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

ORIGINAL RESEARCH
ISSN 2845-7501

REDD1 expression in skeletal muscle as a surrogate biomarker for the efficacy of glucocorticoid receptor blockade - A review of the evidence

Dr.ssa M. Bitonti[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether the expression of REDD1, a protein produced in response to cellular stress conditions, can function in skeletal muscle as an indirect indicator of glucocorticoid receptor activation. In mouse models of restraint stress, type 2 diabetes, and experimental stroke, the increase in corticosterone was accompanied by an increase in REDD1. Treatment with RU-486, a drug that blocks the glucocorticoid receptor, attenuated the increase in REDD1 without reducing hormone concentrations in the blood.In paragraph 4.17 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the specific point that REDD1 reflects glucocorticoid receptor activity and not just the circulating concentration of the hormone. Independent studies support the induction of REDD1 by the receptor and its link to the reduction of the mTORC1 signal, which promotes protein synthesis. However, REDD1 also responds to other cellular stresses, such as reduced oxygen availability, and its use as a biomarker has not been validated in humans.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 25, 2026
Updated: November 25, 2026

DOI 10.5281/zenodo.24529280

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

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 could be used as a surrogate biomarker, that is, as an indirect measure of a biological process that is difficult to observe directly: the blockage of glucocorticoid receptor activity in muscle. Glucocorticoids are stress hormones; in humans, the primary one is cortisol, while in mice, it is corticosterone. When these hormones enter cells and bind to their receptor, the receptor can modify the activity of numerous genes.The publication is relevant to section 4.17 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it examines a specific point in the described chain: whether REDD1 increases when the glucocorticoid signal is active and decreases when the receptor is pharmacologically hindered, even if the amount of the hormone in circulation does not decrease. The study can therefore support REDD1 as an experimental indicator of receptor activity in mouse muscle. It cannot demonstrate that REDD1 is a clinical biomarker already usable in people, nor that every increase in it necessarily depends on cortisol.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study used various mouse models associated with hypercortisolemia, i.e., elevated corticosterone concentrations: restraint stress, type 2 diabetes, and experimental stroke. REDD1 expression was measured in skeletal muscles, and corticosterone concentrations were determined. The animals also received RU-486, also known as mifepristone, used in the study as a glucocorticoid receptor antagonist.The authors compared REDD1 changes across the experimental conditions and evaluated whether RU-486 modified both the circulating hormone and the molecular signal in the muscle. The abstract does not report the group sizes, sex and age of the animals, drug doses and administration times, inclusion or exclusion criteria, specific analytical techniques, statistical significance values, confidence intervals, or a detailed statistical plan. This information is not provided in the available material.

4. RESULTS

In various mouse models, REDD1 expression in skeletal muscle increased alongside changes in corticosterone concentrations. Simply put, when experimental conditions were associated with higher glucocorticoid stress signaling, the muscle also showed increased REDD1 production. The abstract does not report the absolute values of the increase, percentage changes, P-values, or the number of animals used.RU-486 did not reduce plasma corticosterone concentrations, but it strongly attenuated the changes in REDD1 expression induced by stress, diabetes, and stroke. This is the key finding for this section of the book: the REDD1 signal decreased when the receptor was blocked, even without a decrease in the hormone measured in the blood. The study also indicated that receptor blockade attenuated alterations in mTORC1 signaling, a protein complex that partially regulates cellular protein synthesis. Detailed quantitative data for this analysis are not reported in the available abstract.

