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Glucocorticoid-induced REDD1 and autophagy in lymphocytes

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1. ABSTRACT

The analyzed study evaluated whether REDD1, a protein activated under conditions of cellular stress, participates in dexamethasone-induced autophagy in lymphocytes. Autophagy is a recycling process by which the cell degrades and recovers internal components; it can promote survival, but its effect depends on the biological context. The authors observed that reducing or eliminating REDD1 attenuated mTOR inhibition and autophagy following glucocorticoid treatment, while increasing dexamethasone-induced cell death.The research contributes to three sections of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, in which cortisol and glucocorticoids are described as signals capable of activating REDD1, reducing mTOR activity, and promoting an adaptive energy-saving response. Independent evidence confirms that REDD1 can reduce mTOR signaling in cells, muscle, and mouse models. However, a study on thymocytes treated outside the organism obtained different results regarding the necessity of REDD1. The biological chain is therefore well-supported at a mechanistic level, but it cannot be automatically extended to chronic human stress or clinical insulin resistance.

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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 the increase in REDD1, also known as Dig2 or RTP801, contributed to dexamethasone-induced autophagy in lymphocytes. REDD1 is a stress-response protein. mTOR, on the other hand, is a regulatory protein that, when active, promotes cell growth and protein synthesis; when its activity decreases, it can make the initiation of autophagy more likely.The authors' hypothesis was therefore a precise chain: glucocorticoid increase in REDD1 reduction of mTOR signaling increase in autophagy. This is the segment relevant to the book's chapters: it does not by itself demonstrate all the metabolic effects of chronic stress, but it directly examines a possible mechanism by which a glucocorticoid can shift an immune cell from a state of growth to one of adaptation and recycling.The study can document functional relationships in murine cells and thymocytes exposed to dexamethasone. It cannot prove that the cortisol produced during psychological stress or loneliness causes the same effects in the entire human organism, nor that this pathway directly causes insulin resistance or metabolic diseases.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract is available. The authors report having conducted a gene expression analysis to identify genes activated by dexamethasone in lymphocytes. They then experimentally reduced REDD1 using RNA interference, a technique that decreases the production of a specific protein, in lymphocytes treated with glucocorticoids.The verification was extended to murine thymocytes lacking the Dig2/Rtp801/Redd1 gene, i.e., immune cells from genetically modified mice. The observed variables were the inhibition of mTOR, autophagy, and cell death induced by dexamethasone.The sample size, detailed characteristics of the cell lines, dosages, duration of treatments, complete control groups, analytical methods for measuring autophagy, predefined endpoints, and statistical analyses are not reported in the available material. Furthermore, any P-values, confidence intervals, and quantitative measures are not reported in the available material.

4. RESULTS

The initial result was that dexamethasone increased REDD1 expression in lymphocytes. In simple terms, the glucocorticoid activated a protein that signals the presence of a stress condition to the cell. The authors then observed that the reduction of REDD1 via RNA interference decreased both mTOR inhibition and autophagy in lymphocytes exposed to glucocorticoids.Similar results were observed in murine thymocytes lacking REDD1 and treated with dexamethasone. This finding is relevant because it uses both an experimental reduction of the protein in cells and a genetically modified animal model. However, it is not possible to determine the numerical extent of the reduction in mTOR or autophagy from the abstract.The decrease in REDD1 also increased dexamethasone-induced cell death. The authors interpreted this finding as an indication that REDD1-mediated autophagy promotes cell survival in that model. This is an interpretation consistent with the described results, but it does not equate to proving that autophagy is always protective: the effect of autophagy can change depending on the cell type, the duration of the stress, and other signals activated simultaneously.

5. INTERPRETATION

The most immediate biological significance is that a glucocorticoid can activate an adaptation program in lymphocytes. Instead of continuing to invest resources in growth, the cell reduces part of the mTOR signaling and increases the recycling of intracellular components through autophagy.The segment documented by the publication subject to the Evidence Review is: dexamethasone increase in REDD1 reduction of mTOR signaling increase in autophagy. The final step, namely the increased survival of cells with functional REDD1, is suggested by the increase in cell death when REDD1 was reduced.In the book's paragraphs, the statement that REDD1 is necessary to mediate the effects of dexamethasone on mTOR and autophagy summarizes the general direction of the findings. The abstract, however, speaks of a reduction in mTOR inhibition and autophagy following REDD1 suppression. This formulation supports an important and functional role for REDD1, but does not allow for the conclusion that

