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Insulin and REDD1 induction via HIF-1 in adipocytes

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1. ABSTRACT

The analyzed study evaluated whether insulin can increase REDD1 expression in adipocytes, cells specialized in the storage and release of fat. In the available abstract, the authors report that insulin increases REDD1 in murine and human adipocytes through PI3K/mTOR-dependent pathways and the HIF-1 transcription factor. The use of a HIF-1 inhibitor and small interfering RNAs against HIF-1a supported the necessary involvement of this factor in the experimental model.The publication contributes to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, according to which insulin can induce REDD1 via HIF-1a in adipocytes, configuring a possible adaptive brake on mTORC1. Independent studies confirm that insulin increases HIF-1a in adipocytes and that REDD1 can reduce mTORC1 activity through TSC2 and AKT. However, such evidence is primarily cellular or animal-based and indicates that the mechanism depends on the tissue type. They do not, by themselves, demonstrate that this circuit causes insulin resistance in humans.

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.

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 insulin, a hormone that coordinates the use and storage of nutrients, regulates the expression of REDD1 in adipocytes. REDD1, also known as DDIT4, is a protein induced by cellular stress conditions and is capable of reducing the signaling of mTORC1, a protein complex involved in growth and protein synthesis.The hypothesis evaluated was that insulin increases REDD1 via HIF-1a, the regulatory subunit of hypoxia-inducible factor 1, which is a regulator of the activation of certain genes in response to changes in the cellular environment. This is the specific reason why the study is relevant to paragraph 4.10: it documents the initial segment of the narrative, namely insulin HIF-1a increase of REDD1 in adipocytes.The study can demonstrate an experimental effect of insulin on REDD1 expression in adipocyte models and the involvement of HIF-1 in the analyzed system. However, it cannot demonstrate that REDD1 causes clinical insulin resistance in humans, nor that the circuit observed in cultured cells behaves the same way in all tissues or in people with type 2 diabetes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Based solely on the available abstract, the study used murine adipocytes and human adipocytes. The authors exposed these cells to insulin and evaluated the expression of REDD1. They also examined the role of the PI3K/mTOR pathways, a sequence of intracellular signals also activated by insulin and involved in the control of cell growth.To verify the role of HIF-1, the authors used echinomycin, described in the abstract as an HIF-1 inhibitor, and small interfering RNAs directed against HIF-1a. Small interfering RNAs are short molecules used to decrease the production of a specific protein. The number of experiments, the concentrations used, the duration of the incubations, the selection criteria for human adipocytes, the details of the laboratory techniques, the statistical analyses, and the quantitative values are not reported in the available material.

4. RESULTS

The main finding is that insulin increased REDD1 expression in murine and human adipocytes. Simply put, a signal that normally promotes nutrient utilization and storage also activated a protein that can help limit cell growth signaling. The abstract does not report the numerical magnitude of the increase, P-values, or confidence intervals.The authors report that the insulin-induced increase in REDD1 depends on PI3K/mTOR pathways. They also report that pharmacological inhibition of HIF-1 with echinomycin and the reduction of HIF-1α using small interfering RNAs prevented the induction of REDD1 by insulin. In the experimental model, this result places HIF-1 upstream of the increase in REDD1.The data most relevant to the book is therefore directional and specific: in the adipocytes studied, insulin increased REDD1 via HIF-1. The abstract does not report a direct measure of insulin resistance, nor does it demonstrate that the increase in REDD1 produced a stable reduction in the insulin response.

