Supplemental Table-1 Relationships between CREB3L2 and clinicopathological characteristics in the Zhongshan cohort

Variables	Total (n=176)	CREB3L2 low (n=82)	CREB3L2 high (n=94)	χ2	*P*
Age				1.200	0.273
⩽50	76(43.2)	39	37		
>50	100(56.8)	43	57		
AFP				1.354	0.245
⩽20	65(36.9)	34	31		
>20	111(63.1)	48	63		
CEA				0.085	0.770
⩽5	162(92.0)	76	86		
>5	14(8.0)	6	8		
CA199				0.743	0.389
⩽36	134(76.1)	60	74		
>36	42(23.9)	22	20		
Cirrhosis				0.368	0.544
No	29(16.5)	15	14		
Yes	147(83.5)	67	80		
Tumor size					
⩽5	85(48.3)	40	45	0.014	0.904
>5	91(51.7)	42	49		
Differentiation					
I/II	111(63.1)	43	68	7.447	0.006
III/IV	65(36.9)	39	26		
Child grade					
A	166(94.3)	77	89	0.050	0.804
B/C	10(5.7)	5	5		
MVI					
Negative	100(56.8)	43	57	1.200	0.273
Positive	76(43.2)	39	37		
BCLC stage					
0/A	87(49.4)	48	39	5.092	0.024
B/C	89(50.6)	34	55		
ALT					
⩽40	102(58.0)	50	52	0.545	0.448
>40	74(42.0)	32	42		
AST					
⩽37	124(70.5)	62	62	1.686	0.194
>37	52(29.5)	20	32		

Figure legends

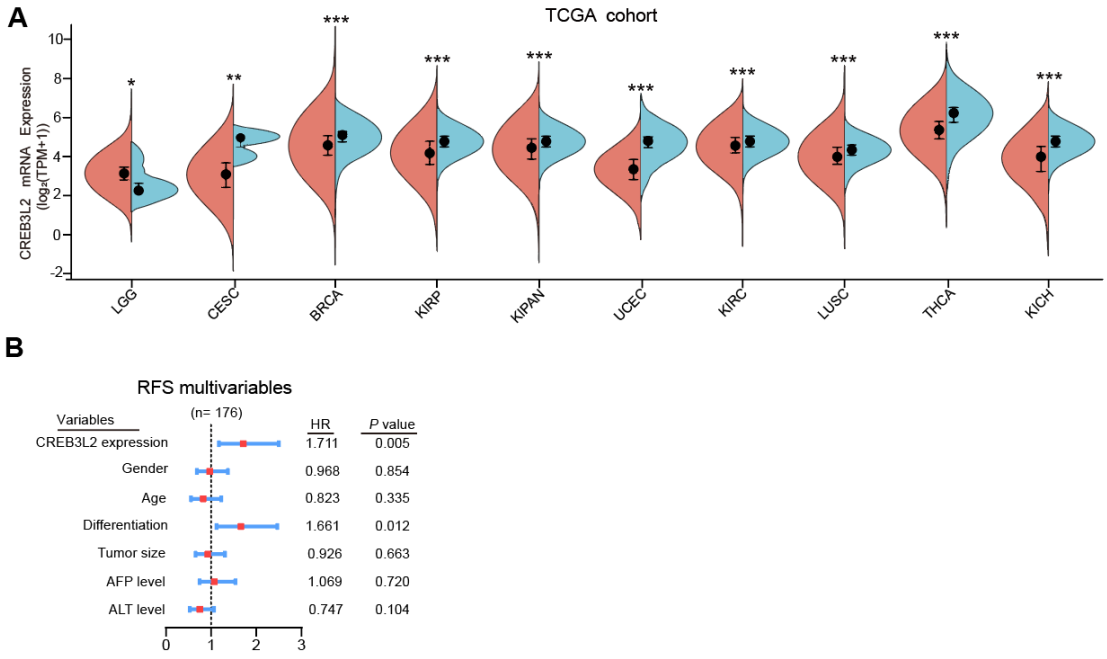
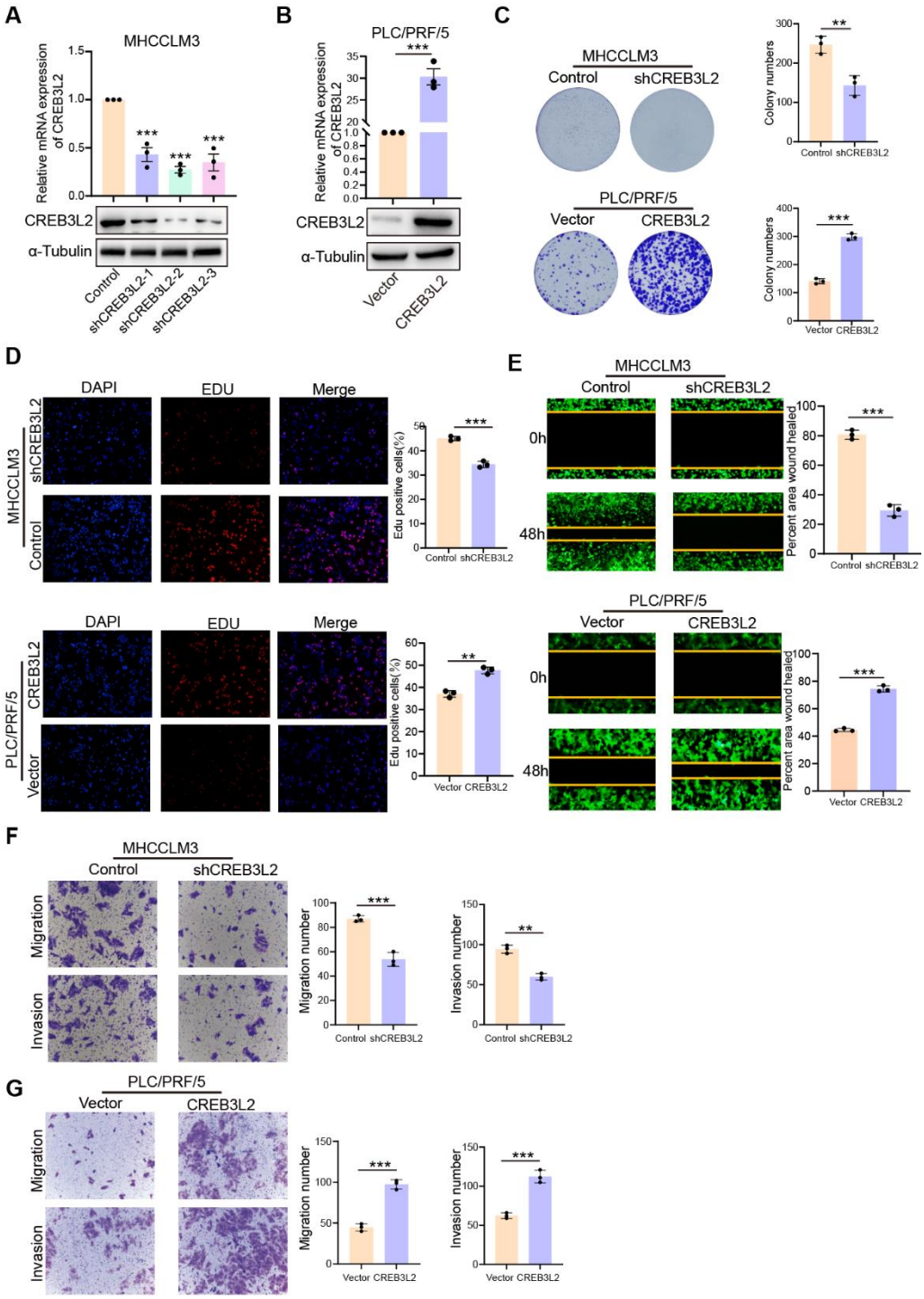


