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REDD1 increases Akt dephosphorylation mediated by protein phosphatase 2A to repress mTORC1 signaling - Evidence review

Dr.ssa M. Bitonti[1]

1 Nutritional Biologist, Italy

ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed study examined how REDD1, a protein induced under various cellular stress conditions, can reduce the activity of mTORC1, a protein complex that promotes cell growth and synthesis when nutrients and growth signals are available. The authors used normal and REDD1-deficient mouse embryonic fibroblasts and observed that REDD1 promotes the action of protein phosphatase 2A, reducing AKT activation at the Thr308 site. This step decreases the inhibition of the TSC complex and reduces, downstream, the activation of mTORC1.In paragraph 4.10 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication is referenced in the description of the regulation of REDD1 stability by mTOR. The only available abstract of the original study does not report experiments on the degradation or protein stability of REDD1; instead, it documents a mechanism by which REDD1 represses mTORC1. Independent studies show that mTORC1 can increase the stability of REDD1 and that REDD1 controls mTOR through the TSC complex. Overall, the narrative is mechanistically consistent, while the implications for clinical insulin resistance require direct evidence in humans.

MISSION

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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.

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2. ANALYZED STUDY

The research question was to understand how REDD1 (regulated in development and DNA damage responses 1, a protein involved in stress responses) manages to reduce the signaling of mTORC1 (mechanistic target of rapamycin complex 1, a complex that supports protein synthesis and cell growth). The hypothesis evaluated was that REDD1 does not act only in a generic way on the TSC1/TSC2 complex, but directly reduces an upstream signal: the activation of AKT, a protein that normally helps release the brake exerted by the TSC complex on mTORC1.The study is relevant to the book's section because it places REDD1 within a regulatory circuit between growth signals, AKT, TSC, and mTORC1. Its specific contribution is the segment REDD1 PP2A reduced phosphorylation of AKT reduced activation of mTORC1. However, based on the available material, it cannot demonstrate that mTOR directly regulates the stability or degradation of REDD1: this particular result does not appear in the provided abstract. Furthermore, as this study was conducted on cells, it does not prove that the same mechanism causes insulin resistance in people.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the publication's abstract. The authors compared normal mouse embryonic fibroblasts with mouse embryonic fibroblasts lacking the REDD1 gene. They also evaluated the physical association between REDD1, AKT, and PP2A using co-immunoprecipitation, a technique that allows for verifying whether proteins present in the same cell extract are part of the same molecular complex.The main variables were the phosphorylation of AKT at Thr308 and Ser473, the phosphorylation of TSC2, and the activation state of Rheb, a small protein that promotes the activation of mTORC1. REDD1 mutants incapable of binding to AKT or PP2A were also evaluated. The number of experiments, the number of biological replicates, inclusion and exclusion criteria, statistical details, P-values, confidence intervals, treatment concentrations, and duration of exposures are not reported in the available material.

4. RESULTS

In simple terms, REDD1 acted as an element that reduces the ability of AKT to transmit growth signals to mTORC1. In detail, REDD1 promoted the dephosphorylation of AKT at Thr308 by PP2A (protein phosphatase 2A, an enzyme that removes phosphate groups from proteins), without reducing the phosphorylation of AKT at Ser473. Phosphorylation is a chemical modification that can turn a protein on or off depending on the site involved.Since the phosphorylation of AKT at Thr308 is necessary to phosphorylate TSC2, the reduction of this signal was accompanied by a reduction in the phosphorylation of TSC2 and lower activation of Rheb. The biological significance proposed by the authors is that TSC2 remains more capable of inhibiting Rheb and, therefore, mTORC1. REDD1 and PP2A were co-immunoprecipitated with AKT in normal fibroblasts, but not in fibroblasts lacking REDD1. Furthermore, the binding of REDD1 to both AKT and PP2A was necessary to repress the signal directed to mTORC1.The abstract does not report numerical values for the observed variations, P-values, or effect sizes. It also does not report measurements of protein stability, ubiquitination, or REDD1 degradation. Therefore, the result documented by the available material concerns the repression of mTORC1 via AKT, not the regulation of REDD1 stability by mTOR.