5. INTERPRETATION

The result suggests the existence of a possible self-regulation circuit. Insulin activates signals that promote anabolism, that is, the use of nutrients to build and store cellular components. At the same time, in the adipocytes studied, REDD1 increases via HIF-1a. Since REDD1 is capable of reducing the mTORC1 signal, this increase may represent a brake that prevents excessive or prolonged activation of growth processes.The segment documented by the publication is insulin HIF-1a REDD1. The subsequent step, REDD1 reduction of mTORC1, is consistent with independent experimental knowledge. However, the term “counter-regulation” must be interpreted with caution: the study did not directly measure a complete feedback circuit, nor did it verify whether REDD1 improves or worsens insulin sensitivity in the body over the long term.The distinction is important because limiting mTORC1 can have different meanings depending on the duration of the stimulus, the tissue, and the metabolic context. A temporary brake can contribute to cellular homeostasis; a persistent alteration cannot automatically be equated to a cause of insulin resistance without specific data in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the upstream pathway comes from a study on differentiated 3T3-L1 adipocytes, a murine cell line widely used to study adipose tissue. Insulin increased both messenger RNA and HIF-1α protein, and increased the activity of an experimental system that signals HIF-1 activation. The authors also found that PI3K and mTOR were necessary for the increase in HIF-1α. This study did not measure REDD1, but it directly confirms the insulin link to HIF-1α in adipocytes [1].A second experimental line clarifies the next step in the chain. In murine embryonic fibroblasts and other cell models, the increase in REDD1 under hypoxic conditions was found to be necessary for the reduction of mTORC1 activity. The mechanism involves the TSC1/TSC2 complex, a regulator that can reduce mTORC1 activation. This confirms that REDD1 can function as a link between an adaptive stimulus and the mTORC1 brake, although it was not a study conducted on adipocytes exposed to insulin [2].Further research has specified how REDD1 can reduce the signal reaching mTORC1. In HEK293 cells and murine embryonic fibroblasts, REDD1 promoted the action of the phosphatase PP2A, an enzyme that removes phosphate groups from proteins. This reduced the phosphorylation of AKT at Thr308, a modification necessary for AKT to effectively inhibit TSC2. Consequently, the activation of Rheb and mTORC1 decreased. The result makes the sequence REDD1 lower AKT/TSC2 signal lower mTORC1 activity biologically consistent, but it remains primarily a cellular demonstration [3].

7. CONFLICTING EVIDENCE

Relevant evidence suggests that the REDD1–TSC1/TSC2–mTORC1 circuit should not be generalized to every organ. In murine fibroblasts and thymocytes, the loss of REDD1 attenuated the hypoxia-induced inhibition of mTORC1. In primary murine hepatocytes, however, hypoxia reduced mTORC1 even in the absence of REDD1 and TSC1/TSC2; in this context, a role for LKB1, AMPK, and raptor emerged. This result does not contradict the observation in adipocytes, but it shows that the way a cell inhibits mTORC1 depends on the tissue and the experimental condition [4].No directly conflicting evidence sufficiently relevant to the insulin-induced increase of REDD1 via HIF-1α in human adipocytes has been identified; this does not prove the absence of contrary results. The main caution concerns, above all, the extension of the mechanism to all tissues and the transition from cellular experiments to clinical consequences such as insulin resistance.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the data from the analyzed study from the independent publications used to confirm or define the steps of the same narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Murine and human adipocytes	Insulin increases REDD1; the effect requires HIF-1 in the studied model.	direct confirmation	moderate
[1]	Experimental cellular	Differentiated 3T3-L1 murine adipocytes	Insulin increases RNA, protein, and HIF-1α activity.	direct confirmation	moderate
[2]	Cellular and animal	Murine fibroblasts, Drosophila cells, and genetic models	REDD1 and TSC1/TSC2 are required to reduce mTORC1 in response to hypoxia.	indirect confirmation	moderate
[3]	Experimental cellular	HEK293 cells and murine embryonic fibroblasts	REDD1 promotes AKT dephosphorylation and reduces mTORC1 activation.	biologically consistent evidence	moderate
[4]	Cellular and animal	Murine fibroblasts, thymocytes, and hepatocytes	In hepatocytes, mTORC1 inhibition by hypoxia is independent of REDD1 and TSC1/TSC2.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports the finding that, in the murine and human adipocytes examined, insulin increases REDD1 through HIF-1. This data is consistent with a possible self-regulation system for cellular anabolism. Independent evidence confirms the link between insulin and HIF-1a in adipocytes and the role of REDD1 in reducing signals directed to mTORC1.The narrative is therefore well-supported at a mechanistic level, but requires caution when extended to the human organism. The circuit varies according to cell type and does not demonstrate on its own that the increase in REDD1 causes clinical insulin resistance. Specific physiological and clinical studies in relevant human tissues are necessary.

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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