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ORIGINAL RESEARCH

Regulation of mTOR function in response to hypoxia by REDD1 and the tumor suppressor complex TSC1/TSC2 - Review of the evidence

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1. ABSTRACT

The analyzed publication investigated how cells reduce mTOR activity when oxygen is scarce. The authors observed that this response requires REDD1, a hypoxia-induced gene, and the TSC1/TSC2 complex, a system that acts as a brake on cell growth. When REDD1 or TSC1/TSC2 were altered, the ability of hypoxia to reduce signals controlled by mTOR decreased.In the context of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study contributes primarily to the narrative that REDD1 links stress from low oxygen availability to the TSC1/TSC2 complex and the reduction of mTORC1 activity. Subsequent studies confirm this axis in cells and fibroblasts, clarifying mechanisms involving TSC2, AKT, and the PP2A protein. However, other research shows that in the liver, hypoxia can inhibit mTORC1 even without REDD1 and TSC1/TSC2. The relationship is therefore well-supported as a cellular mechanism, but it is not universal across tissues nor proven as a general clinical explanation for insulin resistance.

ONLINE ARTICLE

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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 how hypoxia, i.e., a reduced availability of oxygen, manages to slow down mTOR, a protein that coordinates protein synthesis and cell growth. The hypothesis evaluated was that this response did not depend solely on energy scarcity, but required REDD1 and the TSC1/TSC2 complex. This complex can be described as a molecular brake: when active, it reduces the signal that leads to the activation of mTORC1.The relevance to paragraphs 4.10 and 21.9 is direct: the research covered by the article documents the segment hypoxia increase in REDD1 dependence on TSC1/TSC2 reduction in mTORC1 activity. Regarding paragraph 4.6, however, it supports the general role of mTOR as an integrator of stress and growth signals, but it does not directly study mTORC2 nor does it demonstrate that mTORC2 phosphorylates AKT. The study cannot prove that this circuit causes insulin resistance in humans, nor that every form of cellular stress necessarily utilizes REDD1.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study used cellular experiments in which hypoxia was simulated, comparing cells with a functional TSC1/TSC2 complex to cells lacking TSC1 or TSC2. The expression of REDD1 and the activity of several proteins involved in the response to energy availability, including AMPK and LKB1, were also experimentally altered.mTOR activity was assessed through the phosphorylation of S6K and 4E-BP1. Phosphorylation is the addition of a small chemical group to a protein, which often modifies its activity; in this case, a reduction in the phosphorylation of S6K and 4E-BP1 was used as an indicator of lower mTORC1 activity. The authors also evaluated cell proliferation under hypoxic conditions. The number of experiments, the cell lines used, the duration of hypoxia, the oxygen percentage, exclusion criteria, details of statistical analyses, and complete numerical values are not reported in the available material.

4. RESULTS

The main finding is that hypoxia reduced mTOR activity only when both REDD1 and the TSC1/TSC2 complex were present. The loss of TSC1 or TSC2 blocked the inhibitory effect of hypoxia on the S6K and 4E-BP1 targets. Simply put, without this braking system, the cell continued to maintain higher activity in signals normally associated with protein production and growth.Disrupting REDD1 also prevented the reduction in mTOR activity caused by hypoxia. Conversely, experimentally increasing REDD1 was sufficient to decrease S6K phosphorylation, but only if TSC1/TSC2 was functional. This data places REDD1 upstream of the TSC1/TSC2 complex in the observed response.The authors also reported that, under hypoxic conditions, TSC2-deficient cells maintained abnormally high proliferation. They also observed an abnormal accumulation of the hypoxia-inducible factor, HIF, when the TSC1/TSC2 complex was inactive. The study distinguished this pathway from the response to energy depletion: the hypoxia-induced inhibition of mTOR did not require AMPK or LKB1. The abstract does not report percentages, P-values, confidence intervals, or effect sizes; therefore, such data are not available for quantitative assessment.

5. INTERPRETATION

For a cell receiving little oxygen, continuing to grow and produce proteins can increase resource consumption. The results indicate that REDD1 helps activate an adaptive brake, TSC1/TSC2, which reduces mTORC1 activity. This is the scientifically documented step that explains why the publication was cited in the sections dedicated to the REDD1–TSC1/TSC2–mTOR relationship.However, this result does not equate to proving that REDD1 directly "activates" TSC1/TSC2 through physical contact. The study shows a functional dependency: without TSC1/TSC2, REDD1 cannot reduce the signal measured on S6K. Subsequent research has proposed more detailed mechanisms, including the modulation of the interaction between TSC2 and 14-3-3 proteins or the reduction of AKT activation.The publication does not directly demonstrate that REDD1 causes persistent metabolic dysfunction, muscle loss, or clinical insulin resistance. Furthermore, it does not analyze mTORC2. Its contribution to the book's narrative primarily

concerns mTORC1 and cellular adaptation to hypoxia.