5. INTERPRETATION

The result suggests that, in mouse muscle, REDD1 does not merely represent a passive response to the amount of circulating corticosterone. Rather, its expression appears sensitive to glucocorticoid receptor activation. This is an important point because a hormone in the blood and the effect produced in cells do not always coincide: the response also depends on the receptors, tissues, and intracellular signals present at that moment.The segment documented by the research discussed in the article can be summarized as follows: increased glucocorticoid signaling activation of the receptor in the muscle increase in REDD1; blocking the receptor reduction of the increase in REDD1 without a reduction in corticosterone. The authors' interpretation, according to which REDD1 is an excellent surrogate biomarker for the efficacy of RU-486, is reasonable in the context of the mouse models examined. However, this interpretation remains to be validated in other contexts, because REDD1 can also increase in response to hypoxia, fasting, exercise, or other cellular stress signals.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial confirmation of this biological chain comes from experiments on rat muscle and L6 myoblasts, which are muscle progenitor cells cultured in the laboratory. Dexamethasone, a synthetic glucocorticoid, markedly increased REDD1 messenger RNA in both animal muscle and the cells. In cells where REDD1 was reduced via RNA interference, dexamethasone attenuated the mTOR signal to a much lesser extent. This study confirms the glucocorticoid REDD1 reduced mTOR signal pathway, but it does not evaluate REDD1 as a clinical biomarker nor does it demonstrate the mechanism in humans [1].A second experimental study identified REDD1 as a direct target of the glucocorticoid receptor in the skeletal muscle of rodents. It also showed that REDD1 and another regulator, KLF15, can reduce mTOR activity. This result is particularly relevant to the book's narrative because it strengthens the link between receptor activation and increased REDD1, separating it from the mere measurement of the circulating hormone. This evidence also remains preclinical [2].A third study verified whether REDD1 is merely associated with the effects of glucocorticoids or if it actually contributes to determining them. In normal mice, seven days of dexamethasone reduced the weight of the tibialis anterior by 12%, the weight of the gastrocnemius by 10%, and the mean fiber area of the tibialis anterior by 17%. In mice lacking REDD1, such reductions in muscle mass were not observed. After a single administration, the absence of REDD1 also prevented the reduction of protein synthesis and mTORC1 activity. These results provide causal confirmation, in mice, of the role of REDD1 downstream of the glucocorticoid signal [3].Taken together, these independent studies support a coherent network: the glucocorticoid receptor can induce REDD1 in muscle, and REDD1 can contribute to reducing mTORC1, which is a system that promotes protein production. This network makes it biologically plausible that a decrease in REDD1 following receptor antagonism indicates an actual attenuation of the glucocorticoid signal in muscle. However, the strength of this confirmation is limited by the fact that the available evidence is derived from rodents and cells.

7. CONFLICTING EVIDENCE

No directly conflicting evidence sufficiently relevant to the specific finding that RU-486 reduces the increase of REDD1 in muscle without lowering corticosterone has been identified. However, there is a significant limitation to the generalizability of the interpretation: REDD1 is not an exclusive signal of the glucocorticoid receptor.In mouse embryonic fibroblasts and other cell lines, hypoxia—that is, reduced oxygen availability—required the de novo production of REDD1 to reduce mTOR activity. This demonstrates that REDD1 can be induced and function in the control of mTOR even outside the specific cortisol-glucocorticoid receptor pathway [4]. Therefore, an increase in REDD1 alone does not allow for the cause to be attributed with certainty to the stress hormone; the greatest informative value emerges when REDD1 is interpreted together with the biological context and evidence of receptor activation or blockade.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the original study from independent verifications and indicates the level at which each piece of evidence contributes to the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental animal	Murine models of stress, type 2 diabetes, and stroke	RU-486 attenuated the increase in muscle REDD1 without reducing plasma corticosterone.	direct confirmation	moderate
[1]	Animal and cellular	In vivo rat muscle and L6 myoblasts	Dexamethasone increased REDD1; REDD1 reduction attenuated mTOR inhibition in cells.	direct confirmation	moderate
[2]	Animal and molecular	Rodent skeletal muscle	REDD1 was identified as a direct target of the glucocorticoid receptor and linked to the reduction of mTOR.	direct confirmation	moderate
[3]	Genetic animal	Normal mice and REDD1-deficient mice treated with dexamethasone	The absence of REDD1 prevented the reduction of protein synthesis, mTORC1 activity, and muscle mass.	biologically consistent evidence	moderate
[4]	Cellular	Murine embryonic fibroblasts and cell lines	Hypoxia induced REDD1 and reduced mTOR via REDD1, showing that the signal is not exclusive to glucocorticoids.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, in the mouse models considered, that muscle REDD1 responds to glucocorticoid receptor blockade even when circulating corticosterone does not decrease. Independent evidence confirms mechanistically that the receptor can induce REDD1 and that REDD1 can reduce mTORC1 and protein synthesis in muscle. The use of REDD1 as a biomarker for the efficacy of receptor blockade in humans remains preliminary and requires validation across different tissues, diseases, and treatments.

Aggiornato al 25/11/2026. 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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Dexamethasone Represses Signaling through the Mammalian Target of Rapamycin in Muscle Cells by Enhancing Expression of REDD1**
Wang et al., 2006
Journal of Biological Chemistry
DOI: https://doi.org/10.1074/jbc.M610023200

[2] **Crosstalk between Glucocorticoid Receptor and Nutritional Sensor mTOR in Skeletal Muscle**
Shimizu et al., 2011
Cell Metabolism
DOI: https://doi.org/10.1016/j.cmet.2011.01.001

[3] **REDD1 deletion prevents dexamethasone-induced skeletal muscle atrophy**
Britto et al., 2014
American Journal of Physiology-Endocrinology and Metabolism
DOI: https://doi.org/10.1152/ajpendo.00234.2014

[4] **Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex**
Brugarolas et al., 2004
Genes & Development
DOI: https://doi.org/10.1101/gad.1256804