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Hypoxia regulates the TSC1/2-mTOR signal and tumor suppression through REDD1-mediated 14-3-3 displacement - Review of the evidence

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed study examined how oxygen deficiency, known as hypoxia, reduces the activity of mTORC1, a protein complex that promotes protein synthesis and cell growth. In mammalian cells and a mouse model, the authors observed that hypoxia and REDD1 promote the separation between TSC2 and 14-3-3 proteins. This reactivates the TSC1/TSC2 complex, which reduces the mTORC1 signal.In section 4.10 and section 21.9 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that REDD1 is a stress-induced brake capable of limiting the signal directed at mTOR. Independent studies confirm that REDD1 can reduce mTORC1 through TSC1/TSC2 and, in some models, also through a reduction in AKT phosphorylation. However, the original work does not document AKT dephosphorylation during hypoxia and does not directly demonstrate that this mechanism causes insulin resistance in humans. The confirmation is therefore primarily mechanistic and dependent on the cellular context.

MISSION

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2. ANALYZED STUDY

The research question was how hypoxia manages to rapidly reduce the activity of mTORC1, the complex that signals the cell to build proteins, grow, and consume resources. The hypothesis evaluated was that REDD1, a stress-induced protein, acts on the TSC1/TSC2 complex—a physiological brake on mTORC1—by modifying the relationship between TSC2 and 14-3-3 proteins.The relevance to the book's section concerns the REDD1 TSC1/TSC2 mTORC1 inhibition segment. The study shows that REDD1 opposes the growth signal that keeps TSC2 associated with 14-3-3, thereby making it less active. It does not, however, show that REDD1 directly dephosphorylates AKT during hypoxia: in the available material, the authors report that the effect of REDD1 on TSC2 and mTORC1 was not associated with changes in AKT phosphorylation. Furthermore, this is primarily an experimental demonstration in cells and animals, not clinical evidence regarding human insulin resistance.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used mammalian cells, including cells with REDD1 loss or with REDD1 and TSC2 variants incapable of binding 14-3-3. They exposed the cells to hypoxia and evaluated the association between TSC2 and 14-3-3 and mTORC1 activity.The study also evaluated cell proliferation and
anchorage-independent growth, a test that measures the ability of cells to grow without normal attachment to a surface. A mouse model of tumorigenesis was also used. The number of experiments, animal sample size, inclusion criteria, observation times, statistical procedures, significance values, and detailed characteristics of the models are not reported in the available material.

4. RESULTS

The key finding is that hypoxia reduced mTORC1 activity by releasing TSC2 from its association with 14-3-3. In simple terms, REDD1 helped reactivate the TSC1/TSC2 brake when oxygen was scarce. Endogenous REDD1, which is naturally produced by cells, was necessary for both the TSC2/14-3-3 dissociation and the hypoxia-induced inhibition of mTORC1.REDD1 variants that failed to bind 14-3-3 did not effectively induce TSC2/14-3-3 separation or mTORC1 inhibition. Similarly, TSC2 variants unable to bind 14-3-3 did not correctly transmit the hypoxia signal to mTORC1. This supports a functional relationship between REDD1, 14-3-3, TSC2, and mTORC1.The loss of the REDD1 signal promoted proliferation and anchorage-independent growth under hypoxic conditions. In the mouse model, the loss of REDD1 favored tumorigenesis; a reduction in REDD1 was also observed in a subset of human tumors. The available material does not report absolute values, percentages, confidence intervals, P-values, or sample sizes. A particularly important element for the book's text is that the described effect did not depend on a reduction in AKT phosphorylation: REDD1 opposed the result of the PI3K/AKT signal on TSC2 and mTORC1 without modifying AKT phosphorylation in the studied model.

5. INTERPRETATION

When a cell receives insufficient oxygen, continuing to intensely support protein synthesis and growth can be unfavorable. REDD1 therefore appears as a component of the conservation response: it promotes the recovery of the inhibitory function of TSC1/TSC2 and reduces mTORC1. The proposed molecular detail is that REDD1 interacts with 14-3-3 and promotes the detachment of 14-3-3 from TSC2; TSC2 can thus contribute to repressing the activation of mTORC1.This result directly supports the part of the narrative that links hypoxic stress to REDD1, the TSC1/TSC2 complex, and the reduction of mTORC1. It only indirectly supports the link to insulin signaling, because the experiment shows that REDD1 can counteract the downstream effect of the PI3K/AKT pathway, but does not observe AKT dephosphorylation in hypoxia. The sentence in the book regarding AKT dephosphorylation is therefore more precisely supported by subsequent studies conducted in other experimental systems, rather than by the specific mechanism documented in the publication subject to the Evidence Review.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial independent confirmation came from experiments in mouse embryonic fibroblasts, HEK293 cells, and HeLa cells. In this study, hypoxia reduced mTOR activity only when the TSC1/TSC2 complex

