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mTORC2 and co-translational phosphorylation of the nascent AKT polypeptide

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1. ABSTRACT

The analyzed study evaluated whether mTORC2, a protein complex that regulates important cellular signals, acts only on already formed AKT or also during its synthesis. In the available material, consisting only of the abstract, the authors report that mTORC2 can associate with ribosomes engaged in translation and promote the phosphorylation of nascent AKT at the Thr450 site. This modification is associated with reduced co-translational ubiquitination, a process that can direct a protein toward degradation.The result contributes to the narrative of paragraph 4.11 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi: mTORC2 would link protein production to their quality control, helping AKT reach a stable conformation. Independent studies confirm that mTORC2 and its components are necessary for the phosphorylation of the AKT turn motif and for protein maturation processes; other works support the association between mTORC2 and ribosomes. However, independent evidence that the entire process occurs co-translationally in the human organism remains limited.

ONLINE ARTICLE

ARTICLE INFORMATION

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MISSION

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2. ANALYZED STUDY

The research question was whether mTORC2, one of the two main complexes formed by the mTOR protein, has a function during the construction of AKT. AKT is a signaling protein that participates, among other things, in cellular responses to insulin and growth factors. The hypothesis was that mTORC2 does not act only on the complete AKT protein, but could modify AKT as it emerges from the ribosome, the cellular structure that produces proteins.The relevance to paragraph 4.11 is precise: the publication examines the step in which mTORC2 links protein synthesis to quality control, promoting the structural stability of AKT during its formation. The study can document a molecular mechanism in experimental systems; it cannot prove that this mechanism alone determines the insulin response of the entire organism nor establish clinical consequences in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract; therefore, many methodological details are not reported in the provided text. The authors indicate that they studied the localization of mTORC2 in relation to ribosomes that are translating proteins and its interaction with rpL23a, a protein of the large ribosomal subunit located near the exit tunnel of the nascent protein chain.The abstract also reports analyses of AKT phosphorylation during protein translation and its ubiquitination. Phosphorylation is the addition of a phosphate group that can change a protein's behavior, stability, or activity. Ubiquitination is the addition of small proteins called ubiquitins, often used by the cell as a signal to send damaged or misfolded proteins for degradation. The number of experiments, cell lines, selection criteria, complete controls, statistical methods, significance values, and number of replicates are not reported in the available material.

4. RESULTS

The key finding is that mTORC2 can localize together with ribosomes actively engaged in protein synthesis and interact stably with rpL23a. In simple terms, the complex is positioned near the site where a new protein emerges from the cellular machinery that produces it.According to the abstract, during the translation of AKT, mTORC2 promotes the phosphorylation of the Thr450 residue, known as the turn motif. This modification has been associated with a reduction in the cotranslational ubiquitination of AKT—that is, the attachment of a degradation signal while the protein is still being formed. The authors therefore propose that the phosphorylation of Thr450 helps AKT acquire a more stable conformation.The abstract distinguishes Thr450 from the Ser473 residue, known as the hydrophobic motif. Thr450 appears to be accessible during translation, whereas Ser473 is initially hidden within the ribosome tunnel. No absolute values, percentages, concentrations, confidence intervals, or P-values are reported in the available material. Consequently, the result indicates an experimental relationship consistent with a quality control role, but it does not allow for the quantification of the effect's magnitude.

5. INTERPRETATION

For a cell, producing a protein means more than just assembling a sequence of amino acids: the new molecule must also fold into the correct shape to function and avoid being prematurely eliminated. The study analyzed suggests that mTORC2 participates in this phase for AKT, intervening before the protein is fully completed.The segment of the chain documented by the publication is: association of mTORC2 with active ribosomes phosphorylation of nascent AKT at Thr450 reduction of ubiquitination during translation greater potential protein stability. The interpretation that this constitutes a general quality control system stems from the results but remains a conceptual extension: the abstract describes AKT directly and does not demonstrate that all proteins are controlled in the same way.The significance for the book's paragraph is therefore mechanistic. The research does not directly demonstrate the entire metabolic network regulated by AKT, nor does it demonstrate a clinical effect; instead, it supports the initial step that mTORC2 contributes to the structural maturation of AKT during its synthesis.

