SIGNAL TRANSDUCTION

Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1

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Despite the importance of glucose and amino acids for energy metabolism, interactions between the two nutrients are not well understood. We provide evidence for a role of leucyl-tRNA synthetase 1 (LARS1) in glucose-dependent control of leucine usage. Upon glucose starvation, LARS1 was phosphorylated by Unc-51 like autophagy activating kinase 1 (ULK1) at the residues crucial for leucine binding. The phosphorylated LARS1 showed decreased leucine binding, which may inhibit protein synthesis and help save energy. Leucine that is not used for anabolic processes may be available for catabolic pathway energy generation. The LARS1-mediated changes in leucine utilization might help support cell survival under glucose deprivation. Thus, depending on glucose availability, LARS1 may help regulate whether leucine is used for protein synthesis or energy production.

Cells integrate information on nutrient availability to survive under environmental stresses (*1*). Glucose and energy homeostasis is tightly regulated by metabolic organs (*2*). In muscle cells deprived of glucose, activity of anabolic pathways is decreased, and proteins are broken down to supply amino acids to oxidation pathways (*3*). However, it remains to be determined how amino acids are directed to anabolic or catabolic pathways under various conditions. Mechanistic target of rapamycin complex 1 (mTORC1) is a master regulator of anabolic pathways in response to nutrients (*4*). Rag guanosine triphosphatases (GTPases) are proposed to stimulate mTORC1 in response to both glucose and amino acids (*5*). Leucyl-tRNA synthetase 1 (LARS1) covalently couples leucine to its cognate tRNAs using adenosine triphosphate (ATP). LARS1 also senses intracellular leucine and helps convert $RagD^{GTP}$ to $RagD^{GDP}$ (GDP, guanosine diphosphate) (*6*–*8*). The function of LARS1 as both a leucine sensor and an ATP consumer led us to explore its possible role mediating glucose-dependent mTORC1 signaling.

We examined the GTP- or GDP-binding status of Rag GTPases. In the presence of glucose, Rag GTPases mainly existed in active form for mTORC1 activation (fig. S1A). Glucose-induced activation of mTORC1 was decreased in cells transfected with small interfering RNAs (siRNAs) for RagA and RagB, or RagC and RagD (fig. S1B). Overexpression of inactive or active RagB and RagD heterodimers inhibited or activated mTORC1, respectively, regardless of glucose availability (fig. S1, C and D).

We monitored contribution of LARS1 on mTORC1 activity, which was sensitive to the amount of LARS1 in the presence of both glucose and leucine, but not in the presence of leucine alone, suggesting that LARS1 senses leucine with the aid of glucose (fig. S2). Because leucine-to-mTORC1 activation is triggered by the binding of LARS1 and RagD (*6*), we investigated whether glucose might affect this interaction. In cells stimulated with glucose, LARS1 was enriched in lysosomes and localized with lysotracker (Fig. 1, A and B). Fluorescence resonance energy transfer (FRET) and coimmunoprecipitation (co-IP) experiments showed enhanced interaction of overexpressed and tagged LARS1 and RagD in glucose-rich conditions (Fig. 1, C and D). In transgenic (TG), wild-type (WT), and heterozygous (HET) mouse embryonic fibroblasts (MEFs), glucose-induced ribosomal protein S6 kinase (S6K) phosphorylation was positively correlated with the amount of LARS1 (Fig. 1E). However, alanyl-, isoleucyl-, and valyl-tRNA synthetases (AARS1, IARS1, and VARS1) did not show a similar effect (Fig. 1, F and G, and fig. S3), implying that LARS1 may be a specific positive mTORC1 regulator by glucose as well as leucine. S6K phosphorylation was sustained longer in cells overexpressing Myc-LARS1 after glucose withdrawal, whereas it was more rapidly lost in cells depleting LARS1 (Fig. 1H).

Although RagA mediates glucose-induced mTORC1 activation (*5*), the association of LARS1 and RagD was still enhanced in response to glucose in cells overexpressing $RagA^{GTP}$ (fig. S4). Although the mTORC1 pathway is inactivated by tuberous sclerosis complex 2 (TSC2) in glucose starvation (*9*), TSC2 knockout (KO) MEFs deprived of glucose still showed decreased S6K phosphorylation, indicating the existence of another regulation mechanism (fig. S5A). The mTORC1 activity was still positively correlated with the amount of LARS1 in TSC2 KO MEFs (fig. S5B). These results are consistent with glucose-induced activation of mTORC1 through the LARS1-RagD pathway.

