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ORIGINAL RESEARCH

The GTPase Rheb is a direct target of the GAP activity of TSC2 and regulates mTOR signaling - Evidence review

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1. ABSTRACT

The analyzed study examined how the complex formed by TSC1 and TSC2 controls mTOR, a protein that coordinates cell growth and protein synthesis. In the available material, consisting only of the abstract, the authors report that TSC2 acts on Rheb, a small switch protein, promoting its inactivation. When active, Rheb increases the phosphorylation of S6K and 4EBP1, signals linked to protein production; this effect is dependent on mTOR.In section 4.5 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes primarily to documenting the TSC1/TSC2 → Rheb → mTOR segment. The sentence in the book also includes the inhibition of TSC2 by AKT in response to favorable signals: this specific step is confirmed by independent cellular studies. However, evidence indicates that amino acids and energy status do not regulate mTOR exclusively through TSC2. The chain is therefore well-supported on a mechanistic level, but it does not in itself constitute clinical proof in humans.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was to understand how TSC1/TSC2, a complex of two proteins that limits cell growth, communicates with mTOR. The hypothesis evaluated was that TSC2 exerts its effect through Rheb, a GTPase (a protein that functions as a molecular switch: it is active when it binds GTP and inactive when it converts it into GDP).The connection to paragraph 4.5 is precise. The book text describes TSC1/TSC2 as a brake on mTOR and states that when AKT is activated by growth signals, this brake is reduced and the anabolic cascade proceeds. The analyzed study documents, above all, the subsequent part of the chain: TSC2 acts as a GAP (a protein that accelerates the switching off of a GTPase) for Rheb; Rheb is located upstream of mTOR and promotes growth signals.The available material is only the abstract. It does not report a specific experiment in which AKT phosphorylates TSC2, nor does it provide quantitative data on this phosphorylation. Therefore, the publication subject to the Evidence Review does not directly demonstrate the entire insulin AKT TSC2 sequence, but it directly supports the TSC2 Rheb mTOR segment necessary to understand why the functional inhibition of TSC2 can promote the activation of mTOR.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

From the only available abstract, it emerges that the authors evaluated the GAP activity of TSC2 towards Rheb and studied the effects of Rheb on downstream mTOR signaling. They analyzed the phosphorylation of S6K and 4EBP1, two proteins used as indicators of the mTOR pathway activity involved in protein synthesis and cell growth.The authors also verified whether the effect of Rheb depended on mTOR by using rapamycin, a drug that inhibits mTOR, and a dominant-negative form of mTOR, which is a variant designed to hinder the function of the normal protein. The abstract also reports experiments related to nutrient availability and cellular energy status. The number of experiments, cell types, selection criteria, concentrations used, exposure times, statistical analyses, and numerical values are not reported in the available material.

4. RESULTS

The key finding is that TSC2 showed GAP activity towards Rheb. In simple terms, TSC2 promotes the switching off of Rheb, thereby reducing the ability of this switch protein to transmit a growth signal.Conversely, Rheb increased the phosphorylation of S6K and 4EBP1. Phosphorylation is a chemical modification that can change a protein's activity; in this case, both signals indicate an increase in the activity of the mTOR pathway linked to protein synthesis. The effect of Rheb was blocked by rapamycin and dominant-negative mTOR. This places Rheb upstream of mTOR: Rheb promotes the activation of the pathway, while mTOR is necessary for the signal to reach S6K and 4EBP1.The abstract also concludes that Rheb is essential in the regulation of S6K and 4EBP1 in response to nutrients and cellular energy status. However, it does not report absolute values, percentages, P-values, confidence intervals, or experimental details that would allow for an estimation of the effect size. It is therefore not possible to quantify from the available material how large the variation in the observed signals was.

