Reduced REDD1 expression contributes to activation of mTORC1 following electrically induced muscle contraction

Department of Cellular and Molecular Physiology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania

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Gordon BS, Steiner JL, Lang CH, Jefferson LS, Kimball SR. Reduced REDD1 expression contributes to activation of mTORC1 following electrically induced muscle contraction. Am J Physiol Endocrinol Metab 307: E703–E711, 2014. First published August 26, 2014; doi:10.1152/ajpendo.00250.2014.—Regulated in DNA damage and development 1 (REDD1) is a repressor of mTOR complex 1 (mTORC1) signaling. In humans, REDD1 mRNA expression in skeletal muscle is repressed following resistance exercise in association with activation of mTORC1. However, whether REDD1 protein expression is also reduced after exercise and if so to what extent the loss contributes to exercise-induced activation of mTORC1 is unknown. Thus, the purpose of the present study was to examine the role of REDD1 in governing the response of mTORC1 and protein synthesis to a single bout of muscle contractions. Eccentric contractions of the tibialis anterior were elicited via electrical stimulation of the sciatic nerve in male mice in either the fasted or fed state or in fasted wild-type or REDD1-null mice. Four hours postconstrictions, mTORC1 signaling and protein synthesis were elevated in fasted mice in association with repressed REDD1 expression relative to nonstimulated controls. Feeding coupled with contractions further elevated mTORC1 signaling, whereas REDD1 protein expression was repressed compared with either feeding or contractions alone. Basal mTORC1 signaling and protein synthesis were elevated in REDD1-null compared with wild-type mice. The magnitude of the increase in mTORC1 signaling was similar in both wild-type and REDD1-null mice, but, unlike wild-type mice, muscle contractions did not stimulate protein synthesis in mice deficient for REDD1, presumably because basal rates were already elevated. Overall, the data demonstrate that REDD1 expression contributes to the modulation of mTORC1 signaling following feeding- and contraction-induced activation of the pathway.

SKELETAL MUSCLE MASS IS REGULATED by the balance between rates of protein synthesis and protein degradation. Shifting the balance in favor of net protein synthesis results in muscle hypertrophy while a change in favor of net degradation results in muscle atrophy (46). Chronic resistance exercise can lead to muscle hypertrophy, at least in part, by enhancing net synthesis primarily via stimulation of signaling through the mechanistic target of rapamycin in complex 1 (mTORC1) (8, 23, 37). The protein kinase mTORC1 integrates a variety of cellular stimuli to regulate mRNA translation through direct phosphorylation of the 70-kDa ribosomal protein S6 kinase 1 (p70 S6K1) and the eukaryotic initiation factor 4E binding protein 1 (4E-BP1) (13–15, 25). Indeed, phosphorylation of both 4E-BP1 and p70 S6K1 are increased following resistance exercise in humans (19).

In both humans and rats, inhibition of mTORC1 by treatment with rapamycin blunts the nutrient- and exercise-induced stimulation of rates of protein synthesis and mTORC1 signaling (1, 18, 20, 34, 36, 49). Furthermore, chronic inhibition of mTORC1 by rapamycin administration abolishes the overload-induced hypertrophy following synergistic ablation in mice, whereas this effect is not seen in mice expressing a rapamycin-insensitive mutant form of mTOR (4, 23). Unfortunately, the resistance exercise-induced stimulation of protein synthesis and mTORC1 signaling are repressed or nonexistent in populations such as the elderly (22, 26, 27). Thus, a greater understanding of the regulatory mechanisms that govern the anabolic response following resistance exercise is necessary to provide effective therapeutic measures to preserve muscle mass.

Signaling through mTORC1 is regulated by a variety of mechanisms, including changes in expression of regulated in DNA damage and development 1 (REDD1) (9, 16, 47). A number of growth-inhibitory stimuli, including hypoxia, endoplasmic reticulum (ER) stress, starvation, and glucocorticoids, induce REDD1 expression (11, 33, 42, 47). Conversely, REDD1 expression is repressed in response to growth-promoting stimuli (40). Recently, it has been shown that REDD1 mRNA expression in skeletal muscle is repressed in humans following resistance exercise, suggesting a potential role for REDD1 in the exercise-induced stimulation of signaling through mTORC1 and subsequent rates of protein synthesis (21, 38). Although it is known that REDD1 mRNA expression is repressed following resistance exercise, how much, if at all, the change in REDD1 expression causally contributes to the exercise-induced stimulation of signaling through mTORC1 is as yet unexplored. Consequently, the purpose of the present study was to test the hypothesis that contraction-induced stimulation of signaling through mTORC1 and the subsequent increase in muscle protein synthesis are governed by REDD1.