Because glucose seemed to regulate leucine sensing ability of LARS1, we investigated post-translational modification of LARS1. LARS1 was phosphorylated on serine in cells deprived of glucose (fig. S6A). Through siRNA-based screening (*10*–*12*), suppression of adenosine 5′-monophosphate–activated protein kinase (AMPK) or Unc-51 like autophagy activating kinase 1 (ULK1) decreased LARS1 phosphorylation (fig. S6, B and C). ULK1 is activated by AMPK and is constitutively active when overexpressed (*11*, *13*). Overexpression of ULK1 increased LARS1 phosphorylation in cells even without active AMPK (fig. S6D). LARS1 pulled down ULK1 kinase domain in vitro (fig. S7A) and is phosphorylated in vitro by ULK1 WT, but not by catalytically inactive mutant (K46I) (fig. S7B) (*14*), indicating that ULK1 might directly phosphorylate LARS1. LARS1 was identified as a possible ULK1-interacting protein (*15*) and potential member of an autophagy network by mass spectrometry (MS) (*16*). Co-IP and FRET experiments showed that the association of overexpressed and tagged LARS1 and ULK1 was increased in cells deprived of glucose (Fig. 2, A and B, and fig. S7C). However, AARS1 was not bound to ULK1 (Fig. 2C), indicating some specificity of LARS1 and ULK1 interaction.

We focused on LARS1 S391 and S720, which are evolutionally conserved, as residues possibly phosphorylated by ULK1 on the basis of three criteria: LARS1 fragments phosphorylated in vitro, phosphorylated residues identified by MS, and consensus sequence predicting ULK1 substrates (*13*) (fig. S8, A to D). Although LARS1 Ser^{391}→Ala (S391A) and S720A showed decreased autoradiograph intensity compared with WT in in vitro kinase assay, S391A was phosphorylated less than S720A but similarly to 2SA (S391A/S720A) (Fig. 2D), which made us speculate that phosphorylation of S391 might be a prerequisite for that of S720. S391

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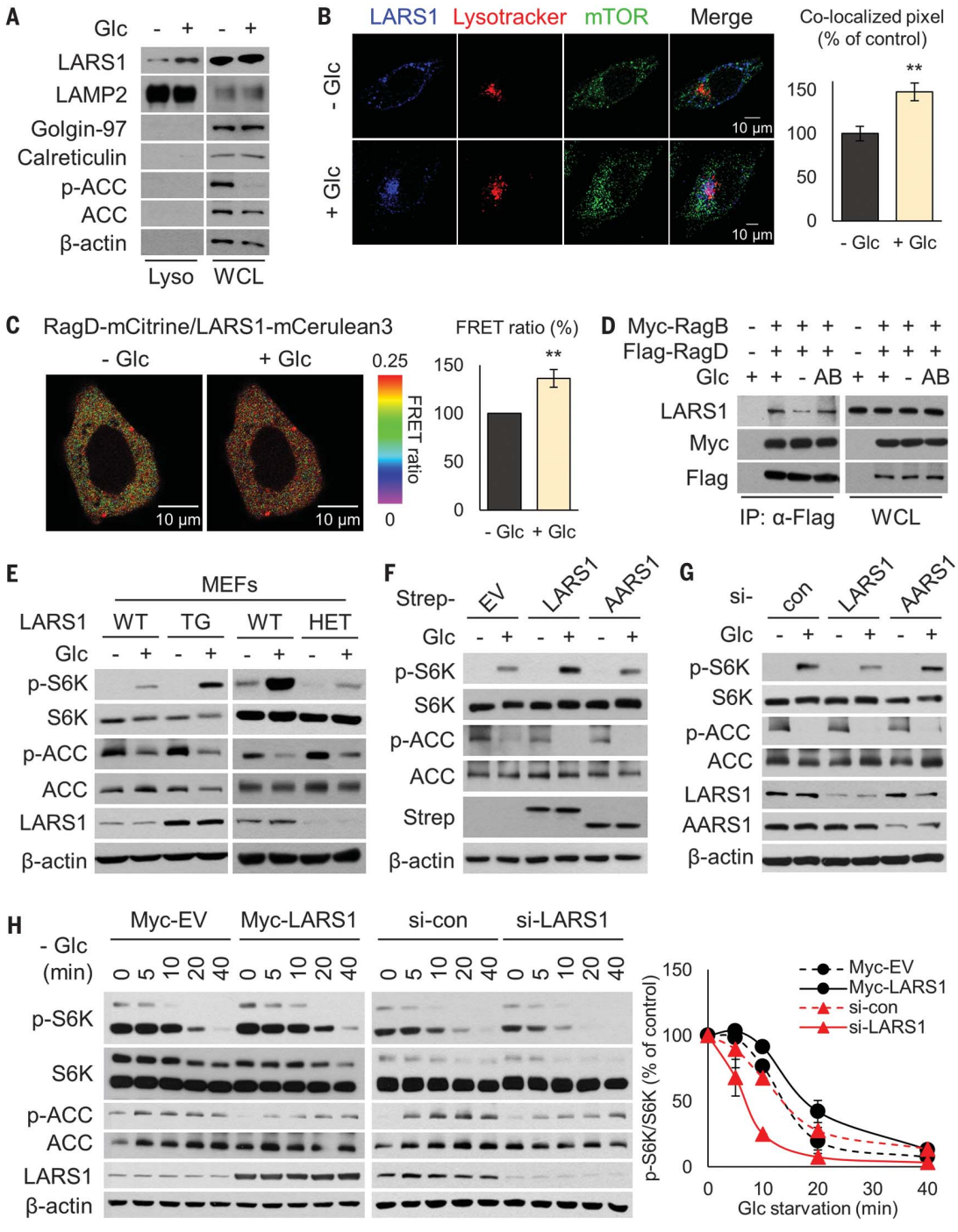

