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Hepatic mTORC2 activates glycolysis and lipogenesis via Akt, glucokinase, and SREBPıc - Evidence review

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1. ABSTRACT

The analyzed study evaluated what happens to metabolism when Rictor, an essential component of the mTORC2 protein complex, is selectively deleted in the liver. In genetically modified mice, the loss of mTORC2 reduced AKT phosphorylation—a chemical modification necessary for the full activity of this protein—and impaired glycolysis, fat synthesis, and the suppression of hepatic glucose production. According to the available abstract, the experimental expression of constitutively active AKT2 corrected glucose flux and lipogenesis.The research contributes to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which posits that mTORC2 supports the metabolic response to insulin through AKT. Independent studies in mice confirm that hepatic Rictor is necessary for proper AKT signaling and for limiting glucose production by the liver. However, independent work reports that activated AKT can correct the glucose defect without fully restoring lipogenesis. The confirmation is therefore moderate, primarily mechanistic and animal-based, rather than clinical.

ONLINE ARTICLE

ARTICLE INFORMATION

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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 whether hepatic mTORC2 directly participates in the insulin response and, specifically, whether it acts through AKT to regulate glucose and lipid fate. mTORC2 is one of the two complexes formed by the mTOR protein; Rictor is an essential component of it. AKT is a protein that receives the insulin signal and helps determine whether the liver should produce glucose, use it, or convert a portion of it into energy reserves.The publication is relevant to sections 4.11 and 22.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it examines precisely the segment of the mTORC2 AKT hepatic metabolism chain. In particular, it supports the claim that the loss of Rictor impairs AKT phosphorylation and hinders the liver's normal transition to post-meal metabolism.The study can demonstrate a causal relationship in the mouse model, as Rictor was selectively deleted in the liver and some effects were subjected to rescue experiments using active AKT2. However, it cannot establish that the same intensity of effect occurs in humans, nor can it prove that all metabolic effects of mTORC2 depend exclusively on AKT.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract; the full text is not accessible. The authors generated mice with selective deletion of Rictor in the liver, referred to as LiRiKO, and compared them with control animals. The study design included the analysis of fed mice, the evaluation of molecular signals in the liver, and experimental interventions in liver cells lacking mTORC2.The main variables reported in the abstract were AKT phosphorylation at serine 473, glucokinase activity, SREBP1c activity, gluconeogenesis, glycolysis, lipogenesis, and certain systemic indicators such as glycemia, insulinemia, and blood lipid concentrations. Glucokinase is an enzyme that helps the liver retain and utilize glucose; SREBP1c is a regulator of the expression of genes involved in fat production.The authors also expressed a constitutively active form of AKT2 in liver cells, i.e., a version experimentally rendered active even in the absence of the normal upstream signal. They also increased glucokinase expression. The group size, age and sex of the animals, inclusion and exclusion criteria, duration of procedures, statistical tests, significance values, and individual quantitative values are not reported in the available material.

4. RESULTS

In fed LiRiKO mice, the deletion of Rictor abolished AKT phosphorylation at serine 473 in the liver. In simple terms, the insulin signal could no longer complete an important step in AKT activation. In the same tissue, glucokinase and SREBP1c activity were reduced.These alterations were associated with a specific metabolic direction: the liver continued to produce glucose through gluconeogenesis even when the organism was fed, while both glycolysis—the use of glucose to produce energy—and lipogenesis—the synthesis of fats from available nutrients—were reduced. At the whole-organism level, the abstract reports an increase in glycemia and insulinemia and a reduction in circulating lipids.The rescue experiment is the most relevant result for the book. The expression of constitutively active AKT2 in liver cells deficient in mTORC2 restored glucose flux and lipogenesis, as stated in the abstract. Increased glucokinase, on the other hand, recovered glucose flux but not lipogenesis. This suggests that glucokinase contributes primarily to glucose management, while additional signals regulated by mTORC2 are required for the lipogenic program.Since only the abstract is available, it is not possible to report absolute values, percentage differences, confidence intervals, P-values, or group sizes related to these results. Therefore, it is not possible to directly evaluate the quantitative magnitude of the effects or the statistical precision of the individual estimates.

