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

ORIGINAL RESEARCH
ISSN 2845-7501

The mammalian target of rapamycin complex 2 controls the folding and stability of AKT and protein kinase C - Review of the evidence

Dr.ssa M. Bitonti[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study examined whether mTORC2, one of the two complexes formed by the mTOR protein, contributes to the maturation of AKT in addition to its activation. The authors report that the loss of essential mTORC2 components reduces constitutive phosphorylation of AKT in the so-called turn motif, promoting instability and degradation of the newly synthesized protein.This finding is relevant to paragraph 4.11 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, which states that mTORC2 ensures the structural maturation of AKT. Independent studies in cells, mouse fibroblasts, and biochemical systems confirm that mTORC2 is necessary for the phosphorylation of the turn motif and for aspects of AKT maturation. However, the relationship between the different AKT phosphorylations, its activity, and its stability is dependent on the modified site and the experimental model. The confirmation therefore primarily concerns a cellular mechanism, not a proven clinical effect in humans.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 23, 2026
Updated: November 23, 2026

DOI 10.5281/zenodo.24462412

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 mTORC2 participates only in the acute regulation of AKT activity or also in its maturation while the protein is being produced. AKT is a kinase, meaning it is a protein that transmits signals by adding phosphate groups to other proteins; it is involved in the response to insulin, cell survival, and metabolism.The hypothesis evaluated was that mTORC2 promotes constitutive phosphorylation of the AKT turn motif. Phosphorylation refers to the addition of a phosphate group, a modification that can change the shape, stability, or function of a protein. In this specific case, the relevant point for the book is that this modification contributes to AKT acquiring a stable conformation during maturation.The publication subject to the Evidence Review is relevant to paragraph 4.11 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it distinguishes between two concepts that are often conflated: the enzymatic activation of AKT and its structural maturation. The study can document molecular mechanisms in experimental models; it cannot, on its own, demonstrate that this mechanism determines specific clinical outcomes in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists exclusively of the abstract. From this material, it can be inferred that the authors evaluated mTORC2 and its components mTOR, SIN1, and Rictor, by analyzing the phosphorylation of AKT and conventional protein kinase C, another family of kinases regulated by similar modifications.The experiments included systems ranging from yeast to mammals, in vitro phosphorylation assays, and assessments of proteasomal degradation. The proteasome is the cellular system that degrades proteins marked for elimination. The involvement of Hsp90, a chaperone protein that helps other proteins maintain or recover a proper conformation, is also reported.Sample size, specific cell lines, inclusion criteria, experimental period, dosages, number of replicates, statistical procedures, P-values, and further technical details are not reported in the available material. As the full text is not accessible in the input, these elements cannot be reconstructed without the risk of attributing unverified data to the study.

4. RESULTS

The key finding is that mTORC2 and its components mTOR, SIN1, and Rictor were necessary for the phosphorylation of AKT and protein kinase C at the turn motif. For AKT, the site indicated is Thr450: this is a position on the protein that, when phosphorylated, promotes the correct folding of the terminal part of the molecule.In simple terms, a newly produced AKT protein is not immediately a definitive and functional structure. According to the authors, the phosphorylation of the turn motif mediated by mTORC2 helps AKT assume a more stable shape. In the absence of this modification, newly synthesized AKT becomes more dependent on Hsp90 and is protected from degradation mediated by ubiquitin and the proteasome. Ubiquitin is a molecular signal that can direct a protein toward the proteasome.The authors also report that mTORC2 separately controls the turn motif and the hydrophobic motif of AKT. In in vitro experiments, mTORC2 was able to phosphorylate both sites. The abstract does not report quantitative values, percentages, confidence intervals, or P-values; such data are therefore not included in the available material.The data directly relevant to the book's text is not the demonstration of the entire insulin response. It is the segment furthest upstream in the chain: loss of mTORC2 or its essential components loss of constitutive phosphorylation of the turn motif lower structural stability of newly synthesized AKT greater vulnerability to degradation.

5. INTERPRETATION

The biological significance of this result is that mTORC2 can act as a quality control system during the production of AKT. Therefore, it does not merely modify an already formed protein to rapidly transmit a signal, but can contribute to making it structurally suitable before it fully performs its functions.The technical detail primarily concerns Thr450, the turn motif of AKT. The phosphorylation of this site is described as constitutive, meaning it is not immediately dependent on a single growth stimulus. This characteristic is consistent with a role in protein maturation. However, this result does not mean that every function of AKT, in every cell and under every