6. INDEPENDENT SUPPORTING EVIDENCE

Close experimental confirmation comes from DeYoung and colleagues, who studied mouse embryonic fibroblasts, U2OS cells, and mouse models. Under hypoxia, REDD1 promoted the dissociation of TSC2 from 14-3-3 proteins, which are regulatory proteins that can hold other proteins in a less active configuration. The loss of REDD1 prevented both this dissociation and the reduction of S6K1 phosphorylation. Experimental increases in REDD1 also countered insulin-induced mTORC1 activation. This directly confirms the passage in the book stating that REDD1 promotes the action of the TSC1/TSC2 complex and reduces mTORC1, but this evidence remains primarily cellular and animal-based [1].A second study outlined a possible alternative or complementary pathway. Dennis and colleagues used mouse embryonic fibroblasts lacking REDD1 and a cell line with inducible REDD1. REDD1 increased the association of the phosphatase PP2A with AKT and reduced AKT phosphorylation at the Thr308 site. Since AKT normally inactivates TSC2 through phosphorylation, the reduction of AKT favored a greater inhibitory effect exerted by TSC2 on mTORC1. The result supports the direction described in the book—REDD1 leading to lower mTORC1 activity—but specifies that the connection may also involve the modulation of AKT and not just a single mechanism acting on TSC2 [2].These findings converge on the main biological significance: when REDD1 increases under specific stress conditions, the mTORC1 signals that support protein synthesis and cell growth decrease. However, the available data do not allow for the automatic transfer of this sequence to all human tissues or for it to be considered a proven cause of clinical insulin resistance.

7. CONFLICTING EVIDENCE

Evidence directly relevant to the mechanism has been identified, which limits its generalizability. Wolff and colleagues compared mouse fibroblasts, thymocytes, and primary liver cells subjected to hypoxia. In fibroblasts and thymocytes, the loss of REDD1 compromised the hypoxia-induced reduction of mTORC1, consistent with the original study. In hepatocytes, however, hypoxia continued to inhibit mTORC1 even in the absence of REDD1 or TSC1/TSC2.In liver cells, the response was found to be more dependent on LKB1, AMPK, and raptor, a component of the mTORC1 complex. This observation does not contradict the REDD1–TSC1/TSC2 circuit in the models where it has been demonstrated, but it shows that hypoxia can utilize different pathways depending on the cell type. Consequently, it is incorrect to present REDD1 as the sole universal switch for mTORC1 in every tissue [3].

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent research that confirms or delimits its significance.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Cells with alterations in REDD1, TSC1, or TSC2; details not reported in the available abstract	Hypoxia requires REDD1 and TSC1/TSC2 to reduce S6K and 4E-BP1 signals associated with mTORC1	direct confirmation	moderate
[1]	Experimental cellular and animal	Mouse embryonic fibroblasts, U2OS cells, and mouse model	REDD1 promotes TSC2/14-3-3 dissociation and reduces S6K1 phosphorylation in response to hypoxia	direct confirmation	moderate
[2]	Experimental cellular	REDD1-deficient mouse embryonic fibroblasts and inducible REDD1 cell line	REDD1 promotes AKT dephosphorylation by PP2A, reducing signaling to mTORC1	indirect confirmation	moderate
[3]	Experimental cellular and animal	Mouse fibroblasts, thymocytes, and primary hepatocytes	In hepatocytes, hypoxia inhibits mTORC1 even without REDD1 and TSC1/TSC2	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports the fact that, in specific cell models subjected to hypoxia, REDD1 and the TSC1/TSC2 complex are necessary to reduce mTORC1 activity. This is the scientific core for which the publication is relevant to the sections of the book dedicated to REDD1 and mTOR.Independent research confirms that REDD1 can reduce mTORC1 signaling through the regulation of TSC2 and AKT. The framework is well-supported at a mechanistic level. However, it remains necessary to distinguish acute cellular adaptation to hypoxia from chronic clinical consequences: the mechanism is not universal across tissues and does not, by itself, prove that REDD1 causes insulin resistance in humans.

Aggiornato al 17/11/2026. 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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