METHODS

Animals. All experiments were performed on male mice 10–12 wk of age, similarly to a previous report (44). C57Bl/6 mice were obtained from Charles River (Horsham, PA). REDD1-null mice were generated by Lexicon Genetics (The Woodlands, TX) (6), and permission to use them was generously granted by Dr. Elena Feinstein (Quark Pharmaceuticals). Breeding pairs on a B6/129F1 background were obtained from Dr. David Williamson (SUNY Buffalo) and bred in The Pennsylvania State University College of Medicine animal facility. A comparison of various physiological measurements between global REDD1-null mice and wild-type mice has been reported elsewhere (51). Male wild-type age-matched B6/129F1 control mice
were obtained from Taconic (Hudson, NY). All mice were housed in a temperature (25°C) and light (12:12-h light-dark)-controlled environment. Mice were provided rodent chow (no. 8604; Harlan-Teklad, Indianapolis, IN) and water ad libitum. The Institutional Animal Care and Use Committee of The Pennsylvania State University College of Medicine approved the animal facilities and all of the experimental protocols, which also complied with NIH guidelines.

Experimental methods. The studies described in this paper consisted of five independent sets of experiments. In all experiments, mice were fasted for 16–18 h beginning at 1700 the night before experimentation. In experiment 1, fasted mice were subjected to muscle contractions as described below, and muscle tissue was harvested 4 h postcontractions. The experiment was repeated once; within each experiment 2–5 mice/group were assessed. In experiment 2, one-half of the fasted mice were randomly selected and allowed access to food for 1 h prior to muscle contractions. The experiment was repeated twice for a total of three independent experiments; within each experiment, 2 or 3 mice/group were assessed. Experiment 3 was identical to experiment 1 except that muscle was harvested 30 min, rather than 4 h, postcontractions. The experiment was repeated once; within each experiment 2–3 mice/group were assessed. Experiments 4 and 5 were identical to experiment 1 except that wild-type and REDD1-null B6/129F1 mice were used instead of wild-type C57Bl/6 mice. Experiment 4 was repeated twice for a total of three independent experiments consisting of 2–3 mice/group within each experiment, and experiment 5 was repeated once with 3–4 mice/group within each experiment.

Muscle contraction protocol. Unilateral eccentric contractions of the tibialis anterior (TA) muscle were conducted as previously described (2, 48, 52). Briefly, mice were anesthetized with isoflurane (2–3%; Piramal Healthcare, Maharashtra, India), and a small incision was made to expose the sciatic nerve. Two wire electrodes were employed to directly stimulate the nerve with a 1-mAmp current (batteries). An incision into the tibialis anterior (TA) muscle were conducted as previously described (22). Briefly, mice were injected intraperitoneally with a flooding dose of 1-[3H]phenylalanine (500 µl volume) 15 min prior to tissue collection. Mice were anesthetized 12 min after intraperitoneal injection, and muscles were harvested 15 min postinjection.

Statistical analysis. All data are presented as means ± SE. Comparisons between stimulation-induced contractions and noncontracting muscle within an animal were performed using a paired Student’s t-test. To correct for multiple testing, P values were adjusted using the Bonferroni method (12). Two-way ANOVA was used to determine the effect of feeding and genotype on the dependent variables. An unpaired Student’s t-test was used post hoc to determine significance. All analyses were performed using Graphpad Prism software (La Jolla, CA). Statistical significance was set at P ≤ 0.05 for all analyses.

RESULTS

Muscle contractions repress REDD1 protein expression. To determine whether REDD1 expression was altered in the model of muscle contractions employed for the studies presented here, we fasted mice overnight to induce skeletal muscle REDD1 protein expression as previously described (40). Eccentric contractions under fasting conditions significantly repressed REDD1 protein expression to 66% (P < 0.01) of noncontracting control values (Fig. 1A). Contrary to the data reported in humans following resistance exercise (21, 38), the repression in REDD1 protein expression was not accompanied by a significant repression in REDD1 mRNA expression, although there was a trend toward a decrease after contraction (P = 0.096; Fig. 1B). Moreover, expression of REDD2 mRNA was repressed 31% (P < 0.05) in the contracting muscle relative to nonstimulated control values (Fig. 1C).

