LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Nutrients suppress phosphatidylinositol 3-kinase/Akt signaling through Raptor-dependent, mTOR-mediated phosphorylation of IRS-1 - Evidence review

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1. ABSTRACT

The analyzed study evaluated how high nutrient availability can weaken the cellular response to insulin. The authors showed that the mTORC1 complex, a system that integrates nutrient and growth signals, can phosphorylate IRS-1, a protein necessary to transmit the signal from the insulin receptor to PI3K and AKT. This modification reduced the activation of PI3K associated with IRS-1. The available material does not provide complete details on experimental models, sample sizes, or quantitative results.In “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that persistent hyperactivation of mTORC1/S6K1 can compromise IRS-1 and promote insulin resistance. Independent studies in humans, cells, and mice confirm important segments of this chain. However, not all IRS-1 phosphorylation sites are directly regulated by S6K1, and chronic inhibition of mTORC1 can have unfavorable metabolic consequences. The overall confirmation is therefore primarily mechanistic, with significant short-term human support.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 18, 2026
Updated: November 18, 2026

DOI 10.5281/zenodo.24348705

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 nutrient abundance could reduce the ability of insulin to activate the PI3K/Akt pathway through a precise intracellular mechanism. In simple terms, the authors investigated whether a system that is normally useful for adapting the cell to energy availability could, when overactive, inhibit insulin signaling.The hypothesis evaluated was that mTOR, a kinase (a protein that modifies other proteins through phosphorylation) sensitive to nutrients, acts together with Raptor, a structural component of mTORC1, to phosphorylate IRS-1. IRS-1 is an adapter protein: it receives the signal from the insulin receptor and helps activate PI3K and AKT, which are essential steps for many of the hormone's metabolic responses.The relevance to "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi therefore concerns the segment of the chain in which nutritional excess increases mTORC1 activity, modifies IRS-1, and reduces signal transmission to PI3K/Akt. The study can document a molecular mechanism for the attenuation of insulin signaling. It cannot, on its own, prove that this mechanism explains the entirety of insulin resistance in humans with obesity or type 2 diabetes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract of the publication. The study used biochemical and cellular experiments to evaluate the relationship between nutrients, mTOR, Raptor, IRS-1, and PI3K/Akt signaling.The authors analyzed the direct link between Raptor and IRS-1 and evaluated the phosphorylation of IRS-1 at serine residues 636 and 639. A serine residue is a specific position on the protein that can receive a phosphate group; this modification can change the protein's behavior. Phosphomimetic mutations—artificial modifications that simulate a protein that is already phosphorylated—were also used to verify the functional effect of the phosphorylation.The study also used Raptor silencing, which is an experimental reduction of its cellular production, and LKB1/AMPK pathway activators, including metformin. AMPK is a sensor of cellular energy status that, in many contexts, reduces mTORC1 activity. The number of experiments, the cell lines used, exposure times, nutrient concentrations, details of statistical analyses, and quantitative values are not reported in the available material.

4. RESULTS

The central finding is that nutrients reduced IRS-1-dependent PI3K/Akt signaling. In simple terms, when the cell received a signal of nutritional abundance, the transmission of information from insulin to its internal effectors became less efficient.According to the abstract, Raptor binds directly to IRS-1 and acts as a platform to allow mTOR to phosphorylate IRS-1 at serines 636 and 639. These sites are close to a region of IRS-1 required to interact with PI3K following insulin stimulation. Mutations that mimicked phosphorylation of serines 636 and 639 blocked the insulin-induced activation of PI3K associated with IRS-1. This data indicates a reduction in PI3K signaling in this model, not a direct demonstration of reduced glucose uptake in the human body.The reduction of Raptor through silencing and the activation of the LKB1/AMPK pathway decreased the phosphorylation of IRS-1 at serines 636/639 and reversed the inhibition of the PI3K/Akt pathway attributed to mTOR. The abstract cites metformin as an activator of the LKB1/AMPK pathway, but does not report dosages, duration of treatment, or quantitative data on the extent of recovery.The authors interpreted these results as a possible molecular link between diabetes-related hyperglycemia, mTOR hyperactivation, and insulin resistance. However, the available material does not report measurements of the total amount of IRS-1, its degradation, GLUT4, or glucose utilization. Therefore, the available publication directly documents primarily the phosphorylation of IRS-1 and the reduction of PI3K/Akt signaling.

5. INTERPRETATION

The biological significance of the study is that the cell possesses an internal brake on insulin signaling. If nutrients and insulin are present after a meal, a temporary brake can help prevent excessive stimulation. However, if the circuit remains highly active, this same regulation can hinder the response to insulin.The pathway documented by the research

discussed in this article is: high nutrients Raptor-dependent mTORC1 phosphorylation of IRS-1 at serines 636/639 reduced activation of PI3K associated with IRS-1 reduced AKT signaling. This is consistent with sections 4.8 and 14.10 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, in which IRS-1 is presented as the vulnerable link between the insulin receptor and the PI3K/AKT pathway.It is important to distinguish this result from the broader chain described in the volume. The available abstract does not directly demonstrate that S6K1 is responsible for the phosphorylation observed at serines 636/639, nor does it directly demonstrate the degradation of IRS-1. Instead, it suggests that the mTORC1 complex, through Raptor, may phosphorylate IRS-1 and reduce the PI3K/Akt signal. Independent evidence is therefore needed to separately verify the role of S6K1, the reduction in IRS-1 expression, and the metabolic consequences.