Fig. 1. Glucose induces the interaction of LARS1 and RagD for mTORC1 activation. (**A**) LARS1 located in lysosome was determined by immunoblot in human embryonic kidney 293T (HEK293T) cells. Glc, glucose; Lyso, lysosome; WCL, whole cell lysates; ACC, acetyl-CoA carboxylase; p, phosphorylation. (**B**) Localization of LARS1 with lysotracker was monitored by immunofluorescence in Hela cells ($n \geq 16$; unpaired t test; $^{**}P < 0.01$; mean ± SEM). (**C**) The interaction of overexpressed and tagged LARS1 and RagD in response to glucose was monitored by live FRET assay in CHO-K1 cells. The ratio of the fluorescence intensity mCitrine-RagD to mCerulean3-LARS1 with the excitation at 457 nm was measured ($n = 4$ per group; unpaired t test; $^{**}P < 0.01$; mean ± SEM). (**D**) LARS1-RagD interaction in response to glucose was determined by co-IP in HEK293T cells. AB, add back. (**E**) Glucose-dependent mTORC1 activities estimated from S6K phosphorylation in LARS1 WT, TG, and HET MEFs. (**F** and **G**) The glucose-dependent mTORC1 activities were also determined by up-regulation (F) and down-regulation (G) of LARS1 and AARS1. Strep, strep-tag; EV, empty vector; si, small interfering RNAs; con, nontarget control. (**H**) The effect of LARS1 on the remaining mTORC1 activity under glucose starvation was observed in HEK293T cells.

phosphorylation seemed to induce conformational changes based on circular dichroism (CD) and limited proteolysis. Although LARS1 WT, S391A, and S391E had similar secondary structure compositions, tertiary structure was different in S391E (Fig. 2E and fig. S9). We made an antibody specific to phosphoLARS1 (S720). It was validated by immunoblotting purified LARS1 with S720 phosphorylation (*17*) and by LARS1 phosphorylated in cells deprived of glucose (Fig. 2, F and G, and fig. S10). ULK1 phosphorylated S720 of LARS1 WT and S391E but not that of S391A (Fig. 2H). ULK1 suppression using siRNAs and SBI-0206965 (*13*) decreased LARS1 S720 phosphorylation (Fig. 2, I and J). Thus, ULK1 may phosphorylate LARS1 at S391 first and then S720 in glucose deprivation.

Because LARS1 S720 is located within a KMSKS motif, which is crucial for ATP binding (fig. S8D) (*18*), we tested the effect of LARS1 phosphorylation on ATP binding. LARS1 mutants with mutations at S720 (S720 mutants) had decreased ATP-binding affinity, whereas S391 mutants still bound to ATP (fig. S11A). Leucine bound to LARS1 better in the presence of ATP, which is consistent with the result that LARS1 S720 mutants had decreased leucine-binding capability (fig. S11B and Fig. 3A). Furthermore, leucine did not bind to five additional mutants substituting S720 for Asp, Val, Asn, Cys, or Arg (fig. S11C), suggesting that serine is critical for the binding of leucine as well as ATP. We monitored catalytic activity of

