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TSC/Rheb/mTOR/S6K activation, insulin resistance, and IRS1/2 depletion

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1. ABSTRACT

The analyzed study evaluated whether constant activation of the TSC/Rheb/mTOR/S6K pathway was sufficient to reduce the cellular response to insulin. In the cell models described in the abstract, the loss of TSC1 or TSC2 or the artificial increase of Rheb resulted in a reduction of IRS1 and IRS2 proteins, which are necessary to transfer the signal from the insulin receptor to PI3K. Consequently, insulin and IGF-I were no longer able to adequately activate AKT, a protein important for metabolic and cell survival responses.The research contributes to the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi because it documents a precise segment of the chain: the hyperactivation of mTOR/S6K can deplete the cell of IRS and disrupt the connection between the insulin receptor, PI3K, and AKT. Independent evidence confirms this negative feedback in cells, animals, and, for some steps, in human muscle. However, it remains necessary to distinguish this experimental mechanism from the clinical consequences in obesity, diabetes, and neurodegenerative diseases.

ONLINE ARTICLE

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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 persistent activation of the cascade formed by TSC, Rheb, mTOR, and S6K was sufficient on its own to make cells resistant to insulin. TSC1 and TSC2 form a complex that normally limits Rheb, a protein that promotes the activation of mTOR. mTOR, in turn, activates S6K, a kinase (an enzyme that modifies other proteins by adding phosphate groups) involved in growth and protein synthesis.The authors' hypothesis was that the hyperactivation of this pathway not only produced growth signals but also activated an internal brake on insulin signaling. The central point is IRS1 and IRS2, adapter proteins that receive the signal from the insulin receptor and transfer it to PI3K (phosphoinositide 3-kinase), upon which the activation of AKT also depends.This is the reason for its relevance to sections 4.8, 14.10, and 15.9 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi: the publication documents that the loss of control exerted by TSC1/TSC2 can reduce IRS1/2 and make the segment of the cascade between the insulin receptor and AKT inefficient. The study can therefore demonstrate a selective cellular mechanism. However, it cannot, on its own, establish how much this mechanism explains insulin resistance in the entire human body, nor can it demonstrate a direct role in Alzheimer's disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract of the publication is available. The authors compared cells with genetic loss of TSC1 or TSC2 with models in which Rheb was artificially expressed. They also evaluated the ability of IRS-dependent signals, namely insulin and IGF-I (insulin-like growth factor 1), to activate AKT; as a comparison, they used PDGF, a growth factor that can activate AKT through pathways independent of IRS.The abstract indicates that IRS1 and IRS2 levels, AKT activation, and the anti-apoptotic response induced by IGF-I or PDGF were measured. Apoptosis is a regulated form of cell death. The number of experiments, the cell lines used, selection criteria, exposure times, treatment concentrations, details of laboratory techniques, statistical analyses, and numerical values are not reported in the available material.

4. RESULTS

The main finding is that the loss of TSC1 or TSC2, or the increased expression of Rheb, was sufficient to produce cellular insulin resistance. In simple terms, the cells still possessed the insulin receptor, but they transmitted its message inward much less effectively.According to the abstract, the constitutive activation—meaning continuous and no longer regulated—of the Rheb/mTOR/S6K axis reduced IRS1 and IRS2. As these proteins became limiting factors, the signal transmission from the insulin receptor to PI3K decreased. Downstream of PI3K, AKT was completely refractory to activation induced by insulin or IGF-I in cells lacking TSC1 or TSC2. Conversely, AKT could still be activated by PDGF, which does not require IRS to transmit its signal.This comparison is particularly informative: it indicates that AKT was not necessarily absent or unusable, but that the defect was localized upstream, in the IRS-dependent link between the insulin receptor and PI3K. Furthermore, in cells without TSC2, the anti-apoptotic program induced by IGF-I was severely compromised, while the one induced by PDGF was not. The abstract does not report absolute values, percentages, confidence intervals, or P-values; such data are therefore not reported in the available material.

5. INTERPRETATION

The biological significance is that a pathway normally useful for coordinating nutrient availability and growth can, if kept constantly active, weaken the very insulin signal that helps regulate it. In a useful simplification, mTOR/S6K also acts as a brake: when the brake is transient, it contributes to homeostasis; when it remains engaged for too long, it limits the response to insulin.The segment documented by the analyzed study is inactive TSC1/TSC2 or increased Rheb hyperactivation of Rheb/mTOR/S6K reduction of IRS1/2 reduced IRS-dependent signaling toward PI3K and AKT. This corresponds directly to the passage in the book's chapters regarding the loss of IRS proteins and the selective impairment of AKT activation by insulin.However, the available material does not allow for a detailed verification of some additional elements reported in the book, such as the recovery of IRS1/2 levels with rapamycin, the

reduction of IRS mRNA, or the experimental overexpression of IRS1. These aspects should not be attributed with certainty to the analyzed study based solely on the available abstract. Furthermore, the demonstration concerns cellular models: it is not equivalent to proof that every form of human insulin resistance is primarily influenced by this single circuit.

