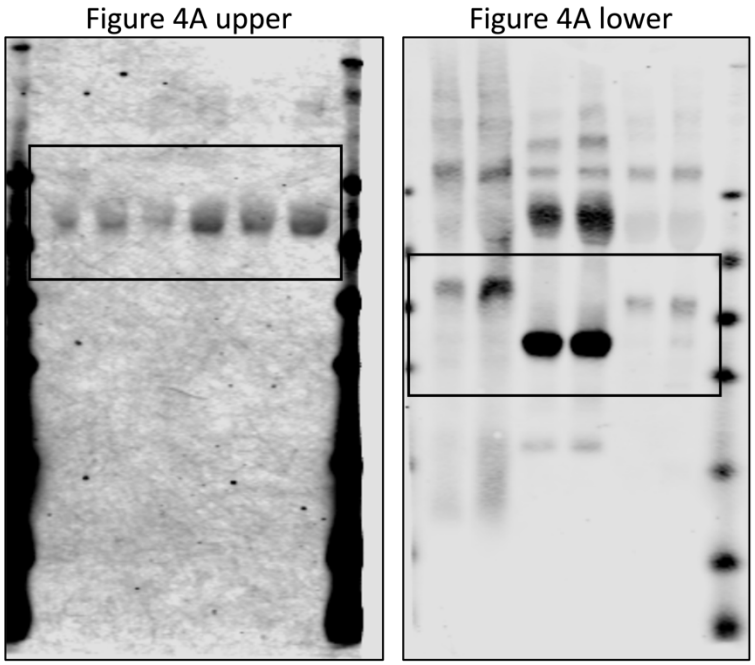

Fig. S9. Uncropped western blots for Fig. 4.