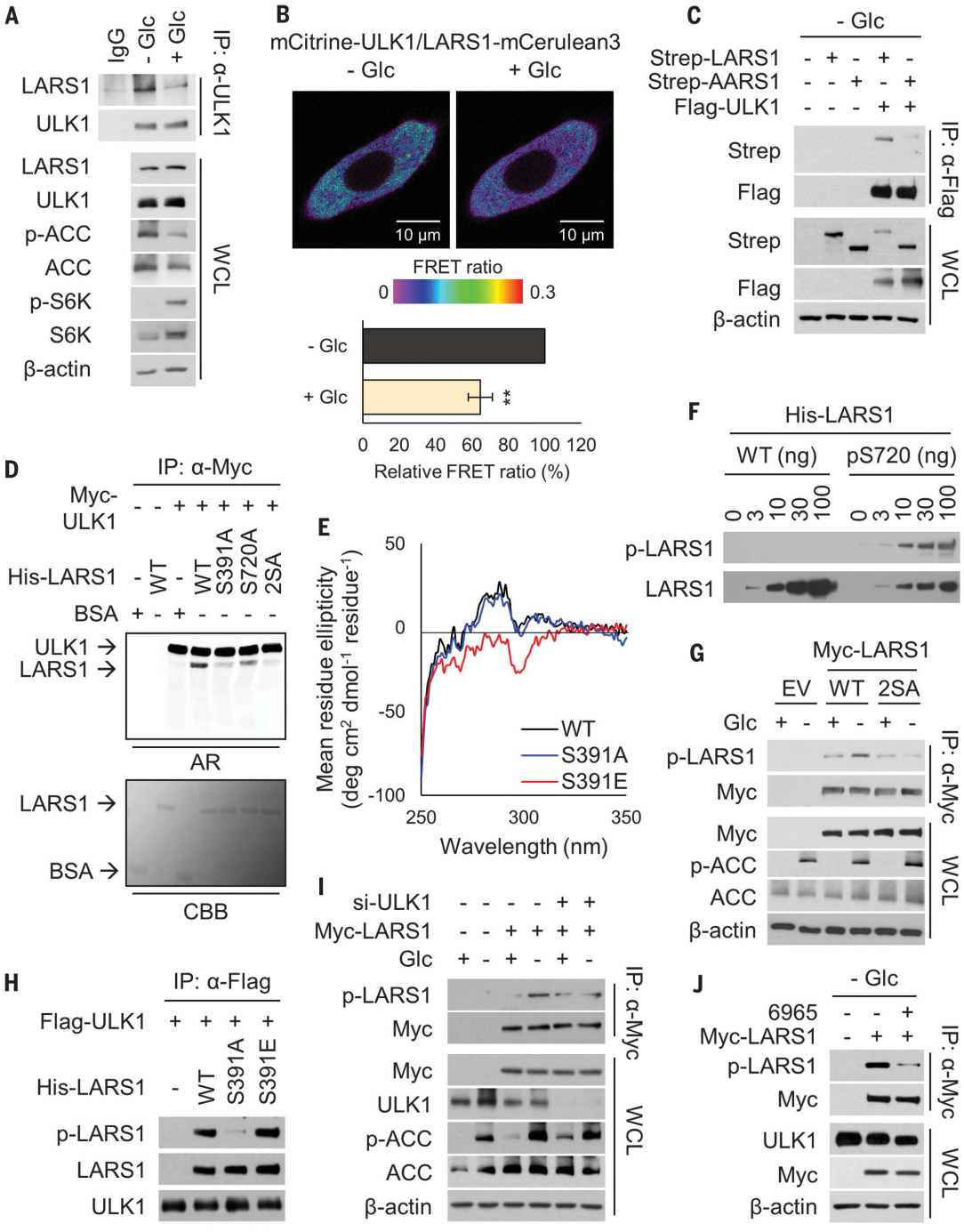

Fig. 2. Glucose starvation–dependent phosphorylation of LARS1 by ULK1. (**A**) Co-IP of LARS1 with ULK1 in response to glucose was monitored in HEK293T cells. IgG, immunoglobulin G. (**B**) The interaction of LARS1 with ULK1 in response to glucose was determined by live FRET assay in CHO-K1 cells (n = 3 per group; unpaired t test; $^{**}P < 0.01$; mean ± SEM). (**C**) Co-IP of ULK1 with LARS1 or AARS1 was determined in HEK293T cells. (**D**) In vitro kinase assay using [^{32}P]ATP. Radioactive labeling of ULK1 and LARS1 was determined by autoradiography. BSA, bovine serum albumin; AR, autoradiograph; CBB, Coomassie brilliant blue. S, serine; A, alanine. (**E**) Near-ultraviolet CD spectrum of His-LARS1 WT and mutants. E, glutamate. (**F**) Immunoblot of purified His-LARS1 WT and pS720. (**G**) Glucose starvation–induced LARS1 S720 phosphorylation in HEK293T cells. (**H**) Immunoblot of S720 phosphorylation after kinase assay using LARS1 WT and mutants. (**I** and **J**) Phosphorylation of LARS1 S720 with the suppression of ULK1 by siRNAs (I) or inhibitor (J) was determined in HEK293T cells. 6965, SBI-0206965.

LARS1. Leu-AMP and Leu-tRNA production of LARS1 2SE (S391E/S720E) and S720E were blocked, whereas LARS1 S391A and S391E showed comparable activity to WT. 2SA and S720A retained ~10% of WT activity, implying a possible weak interaction with leucine (fig. S11D and Fig. 3B). Cells overexpressing LARS1 2SE and S720E showed reduced leucine incorporation (fig. S11E). Thus, ULK1-mediated LARS1 phosphorylation appears to reduce ATP and leucine binding, leading to inhibition of leucylation.

