LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Glucocorticoid-dependent REDD1 expression reduces muscle metabolism to allow adaptation to energy stress - Evidence review

Dr.ssa M. Bitonti[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated how REDD1, a stress-induced protein, contributes to skeletal muscle adaptation when available energy or oxygen is reduced. In mice lacking REDD1, fasting, hypoxia, and intense exercise resulted in greater activation of energy-deficiency signals, a greater reduction in glycogen stores, and poorer exercise tolerance. Experiments on murine muscle and human myoblasts also indicated that REDD1 reduces oxygen consumption, protein synthesis, and AKT/mTORC1 pathway activity.In the book “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, this publication helps explain how glucocorticoids can increase REDD1 and temporarily limit cellular anabolism. Independent studies confirm that dexamethasone, fasting, and energy stress induce REDD1 and reduce mTOR signaling. However, the evidence primarily concerns cells and animal models; it does not prove that chronic cortisol produces identical metabolic effects in humans.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 24, 2026
Updated: November 24, 2026

DOI 10.5281/zenodo.24498729

MISSION

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Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether REDD1, a protein known to limit the mTORC1 pathway, played only a catabolic role in muscle or also contributed to the survival of muscle fibers during an energy crisis. mTORC1 is a cellular complex that promotes protein synthesis, growth, and nutrient storage when energy and substrates are available.The publication is relevant to sections 4.14 and 22.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it analyzes the segment of the glucocorticoids REDD1 reduced AKT/mTORC1 signaling lower energy expenditure chain. It does not directly evaluate insulin resistance in humans nor does it demonstrate the effects of chronic psychological cortisol. Instead, it documents, primarily in mouse muscle, how the induction of REDD1 can curb energetically expensive anabolic processes during fasting, hypoxia, and exercise.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study used wild-type male mice, meaning they had functional REDD1, and knockout mice, which lacked the REDD1 gene. The animals were primarily six months old; some basal metabolism measurements were also taken at two and twelve months. The mice were subjected to hypobaric hypoxia equivalent to approximately 6,500 meters of altitude for two weeks, fasting for 16 or 48 hours, or exercise on a treadmill for 90 minutes.The researchers measured muscle weight, glycogen, AMPK phosphorylation, and components of the AKT/mTORC1 pathway. AMPK is a cellular sensor that increases when immediately available energy becomes insufficient. Mitochondrial respiration, whole-organism oxygen consumption, body temperature, and aerobic performance were also measured.Mechanistic experiments included permeabilized mouse muscle fibers, primary human myoblasts from a biopsy of a single healthy volunteer, and treatment with dexamethasone. Cell fractionation techniques, western blot, small interfering RNA silencing, protein proximity analysis, and ATP measurements were used. Data were analyzed using t-tests and two-way analysis of variance; the significance threshold was $P < 0.05$.

4. RESULTS

The main finding is that the absence of REDD1 did not protect muscle from energy stress. On the contrary, in knockout mice, hypoxia and fasting increased muscle mass loss more significantly than in wild-type mice. During hypoxia, animals lacking REDD1 showed greater AMPK activation and did not develop the increase in muscle glycogen stores observed in the controls.After fasting, exercise, or hypoxia, the absence of REDD1 was associated with greater glycogen depletion and increased AMPK phosphorylation. In practical terms, muscle without REDD1 appeared to consume its reserves more rapidly when energy and oxygen were limited. Knockout mice also had a lower maximum aerobic speed compared to controls.Oxygen consumption in isolated mitochondria did not differ significantly between wild-type and knockout mice. However, in permeabilized muscle fibers, oxygen consumption was higher without REDD1, whereas experimental increases in REDD1 reduced it. This suggests that REDD1 does not necessarily modify the intrinsic capacity of the mitochondrion, but may influence how it communicates with other cellular structures.In human myoblasts, silencing REDD1 increased IP3R/VDAC interactions by 36% and IP3R/GRP75 interactions by 41%. These complexes are indicators of the membrane-associated structures between mitochondria and the endoplasmic reticulum, known as MAMs. In mouse muscles treated with dexamethasone, the loss of REDD1 increased the VDAC/IP3R signal by 90%, consistent with a greater extent of MAMs.The loss of REDD1 also increased the phosphorylation of PRAS40 and the S6 protein in the cellular fraction containing MAMs. This means that the brake exerted by REDD1 on mTORC1 was attenuated. In myoblasts subjected to glucose deprivation and blockage of ATP production, silencing REDD1 increased protein synthesis. Finally, knockout mice showed higher whole-body oxygen consumption and carbon dioxide production, with no relevant differences in food Intake, spontaneous activity, or respiratory quotient.