6. INDEPENDENT CONFIRMING EVIDENCE

Confirmation very close to the described mechanism comes from an independent cellular study on the TSC1/TSC2 complex. The authors showed that TSC1/TSC2 promotes insulin signaling toward PI3K by repressing a negative feedback loop from mTOR/S6K to IRS1. In other words, when TSC1/TSC2 control is lost, the growth signal can reduce the availability or functionality of the IRS adapter and weaken the communication between the insulin receptor and PI3K. The model is experimental and cellular, but it directly confirms the central molecular step of the narrative [1].A second study identified a specific site on IRS1, serine 1101, which can be directly phosphorylated by S6K1. Phosphorylation is a chemical modification that can change a protein's activity. In cells and mice fed a high-fat diet, increased S6K1 activity was associated with greater IRS1 phosphorylation and reduced insulin signaling functionality. The part most relevant to the book's narrative is that, in humans subjected to amino acid infusion, S6K1 activation was accompanied by IRS1 phosphorylation, reduced IRS1 function, and insulin resistance in skeletal muscle. This data supports the link in humans between nutrient abundance, S6K1, and the weakening of insulin signaling, although it does not demonstrate the quantitative depletion of IRS1/2 observed in the original study [2].An animal model of chronic hyperinsulinemia showed that prolonged exposure to high insulin levels can be associated with increased mTOR and p70 S6K activity, serine phosphorylation of IRS1/2, and reduced insulin signaling in the liver and muscle. In that model, rapamycin prevented hyperinsulinemia-induced insulin resistance in both tissues. The result strengthens the causal plausibility of the mTOR/S6K–IRS circuit, but it remains data obtained in animals and with a drug that may have broader effects than just the inhibition of S6K1 [3].Overall, the independent evidence converges on a biologically coherent sequence: persistent nutrients or anabolic signals can keep mTOR/S6K1 active; S6K1 can modify IRS1 in an inhibitory manner; the lower efficiency of IRS limits signal transfer toward PI3K and AKT. The demonstration of the quantitative loss of IRS1/2 is more robust in cellular models than in human studies.

7. CONFLICTING EVIDENCE

The most sensitive part of the narrative concerns the interpretation of rapamycin as a means to stably restore insulin sensitivity. In mice treated chronically with rapamycin, an mTOR inhibitor, a reduction in glucose tolerance and insulin action has been observed instead. The authors attributed this effect primarily to the impairment of mTORC2, a second mTOR complex necessary, among other things, for the normal suppression of hepatic glucose production by insulin [4].This evidence does not contradict the mTORC1/S6K1 negative feedback toward IRS described in the original study. However, it shows that the overall effect of pharmacological mTOR inhibition depends on the duration of treatment, the tissue, the dose, and the involvement of mTORC2. Consequently, the recovery of the IRS/PI3K/AKT signal observed in some experimental models cannot be automatically translated into a general clinical prediction. No directly conflicting evidence sufficiently relevant to the reduction of IRS1/2 induced by the loss of TSC1/TSC2 has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

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

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular	Cells with TSC1 or TSC2 loss or increased Rheb expression	Rheb/mTOR/S6K hyperactivation reduced IRS1/2 and rendered AKT refractory to insulin and IGF-I, but not to PDGF.	direct confirmation	moderate
[1]	Cellular and molecular	Experimental models with TSC1/TSC2, IRS, and PI3K regulation	TSC1/TSC2 limits mTOR/S6K feedback to IRS and promotes insulin signaling to PI3K.	direct confirmation	moderate
[2]	Cellular, animal, and experimental human	Cells; obese mice or mice on a high-fat diet; human skeletal muscle after amino acid infusion	S6K1 activation increased inhibitory phosphorylation of IRS1 and reduced IRS1 function; in humans, it was associated with muscle insulin resistance.	direct confirmation	moderate
[3]	Animal	Rats with chronic hyperinsulinemia; liver and muscle	Hyperinsulinemia increased mTOR/S6K activity and IRS1/2 phosphorylation; rapamycin prevented insulin resistance in the model.	indirect confirmation	moderate
[4]	Animal	Mice treated chronically with rapamycin	Chronic rapamycin compromised glucose tolerance and insulin action through loss of mTORC2 function.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports a specific part of the narrative: unregulated activation of the TSC/Rheb/mTOR/S6K axis can reduce IRS1 and IRS2 and impair the AKT response to insulin and IGF-I. Independent evidence makes this circuit quite well-supported at a mechanistic level and shows that the relationship between S6K1, IRS1, and insulin resistance is also detectable in human muscle under experimental conditions.The strength of the conclusion decreases when extending the model to all forms of type 2 diabetes, the entire organism, or Alzheimer's disease. In particular, the response to drugs that inhibit mTOR is not uniform and depends on the duration of exposure and the involvement of mTORC2. The mechanism is therefore well-supported as a component of the pathophysiology of insulin resistance, but it requires specific clinical validation for each pathological context.

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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