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ORIGINAL RESEARCH
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REDD1 deletion prevents dexamethasone-induced skeletal muscle atrophy - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether REDD1, a stress-induced protein, is necessary for dexamethasone to cause muscle loss. In mice lacking the REDD1 gene, dexamethasone treatment did not reduce the weight of specific muscles or fiber size, and it did not suppress protein synthesis or mTORC1 activity. The model is animal-based and does not allow us to determine whether the same effect occurs in people treated with glucocorticoids.The research contributes to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, according to which glucocorticoids can reduce muscle anabolic signaling through REDD1 and mTORC1. Independent studies confirm that dexamethasone induces REDD1 and reduces mTOR signaling in muscle; other data show that REDD1 participates in autophagy in lymphocytes. However, REDD1 may also play an adaptive role during fasting and hypoxia. The confirmation is therefore primarily mechanistic and animal-based.

ONLINE ARTICLE

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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 (regulated in development and DNA damage response 1, a protein activated under cellular stress conditions) is a necessary step in muscle loss caused by dexamethasone. The hypothesis was that the glucocorticoid induces REDD1 and that this protein reduces the activity of mTORC1 (a molecular complex that promotes protein synthesis and cell growth), thereby limiting the building of new muscle proteins.The publication is relevant to sections 4.14, 4.17, and 22.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it directly documents the glucocorticoid REDD1 reduction of mTORC1 and protein synthesis muscle atrophy segment. However, it does not demonstrate that daily psychological stress, chronic endogenous cortisol, or insulin resistance in humans necessarily produce the same biological sequence.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study compared wild-type mice, meaning those with REDD1 normally present, and knockout mice, which lack the REDD1 gene. Under basal conditions, the authors compared the mass and characteristics of the skeletal muscle. To induce atrophy, they administered dexamethasone orally for seven days and measured the weight of the tibialis anterior and gastrocnemius muscles, as well as the size of the tibialis anterior fibers.In an acute experiment, following a single administration of dexamethasone and five hours of observation, protein synthesis and mTORC1 activity were evaluated in the gastrocnemius. mTORC1 activity was estimated through the phosphorylation of S6, 4E-BP1, and ULK1: phosphorylation is a chemical modification that can indicate whether a signaling protein is active or inactive. The total number of animals, sex, precise dosage, inclusion criteria, detailed statistical analyses, and P-values are not reported in the available material, which consists only of the abstract.

4. RESULTS

In the absence of treatment, mice with and without REDD1 did not differ in muscle mass or muscle type. This finding indicates that eliminating REDD1 did not result in an obvious muscle defect under the baseline conditions observed.After seven days of dexamethasone, the weight of the tibialis anterior and gastrocnemius muscles decreased only in wild-type mice. The size of the tibialis anterior fibers also decreased only in animals with REDD1. In knockout mice, these indicators of atrophy did not decrease, as reported in the abstract.Following a single administration of dexamethasone and five hours of observation, protein synthesis and mTORC1 activity decreased in wild-type mice. In mice lacking REDD1, these reductions were not observed. The signals analyzed included S6, 4E-BP1, and ULK1, which are proteins downstream of mTORC1 and are useful for assessing the protein synthesis program and autophagy regulation, respectively. The abstract does not report absolute values, percentage differences, confidence intervals, or P-values.The authors did not attribute the effect of REDD1 to the modulation of the binding between TSC2 and 14-3-3. Instead, they proposed a link between REDD1, AKT, and PRAS40. This is a mechanism hypothesized based on experimental data and not a demonstration that every effect of dexamethasone on muscle depends exclusively on this sequence.