5. INTERPRETATION

A cell does not activate growth simply because it receives an external signal: it must also verify that it has sufficient resources. The TSC1/TSC2 complex contributes to this regulation by acting as a brake on Rheb. When the brake is active, Rheb remains less active and mTOR receives less stimulation; when the brake is reduced, Rheb can promote mTOR signaling.The study's specific contribution to the book's narrative is therefore the functional link TSC2 Rheb mTOR. This relationship makes it biologically plausible that the inhibition of TSC2 by AKT, described in the paragraph, leaves greater activity for Rheb and allows the anabolic cascade to continue.However, it is necessary to distinguish between levels of evidence. The data in the abstract concern molecular and cellular mechanisms, not people with insulin exposure or specific nutritional conditions. Furthermore, the available text does not allow us to attribute to the analyzed study the direct demonstration of the inhibitory phosphorylation of TSC2 by AKT. This step requires the support of targeted independent publications.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial confirmation of the AKT TSC2 pathway comes from biochemical and cellular experiments by Manning and colleagues. The authors identified TSC2 as a target of the PI3K/AKT pathway, where PI3K is an enzyme that transmits signals from growth factors like insulin to the cell. AKT phosphorylated TSC2 in vitro and in cells; furthermore, a non-phosphorylatable variant of TSC2 reduced S6K1 activation. This result supports the direction proposed in the book: AKT activation reduces the inhibitory function of TSC2 and facilitates signaling toward mTOR. This is a mechanistic confirmation in cellular models, not clinical evidence in humans [1].Garami and colleagues independently reconstructed the central segment of the chain. In cellular experiments, insulin increased Rheb activation through a PI3K-dependent pathway; TSC1/TSC2 inhibited this activation. The authors also showed that Rheb increased S6K1 phosphorylation and that a pathological mutation in the GAP domain of TSC2 failed to effectively turn off Rheb. This study confirms the insulin signal/PI3K TSC1/TSC2 Rheb mTOR signaling sequence, while remaining experimental cellular evidence [2].A further study clarified a potential detail of the mechanism. In cultured cells, growth signals induced the phosphorylation of TSC2 by AKT and its translocation from the cell membrane to the cytosol, the fluid interior of the cell. This shift reduced the repression of Rheb. The authors observed that the phosphorylation of TSC2 at specific sites did not directly alter its intrinsic GAP activity toward Rheb; instead, it appeared to change its localization and availability to act as a brake. This confirms the general direction of the narrative, but shows that the expression "AKT inhibits TSC2" summarizes a more complex regulatory process [3].

7. CONFLICTING EVIDENCE

An important distinction concerns the different signals that converge on mTOR. Smith and colleagues studied cells lacking TSC2 and observed that amino acid deprivation still reduced the phosphorylation of S6K1, the S6 protein, and 4E-BP1. Even some effects of cellular stress and energy reduction were maintained in the absence of TSC2. These results indicate that the regulation of mTOR by amino acids and certain stress conditions does not necessarily require TSC2 [4].This evidence does not contradict the TSC2 Rheb mTOR segment documented by the original study, nor the inhibition of TSC2 by AKT in response to growth factors. However, it reduces the generalizability of the statement that groups insulin, amino acids, and energy availability as if they all acted through the same AKT TSC2 pathway. Insulin and other growth signals have a well-documented pathway through AKT and TSC2; amino acids and energy status also utilize parallel controls.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to confirm or define the narrative passage of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	Experimental models not detailed in the available abstract	TSC2 acts as a GAP for Rheb; Rheb increases mTOR-dependent S6K and 4EBP1 signaling.	direct confirmation	moderate
[1]	Cellular and biochemical	Mammalian cells and in vitro assays	AKT phosphorylates TSC2; a non-phosphorylatable TSC2 reduces signaling to S6K1.	direct confirmation	moderate
[2]	Cellular and biochemical	Mammalian cells and recombinant proteins	Insulin increases Rheb in a PI3K-dependent manner; TSC1/TSC2 inhibits Rheb and signaling to S6K1.	direct confirmation	moderate
[3]	Cellular	Cultured cells	AKT phosphorylates TSC2 and promotes its translocation to the cytosol, reducing the repression of Rheb.	biologically consistent evidence	moderate
[4]	Cellular	TSC2-deficient cells	Amino acid deprivation reduces mTOR signaling even in the absence of TSC2.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports that TSC2 inhibits Rheb and that Rheb promotes mTOR-dependent signals associated with cell growth. This is the segment of the book's narrative that is effectively documented by the available publication.Independent literature confirms that AKT can reduce TSC2 function and that the TSC1/TSC2 complex limits Rheb activation in response to growth signals. The chain is therefore well-supported at a mechanistic level. Caution remains necessary when considering amino acids, energy, and insulin as identical regulators, as mTOR integrates parallel pathways that are dependent on the biological context.

Aggiornato al 17/11/2026. 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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