5. INTERPRETATION

In simple terms, REDD1 can act as a temporary brake: when energy is scarce, it reduces useful but

energy-expensive cellular activities, such as protein synthesis and glycogen storage. This can prevent the muscle from depleting ATP—the molecule that provides immediate energy for cellular processes—too quickly.The pathway documented by the publication subject to the Evidence Review is glucocorticoids and energy stress increased REDD1 reduced AKT/mTORC1 activity and lower energy demand. The study does not prove that REDD1 is the only mechanism by which dexamethasone or cortisol reduces mTORC1. Furthermore, dexamethasone is a synthetic glucocorticoid administered experimentally; its effects cannot be automatically superimposed onto those of chronic cortisol exposure in humans.The result also clarifies an apparent contradiction. Under conditions of adequate energy availability, a persistent reduction in mTORC1 can promote muscle mass loss. During fasting, hypoxia, or intense exercise, however, a transient reduction in anabolic processes can be adaptive. The direction of the effect therefore depends on the context, the duration of the stimulus, and the tissue analyzed.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial direct confirmation of the dexamethasone REDD1 mTOR inhibition pathway comes from a study on rat muscle and L6 myoblasts. Dexamethasone markedly increased REDD1 messenger RNA and reduced the phosphorylation of S6K1 and 4E-BP1, two downstream targets of mTORC1 linked to the initiation of protein synthesis. When REDD1 was reduced via RNA interference, dexamethasone lost much of its ability to inhibit mTOR signaling. The study also showed that glucocorticoid treatment was dependent on the TSC2/Rheb configuration, consistent with the chain reported in the book [1].A second study analyzed fasting in rats. After food deprivation, REDD1 in skeletal muscle increased up to approximately fivefold compared to controls and returned toward baseline levels upon refeeding. The increase was associated with higher corticosterone and lower mTORC1 signaling. Pharmacological blockade of the glucocorticoid receptor almost completely reduced the induction of REDD1, supporting the link between glucocorticoid signaling and anabolic repression during nutritional deficiency [2].A third study, conducted in mouse embryonic fibroblasts and cellular systems with manipulated REDD1, defined the link between energy stress and the TSC1/TSC2 complex. ATP depletion induced REDD1; in cells lacking the protein, the reduction in S6K and 4E-BP1 phosphorylation was defective. The effect required TSC2 and was countered by Rheb, a downstream activator of the TSC complex. This confirms the molecular pathway REDD1 TSC1/TSC2 mTORC1 inhibition, although it is not a study on human muscle [3].Taken together, these studies are independent of the analyzed publication and converge on the fact that REDD1 is a stress mediator capable of reducing mTORC1 signaling. The confirmation is more direct for the effects of glucocorticoids and fasting in rodent muscle; it is, however, indirect for the idea that chronically elevated cortisol in humans determines the same biological sequence.

7. CONFLICTING EVIDENCE

An important conflicting element concerns the relationship between REDD1 and mitochondrial respiration. In a study on mouse embryonic fibroblasts, immune cells, and mice lacking REDD1, the loss of the protein was associated with lower basal oxygen consumption, lower mitochondrial ATP production, accumulation of defective mitochondria, and reduced exercise capacity. The authors attributed the phenomenon to a defect in autophagy, i.e., the process of recycling cellular components [4].This result is the opposite of the increased oxygen consumption observed in the study analyzed in muscle fibers and the whole organism of knockout mice. The difference does not negate the REDD1-mTORC1 link, but it indicates that the role of REDD1 in metabolism depends on the cell type, the level of stress, the function of autophagy, and the experimental model. No sufficiently relevant directly conflicting evidence has been identified regarding the fact that glucocorticoids induce REDD1 and reduce mTORC1 signaling in muscle; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication that is the subject of the review from the independent research used to confirm or define the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Wild-type and knockout mice; muscle fibers; human myoblasts	REDD1 reduces oxygen consumption, AKT/mTORC1 signaling, and energy demand during stress.	direct confirmation	moderate
[1]	Animal and cellular	Rat muscle and L6 myoblasts	Dexamethasone increases REDD1 and reduces S6K1 and 4E-BP1 phosphorylation; REDD1 silencing attenuates the effect.	direct confirmation	moderate
[2]	Animal	Rat skeletal muscle during fasting and refeeding	Fasting increases REDD1 and corticosterone and reduces mTORC1; glucocorticoid receptor blockade reduces REDD1.	direct confirmation	moderate
[3]	Cellular	Mouse embryonic fibroblasts with manipulated REDD1 and TSC2	REDD1 is required to reduce phosphorylation of mTOR targets after energy depletion.	indirect confirmation	moderate
[4]	Animal and cellular	Fibroblasts, splenocytes, and REDD1-deficient mice	Loss of REDD1 reduces mitochondrial respiration and ATP in a model dominated by autophagic defect.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed convincingly argues that REDD1 is not merely a stress indicator or a mediator of muscle loss, but also a regulator of energy balance during fasting, hypoxia, and exercise. The temporary reduction of AKT/mTORC1, protein synthesis, and oxygen consumption appears to be an adaptive response in mouse muscle.Independent evidence strongly confirms the link between glucocorticoids, REDD1 induction, and mTORC1 repression. However, significant limitations remain: much of the data comes from rodents and cells, the metabolic effects of REDD1 are dependent on the biological context, and there is a lack of direct demonstration that chronically elevated cortisol produces the same sequence in human muscle.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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