We investigated mTORC1-stimulating activity of LARS1. LARS1 mutants showed reduced translocation to lysosome (fig. S12A), and 2SE and S720E did not interact with RagD, whereas 2SA and S720A showed weak binding. LARS1 S391 mutants also showed weaker interaction compared with WT despite its leucine-binding capability (Fig. 3C and fig. S12, A and B). LARS1 mutants did not restore S6K phosphorylation completely, whereas WT did. It was more decreased in cells expressing 2SE and S720E than the other mutants (Fig. 3D). Weaker effects of 2SA and S720A might reflect incomplete blocking of LARS1 and leucine binding. Cells expressing LARS1 mutants showed decreased cell size and increased autophagy compared with WT-expressing cells, as measured by forward scattering, amounts of microtubule-associated protein 1 light chain 3 (LC3)–phosphatidylethanolamine conjugate (LC3 II), and green fluorescent protein (GFP)–LC3 puncta formation (fig. S12, C to G, and Fig. 3E). Thus, changing leucine binding capability of LARS1 may regulate leucylation and

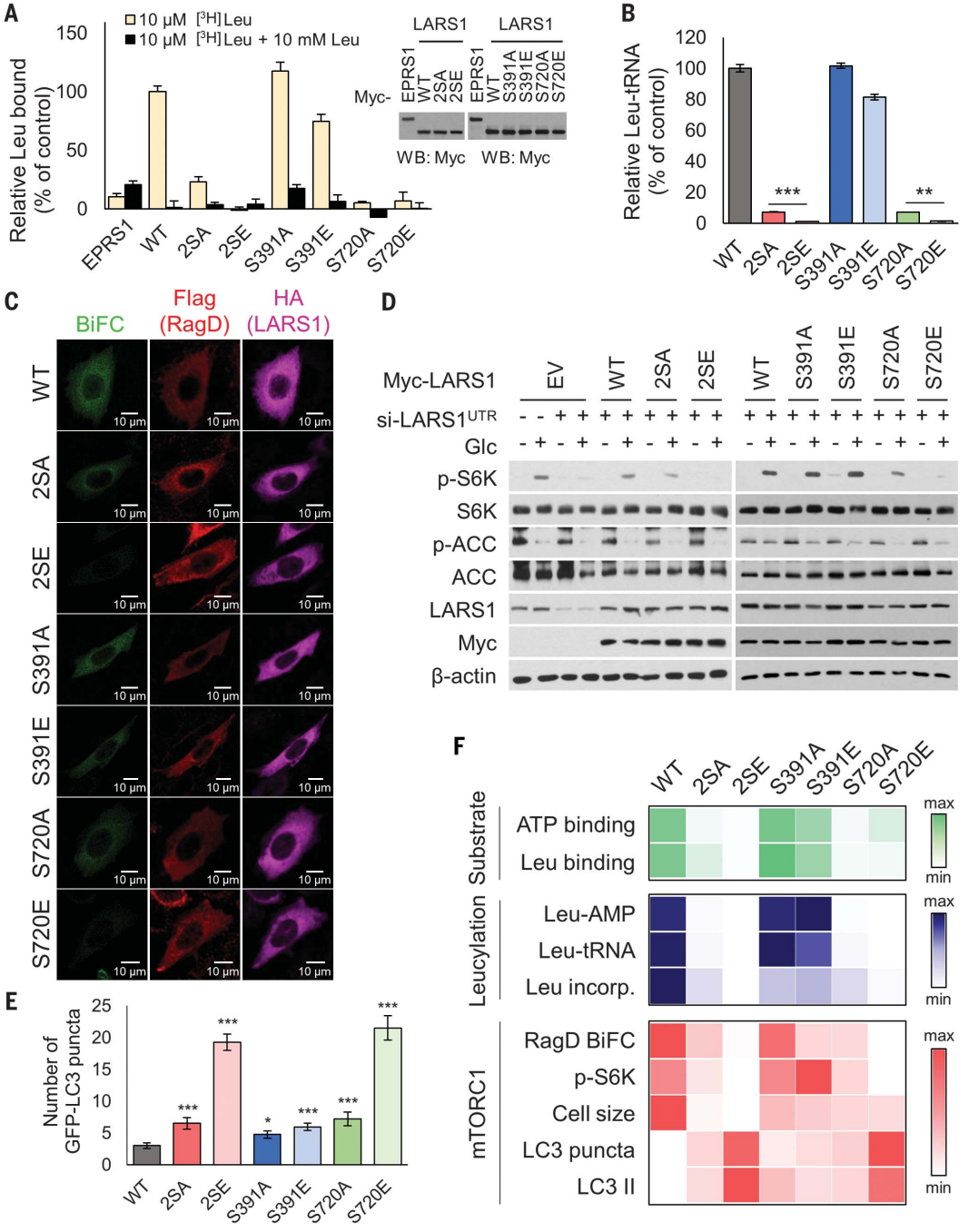

Fig. 3. Effects of LARS1 phosphorylation on catalytic and noncatalytic activities for protein synthesis. (**A**) The amount of leucine bound to LARS1 WT and mutants was quantified. The abundance of EPRS1, LARS1 WT, and mutants was determined by immunoblot (n = 3 per group; unpaired t test; mean ± SEM). EPRS1, glutamyl-prolyl-tRNA synthetase 1; WB, Western blot. (**B**) The catalytic activity of LARS1 WT and mutants was determined by Leu-tRNA production (n = 3 per group; mean ± SEM). (**C**) The interaction of LARS1 WT and mutants with RagD was determined by bimolecular fluorescence complementation (BiFC) in CHO-K1 cells. (**D**) The effect of LARS1 WT and mutants on mTORC1 activation was estimated by phosphorylation of S6K in HEK293T cells. (**E**) The effect of LARS1 WT and mutants on the formation of GFP-LC3 puncta was evaluated in HEK293T cells ($n \geq 51$; mean ± SEM). (**F**) The contribution of LARS1 WT and mutants on substrate binding, leucylation activity, and mTORC1 stimulation activity was summarized as a heat map. Experimental detail in figs. S11 and S12. Unpaired t test; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

