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	Gene name	Fold increase	P value	
SH2 domain-containing protein	p85a	3.49	0.0062(***)	Positive control
	C1-Ten	2.63	0.0057(**)	
	GRAP	1.99	0.0075(**)	
	Shc	1.93	0.005(**)	
	RIN3	1.84	0.0324(*)	
	SUPT6H	1.51	0.0541(*)	
	LYN	1.44	0.0223(*)	
	EAT2	1.82	0.2045	
	Crkl	1.60	0.0994(&)	
	NCK2	1.42	0.0961(&)	
	TYK2	1.32	0.1584	
	NCK1	1.26	0.3717	
	SH3BP2	1.24	0.1735	
	CHN1	1.19	0.3275	
	TEC	1.06	0.6528	
	RASA1	1.05	0.7504	
	Src	1.00	0.9896	
	Abl1	0.88	0.6256	
	Vav3	0.84	0.3529	
	cTEN	No expression		
	MATK	No expression		
	PKCθ	1.84	0.0008(***)	Postive control
	PKCε	1.48	0.0289(*)	Postive control
	PTP1B	1.45	0.1578	
	PTEN	0.83	0.3795	
	RhoA	1.12	0.5347	

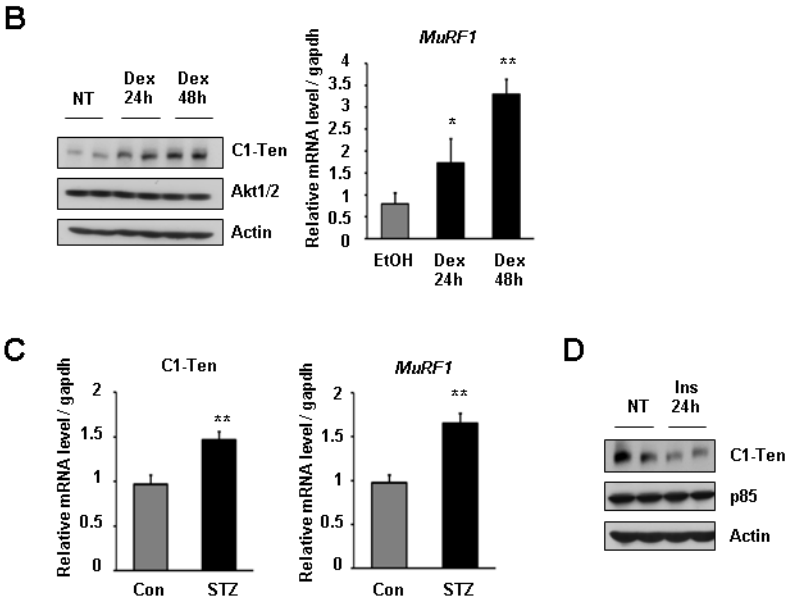

FIG S1 Upregulation of C1-Ten expression in catabolic muscle. (A) Expression analysis of SH2 domain-containing proteins in diabetic skeletal muscle. (B) C1-Ten expression was measured in L6 myotubes exposed to 100 nM dexamethasone at day 8 of differentiation (left

panel). Right panel, upregulation of *MuRF1* mRNA in L6 myotubes treated with 100 nM dexamethasone (n = 3). (C) C1-Ten level (left panel) and *MuRF1* level (right panel) in gastrocnemius muscles of streptozotocin (STZ)-treated rats. STZ (100 mg/kg) was dissolved in 0.1 M citrate buffer (pH 4.5) and injected into male rats (~180 g) by the tail vein. 3 days later, the rats were anesthetized, and muscle tissue was harvested (n = 5). *P*-value, compared to the control pair-fed rats. (D) C1-Ten level was measured in L6 myotubes treated with 100 nM insulin for 24 hr at day 6 of differentiation.

