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Prolonged rapamycin treatment inhibits mTORC2 and Akt/PKB assembly - Review of the evidence

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1. ABSTRACT

The analyzed publication evaluated whether rapamycin, a drug historically considered an mTORC1 inhibitor, can also influence mTORC2, the protein complex that contributes to the full activation of AKT. The authors reported that prolonged treatment reduces the assembly of new mTORC2 complexes and, in many cell types, lowers AKT signaling. They also observed that a rapamycin-resistant AKT variant attenuated the drug's pro-apoptotic and anti-tumor effects in experimental cells.The work is cited in “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi to support two connected points: the possibility that prolonged exposure to rapamycin reduces AKT phosphorylation via mTORC2 and the potential relevance of this phenomenon for anti-tumor and metabolic effects. Independent studies confirm that the loss of mTORC2 can impair insulin signaling in vivo and in human adipose cells. However, other experiments show that in some tumor cells, AKT can increase despite the reduction in mTORC2 assembly due to compensatory circuits. The most prudent conclusion is therefore that the mechanism is biologically grounded, but highly dependent on the cell type, dose, and duration of exposure.

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.

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 rapamycin acts solely on mTORC1, the complex that primarily regulates protein synthesis, or if it could also alter mTORC2 over time. The latter is a multiprotein complex that contributes to the phosphorylation of AKT/PKB, a protein that integrates survival, growth, and metabolic signals.The hypothesis evaluated was that prolonged exposure to the drug hinders the formation of mTORC2. According to the available abstract, this reduction would lead to insufficient levels of mTORC2 in many cell types to maintain the AKT signal. The relevance to "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi therefore concerns the segment of the chain: prolonged rapamycin reduced mTORC2 assembly reduced AKT phosphorylation.The study can demonstrate a molecular and cellular effect of rapamycin in the examined models. However, it cannot establish that the same effect occurs in all tissues, in all neoplasms, or in every person treated with rapamycin. It also does not prove that the reduction of AKT is the sole cause of the potential antitumor or metabolic effects of the drug.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material contains only the abstract of the publication. The study compared the behavior of mTORC1 and mTORC2 under rapamycin treatment conditions and evaluated the AKT/PKB signal. The authors also used cells expressing a rapamycin-resistant mutant variant of AKT to verify whether maintaining the AKT signal would alter the cellular effects of the treatment.The detailed experimental design, the number and complete identity of the cell types, drug concentrations, precise duration of treatments, laboratory procedures, statistical analyses, numerical values, and exclusion criteria are not reported in the available material. No clinical follow-ups, human participants, or therapeutic trials on patients are reported.

4. RESULTS

The main finding is that prolonged treatment with rapamycin inhibited the assembly of mTORC2. In simple terms, the drug would not only have slowed down the activity of the existing complex, but would have hindered the formation of new functional complexes. In many cell types, this reduced mTORC2 below the level necessary to maintain AKT/PKB signaling.AKT is a protein that receives signals from nutrients, insulin, and growth factors. Its phosphorylation, i.e., the addition of a phosphate group at regulatory sites, is one of the modifications that allow for its full activity. The abstract therefore reports a reduction in AKT signaling after prolonged exposure to rapamycin, but does not report percentages, exact times, P-values, or confidence intervals.The authors also observed that the pro-apoptotic effects—that is, those favoring programmed cell death—and the anti-tumor effects of rapamycin were attenuated in cells with an AKT variant resistant to rapamycin. This finding supports the interpretation that the reduction in AKT signaling contributes to the effects observed in the experimental model. However, it does not allow for the quantification of how much this contribution weighs in human tumors.

5. INTERPRETATION

The biological significance is that rapamycin may have different consequences than expected if administered over the long term. Initially, the best-known effect concerns mTORC1; with prolonged exposure, in some models, mTORC2 may also be involved. Since mTORC2 contributes to the activation of AKT, the reduction of its integrity can weaken signals that promote cell survival and insulin response.The step documented directly by the publication that is the subject of the Evidence Review is: prolonged rapamycin reduced mTORC2 assembly reduced ability to maintain the AKT signal. This is the point that explains its presence in the sections of the book dedicated to the relationship between mTORC2 and AKT. The hypothesis that this mechanism contributes to anti-tumor effects is consistent with the cellular model, but requires caution: the effect is not necessarily uniform across different tumors.Subsequent literature also clarifies why it is incorrect to turn this mechanism into a universal rule. mTORC2 is important for the maturation and stability of AKT [1]. However, rapamycin can simultaneously remove some upstream brakes on the PI3K-AKT pathway, allowing for a compensatory increase in

AKT phosphorylation in specific tumor cells [2].