condition, depends on this step in the same way.In section 4.11 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication is used to support the claim that mTORC2 ensures the structural maturation of AKT. This formulation is consistent with the mechanism reported in the abstract. It would, however, be an unproven extension to attribute all the hepatic metabolic, pharmacological, or oncological consequences discussed in other parts of the section to this study alone.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct and independent confirmation comes from genetic experiments conducted on mouse embryonic fibroblasts lacking Rictor, SIN1, or mTOR. In these cells, the ablation of mTORC2 components abolished the phosphorylation of the AKT turn motif and also reduced phosphorylation of the hydrophobic motif. The work therefore confirms that the integrity of mTORC2 is necessary for the constitutive modification of the AKT turn motif. The main limitation is that the model is cellular and murine, not clinical [1].A subsequent structural and biochemical study clarified how mTORC2 recognizes AKT through three-dimensional interactions distant from the catalytic site. The authors demonstrated the specificity of mTORC2 for AKT and other AGC family kinases and confirmed that Thr450 is a phosphorylation site directly attributable to mTORC2. This evidence strengthens the mechanistic link between the complex and AKT maturation, while still being based on reconstituted proteins and experimental systems [2].A further cellular study identified a different regulatory site in the AKT tail, the TOR-interaction motif. The results do not negate the role of the turn motif, but show that mTORC2 coordinates multiple steps in the maturation of AGC kinases. In cells lacking mTORC2, experimental increase of PDK1 restored phosphorylation of the activation loop and the hydrophobic motif, but not that of the turn motif. This data specifically supports the idea that the turn motif maintains a peculiar dependence on mTORC2 [3].Taken together, these studies converge on the relevant point for this book: the function of mTORC2 does not coincide exclusively with the acute modulation of the AKT signal. It also includes modifications that influence the conformation, stability, and maturation of the protein. The convergence is strong at the molecular and cellular level, while it does not provide a direct measure of the effects in patients.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance regarding the dependence of the AKT turn motif on mTORC2 has been identified; this does not prove the absence of contrary results.However, there is a significant experimental clarification. In starfish oocytes, TORC2-dependent phosphorylation of the turn motif contributed to AKT stability, but reduced phosphorylation of the activation loop and AKT's sensitivity to PDK1. In that model, therefore, the turn motif did not act as a simple linear amplifier of AKT enzymatic activity [4].This evidence does not contradict the core narrative of the book, namely mTORC2's contribution to the structural maturation of AKT. It does, however, indicate that protein stability and the intensity of the catalytic signal are not synonymous: a modification that helps AKT mature may have different consequences on other regulatory sites, depending on the species, cell type, and stimulus.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to evaluate the book's passage.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular, biochemical, and comparative	Models from yeast to mammals; full details not available in the abstract	mTORC2 promotes phosphorylation of the AKT turn motif and supports its folding and stability	direct confirmation	moderate
[1]	Cellular and genetic	Mouse embryonic fibroblasts with deletion of Rictor, SIN1, or mTOR	Loss of mTORC2 components abolishes phosphorylation of the AKT turn motif	direct confirmation	moderate
[2]	Structural and biochemical	Reconstituted mTORC2 and AKT; experimental cellular systems	mTORC2 selectively recognizes AKT and directly phosphorylates regulatory sites, including Thr450	direct confirmation	moderate
[3]	Cellular and biochemical	mTORC2-deficient cells, mouse fibroblasts, and in vitro assays	Recovery of other AKT sites does not restore the turn motif without mTORC2	indirect confirmation	moderate
[4]	Cellular in model organism	Starfish oocytes with experimentally expressed human AKT	The turn motif stabilizes AKT but reduces activation loop phosphorylation in the studied model	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The passage in the book stating that mTORC2 contributes to the structural maturation of AKT is mechanistically supported. The analyzed study links the loss of turn motif phosphorylation to the instability and degradation of AKT, while independent studies confirm the dependence of this site on the integrity of mTORC2.However, the evidence does not justify automatically translating this mechanism into a clinical conclusion regarding insulin response, metabolic diseases, or tumors. Other AKT phosphorylations have distinct roles and can produce different effects depending on the experimental context. Further validation in human tissues and under defined pathophysiological conditions is necessary.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Essential function of TORC2 in PKC and Akt turn motif phosphorylation, maturation and signalling**
Ikenoue et al., 2008
The EMBO Journal
DOI: https://doi.org/10.1038/emboj.2008.119

[2] **Structural basis for the recruitment and selective phosphorylation of Akt by mTORC2**
Taylor et al., 2026
Science
DOI: https://doi.org/10.1126/science.adv7111

[3] **mTORC2 controls the activity of PKC and Akt by phosphorylating a conserved TOR interaction motif**
Baffi et al., 2021
Science Signaling
DOI: https://doi.org/10.1126/scisignal.abe4509

[4] **Turn motif phosphorylation negatively regulates activation loop phosphorylation in Akt**
Hiraoka et al., 2011
Oncogene
DOI: https://doi.org/10.1038/onc.2011.155