mTORC1-dependent physiology under glucose starvation (Fig. 3F).

Because autophagy contributes to starvation responses and is regulated by mTORC1 and ULK1 (*19*), we examined functional relationship of LARS1 and autophagy. LARS1 negatively affected the autophagy response to glucose deprivation (fig. S13, A and B). Conversely, when inhibiting autophagy with bafilomycin A, LARS1 phosphorylation and LARS1-mediated mTORC1 regulation were still observed to be dependent on glucose availability (fig. S13, C to E).

Amino acids are used not only as building blocks for protein synthesis but also as a carbon source for energy production (*3*), and leucine catabolism is inhibited by glucose (*20*). Therefore, we examined the direction of leucine usage in glucose deprivation. We used rhabdomyosarcoma (RD) cell lines, for high expression of leucine catabolic enzymes (LCEs) in muscle (*21*). Leucine increased ATP concentration and decreased cytotoxicity in cells deprived of glucose (fig. S14). mRNAs of some LCEs were more abundant in the absence of glucose (fig. S15, A and B). Suppression of LCEs decreased ATP concentration and increased cytotoxicity under glucose restriction (fig. S15, C to E), implying the significance of leucine catabolism in glucose starvation.

To monitor the effect of LARS1 phosphorylation on leucine catabolism, the fraction of ^{13}C-labeled citrate and malate converted from $^{13}C_6$-leucine was determined (fig. S16A). These fractions were increased in cells expressing LARS1 2SE compared with WT, suggesting an increased leucine contribution to tricarboxylic acid cycle intermediates (Fig. 4, A and B, and fig. S16, B and C). Investigation of glutamine