was functional; the loss of TSC1, TSC2, or REDD1 prevented the reduction in the phosphorylation of S6K and 4E-BP1, two downstream targets of mTORC1. Experimental increase of REDD1 also reduced S6K phosphorylation in a TSC1/TSC2-dependent manner. This directly confirms the pathway hypoxia REDD1 TSC1/TSC2 reduced mTORC1 activity, although it remains primarily cellular evidence [1].A second study, conducted in mouse fibroblasts with and without REDD1 and with experimental manipulations of gene expression, extended the model to energy stress. The presence of REDD1 was necessary for the normal reduction of S6K and 4E-BP1 phosphorylation following ATP depletion or activation of AMPK, a protein that signals low energy availability. REDD1 induction reduced cell size, while its inhibition increased it. The result reinforces the role of REDD1 as a brake on mTORC1 under stress conditions, but it does not prove that all forms of stress use the same molecular detail as hypoxia [2].The part of the book text discussing AKT dephosphorylation finds independent confirmation in work performed in inducible HEK293 cells and mouse embryonic fibroblasts. REDD1 promoted the action of the phosphatase PP2A, an enzyme that removes phosphate groups, increasing the dephosphorylation of AKT at the Thr308 site. The reduction of this signal was accompanied by lower TSC2 phosphorylation, lower Rheb activation, and repression of mTORC1. This is a mechanistic confirmation of the possibility that REDD1 limits AKT and mTORC1, but it concerns a different model from the hypoxic one in the original study and does not imply that the PP2A-AKT pathway is always necessary [3].Taken together, these studies converge on the role of REDD1 as a negative regulator of mTORC1. The convergence is more robust for the sequence REDD1 TSC1/TSC2 mTORC1; it is more circumscribed and model-dependent for the sequence REDD1 PP2A AKT TSC2 mTORC1.

7. CONFLICTING EVIDENCE

Important contextual evidence comes from a study that compared multiple cell types and tissues. The authors observed that the induction of REDD1 by hypoxia and the signal transmission to mTORC1 were not uniform: in some cellular contexts, REDD1 and TSC1/TSC2 contributed significantly, while in liver cells, the phosphorylation of raptor—a component of mTORC1—mediated by AMPK also proved essential. This does not negate the mechanism documented in the original study, but it shows that hypoxia can reduce mTORC1 through different pathways depending on the cell type [4].No directly conflicting evidence sufficiently relevant to the fact that REDD1 can reduce mTORC1 through TSC1/TSC2 has been identified; this does not prove the absence of contrary results. The available evidence primarily indicates that the relative weight of REDD1, TSC1/TSC2, AKT, and AMPK changes according to the tissue, the state of cellular transformation, and the type of stress.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent research and summarizes the level at which each contributes to the REDD1-TSC1/TSC2-mTORC1 narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	Mammalian cells and murine model	In hypoxia, REDD1 promotes TSC2/14-3-3 dissociation and reduces mTORC1; loss of REDD1 promotes cell growth and tumorigenesis	biologically consistent evidence	moderate
[1]	Cellular	Murine embryonic fibroblasts, HEK293 and HeLa	Hypoxia and REDD1 reduce mTOR activity in a TSC1/TSC2-dependent manner	direct confirmation	moderate
[2]	Cellular	Murine embryonic fibroblasts with REDD1 manipulation	REDD1 reduces phosphorylation of mTORC1 targets and limits cell growth during energy stress	indirect confirmation	moderate
[3]	Cellular	Inducible HEK293 and murine embryonic fibroblasts	REDD1 promotes PP2A-mediated dephosphorylation of AKT Thr308 and represses mTORC1	indirect confirmation	moderate
[4]	Cellular and animal	Murine cells and tissues of different types	Hypoxic regulation of mTORC1 depends on cell type and may involve pathways beyond REDD1-TSC1/TSC2	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports the fact that REDD1 participates in the response to hypoxia by reducing mTORC1 through the TSC1/TSC2 complex and the regulation of the TSC2/14-3-3 interaction. This mechanistic core is confirmed by independent evidence. The idea that REDD1 may also promote the dephosphorylation of AKT is supported in other cellular models, but it is not the specific result observed in the original study.The narrative that REDD1 acts as a brake on the cellular anabolic state is therefore well-supported at a mechanistic level. However, it is not possible to deduce from these data that the activation of REDD1 directly causes insulin resistance in humans, nor that the REDD1-mTOR relationship always has the same effect in all tissues or under every stress condition.

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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