6. INDEPENDENT CONFIRMING EVIDENCE

Particularly relevant confirmation for the metabolic section of the book comes from an experimental study in mice. Chronic exposure to rapamycin altered mTORC2 in vivo and was associated with a worsening of glucose tolerance and insulin action. The authors also showed that mTORC2 was necessary for insulin to suppress hepatic gluconeogenesis, i.e., the production of glucose by the liver. The result supports the passage stating that the prolonged loss of mTORC2 function can reduce insulin signaling through AKT. The limitation is that this is primarily a mouse model, not a direct demonstration of an identical clinical effect in all people [3].A second study analyzed adipocytes, i.e., adipose tissue cells, obtained from human subcutaneous and omental biopsies. At a therapeutic concentration of 0.01 µM, rapamycin reduced basal and insulin-stimulated glucose uptake by 20–30% after 15 minutes or 20 hours of culture. In subcutaneous cells, AKT phosphorylation at serine 473 and mTOR-RICTOR and mTOR-SIN1 interactions also decreased, consistent with reduced mTORC2 formation. This is a finding biologically very close to the book's narrative, although it remains an ex vivo experiment on isolated cells and not a clinical trial [4].Further evidence clarifies why the reduction of mTORC2 is relevant for AKT. In cellular experiments and in vivo models, the absence of essential mTORC2 components reduced phosphorylations necessary for the correct maturation of AKT. The consequence was lower stability of the newly synthesized protein. This study does not test rapamycin, but it confirms the step in the chain according to which an intact mTORC2 contributes to making AKT structurally and functionally competent [1].

7. CONFLICTING EVIDENCE

Not all cells respond to prolonged rapamycin treatment with a reduction in AKT phosphorylation. In lung cancer cell lines, one experiment found that 24 hours of rapamycin reduced the association of RICTOR with mTOR, a sign consistent with decreased mTORC2 assembly, yet it still increased AKT phosphorylation. The effects also varied with the dose: in PC-3 cells, 1 nM increased AKT phosphorylation, while 100 nM reduced it [2].This result does not disprove the fact that rapamycin can hinder mTORC2 assembly. Instead, it shows that the final level of AKT phosphorylation also depends on feedback loops. By blocking mTORC1, the cell can increase upstream signals, including those that activate PI3K and AKT. In the context of cancer, therefore, less mTORC2 assembly does not automatically guarantee lower overall AKT activity or a greater antitumor effect.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from independent research that confirms or defines its biological significance.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and molecular	Cell types not specified in the available abstract	Prolonged rapamycin reduced mTORC2 assembly and AKT signaling in many cell types; antitumor effects were attenuated by rapamycin-resistant AKT.	biologically consistent evidence	preliminary
[1]	Cellular and in vivo	Mammalian cells and experimental models	mTORC2 is required for phosphorylations that promote AKT maturation and stability.	indirect confirmation	moderate
[3]	Animal and genetic	Mice treated chronically with rapamycin and models with mTORC2 alteration	Loss of mTORC2 compromised insulin suppression of hepatic gluconeogenesis and contributed to insulin resistance.	direct confirmation	moderate
[4]	Human ex vivo cellular	Adipocytes from human subcutaneous and omental biopsies	Rapamycin reduced glucose uptake, AKT phosphorylation, and interactions necessary for mTORC2 formation.	direct confirmation	moderate
[2]	Tumor cellular	Lung and prostate tumor cell lines	Rapamycin reduced mTORC2 assembly but, under certain conditions, increased AKT phosphorylation due to compensatory feedback.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that rapamycin, when exposure is prolonged, can impair the assembly of mTORC2 and reduce AKT signaling in specific cell types. Independent evidence confirms that mTORC2 is important for AKT function and that its loss can impair the insulin response in experimental models and human adipose cells. The potential contribution to anti-tumor effects is biologically plausible, but not uniform: some tumors activate feedback loops that maintain or increase AKT. The book's narrative is therefore moderately supported and always requires a context-dependent reading.

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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