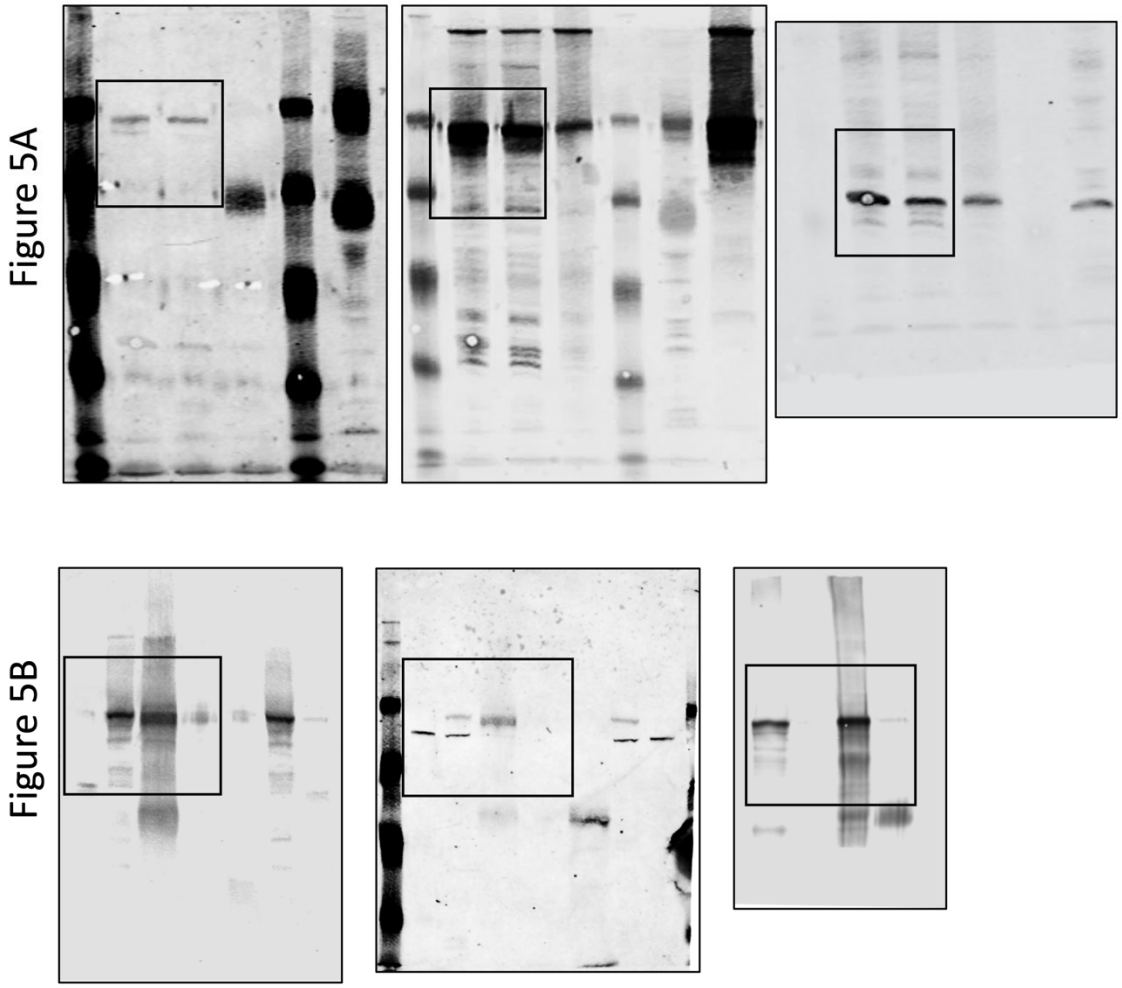

Fig. S10. Uncropped western blots for Fig. 5.

Table S1. Targets of the upregulated autoantibody (AAb)-antigen (Ag) complexes validated in 3 independent SCLC cohorts broken down time to diagnosis and stage at diagnosis. Coef, coefficient; dx, diagnosis.

Validated AAb-Ag Complex Targets	Target Entry Identifier	Mean control coef	Mean 1-2 years to dx coef (p-value)	Mean <1 year to dx coef (p-value)	Mean limited stage coef (p-value)	Mean extensive stage coef (p-value)
CDH5	P33151	-3.1E-16	0.23 (0.270)	1.32 (0.002)	0.58 (0.006)	0.56 (0.003)
CD133	O43490	1.72E-16	0.45 (0.244)	1.26 (0.0003)	0.57 (0.006)	0.69 (0.002)
SPINK1	P00995	0.036	1.22 (0.19)	1.19 (0.01)	0.50 (0.01)	0.63 (0.002)
CDH23	Q9H251	0.122	1.44 (0.02)	0.52 (0.18)	0.54 (0.04)	0.59 (0.01)
NLRP7	Q8WX94	-2E-16	0.73 (0.06)	0.99 (0.007)	0.58 (0.007)	1.02 (0.0008)
TFRC	P02786	-0.091	-0.38 (0.19)	0.39 (0.08)	0.55 (0.0009)	0.60 (0.0001
SPINT2	O43291	-3.7E-17	0.46 (0.20)	1.10 (0.01)	0.90 (0.0004)	0.69 (6.84E-05)
NADSYN1	Q6IA69	-2.3E-16	0.85 (0.01)	0.90 (0.045)	0.71 (0.002)	0.75 (0.0002)
HIF1A	Q16665	3.01E-16	0.62 (0.10)	1.24 (0.02)	0.64 (0.002)	0.93 (9.15E-05)
GRAP2	O75791	0.0053	1.36 (0.12)	1.00 (0.02)	0.65 (0.002)	0.76 (0.0008)
MAPRE1	Q15691	-0.003	0.23 (0.30)	1.25 (0.003)	0.64 (0.002)	0.77 (0.001)
INHA	P05111	-1.8E-16	0.46 (0.04)	1.03 (0.01)	2.25 (6.06E-07)	2.54 (4.6E-07)
PTEN	P60484	-1E-16	0.87 (0.07)	1.03 (0.03)	1.30 (3.76E-05)	1.48 (9.6E-06)
CTSB	P07858	0.007	0.87 (0.02)	0.81 (0.004)	1.07 (2.41E-06)	1.45 (3.97E-06)
B3GNT6	Q6ZMB0	-0.002	0.91 (0.008)	0.96 (0.05)	1.13 (4.73E-05)	1.04 (0.0008)
PLD3	Q8IV08	5.8E-08	1.14 (0.003)	1.03 (0.0007)	1.43 (7.99E-11)	1.27 (1.4E-07)
TIMP2	P16035	-8.2E-08	1.37 (0.001)	1.42 (0.0002)	0.85 (5.32E-05)	0.71 (0.0006)
NUDT5	P50583	0.0067	0.55 (0.10)	1.04 (0.003)	1.23 (1.44E-07)	1.32 (8.23E-07)
ANAPC2	Q9UJX6	-0.00916	0.58 (0.06)	0.37 (0.10)	0.35 (0.01)	0.45 (0.02)
GPLD1	P80108	0.0076	0.86 (0.04)	0.72 (0.06)	0.95 (5.86E-07)	1.07 (2.18E-05)
PTPRU	Q92729	-8.4E-17	0.73 (0.004)	0.67 (0.02)	0.27 (0.11)	0.38 (0.05)
CA9	Q16790	-0.01862	0.30 (0.22)	1.00 (0.02)	0.61 (0.001)	0.61 (0.0005)