6. INDEPENDENT CONFIRMING EVIDENCE

The closest confirmation to the book's narrative comes from a crossover study in humans conducted on seven healthy men. During amino acid infusion, compared to saline infusion, total plasma amino acid availability was approximately tripled. In skeletal muscle, insulin increased S6K1 activity to a greater extent, while inhibitory phosphorylations of IRS-1 at serines 312 and 636/639 increased, and insulin-induced PI3K activity decreased. Functionally, the rate of glucose disappearance was approximately 33% lower during amino acid infusion, 50 ± 4 versus 75 ± 6 micromoles per kilogram per minute, with P = 0.002. This study confirms in humans, under acute and experimental conditions, the sequence: elevated amino acids increased mTOR/S6K1 activity increased IRS-1 phosphorylation decreased PI3K activity and reduced glucose utilization [1]. The main limitation is the very small sample size, the short exposure, and the fact that the participants were healthy men, not people with type 2 diabetes.A second independent study further investigated the step related to the functional and quantitative reduction of IRS-1. In mouse embryonic fibroblasts lacking TSC2, a condition that keeps mTOR/S6K activity high, the authors observed reduced insulin signaling toward PI3K. The mechanism involved both the repression of IRS-1 gene expression and the direct phosphorylation of IRS-1 by S6K1. Rapamycin and S6K1 silencing reduced IRS-1 phosphorylation and restored part of the signaling. This evidence directly confirms, albeit in murine cells, the pathway: elevated mTOR/S6K1 lower IRS-1 availability or function lower PI3K signal [2]. The limitation is that a genetic loss of TSC2 does not fully replicate human nutritional excess.A third study provided causal verification at the whole-organism level in animals. Mice lacking S6K1 showed protection against age-induced or high-fat diet-induced obesity and increased insulin sensitivity. This finding supports the idea that S6K1 is not just an indicator of nutritional abundance, but contributes to the metabolic consequences of mTORC1 hyperactivation [3]. This confirmation is important for the causal direction of the chain, but it does not allow for the automatic transfer of the mouse's permanent genetic effect to human physiology or treatment.

7. CONFLICTING EVIDENCE

The mTORC1/S6K1 IRS-1 pathway should not be interpreted as if every serine on IRS-1 is regulated in the same way and in every tissue. In primary human adipocytes isolated from six subjects, a study examined serine 307 of IRS-1, which corresponds to serine 302 in mice. Although phosphorylation at this site was sensitive to rapamycin, an inactive S6K1 construct and the selective inhibitor PF-4708671 reduced S6 phosphorylation without reducing IRS-1 phosphorylation at serine 307. The authors therefore concluded that S6K1 is likely not the physiological kinase for that specific site in human adipocytes [4].This evidence does not directly contradict the original study, which concerns serines 636/639 and a Raptor-dependent mechanism. However, it scales back the general claim that S6K1 is necessarily responsible for every inhibitory phosphorylation of IRS-1. The control of IRS-1 is site-dependent, cell-type-dependent, and context-dependent. No sufficiently relevant directly conflicting evidence has been identified regarding Raptor-dependent mTORC1-mediated phosphorylation of IRS-1 at serines 636/639; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent evidence selected based on the specific passages in the volume's chapters.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	Cellular model not reported in available material	Raptor/mTOR phosphorylates IRS-1 at serines 636/639; this modification reduces PI3K activation associated with IRS-1.	direct confirmation	moderate
[1]	Experimental in humans, crossover	Seven healthy men undergoing amino acid or saline infusion	Amino acids increased S6K1 and inhibitory phosphorylation of IRS-1, reduced PI3K activity, and decreased glucose clearance by 33%.	direct confirmation	moderate
[2]	Cellular and molecular	Mouse embryonic fibroblasts with TSC2 loss	mTOR/S6K hyperactivation reduced IRS-1 expression and function, impairing insulin signaling toward PI3K.	direct confirmation	moderate
[3]	Genetic animal	S6K1-deficient mice	The absence of S6K1 increased insulin sensitivity and protected against age- or high-fat diet-induced obesity.	indirect confirmation	moderate
[4]	Cellular on human tissue	Primary human adipocytes isolated from six subjects	S6K1 was not found to be responsible for IRS-1 phosphorylation at serine 307, although this site is regulated in a rapamycin-sensitive manner.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication directly supports the claim that nutrients can reduce insulin signaling through Raptor-dependent mTORC1-mediated phosphorylation of IRS-1. Independent evidence confirms that increased mTOR/S6K1 signaling can be associated with greater IRS-1 phosphorylation, lower PI3K activity, and reduced metabolic action of insulin.The volume's narrative is well-supported at a mechanistic level and also has experimental support in humans. It remains necessary to avoid oversimplifications: IRS-1 possesses many regulatory sites, not all of which depend directly on S6K1, and metabolic effects depend on the duration of activation, the tissue, and the model studied. The link to chronic insulin resistance in humans therefore requires further longitudinal and clinical validation.

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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