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Self-regulation of the integrity of the mechanistic target of rapamycin complex 2 (mTOR) is controlled by an ATP-dependent mechanism - Review of the evidence

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1. ABSTRACT

The analyzed study evaluated whether the cell's energy status, represented by the availability of ATP (adenosine triphosphate, the immediate source of cellular energy), influences the mTORC2 complex and the maturation of AKT, a protein involved in the insulin response and cell survival. In cellular experiments, glucose deprivation or acute reduction of ATP prevented the phosphorylation of SIN1 and AKT at a structural site, which was associated with reduced integrity of mTORC2. The study also indicated that optimal activity of the complex required ATP concentrations above 1.2 mM.This evidence contributes to the passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, which states that mTORC2 links AKT maturation to the cellular metabolic state. Independent research confirms that SIN1 is essential for the assembly of mTORC2 and for specific phosphorylations of AKT, and that insulin can regulate the complex through the PI3K-AKT pathway. However, other studies show that some forms of nutrient deprivation can also activate mTORC2 in specific experimental contexts. The confirmation is therefore primarily mechanistic and does not directly demonstrate clinical effects in humans.

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MISSION

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2. ANALYZED STUDY

The research question was whether cellular energy availability regulates the activity and stability of mTORC2, one of the two complexes formed by the mTOR protein. The hypothesis was that a drop in ATP would reduce a basal function of mTORC2 necessary to keep the complex intact and to modify AKT during its maturation.The relevant point for paragraph 4.11 is specific: the publication does not address the entire metabolic response of the organism to insulin, but documents a segment upstream of the chain. In particular, it shows that an adequate level of ATP supports the phosphorylation of SIN1, a structural component of mTORC2, and that of AKT at the Thr-450 residue. Phosphorylation is the addition of a small chemical group that can change the stability, position, or function of a protein.The work can therefore support the idea that cellular energy status modulates mTORC2 and the structural maturation of AKT. However, it cannot demonstrate that the same mechanism occurs with identical intensity in all human tissues, nor that an energy reduction directly determines a clinical outcome or a disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study used cellular models and compared conditions of normal glucose availability with glucose deprivation or acute ATP reduction. The authors also analyzed cells with SIN1 variants, including a phosphomimetic variant, which is designed to mimic a permanently phosphorylated protein.The main variables reported in the abstract were mTORC2 activity, SIN1 phosphorylation at the Ser-260 residue, AKT phosphorylation at the Thr-450 residue, the integrity of the mTORC2 complex, and cell proliferation under low-glucose conditions. An ATP titration was performed to evaluate the concentration required for complex activity.The number of experiments, the cell lines used, the selection criteria, the number of biological replicates, the detailed analytical techniques, the statistical procedures, and the significance values are not reported in the available material.

4. RESULTS

The main finding is that mTORC2 showed marked sensitivity to ATP availability. Optimal activity of the complex required an ATP concentration greater than 1.2 mM. In simple terms, when the energy immediately available to the cell fell below a certain threshold, the complex that contributes to AKT maturation lost efficiency.Glucose deprivation, but not amino acid deprivation, prevented mTOR-dependent phosphorylation of SIN1 at the Ser-260 residue and of AKT at the Thr-450 residue. This finding points in a precise direction: glucose deficiency associated with reduced ATP decreased two protein modifications that the authors link to the maintenance of mTORC2 and the stability of AKT.The authors also observed that a phosphomimetic variant of SIN1, in a low-glucose medium, was associated with greater abundance of mTORC2, increased AKT phosphorylation, and greater cell proliferation compared to cells expressing unmodified SIN1. The abstract does not report absolute values, percentages, confidence intervals, or P-values for these comparisons.These results are consistent with the passage in the book because they link energy availability to the ability of mTORC2 to maintain an essential component of the complex, SIN1, and a structural modification of AKT. However, these remain results obtained in cultured cells, not in people.

5. INTERPRETATION

In common language, mTORC2 can be viewed as a protein structure that helps AKT reach a stable and functional form. The study suggests that this structure requires sufficient energy to remain well-assembled. If ATP levels decrease, SIN1 loses a phosphorylation at the Ser-260 site, mTORC2 becomes less intact, and AKT loses the phosphorylation at the Thr-450 site.The documented pathway is therefore: ATP availability SIN1 phosphorylation mTORC2 integrity structural phosphorylation of AKT. This phosphorylation does not necessarily coincide with the acute activation of AKT by insulin. Thr-450 is described as a turn motif site, a region that contributes to the correct conformation and stability of the protein, whereas other sites, such as Ser-473, are more often used to assess AKT activation in response to external signals.The interpretation that the complex prevents