Phosphorylation of p70 S6K1 and 4E-BP1 as well as rates of protein synthesis are inversely associated with REDDI protein expression. In parallel with the repression of REDD1 protein expression shown above, phosphorylation of p70 S6K1 (Thr389) was increased 301% (P < 0.05) and 4E-BP1 (Ser65) was increased 55% (P < 0.05) in the contracting muscle relative to the respective noncontracting control (Fig. 2, A and B). These signaling events occurred in parallel with a 14% increase in rates of protein synthesis (Fig. 2C). Together, these results demonstrate that the contraction-induced repression in REDD1 protein expression was inversely associated with the elevated phosphorylation of p70 S6K1 (Thr389) and 4E-BP1.
as well as rates of skeletal muscle global protein synthesis in this model.

Feeding and muscle contractions synergistically repress REDD1 expression in association with synergistic elevation in mTORC1 signaling. Previous work from our laboratory demonstrated that feeding a previously fasted animal rapidly repressed REDD1 protein expression in concert with elevated signaling through mTORC1 (40). Furthermore, feeding in combination with resistance exercise elevates signaling through mTORC1 above that observed after resistance exercise (Ser65) as well as rates of skeletal muscle global protein synthesis in this model.

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alone (19, 29, 35). Therefore, we assessed whether or not feeding in combination with muscle contractions would synergistically repress REDD1 protein expression in association with enhanced signaling through mTORC1. Following an overnight fast, a subset of mice was allowed access to a food pellet for 1 h prior to the onset of stimulation-induced contractions (fed group). On average, mice in the fed group consumed 0.98 ± 0.06 g of food in the 1-h time frame. Consistent with previous work (40), refeeding fasted mice repressed REDD1 protein expression in the noncontracting muscle to 22% (P < 0.05) of the value observed in the noncontracting muscle of fasted mice (Fig. 3A). In concert with repression of REDD1 protein expression, refeeding stimulated signaling through mTORC1 in the noncontracting muscle, as phosphorylation of p70 S6K1 (Thr389) and 4E-BP1 (Ser65) was increased by 92% (P < 0.05) and 310% (P < 0.05), respectively, compared with the fasted noncontracting control values (Fig. 3C).

In fasted animals, stimulation-induced contractions repressed REDD1 protein expression to 67% (P < 0.01) of the noncontracting control value (Fig. 3A). This effect paralleled the 89% (P < 0.01) and 101% (P < 0.025) elevations in phosphorylation of p70 S6K1 (Thr389) and 4E-BP1 (Ser65), respectively, compared with fasted noncontracting control values. Muscle contractions in fed mice further repressed REDD1 protein expression to only 11% (P < 0.01) of the fasted noncontracting control values (Fig. 3A) while further elevating phosphorylation of p70 S6K1 (Thr389) and 4E-BP1 (Ser65) to 329% and 462% (P < 0.025), respectively, relative to the fasted noncontracting control values (Fig. 3, B and C).

Signaling through mTORC1 and repression of REDD1 protein occurs within 30 min following muscle contractions. O’Neil et al. (44) demonstrated that signaling through mTORC1 occurs immediately following eccentric contractions of the TA muscle. Furthermore, feeding-induced turnover of REDD1 protein following an overnight fast occurs within 45 min, indicating potential for rapid turnover of REDD1 at earlier time points in parallel with the increased signaling through mTORC1. To determine whether REDD1 protein expression was repressed at time points earlier than 4 h, fasted mice were subjected to contractions and muscles were harvested 30 min later. In these mice, contractions repressed REDD1 protein expression to 67% (P < 0.05) of noncontracting control values (Fig. 4A). In parallel with the repression in REDD1 protein, phosphorylation of p70 S6K1 (Thr389) was elevated 382% (P < 0.05) in contracting muscle relative to noncontracting control values (Fig. 4B). However, there was no difference in either REDD1 or REDD2 mRNA expression 30 min postcontractions (Fig. 4, C and D).

Signaling through mTORC1 following contractions in fasted mice is increased in REDD1-null compared with wild-type mice. All data presented thus far demonstrate an inverse association between REDD1 protein expression and signaling through mTORC1. To examine the causal role of REDD1 in regulating signaling through mTORC1 following contractions, wild-type mice or mice lacking REDD1 were fasted overnight. The following morning, both groups were subjected to stimulation-induced muscle contractions and euthanized 4 h later. In the noncontracting muscle of wild-type mice, REDD1 protein was abundantly expressed, whereas it was undetectable in muscle of REDD1-null mice (Fig. 5A). Similar to the results obtained using C57Bl/6 mice, stimulation-induced muscle con-
tractions in wild-type B6/129F1 mice repressed REDD1 protein expression to 66% ($P < 0.01$) of the noncontracting control values (Fig. 5A). The repression in REDD1 protein expression was accompanied by 232% ($P < 0.025$) and 167% ($P < 0.01$) increases in phosphorylation of p70 S6K1 (Thr389) and 4E-BP1 (Ser65), respectively, relative to the noncontracting control values in wild-type mice (Fig. 5, B and C).