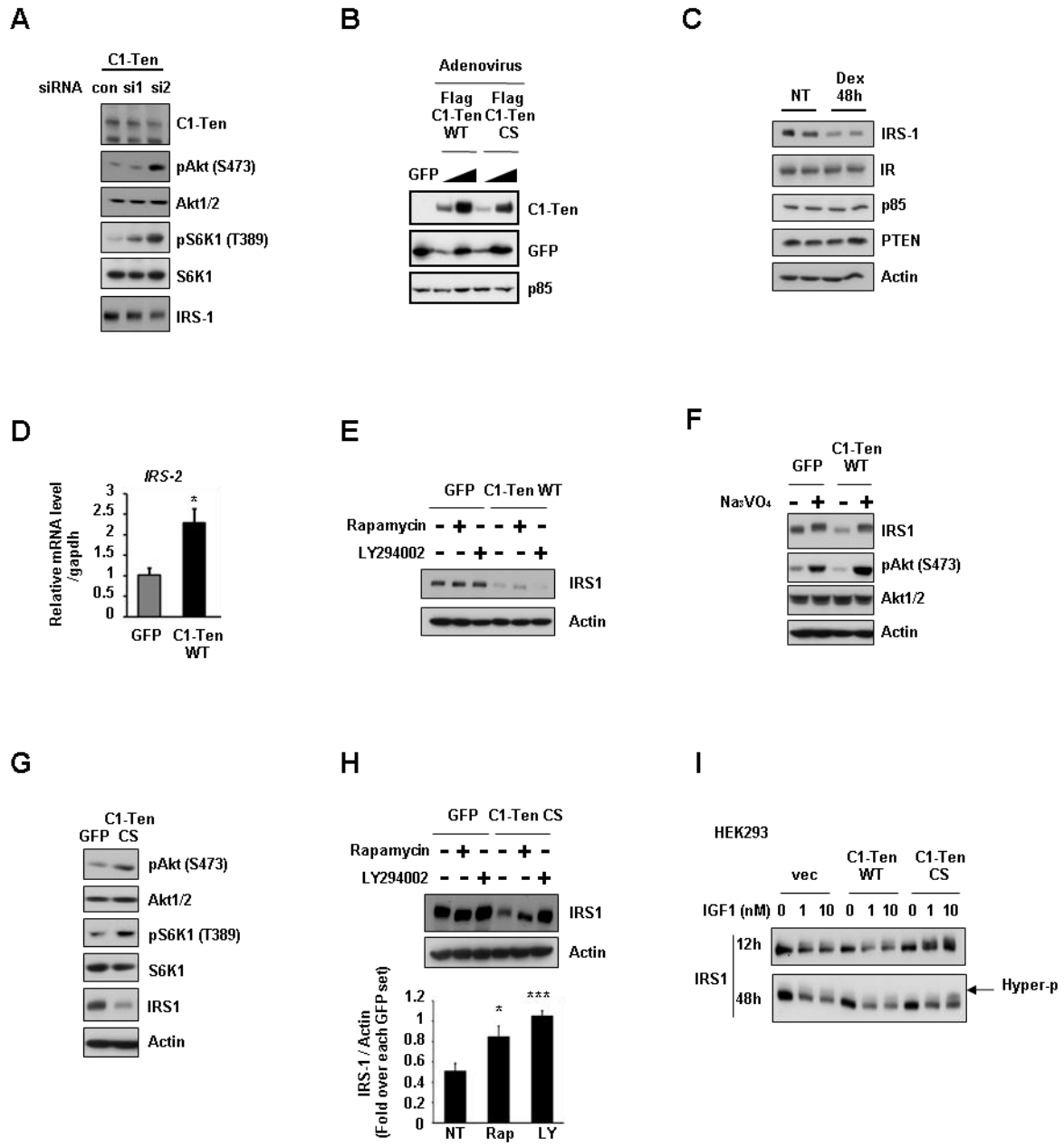

FIG S2 C1-Ten WT and C1-Ten CS reduce IRS-1 via different mechanisms. (A) Effect of C1-Ten depletion on Akt/S6K1 signaling. si1 and si2 were used to deplete C1-Ten. Knockdown was done for 24 hr on day 6 of differentiation. (B) Expression of recombinant adenovirus vectors Ad-GFP, Ad-C1-Ten WT, and Ad-C1-Ten CS. L6 myotubes, on day 8 of culture, were infected for 48 hr, followed by immunoblotting. (C) After L6 myotubes at 8 days of culture were treated with 100 nM dexamethasone, IRS-1, IR, p85, and PTEN levels were measured. (D) qRT- PCR of IRS-2 mRNA, normalized to *gapdh* (n = 3). (E) mTOR- and PI3K-indepndent degradation of IRS-1 by C1-Ten WT. GFP- and C1-Ten WT-expressing

myotubes were treated with 200 nM rapamycin or 10 μM LY294002 for 2 hr. (F) The effect of vanadate on C1-Ten-induced IRS-1 degradation was evaluated by the treatment of L6 myotubes with 2 mM Na_3VO_4 for 4 hr. (G) The effect of C1-Ten CS on IRS-1 and downstream signaling events. (H) The mTOR- and PI3K-dependent degradation of IRS-1 by C1-Ten CS was determined by treating GFP- and C1-Ten CS- expressing myotubes with 200 nM rapamycin or 10 μM LY294002 for 2 hr. Top panel, representative immunoblot; bottom panel, fold-change in IRS-1 was normalized to Actin relative to each GFP set (n = 4). *P*-value compared with NT set. (I) Effect of long-term IGF-1 stimulation on IRS-1 in C1-Ten-expressing HEK293 cells. HEK293 cells expressing each Flag construct were treated with 1 nM or 10 nM IGF-1.