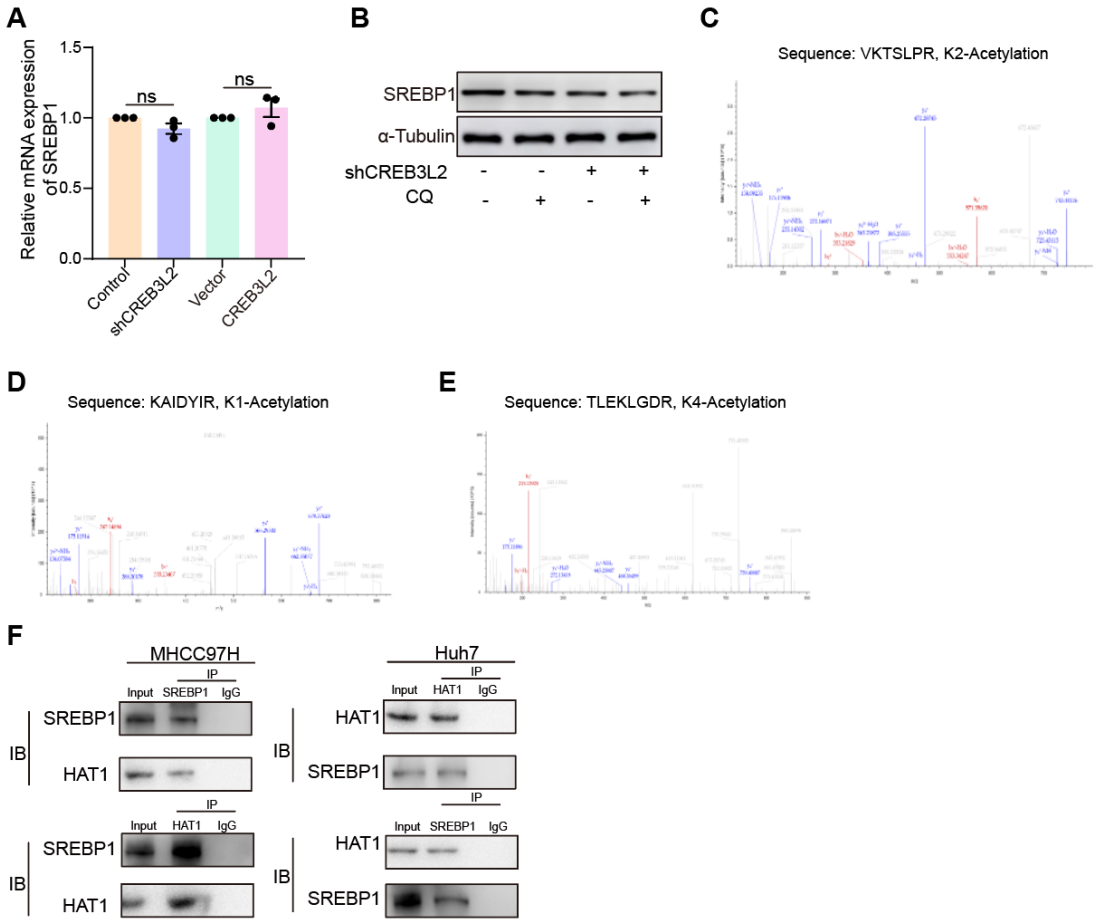
Figure S1 CREB3L2 is upregulated and correlates with poor prognosis in HCC.