anabolic programs when energy is insufficient is biologically plausible, but it should be considered an interpretive model. The study does not directly measure all anabolic programs, does not evaluate the organism as a whole, and does not demonstrate that this response constitutes a universal mechanism in human tissues.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Initial independent confirmation concerns the structural role of SIN1. In SIN1-deficient cells, Jacinto and colleagues observed the loss of the interaction between Rictor and mTOR, which are necessary components for mTORC2, and the abolition of AKT phosphorylation at the Ser-473 site. The work therefore confirms the central premise that the integrity of the complex depends on SIN1 and determines specific modifications of AKT. It does not evaluate ATP or the Ser-260 site; therefore, it supports the intact mTORC2 AKT regulation segment, rather than the complete energy chain [1].A second study, conducted in 3T3-L1 adipocytes and HEK293 cells, analyzed the response to insulin using quantitative proteomics and functional assays. The authors identified the phosphorylation of SIN1 at the Thr-86 residue by AKT. Replacing this residue with a non-phosphorylatable variant reduced the mTORC2 response and AKT phosphorylation, while a phosphomimetic variant increased the complex's activity. This evidence confirms that SIN1 is not merely a passive component: selective modifications of SIN1 can regulate mTORC2 and, downstream, AKT. The site studied is different from Ser-260 and the model remains cellular, but the result reinforces the biological coherence of the SIN1–mTORC2–AKT relationship [2].A further study showed that the PI3K product, the lipid PtdIns(3,4,5)P3, binds to the PH domain of SIN1 and removes an internal brake on mTORC2 activity. Mutations that prevented this binding decreased mTORC2 activity and AKT phosphorylation at the Ser-473 site. This data completes the context described in the book's paragraph: in addition to the energy state, insulin signaling through PI3K can also render mTORC2 capable of phosphorylating AKT. It does not test ATP dependence and does not demonstrate metabolic effects in humans [3].Taken together, these independent works do not exactly replicate the ATP experiment, but they build a convergent chain: SIN1 is necessary for the structure of mTORC2; modifications of SIN1 change the activity of the complex; mTORC2 regulates functional sites of AKT; and signals produced by PI3K can activate the complex. The confirmation remains experimental and cellular.

7. CONFLICTING EVIDENCE

There are findings that require caution when interpreting nutrient deprivation as an unambiguous signal for the downregulation of mTORC2. In cellular models subjected to a decrease in glutamine catabolites, Moloughney and colleagues observed an increase in mTORC2 activity associated with a metabolic adaptation aimed at supporting the hexosamine biosynthesis pathway. In that context, therefore, nutrient limitation activated rather than reduced an mTORC2 function [4].This evidence does not invalidate the result of the original study, as it primarily concerns glutamine catabolites, other downstream targets, and a different experimental design. However, it shows that the mTORC2 response depends on the nature of the stress, its duration, the cell type, the availability of growth signals, and the specific phosphorylation site measured. In particular, it is incorrect to automatically equate the reduction of structural AKT phosphorylation at the Thr-450 site with a decrease in all forms of mTORC2 signaling.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent research. All available evidence is predominantly cellular or molecular; these are not clinical studies on humans.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	Cultured cells; details not reported in available material	Reduction of glucose or ATP decreases SIN1 Ser-260 and AKT Thr-450 phosphorylation; ATP levels above 1.2 mM required for optimal activity.	direct confirmation	moderate
[1]	Cellular and genetic	Cells with SIN1 deletion	Absence of SIN1 disrupts Rictor-mTOR interaction and abolishes AKT Ser-473 phosphorylation.	indirect confirmation	moderate
[2]	Cellular, proteomic, and functional	3T3-L1 adipocytes, HEK293 cells, and mouse embryonic fibroblasts	Phosphorylation of SIN1 Thr-86 by AKT increases mTORC2 activity and supports AKT phosphorylation.	biologically consistent evidence	moderate
[3]	Cellular and biochemical	Human cell lines, mouse fibroblasts, and mouse xenografts	PtdIns(3,4,5)P3 bound to SIN1 activates mTORC2; SIN1 mutations reduce AKT Ser-473 phosphorylation.	indirect confirmation	moderate
[4]	Cellular and metabolic	HeLa cells, mouse embryonic fibroblasts, and mouse lymphoma model	Reduction of glutamine catabolites increases mTORC2 signaling under specific nutrient-limiting conditions.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the finding that, in the cells examined, a reduction in ATP compromises a basal function of mTORC2 and decreases the phosphorylation of SIN1 and AKT at the Thr-450 site. This result is consistent with the narrative that mTORC2 links AKT maturation to the cellular energy state.Independent evidence convincingly confirms the role of SIN1 in the integrity and regulation of mTORC2, as well as the functional relationship between mTORC2 and AKT. However, the complex's response to nutrient limitations is not uniform: it depends on the nutrient involved, the cell type, the duration of the stress, and the specific molecular site observed. The narrative is therefore supported at a mechanistic level, but requires direct validation in human tissues and under physiological conditions.

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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