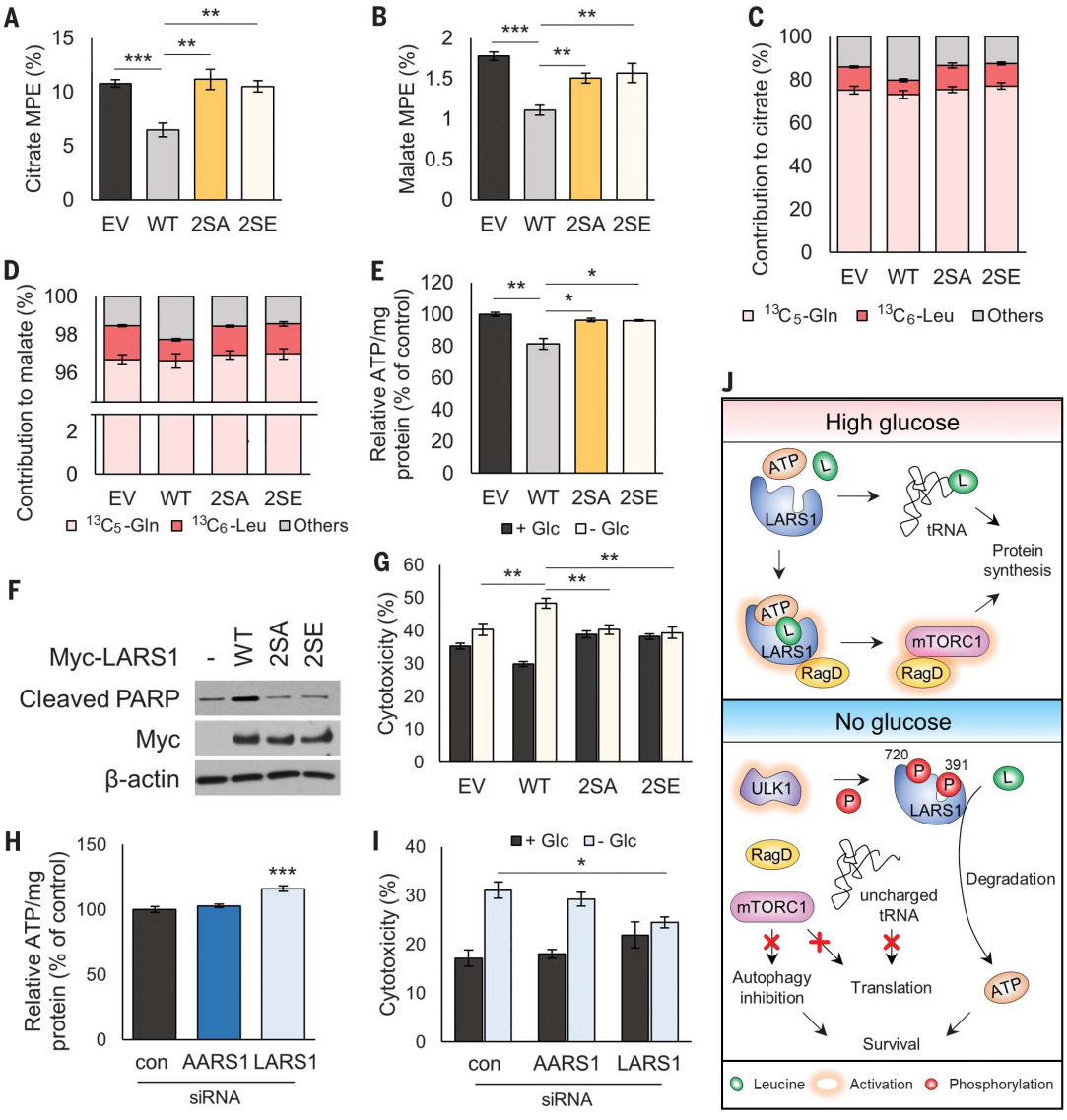

Fig. 4. LARS1 phosphorylation makes leucine more available for catabolism. (**A** to **D**) RD cells stably expressing LARS1 WT and mutants (RD^{LARS1} stable cells) were transfected with $siLARS1^{UTR}$ to suppress endogenous LARS1 and incubated with $^{13}C_6$-leucine or $^{13}C_5$-glutamine. The fraction of ^{13}C-labeled citrate and malate was measured by liquid chromatography–mass spectrometry ($n \geq 3$; mean ± SEM). MPE, molar percent enrichment. The contribution to total citrate or malate from leucine and glutamine was visualized in (C) and (D). (**E**) ATP levels were determined in RD^{LARS1} stable cells with $siLARS1^{UTR}$ using luminescence assay ($n = 3$ per group; mean ± SEM). (**F** and **G**) RD^{LARS1} stable cells were transfected with $siLARS1^{UTR}$ and glucose starvation–induced cell death was determined by the PARP cleavage and LDH assay ($n = 5$ per group; mean ± SEM). (**H**) The amount of ATP in RD cells starved of glucose was quantified by luminescence assay ($n = 6$ per group; mean ± SEM). (**I**) Cytotoxicity was determined by LDH assay in RD cells ($n = 5$ per group; mean ± SEM). (**J**) Schematic model of LARS1 roles in the control of glucose-dependent leucine metabolism. Unpaired t test; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

degradation (fig. S17A) (*22*) indicated that oxidative glutamine metabolism was decreased in cells expressing LARS1 WT compared with 2SE as monitored by m+4 citrate and m+4 malate (fig. S17, B and C) (*23*). When analyzing the source of total citrate and malate, the contribution of leucine seemed to be the second most common (Fig. 4, C and D).

ATP concentration was increased in cells expressing LARS1 2SE compared with WT under glucose deprivation (Fig. 4E). Monitoring the poly(ADP-ribose) polymerase (PARP) cleavage and activity of lactate dehydrogenase (LDH) showed that cytotoxicity was decreased in cells expressing LARS1 mutants (Fig. 4, F and G). Whereas AARS1 did not show the similar effect (Fig. 4, H and I), both the fraction of leucine-derived citrate and malate and the ATP concentration were increased and cytotoxicity was decreased by the depletion of IARS1 and VARS1 (fig. S18). Thus, although leucine regulates the mTORC1 pathway through specific LARS1 and RagD interaction, three branched-chain amino acids (BCAAs) appear to be similarly important for protecting cells under glucose starvation because degradation of one BCAA is positively correlated with that of others (*21*, *24*).

