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Signaling and functions of the mTOR complex 2 - Review of the evidence

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1. ABSTRACT

The analyzed study is a narrative review that examined the knowledge available in 2011 regarding the mTORC2 complex, one of the two main forms through which the mTOR protein acts. Its objective was to clarify how mTORC2 contributes to cell growth, metabolism, and survival, with particular attention to the regulation of AKT, a central protein in the response to insulin and growth factors.In section 4.11 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, this publication contributes to the narrative that mTORC2 is not a simple secondary regulator of mTOR, but participates in the full functionality of AKT. Independent experimental studies have confirmed that the complex containing RICTOR promotes the phosphorylation of AKT at a site essential for many cellular responses. However, the data also indicate that the importance of this signal varies between tissues and AKT targets. The confirmation is therefore primarily mechanistic and preclinical, not a clinical demonstration in humans.

ONLINE ARTICLE

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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 to understand which functions distinguish mTORC2 from mTORC1 and what the specific contribution of mTORC2 is to the signals that control cell growth, metabolism, and survival. The hypothesis discussed by the authors was that mTORC2 plays a significant role in the regulation of AKT, a kinase—that is, a protein that activates or modifies other proteins through phosphorylation.The relevance to section 4.11 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns precisely this point: mTORC2 is presented as an important regulator of the kinase family that includes AKT. The study analyzed can support this biological framework because it summarizes experimental evidence on the relationship between mTORC2 and AKT. However, as it is a narrative review, it does not constitute a single independent experiment and does not, by itself, demonstrate metabolic or clinical consequences in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The publication is a narrative literature review and not an experimental study involving participants, animals, or cell cultures enrolled directly by the authors. The authors discussed results obtained through pharmacological inhibitors of the mTOR kinase and mouse models with genetic deletion of mTOR complex components.The bibliographic search strategy, inclusion and exclusion criteria for studies, the number of publications evaluated, the exact search period, and quantitative synthesis methods are not reported in the available material. Therefore, there is no overall sample size, predefined endpoints, aggregate statistical analyses, or follow-up, which would otherwise be expected in a systematic review or meta-analysis.

4. RESULTS

The main message of the review is that mTOR forms two distinct protein complexes, mTORC1 and mTORC2. In simple terms, these are two groups of proteins that share mTOR but perform partially different tasks. mTORC1 was already more widely studied because rapamycin more easily inhibits its activity; mTORC2 was less defined, but new pharmacological tools and genetic models are clarifying its functions.Regarding the passage relevant to the book, the authors report that mTORC2 participates in the regulation of AKT. Phosphorylation is the addition of a small chemical group that can modify a protein's behavior. In the case of AKT, the phosphorylation of serine 473, referred to as Ser473, contributes to its complete activation in many experimental contexts. The abstract does not report numerical values, sample sizes, P-values, or quantitative measures of the individual studies discussed.The review also points out that the effects of mTORC2 need to be re-evaluated in tumors, metabolic disorders, and aging. This is an indication of biological relevance, not proof that altering mTORC2 produces a therapeutic benefit in people with such conditions.

5. INTERPRETATION

The biological significance is that AKT does not act as an isolated switch. For many of its responses, it must receive coordinated signals from multiple proteins. mTORC2 represents one of the systems that make this regulation possible, specifically by promoting the phosphorylation of AKT at Ser473. This helps to understand why the insulin pathway cannot be generically attributed to mTOR without distinguishing between the two complexes.The conclusion supported by the analyzed study is therefore: mTORC2 contributes to the functional regulation of AKT. It does not, however, demonstrate that every effect attributed to AKT always depends on mTORC2, nor that this relationship has identical importance in all tissues. Experimental literature shows, in fact, that some target proteins of AKT depend more on phosphorylation at Ser473 than others.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation has come from experiments in human and Drosophila cells. Sarbassov and colleagues reduced the expression of mTOR or RICTOR and observed a reduction in the phosphorylation of AKT at Ser473. Furthermore, the RICTOR-mTOR complex isolated from cells directly phosphorylated AKT in a test tube. The result

supports the central premise of the book because it identifies mTORC2 as a direct regulator of a site necessary for the full activity of AKT. The limitation is that these are cellular models and biochemical experiments, not clinical data [1].A second confirmation comes from mice with a genetic deletion of Rictor, a characteristic component of mTORC2. In tissues and embryos lacking Rictor, the authors detected a reduction in the phosphorylation of the hydrophobic motif of AKT and alterations in the signaling toward FOXO, a family of proteins that regulates genes involved in metabolism and cell survival. Since the model selectively modifies an essential component of mTORC2, this study strengthens the causal link between the integrity of the complex and specific functions of AKT in a living organism. However, it remains a murine developmental model and not a human trial [2].A further study in the muscles of mice lacking Rictor confirms that the loss of mTORC2 eliminates insulin-induced AKT phosphorylation at Ser473 and reduces insulin-stimulated glucose transport. The same work, however, shows that AKT phosphorylation at Thr308 and some downstream signals may remain preserved. This observation is important because it confirms the role of mTORC2 but indicates that AKT does not necessarily become inactive in a uniform manner: dependence on the complex varies with the substrate and the tissue [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified that denies the role of mTORC2 in the phosphorylation of AKT at Ser473. However, there is evidence that limits an overly broad interpretation of the mechanism. In the muscle of Rictor-deficient mice, the loss of AKT phosphorylation at Ser473 did not reduce AKT phosphorylation at Thr308 and did not abolish all signaling to the target proteins studied [3].This does not refute the mTORC2-AKT relationship. Rather, it indicates that the statement “mTORC2 regulates AKT” must be interpreted in its correct context: mTORC2 is essential for certain modifications and functions of AKT, but the overall response depends on the specific cell, tissue, stimulus, and molecular target being considered.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to evaluate the section of the book regarding the regulation of AKT by mTORC2.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature summary on cellular, animal, and pharmacological models	Describes mTORC2 as a regulator of AKT and its cellular functions	biologically consistent evidence	moderate
[1]	Cellular and biochemical	Human cells, Drosophila cells, and in vitro assays	Reduction of RICTOR or mTOR decreases AKT phosphorylation at Ser473; the complex phosphorylates AKT in vitro	direct confirmation	moderate
[2]	Animal and cellular	Mice, embryos, and fibroblasts with loss of Rictor or other mTOR components	Rictor and mLST8 are required for phosphorylation of the AKT hydrophobic motif and for AKT-FOXO signaling	direct confirmation	moderate
[3]	Animal	Mice with Rictor deletion in skeletal muscle	Loss of Rictor reduces AKT Ser473 and insulin-induced glucose transport, but preserves some AKT signaling	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The publication analyzed is consistent with its use in the section dedicated to mTORC2 and AKT. The scientific point best supported is that mTORC2, through components such as RICTOR, promotes the phosphorylation of AKT at Ser473 and modulates specific downstream responses.Independent evidence confirms this relationship at the cellular level and in mouse models. The most prudent formulation is that mTORC2 represents an important regulator of AKT functionality, with selective effects depending on the tissue and molecular target. Direct extension to diseases or treatments in humans requires further 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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