5. INTERPRETATION

For a cell, the result suggests an attention system: when REDD1 is present, it makes one of the signals that promote growth and the synthesis of new proteins less effective. The molecular detail is REDD1 PP2A dephosphorylation of AKT at Thr308 reduced phosphorylation of TSC2 reduced activation of Rheb reduced mTORC1 signaling. This sequence is consistent with a regulatory brake, not an absolute and permanent blockage of the insulin response.The step directly documented by the analyzed study is therefore the repression of mTORC1 by REDD1 through PP2A and AKT. The book's paragraph also contains a different point, namely that mTOR modulates the stability and degradation of REDD1. This point is not verifiable in the abstract of the original study, but it has been evaluated through independent evidence. The distinction is important: a

biological circuit can be composed of multiple real relationships without a single publication demonstrating them all.

6. INDEPENDENT CONFIRMATORY EVIDENCE

The most direct confirmation of the book's statement on protein stability comes from an independent cellular study by Tan and Hagen. In cultured cells, inhibition of mTORC1 with rapamycin or PP242 reduced the stability and abundance of REDD1; conversely, activation of mTORC1 increased REDD1 levels. The authors proposed a feedback loop in which active mTORC1 limits the proteasomal degradation of REDD1. This directly confirms the idea that mTORC1 can help regulate REDD1 stability, although it does not demonstrate what consequences this circuit has in the human body [1].A second independent study verified the functional segment REDD1 TSC1/TSC2 mTOR. In murine fibroblasts and cell lines with inducible REDD1, REDD1 was necessary to reduce the phosphorylation of S6K and 4E-BP1, two targets of mTORC1 that reflect reduced growth signaling. The effect required TSC2 and was hindered by the overexpression of Rheb; the induction of REDD1 also reduced the average cell size. The study therefore confirms that REDD1 acts in the TSC-Rheb-mTOR circuit, but it remains experimental cellular evidence [2].The insulin context described in the paragraph is supported by a study in murine and human adipocytes. Insulin increased REDD1 expression through HIF-1α (hypoxia-inducible factor 1 alpha, a transcription factor activated in response to conditions of reduced oxygen availability and other stimuli). Silencing HIF-1α or inhibiting it prevented the increase in REDD1 induced by insulin. This result is consistent with a cellular counter-regulation of anabolic signaling, but it does not prove that such a response is necessarily harmful or responsible for type 2 diabetes in humans [3].

7. CONFLICTING EVIDENCE

Independent research confirms that REDD1 is a highly unstable protein and that its degradation modifies mTORC1 signaling, but it proposes a partially different mechanism. In several cell lines, Katiyar and colleagues attributed REDD1 degradation to a ubiquitination complex including CUL4A-DDB1, with an estimated half-life of approximately 5–7 minutes following hypoxic induction. The study by Tan and Hagen, however, did not detect a role for CUL4A in the observed regulation of REDD1 stability [4].This difference does not negate the fact that REDD1 is regulated via protein degradation, nor that mTORC1 can influence its stability. It does, however, indicate that molecular details may depend on the cell line, the type of stress, and experimental conditions. No sufficiently relevant directly conflicting evidence has been identified regarding the general direction of the mTORC1-REDD1 circuit; this does not prove the absence of contradictory results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to evaluate the specific narrative of the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and molecular	Normal and REDD1-deficient murine embryonic fibroblasts	REDD1 promotes PP2A, reduces AKT phosphorylation at Thr308, and represses signaling to mTORC1.	biologically consistent evidence	preliminary
[1]	Cellular	Cultured cell lines	mTORC1 inhibition reduces REDD1 stability; mTORC1 activation increases its levels.	direct confirmation	moderate
[2]	Cellular and genetic	Murine fibroblasts and lines with inducible REDD1	REDD1 requires TSC2 to reduce downstream mTORC1 signaling and reduces cell size.	indirect confirmation	moderate
[3]	Cellular	Murine 3T3-L1 adipocytes and human adipocytes	Insulin increases REDD1 via HIF-1α.	biologically consistent evidence	moderate
[4]	Cellular	HEK293, HCT-116, MCF-7, and U2OS cells	REDD1 is rapidly degraded; involvement of CUL4A-DDB1 is proposed.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study clearly supports that REDD1 can reduce mTORC1 signaling by promoting the dephosphorylation of AKT by PP2A. This mechanism is well-integrated into the REDD1-TSC-Rheb-mTORC1 chain described in the paragraph. However, the specific statement regarding the stability and degradation of REDD1 is not reported in the abstract of the original study alone.Independent evidence confirms that mTORC1 can influence REDD1 stability and that REDD1 acts as a regulator of mTORC1 under conditions of stress or insulin stimulation. This confirmation is primarily mechanistic and cellular. The link to insulin resistance and metabolic disease in humans remains plausible, but it requires direct clinical validation and cannot be automatically inferred from cellular experiments.

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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