6. INDEPENDENT CONFIRMING EVIDENCE

Particularly relevant confirmation comes from an independent cellular study that examined mTORC2, Sin1, and Rictor, essential components of the complex. The authors observed that their absence reduced the phosphorylation of the AKT turn motif and that this phosphorylation promoted the correct folding of the protein's terminal portion, associating it with greater stability of the newly synthesized AKT molecules [1]. This work directly confirms the narrative regarding AKT maturation and stability, although it does not, on its own, demonstrate the association with the ribosome during every phase of translation.A second study, conducted in cellular models with inactivation of Rictor, Sin1, or mTOR, found the abolition of AKT turn motif phosphorylation and a reduction in the phosphorylation of other regulatory sites. The work also linked mTORC2 to the maturation of kinases in the same family as AKT, especially PKC. For AKT, the data consistently support that mTORC2 is necessary for the modification of the turn motif; however, AKT stability is inferred primarily by analogy with the other kinases studied [2].A third study provided confirmation of the upstream step: in a system comprising yeast and mammalian cells, active mTORC2 was found to be physically associated with ribosomes. Furthermore, insulin-induced signaling through PI3K increased the binding between mTORC2 and ribosomes [3]. This result does not measure the cotranslational phosphorylation of Thr450, but it makes it biologically more plausible that the complex can act near proteins in formation.Taken together, these independent pieces of evidence support three levels of the same chain: the necessity of mTORC2 for AKT phosphorylation, the link between turn motif phosphorylation and protein maturation, and the physical association between mTORC2 and ribosomes. However, these are experimental studies in cells or model systems; they do not constitute direct proof in humans.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results. However, there is a significant mechanistic limitation. The study by Ikenoue and colleagues showed that the loss of mTORC2 components eliminates the phosphorylation of the AKT turn motif, but in their in vitro assays, immunoprecipitated mTOR did not directly phosphorylate that site [2]. The authors pointed to possible technical explanations, such as the loss of a necessary component of the complex or non-conserved characteristics of the experimental substrate.This observation does not contradict the fact that mTORC2 is necessary for the phosphorylation of Thr450 in cells. However, it reduces certainty regarding the finer details of the chain, specifically whether mTORC2 is always the enzyme that directly adds the phosphate to Thr450 or if it also contributes through an intermediate step dependent on the experimental context.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study subject to the Evidence Review from the independent publications used to confirm the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	Experimental systems not detailed in the available abstract alone	mTORC2 associated with active ribosomes promotes AKT Thr450 phosphorylation and reduces cotranslational ubiquitination	direct confirmation	moderate
[1]	Cellular and biochemical	Cell lines and murine embryonic fibroblasts	mTORC2 and its components are necessary for turn motif phosphorylation and the stability of newly synthesized AKT	direct confirmation	moderate
[2]	Cellular and biochemical	Cells with Rictor, Sin1, or mTOR inactivation	Loss of mTORC2 eliminates AKT turn motif phosphorylation; the role in maturation is demonstrated primarily for PKC	biologically consistent evidence	moderate
[3]	Cellular and genetic	Yeast and mammalian cells, including tumor cells	Active mTORC2 is associated with ribosomes, and insulin-induced PI3K signaling increases this association	indirect confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed specifically supports the claim that mTORC2 may participate in the maturation of AKT while the protein is being synthesized. The key finding is the phosphorylation of Thr450, which is associated with a reduction in cotranslational ubiquitination and, therefore, greater potential stability of AKT.Independent evidence confirms quite well that mTORC2 is necessary for the phosphorylation of the AKT turn motif and that this modification is linked to protein folding and stability processes. The association between mTORC2 and ribosomes is also confirmed in experimental models. The conclusion remains primarily mechanistic: it requires validation in human tissues and should not be interpreted as direct proof of a therapeutic or metabolic effect 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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