(A) Relative expression of CREB3L2 in brain Lower Grade Glioma(LGG), cervical squamous cell carcinoma and endocervical adenocarcinoma(CESC), breast invasive carcinoma(BRCA), kidney renal papillary cell carcinoma(KIRP), pan-kidney cohort (KIPAN), uterine Corpus Endometrial Carcinoma(UCEC), kidney renal clear cell carcinoma(KIPC), lung squamous cell carcinoma(LUSC), thyroid carcinoma(THCA), kidney Chromophobe(KICH).**(B)** Multivariable Cox analysis of clinical prognostic parameters for RFS. *,$P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.



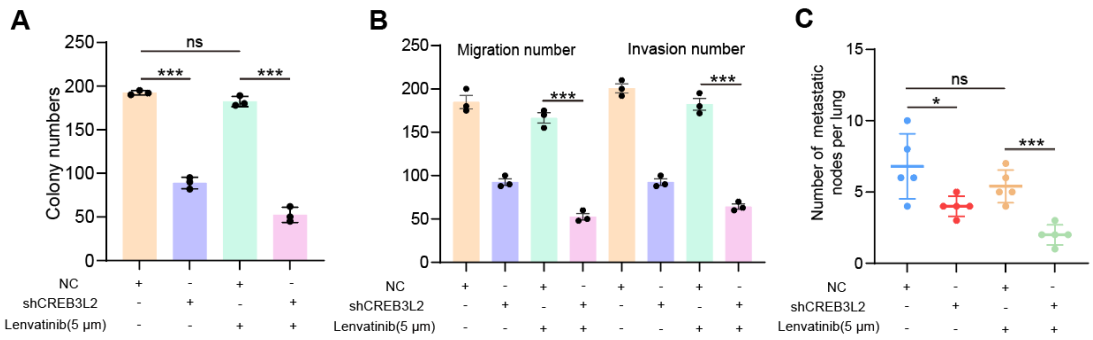
FigureS2　CREB3L2 facilitates HCC cell proliferation and metastasis in vitro

The transfection efficiency of knockdown and overexpression of CREB3L2 in LM3 and PLC cells was confirmed through qPCR **(A)** and Western blotting **(B)**. **(C-D)** Colony formation and EDU assays were performed after CREB3L2 was knocked down or overexpressed in LM3 and PLC cells. **(E-G)** After knockdown or overexpression of CREB3L2, the migration and invasion capabilities of HCC cells were assessed using scratch and transwell assays. *,$P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.



FigureS3 CREB3L2 attenuates ubiquitinated degradation of SREBP1 protein by enhancing HAT1-mediated acetylation

(A) The effect of CREB3L2 on SREBP1 mRNA levels in HCC cells.(B) The protein expression level of SREBP1 in 97H-shCREB3L2 cells in the presence of CQ. (C-E) Prediction of acetylation sites on SREBP1 through mass spectrometry analysis.(F) Co-IP demonstrated the combination of HAT1 and SREBP1 in Huh7 cells.



FigureS4 Targeting CREB3L2 reverses lenvatinib resistance in HCC

(A-B) Inhibition of CREB3L2 expression markedly enhances the effects of lenvatinib on cell proliferation, migration, and invasion. **(C)** The specific differences regarding the metastatic pulmonary nodules among distinct groups.