REDD1 is the only possible mechanism in every lymphocyte or in every experimental condition.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the glucocorticoid REDD1 mTOR reduction pathway comes from a study on rat skeletal muscle and L6 myoblasts, muscle precursor cells cultured in the laboratory. Dexamethasone markedly increased REDD1 RNA, reduced the phosphorylation of S6K1 and 4E-BP1—two indicators of mTOR activity—and silencing REDD1 attenuated the drug's inhibitory effect on mTOR. The experiments also placed REDD1 upstream of the TSC complex and Rheb, which are regulators of the mTOR pathway. The model differs from lymphocytes, but it functionally confirms the same direction of signaling induced by dexamethasone [1].A second independent study showed that REDD1 is a regulator of the response to energy stress. In cells lacking REDD1, the dephosphorylation of S6K and 4E-BP1 after ATP depletion was severely defective; conversely, induced expression of REDD1 rapidly reduced the phosphorylation of these targets and decreased cell size. This work does not use glucocorticoids and does not evaluate autophagy in lymphocytes, but it confirms the central step that REDD1 can act as a brake on the TSC-mTOR pathway when energy resources are scarce [2].Confirmation in a whole organism comes from mice with or without REDD1 treated with dexamethasone. After seven days, a reduction in the weight of certain muscles and in fiber size was observed in normal mice, but not in mice lacking REDD1. Furthermore, the absence of REDD1 prevented the reduction in protein synthesis and mTORC1 activity observed in the muscles of normal mice after dexamethasone. The result confirms that, in murine muscle, REDD1 is an important mediator of the catabolic effects of the glucocorticoid; however, it does not prove that the same outcome occurs in human lymphocytes [3].Taken together, these studies build a convergent chain: dexamethasone can increase REDD1; REDD1 can reduce mTOR signaling; the reduction of mTOR promotes a less anabolic cellular state. For the final part of the book's narrative, namely the activation of autophagy in lymphocytes, the publication subject to the Evidence Review remains the most specific source. The independent confirmations considered here primarily strengthen the upstream mechanism, not a clinical demonstration in humans.

7. CONFLICTING EVIDENCE

Significant conflicting evidence comes from primary murine thymocytes treated with dexamethasone ex vivo. In this study, the deletion of REDD1 did not alter mTORC1 inhibition or glucocorticoid-induced cell death. REDD1 was still increased by the treatment, but it did not prove essential for these two outcomes in the experimental model used [4].This divergence does not eliminate the correspondence between the analyzed study and the book's sections. Rather, it indicates that dexamethasone can reduce mTOR through multiple parallel pathways and that the relative weight of REDD1 depends on the context. The authors of the conflicting study highlighted substantial differences compared to the original work: treatment of mice in vivo followed by thymocyte isolation in the first case, and direct exposure of thymocytes to the drug ex vivo in the second.The result necessitates a cautious formulation. REDD1 is well-supported as a negative regulator of mTOR during stress and after glucocorticoid exposure in various models, but it cannot be considered the sole mediator of mTOR inhibition or thymocyte survival under all conditions.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to confirm or define the scope of the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	Lymphocytes treated with glucocorticoids and REDD1-deficient murine thymocytes	Reducing REDD1 attenuates dexamethasone-induced mTOR inhibition and autophagy; increases cell death.	direct confirmation	moderate
[1]	Cellular and animal	Rat skeletal muscle and L6 myoblasts	Dexamethasone increases REDD1 and reduces mTOR signaling; silencing REDD1 attenuates this reduction.	direct confirmation	moderate
[2]	Cellular	Cells with normal, reduced, or absent REDD1 subjected to energy stress	REDD1 promotes the reduction of mTOR signaling during energy depletion and limits cell growth.	indirect confirmation	moderate
[3]	Animal	Normal mice and REDD1-deficient mice treated with dexamethasone	The absence of REDD1 protects against mTORC1 inhibition, reduced protein synthesis, and muscle atrophy.	direct confirmation	moderate
[4]	Cellular ex vivo	Primary thymocytes from normal or REDD1-deficient mice	The absence of REDD1 does not alter dexamethasone-induced mTORC1 inhibition or death in the model used.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that REDDı participates in the lymphocyte response to dexamethasone, linking the increase in this protein to the reduction of mTOR signaling and autophagy. Independent evidence confirms REDDı as a negative regulator of mTOR during energy stress and following glucocorticoid exposure, particularly in cells and murine models.The most balanced conclusion is that the glucocorticoids REDDı mTOR reduction pathway is well-supported at a mechanistic level. The subsequent link to protective autophagy in lymphocytes is plausible and directly documented in the original work, but it remains dependent on the experimental model. It is not possible to automatically translate these results to the clinical consequences of chronic stress in humans.

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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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