Because nutrient deprivation induces cell death caused by metabolic imbalance, understanding metabolic changes is crucial (*3*, *25*, *26*). We propose that LARS1 mediates defense under glucose starvation by rebalancing leucine metabolism. Upon sensing leucine in the presence of glucose, LARS1 supports translation by leucylating tRNA and by activating mTORC1. However, in the absence of glucose, LARS1 phosphorylated by ULK1 loses its leucine binding capability, decreasing both activities, thus leading to the inhibition of protein synthesis and activation of autophagy. In this way, phosphorylated LARS1 may save ATP consumption and allow leucine to be used for ATP generation, which together provide the tolerance against glucose starvation (Fig. 4J).

In muscle, the major energy source changes from glucose to ketone bodies during starvation (*27*). Because leucine is a potent mTORC1 activator and is an exclusively ketogenic amino acid (*28*), changing leucine metabolism might help defend against glucose starvation in muscle.

REFERENCES AND NOTES

1. P. B. Soeters, *Nestle Nutr. Inst. Workshop Ser.* **82**, 17–25 (2015).
2. J. D. Rabinowitz, E. White, *Science* **330**, 1344–1348 (2010).
3. A. Valerio, G. D'Antona, E. Nisoli, *Aging* **3**, 464–478 (2011).
4. R. A. Saxton, D. M. Sabatini, *Cell* **168**, 960–976 (2017).
5. A. Efeyan *et al.*, *Nature* **493**, 679–683 (2013).
6. J. M. Han *et al.*, *Cell* **149**, 410–424 (2012).
7. J. H. Kim *et al.*, *Nat. Commun.* **8**, 732 (2017).
8. M. Lee *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **115**, E5279–E5288 (2018).

9. K. Inoki, T. Zhu, K. L. Guan, *Cell* **115**, 577–590 (2003).
10. S. Horman *et al.*, *Curr. Biol.* **12**, 1419–1423 (2002).
11. F. McAlpine, L. E. Williamson, S. A. Tooze, E. Y. Chan, *Autophagy* **9**, 361–373 (2013).
12. S. Shin *et al.*, *Mol. Cell* **59**, 382–398 (2015).
13. D. F. Egan *et al.*, *Mol. Cell* **59**, 285–297 (2015).
14. E. Y. Chan, A. Longatti, N. C. McKnight, S. A. Tooze, *Mol. Cell. Biol.* **29**, 157–171 (2009).
15. A. D. Rouillard *et al.*, *Database* **2016**, baw100 (2016).
16. C. Behrends, M. E. Sowa, S. P. Gygi, J. W. Harper, *Nature* **466**, 68–76 (2010).
17. H. S. Park *et al.*, *Science* **333**, 1151–1154 (2011).
18. J. J. Burbaum, P. Schimmel, *J. Biol. Chem.* **266**, 16965–16968 (1991).
19. J. Kim, M. Kundu, B. Viollet, K. L. Guan, *Nat. Cell Biol.* **13**, 132–141 (2011).
20. D. Shao *et al.*, *Nat. Commun.* **9**, 2935 (2018).
21. J. T. Brosnan, M. E. Brosnan, *J. Nutr.* **136** (suppl.), 207S–211S (2006).
22. C. Yang *et al.*, *Mol. Cell* **56**, 414–424 (2014).
23. B. Kim, J. Li, C. Jang, Z. Arany, *EMBO J.* **36**, 2321–2333 (2017).
24. R. Paxton, R. A. Harris, *Arch. Biochem. Biophys.* **231**, 48–57 (1984).
25. A. Y. Choo *et al.*, *Mol. Cell* **38**, 487–499 (2010).
26. G. Leprivier *et al.*, *Cell* **153**, 1064–1079 (2013).
27. J. M. Argilés, N. Campos, J. M. Lopez-Pedrosa, R. Rueda, L. Rodriguez-Mañas, *J. Am. Med. Dir. Assoc.* **17**, 789–796 (2016).
28. M. G. Carlson, W. L. Snead, P. J. Campbell, *Am. J. Clin. Nutr.* **60**, 29–36 (1994).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S18
References (*29*–*33*)

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Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1

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A tRNA synthase in metabolic control

Leucyl-tRNA synthetase 1 (LARS1), which covalently couples leucine to its cognate transfer RNAs (tRNAs), appears to have broader roles in the control of leucine metabolism. The enzyme also serves as a leucine sensor for the mechanistic target of rapamycin complex 1 (mTORC1), which regulates protein synthesis, metabolism, autophagy, and cell growth. Yoon *et al.* show that in cells deprived of glucose, LARS1 is phosphorylated by Unc-51 like autophagy activating kinase 1 (see the Perspective by Lehman and Abraham). This phosphorylation decreases leucine binding to LARS1 and, in turn, should decrease translation, reduce activation of mTORC1, and perhaps free up leucine for use in the generation of adenosine triphosphate in glucose-starved cells.

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