5. INTERPRETATION

The central biological significance is that mTORC2 appears to help the liver recognize the fed state. After a meal, insulin should reduce hepatic glucose production and promote its utilization or storage. In the studied model, the absence of Rictor disrupted this adaptation: the liver retained programs typical of fasting and reduced those that utilize glucose or produce lipids.The segment documented directly by the publication subject to the Evidence Review is hepatic mTORC2 AKT phosphorylation regulation of

glucose and lipid metabolism. Experimental rescue with AKT2 reinforces the interpretation that AKT is a relevant effector of mTORC2 for glucose control. The failure to rescue lipogenesis with glucokinase alone, however, shows that glucose utilization and fat synthesis do not coincide and do not depend on the same steps.The data does not demonstrate that every metabolic alteration associated with mTORC2 is mediated solely by AKT. Furthermore, it describes genetically modified mice and liver cells, not people with insulin resistance or diabetes. The book's statement that AKT is the main metabolic effector of mTORC2 is consistent with the result on glucose control, but requires caution if extended to the entirety of lipogenesis.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial independent confirmation comes from a study in mice treated chronically with rapamycin, a drug capable over time of also interfering with the formation of mTORC2. The authors observed that the loss of mTORC2 function was associated with hepatic insulin resistance, meaning a reduced ability of insulin to suppress glucose production by the liver. The deletion of Rictor reproduced the metabolic defect, whereas the reduction of mTORC1 did not explain it in the same way. This confirms the passage in the book stating that mTORC2 is necessary for maintaining insulin sensitivity through AKT and for controlling gluconeogenesis [1]. The limitation is that pharmacological treatment can produce systemic effects and the model remains murine.A second study used mice with hepatic Rictor deletion and confirmed that the lack of this protein reduces the phosphorylation of AKT at serine 473, decreases the phosphorylation of downstream targets, and is associated with glucose intolerance. During the euglycemic-hyperinsulinemic clamp, a technique that measures how much insulin is needed to keep glycemia stable, the effect of a glucagon receptor agonist in improving insulin sensitivity was present in controls but was lost in mice lacking hepatic Rictor [2]. The result directly confirms, in a different murine model, that hepatic mTORC2 supports the insulin response and AKT activation. However, it does not evaluate genetic correction with active AKT2 nor does it demonstrate a clinical effect in humans.Taken together, these independent studies support a coherent network: Rictor maintains mTORC2 function; mTORC2 promotes AKT phosphorylation; AKT and its targets help insulin reduce glucose output from the liver. The part of the narrative regarding lipogenesis is biologically plausible and present in the original study, but it requires more careful distinction because not all independent data attribute the lipogenic recovery to AKT alone.

7. CONFLICTING EVIDENCE

An independent study examined mice with hepatic Rictor deletion and confirmed some key elements of the narrative: reduced insulin response, lower AKT phosphorylation, an inability to normally suppress glucose production by the liver, and reduced expression of genes involved in fat synthesis [3]. However, it provided a significant result for refining the interpretation: hepatic expression of active AKT2 corrected glucose intolerance and insulin resistance, but did not restore lipogenesis in the absence of mTORC2.This evidence does not contradict the role of AKT in controlling glucose production. Instead, it scales back the idea that AKT alone fully explains the lipogenic component of mTORC2 function. The authors proposed the existence of an additional branch, parallel or complementary to AKT, necessary to fully activate the lipid synthesis program. In any case, this is a comparison between different animal models and experimental strategies; it does not clarify which mechanism prevails in the human liver.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent verifications and indicates the level at which each study supports the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Mice with hepatic Rictor deletion and liver cells	Loss of mTORC2 reduces AKT Ser473, glycolysis, and lipogenesis; active AKT2 restores glucose flux and lipogenesis in the abstract.	direct confirmation	moderate
[1]	Animal and pharmacological	Mice treated chronically with rapamycin and Rictor-loss models	mTORC2 dysfunction is associated with hepatic insulin resistance and reduced suppression of gluconeogenesis.	direct confirmation	moderate
[2]	Animal and cellular	Mice with hepatic Rictor deletion, primary hepatocytes, and euglycemic-hyperinsulinemic clamp	Loss of Rictor reduces AKT Ser473, alters downstream signaling, and worsens glucose control.	direct confirmation	moderate
[3]	Animal and cellular	Mice with hepatic Rictor deletion, standard or high-fat diet, hepatocytes	Active AKT2 corrects the glucose defect but does not reactivate lipogenesis without mTORC2.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that hepatic mTORC2, through Rictor, is necessary for the full activation of AKT and for the liver's proper adaptation to insulin signals. Independent evidence confirms the segment regarding the reduction of hepatic glucose production and insulin sensitivity in mouse models quite well. The role of AKT in regulating lipogenesis, however, is more complex: it appears important, but does not seem sufficient in every experimental model. The narrative is therefore moderately supported at a mechanistic level and requires validation in humans.

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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