In REDD1-null mice, phosphorylation of p70 S6K1 (Thr389) and 4E-BP1 (Ser65) were 359% ($P < 0.05$) and 578% ($P < 0.05$) greater, respectively, relative to the noncontracting control values in wild-type mice (Fig. 5, B and C). Stimulation-induced muscle contractions in mice lacking REDD1 significantly enhanced phosphorylation of both p70 S6K1 (Thr389) and 4E-BP1 (Ser65) to 1,130% ($P < 0.01$) and 864% ($P < 0.01$), respectively, relative to the noncontracting control value in wild-type mice (Fig. 5, B and C). However, the magnitude of the contraction-induced increase in mTORC1 signaling in REDD1-null mice was similar to that observed in wild-type animals.

To determine whether loss of REDD1 was sufficient to maximize signaling through mTORC1, we performed a p70 S6K1 gel shift assay. Loss of REDD1 was sufficient to increase the abundance of p70 S6K1 in slower migrating, hyperphosphorylated forms in control muscle relative to fasted wild-type control muscle. This effect was amplified in muscle of REDD1-null mice subjected to contractions (Fig. 5D). However, even after contractions, a significant proportion of p70 S6K1 was present in the hypophosphorylated α-form, suggesting that mTORC1 was not maximally stimulated, as is observed in insulin-treated skeletal muscle (2).

REDD1 governs rates of protein synthesis. The observed effects of REDD1 on signaling through mTORC1 suggest that rates of protein synthesis would also be modulated by changes in REDD1 expression. To test this, fasted wild-type and REDD1-null mice were subjected to stimulation-induced muscle contractions. Four hours postcontractions, rates of protein synthesis were assessed using the flooding dose method. In wild-type mice, stimulation-induced contractions enhanced...
rates of synthesis 22% ($P < 0.025$) relative to the noncontracting control muscle (Fig. 6). Rates of protein synthesis were significantly greater ($P < 0.05$) in the noncontracting control muscle of REDD1-null mice relative to the noncontracting control muscle of wild-type mice, and contractions did not significantly increase these rates. However, the rates of synthesis in muscle of REDD1-null mice were significantly greater ($P < 0.05$) after contraction relative to the muscle of wild-type mice.

**DISCUSSION**

The present study examined the role of REDD1 in regulating mTORC1 signaling and protein synthesis following a single bout of muscle contractions. The results show that reductions in REDD1 protein expression are associated with higher absolute signaling through mTORC1 following contractions. Furthermore, the data show a direct effect of REDD1 abundance on in-vivo-determined rates of protein synthesis and mTORC1 signaling in skeletal muscle. These findings are consistent with a model in which REDD1 acts to govern signaling through mTORC1 and the rate of global protein synthesis.

The precise mechanism of action by which REDD1 represses signaling through mTORC1 is still not fully understood. However, a recent study (17) reported that REDD1 acts to target protein phosphatase 2A to Akt, leading to dephosphorylation of the kinase on Thr308 and reduced phosphorylation of residues on the tuberous sclerosis complex (TSC2) that are known to be phosphorylated by Akt. As expected based on previous studies showing that phosphorylation of TSC2 by Akt represses its GTPase activator protein function toward the ras homolog enriched in brain [Rheb; (7, 28)], the proportion of Rheb in the GTP-bound form was repressed by REDD1 expression (17). Because Rheb-GTP, but not Rheb-GDP, activates mTORC1 (7, 13, 28), it is likely that REDD1 represses mTORC1 signaling by increasing Rheb GTPase activity, thereby reducing Rheb GTP loading.

Regardless of the mechanism involved in REDD1-mediated repression of mTORC1 signaling, the finding in the present
However, in the present study, the rate of protein synthesis was not enhanced in the muscle of REDD1-null mice after contractions relative to muscle of REDD1 wild-type mice despite significantly greater signaling through mTORC1. However, basal rates of protein synthesis were already significantly elevated in the control muscle of REDD1-null mice relative to the noncontracting control muscle of wild-type mice in association with increased signaling through mTORC1. A similar discrepancy between changes in mTORC1 signaling and protein synthesis has been reported in rats administered leucine by oral gavage (10). In that study, oral administration of 0.135 g leucine/kg body wt was sufficient to maximally stimulate muscle protein synthesis. However, mTORC1 signaling, as assessed by phosphorylation of either p70 S6K1 or 4E-BP1, was still increasing linearly at 10 times that dose. The question therefore arises as to why the amplitude of mTORC1 signaling extends so far beyond what is required for maximal stimulation of protein synthesis. One possibility is that the greater activation of mTORC1 is necessary to promote ribosome biogenesis. In that regard, activation of mTORC1 promotes both the translation of mRNAs encoding ribosomal proteins as well as stimulating ribosomal DNA transcription (39). Thus, it is tempting to speculate that the additional increase in mTORC1 signaling beyond what is necessary to maximally stimulate mRNA translation acts to enhance the capacity for protein synthesis by stimulating ribosome biogenesis.