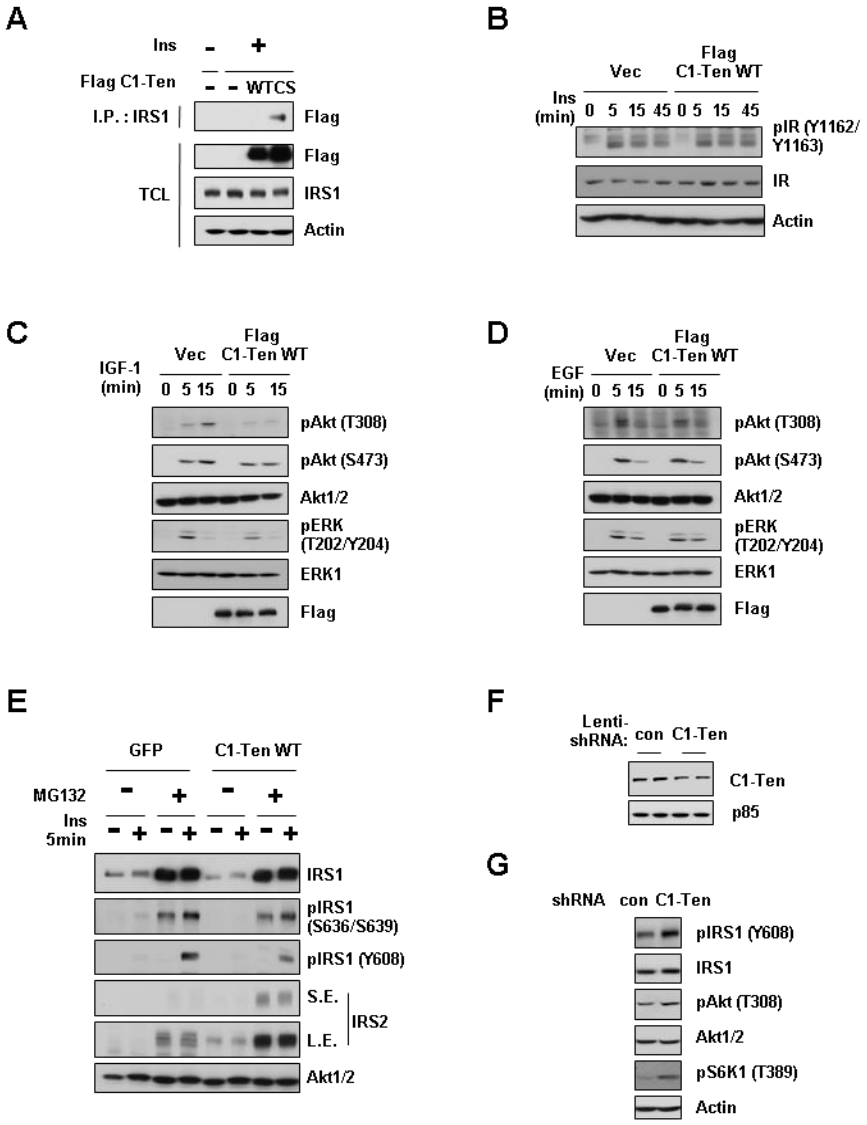

FIG S3 C1-Ten regulates IRS-1-mediated signaling. (A) Stable interaction of C1-Ten CS with IRS-1. Immunoprecipitation (IP) was performed with IRS-1 antibody and subjected to immunoblotting (IB) with anti-flag antibody. (B) Effect of C1-Ten on insulin receptor tyrosine phosphorylation. HEK293 cells were transfected with Flag vector alone or Flag C1-Ten WT. After 24 hr, the cells were serum starved for 18 hr, then treated with 50 nM insulin for indicated times. (C) Effect of C1-Ten on IGF-1 signaling in HEK293 cells. Cells were treated with 10 nM IGF-1. (D) Effect of C1-Ten on EGF signaling in HEK293 cells. Cells were treated with 2 nM EGF. (E) The effect of C1-Ten on the serine and tyrosine phosphorylation of IRS-1 was determined by treating serum-starved L6 myotubes with 20 μM MG132 for 2 hr, followed by stimulation with 50 nM insulin for 5 min. (F) C1-Ten knockdown in Glut4-expressing L6 myoblasts via lentivirus transduction. (G) Effects of C1-Ten knock-down on IRS-1-mediated signaling in L6 myoblasts.

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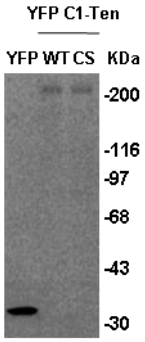

FIG S4 Expression of YFP constructs used for *in vivo* electroporation. (A) HEK293 cells were transfected with YFP vector, YFP C1-Ten WT, or YFP C1-Ten CS. After 48 hr, the cells were harvested and used for immunoblotting with GFP antibody.