Table S2. Autoantibody identified antigens are not commonly mutated in SCLC cell lines or tumors.

	Cancer Cell Line Encyclopedia (CCLE) *(24-25)* (n=51)		**George *et al. (26)* (n=110)**	
Gene	**Number of Variants**	**Variant Classification**	**Number of Variants**	**Variant Classification**
TFRC	1	1 missense	3	3 missense
CD133	6	1 slice site, 2 missense, 3 silent	2	1 nonsense, 1 missense
SPINT2	None		None	
CA9	4	1 silent, 3 missense	2	2 missense
PLD3	None		None	

Table S3. Peptide Sequences. Wildtype (WT) or post-translationally modified (PTM) peptide sequences

Peptide	WT Sequence	PTM Sequence
SPINT2-1	NVTDGSC	NVT{isoAsp}GSC
SPINT2-2	GGCDGNSN	GGC{isoAsp}GNSN
SPINT2-3	GGCDGNSN	GGCDG{isoAsp}SN
SPINT2-4	NAADSSVC	NAA{isoAsp}SSVC
SPINT2-5	CGNKNSYR	CGNK{isoAsp}SYR
SPINT2-6	RRQDSEDC	RRQ{isoAsp}SEDC
SPINT2-7	VERNSCN	VER{isoAsp}SCN
SPINK1-1	CYNELNGCTKI	CYNEL{isoAsp}GCTKI
SPINK1-2	LCFENRKRQT	LCFE{isoAsp}RKRQT
TIMP2-1	TQKKSLNHRYQMGC	TQKKSL{isoAsp}HRYQMGC
TIMP2-2	CVTEKNINGHQAKF	CVTEKNI{isoAsp}GHQAKF
TIMP2-3	CKAEGDGKMHI	CKAEG{isoAsp}GKMHI
TIMP2-4	CIKRSDGSCAW	CIKRS{isoAsp}GSCAW
TIMP2-5	CEKEVDSGNDI	CEKEV{isoAsp}SGNDI
TFRC-1	CDFPAARRLYW	CDFPAA{Cit}RLYW
TFRC-2	CDFPAARRLYW	CDFPAAR{Cit}LYW
TFRC-3	CNKVARAAA	CLYSA{Cit}GDF
TFRC-4	LNDRVMRVEYC	LNDRVM{Cit}VEYC
TFRC-5	LNDRVMRVEYC	LND{Cit}VMRVC
TFRC-6	CLYSARGDFFRATS	CGDFF{Cit}ATS
TFRC-7	CNKVARAAA	CNKVA{Cit}AAA