While others have reported repressed REDD1 mRNA expression following resistance exercise in humans (21, 38), we found no statistically significant effect of eccentric contractions on REDD1 mRNA expression despite significant reductions in REDD1 protein expression at both 30 min and 4 h postcontractions. Though this is the first known report to demonstrate altered REDD1 protein expression following muscle contractions, it is unlikely that REDD1 protein expression would not follow the mRNA patterns observed in the previous human studies, due to the rapid turnover of REDD1 (5–10 min half-life) (30, 32). However, the difference in the type of contractions utilized in the present study (purely eccentric contractions) compared with those used in previous human studies (combined eccentric and concentric) (21, 38) may partially explain the discordant findings. Although not reported here, we found that REDD1 protein expression was also repressed in the gastrocnemius following purely concentric contractions with no measureable change in REDD1 mRNA expression (unpublished data). The mechanisms responsible for the changes in REDD1 protein expression following contractions are unknown but may involve ubiquitin proteasome-mediated degradation. In cells in culture, the half-life of REDD1 has been estimated to be less than 10 min (30), and inhibition of proteasome activity using MG 132 significantly increases the half-life of REDD1 (30). Furthermore, proteasome activity and expression of components of this pathway are increased in both humans and animals following resistance exercise, muscle overload, or muscle contractions (3, 43, 45). Though speculative, the increased turnover of REDD1 and the maintenance of its reduced expression following muscle contractions may be due to increased proteasome-mediated degradation.

In agreement with previous reports (21, 38), in the present study, a reduction in REDD2 mRNA expression was observed 4 h after completion of muscle contraction. Similar to REDD1, REDD2 is thought to act as a repressor of mTORC1 signaling...
by promoting TSC2-mediated repression of Rheb GTP loading (41). Indeed, ectopic expression of REDD2 in C2C12 myoblasts is associated with resistance to both leucine and stretch-induced stimulation of mTORC1 in a TSC2-dependent manner (41). Unfortunately, assessment of potential changes in REDD2 protein expression was not possible in the present study due to the lack of an appropriate antibody. However, it is tempting to speculate that the increased efficacy of muscle contraction in stimulating mTORC1 signaling in REDD1-null mice is, at least in part, due to a contraction-mediated reduction in REDD2 protein expression.

The physiological consequences of impaired signaling through mTORC1 are clearly illustrated in both human and animal models. Treating humans or rats with the partial mTORC1 inhibitor rapamycin prior to resistance exercise represses the ensuing signaling through mTORC1 and rates of protein synthesis (20, 36). Furthermore, Goodman et al. (23) and Bodine et al. (4) showed that chronic inhibition of mTORC1 signaling using rapamycin in mice completely blocks muscle hypertrophy following synergistic ablation-induced overload. The practical physiological importance for understanding the mechanisms that activate and govern mTORC1 signaling can be seen with aging, as signaling through mTORC1, rates of protein synthesis, and skeletal muscle hypertrophy are either abolished or severely blunted following resistance exercise/muscle overload (22, 26, 27). Though speculative, delayed or unchanged expression of REDD1 following resistance exercise with aging may be one potential explanation for this effect.

When viewed in the context of previous studies (e.g., Refs. 16, 17), the results of the present study support a model in which muscle contractions activate mTORC1 through both REDD1-dependent and -independent pathways. In this model, the reduction in REDD1 protein expression that is observed in response to muscle contractions would, by itself, lead to a stimulation of mTORC1 signaling, although absolute mTORC1 activity would remain relatively modest in the absence of the REDD1-independent input. Perhaps more importantly, the reduction in REDD1 protein expression would increase basal mTORC1 activation, such that signaling to the complex through the proposed REDD1-independent pathway would lead to a greater absolute level of activity when REDD1 expression is low compared with when it is high. Further support for this model is provided by the studies presented herein in which refeeding fasted animals prior to electrically induced muscle contractions resulted in a greater reduction in REDD1 protein expression and a greater stimulation of mTORC1 signaling compared with either refeeding or contractions alone. In the future, delineation of the mechanism(s) through which muscle contractions act(s) to reduce REDD1 protein expression will provide the basis for studies allowing this model to be tested directly.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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