5. INTERPRETATION

In simple terms, dexamethasone reduced the muscle's ability to produce proteins in mice and promoted mass loss; removing REDD1 prevented these changes in the experimental model. REDD1 therefore appears to be a functional mediator, not just an indicator associated with glucocorticoid stress.The documented pathway is glucocorticoid REDD1 reduced mTORC1 activity reduced protein synthesis muscle atrophy. mTORC1 functions as an integration point: when active, it promotes protein translation; when inhibited, the muscle has less anabolic drive. The reduction in S6 and 4E-BP1 phosphorylation is consistent with this decrease in the synthesis program.Compared to "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study directly supports the idea that REDD1 protects the link between glucocorticoids and anabolic suppression in muscle. However, it cannot prove that REDD1 is the primary cause of systemic insulin resistance, nor that blocking REDD1 is safe or useful in humans.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial independent confirmation of the dexamethasone REDD1 mTOR reduction pathway comes from a study on rat skeletal muscle and L6 myoblasts, which are immature cells cultured in the laboratory. Dexamethasone reduced the phosphorylation of S6K1 and 4E-BP1, two mTOR targets linked to protein synthesis, and markedly increased REDD1 messenger RNA. In myoblasts, silencing REDD1 using interfering RNA attenuated the drug-induced inhibition of mTOR. This study is significant because it demonstrates a functional relationship, although the cellular component does not replicate the entire muscle of an organism [1].A second independent study identified REDD1 as a direct target of the glucocorticoid receptor in skeletal muscle. In experimental rodent models, the authors also identified KLF15 as another catabolic regulator. REDD1 and KLF15 reduced mTOR activity through different pathways, while mTOR activation counteracted catabolic processes triggered by glucocorticoids. This evidence expands the chain: the glucocorticoid receptor signal can activate programs that converge on the mTOR brake and the reduction of fiber size [2].Regarding the step related to autophagy, i.e., the recycling of cellular components, a study on murine lymphocyte and thymocyte lines observed that dexamethasone increases REDD1, reduces mTOR activity, and promotes autophagy. Silencing or the absence of REDD1 attenuated both mTOR inhibition and autophagy. The result confirms the biological consistency of the glucocorticoid REDD1 mTOR autophagy sequence, but it concerns immune cells and does not prove that autophagy is the primary determinant of atrophy in skeletal muscle [3].

7. CONFLICTING EVIDENCE

No sufficiently relevant, directly conflicting evidence has been identified that denies the fact that, in the mouse model treated with dexamethasone, REDD1 participates in the reduction of mTORC1 activity and muscle loss. However, there is a significant limitation to generalization: in a different study on mice and human myoblasts, REDD1 reduced oxygen and ATP consumption during fasting, hypoxia, or exercise, helping to preserve energy reserves. Under these conditions, the absence of REDD1 increased basal metabolism and made adaptation to energy stress less effective [4].This evidence does not directly contradict the effect of dexamethasone on atrophy, because the experimental context is different. However, it shows that REDD1 is not simply a “harmful” protein: it can limit anabolism in an adaptive way when the cell needs to save energy. Therefore, the hypothesis of inhibiting it as a strategy against atrophy would require specific assessments of safety, tissue, duration, and clinical condition.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent evidence and summarizes the level at which each source supports the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Genetic knockout animal	Wild-type and REDD1-deficient mice treated with dexamethasone	The absence of REDD1 prevented the dexamethasone-induced reduction in muscle mass, fiber size, protein synthesis, and mTORC1 activity.	direct confirmation	moderate
[1]	Animal and cellular	In vivo rat muscle and L6 myoblasts	Dexamethasone increased REDD1 and reduced mTOR signaling; silencing REDD1 attenuated this effect.	direct confirmation	moderate
[2]	Animal and molecular	Rodent skeletal muscle	REDD1 was identified as a target of the glucocorticoid receptor and as an inhibitor of mTOR in muscle.	indirect confirmation	moderate
[3]	Cellular and animal	Lymphocytes, murine thymocytes, and knockout mice	Reducing REDD1 attenuated dexamethasone-induced mTOR inhibition and autophagy.	biologically consistent evidence	moderate
[4]	Animal and cellular	Knockout mice and human myoblasts	During energy stress, REDD1 reduced oxygen and ATP consumption, promoting metabolic adaptation.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that REDD1 is necessary, in the mouse model used, for a significant portion of dexamethasone-induced atrophy: the reduction of mTORC1, protein synthesis, and muscle mass. The glucocorticoid–REDD1–mTOR pathway is confirmed by independent evidence, primarily experimental.The section of the book regarding the loss of muscle anabolic signaling is therefore well-supported at a mechanistic level. Extending this conclusion to muscle autophagy requires caution, as the most direct independent evidence comes from lymphocytes. It has not been demonstrated that REDD1 alone explains insulin resistance in humans, nor that its inhibition can be proposed as a treatment without further clinical studies.

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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