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ORIGINAL RESEARCH

Inhibition of the mammalian target of rapamycin (mTOR) as a potential antiepileptogenic therapy: from tuberous sclerosis to common acquired epilepsies - A review of the evidence

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study is a review article evaluating mTOR inhibition (the mammalian target of rapamycin, a protein that coordinates cell growth and protein synthesis) as a potential strategy to prevent the development of epilepsy. The available text primarily describes evidence obtained in mouse models of tuberous sclerosis, in which mTOR inhibitors prevented seizures and brain abnormalities associated with the epileptogenic process.In the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that the loss or malfunction of TSC1 and TSC2, hamartin and tuberin respectively, deregulates mTOR and can have significant clinical consequences in tuberous sclerosis. Independent evidence confirms that the TSC1/TSC2 complex limits cellular signals controlled by mTOR and that pharmacological inhibition of this pathway can reduce some manifestations of the disease in humans. However, significant limitations remain: not all clinical consequences depend solely on mTOR, and the response to drugs is not uniform.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether mTOR inhibition could become an antiepileptogenic therapy—that is, one capable not only of reducing existing seizures but also of modifying the biological processes that promote the onset of epilepsy. The central hypothesis is that intervening in a signaling pathway located upstream of many cellular alterations could limit the brain modifications that make seizures more likely.The connection to the book's section concerns tuberous sclerosis, a genetic condition in which alterations of TSC1 or TSC2 compromise the protein complex that normally limits mTOR activity. The study analyzed uses this disease as an example of the biological relevance of mTOR in cell growth abnormalities and epilepsy. However, based on the available material, it does not directly measure the relationship between insulin, AKT, and TSC2 described in the book's section; nor can it prove that every clinical manifestation of tuberous sclerosis derives exclusively from mTOR activation.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the publication's abstract. From this, it is clear that it is a scientific review article, not a new clinical trial or a single experiment with participants enrolled by the authors. The objective was to integrate the evidence available at the time regarding the role of mTOR in epileptogenesis, that is, the set of changes that predispose the brain to epileptic seizures.The abstract refers to murine models of tuberous sclerosis and other animal models of acquired epilepsy, including those following status epilepticus or traumatic brain injury. The number of animals, selection criteria, dosages of mTOR inhibitors, duration of observations, detailed endpoints, and statistical analyses are not reported in the available material. Furthermore, a systematic literature search strategy is not reported; therefore, it is not possible to evaluate from the abstract how the discussed studies were selected.

4. RESULTS

The main result reported in the abstract is qualitative: in mouse models of tuberous sclerosis, mTOR inhibitors prevented the development of epilepsy and certain brain abnormalities associated with epileptogenesis. In simple terms, reducing an overly active cellular signal limited both seizures and certain brain alterations linked to their onset in the animals.The publication also notes that mTOR may be involved in epileptogenesis in other conditions, such as focal cortical dysplasia and acquired brain injuries. However, the abstract does not report numerical values, percentage reductions in seizures, P-values, confidence intervals, or experimental details that would allow for the quantification of these effects.For the book passage, the most relevant data is as follows: tuberous sclerosis is presented as an example where the alteration of the TSC1/TSC2 system is associated with abnormal mTOR activity and significant neurological consequences. This supports the role of the TSC1/TSC2 complex as a biological regulator of mTOR, but it does not, on its own, demonstrate all the clinical consequences mentioned in the paragraph.

5. INTERPRETATION

The biological significance is that TSC1 and TSC2 act together as a brake: when they function, they help prevent growth and protein synthesis signals from remaining active longer than necessary. mTOR is one of the main nodes controlled by this brake. If the TSC1/TSC2 complex is defective, the cell may persistently receive signals that promote protein production, increased size, and the growth of disorganized tissues.In technical terms, the TSC1/TSC2 complex primarily limits mTORC1, one of the two main functional forms of mTOR. Excessive activation of mTORC1 alters phosphorylation—the addition of chemical groups that regulate protein activity—of targets involved in protein synthesis. The analyzed study interprets this dysregulation as a plausible explanation for brain abnormalities and epilepsy in tuberous sclerosis.This interpretation is consistent with the book's paragraph, but requires precision. The publication subject to the Evidence Review primarily documents biological plausibility and preclinical results in animals; it does not constitute definitive clinical proof that mTOR inhibition prevents epilepsy in all people with tuberous sclerosis or that TSC1/TSC2 malfunction produces the same effect in all organs.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct mechanistic confirmation comes from cellular experiments in which hamartin and tuberin were expressed together. The TSC1/TSC2 complex reduced the activation of 4E-BP1 and S6K1, two proteins located downstream of mTOR that promote protein synthesis. Furthermore, a TSC2 variant identified in people with tuberous sclerosis failed to adequately repress 4E-BP1 phosphorylation. This study directly supports the concept that TSC1/TSC2 acts as a brake on signals regulated by mTOR. The limitation is that the main model was cellular and does not measure the clinical outcomes of the disease [1].Verification in humans was provided by a non-randomized prospective study conducted on 25 people with tuberous sclerosis or sporadic lymphangioleiomyomatosis, a related disease that can also involve alterations in TSC genes. During twelve months of treatment with sirolimus, an mTOR inhibitor, the mean volume of renal angiomyolipomas was 53.2% of the initial value, with a statistically significant reduction. One year after discontinuation, the mean volume had risen back to 85.9% of the baseline. The result is consistent with the fact that mTOR activity contributes to the growth of some lesions associated with this biology, but the design without a control group and the mixed population limit the causal strength of the inference [2].Neurological relevance in humans was evaluated in a randomized, double-blind, placebo-controlled clinical trial on 366 people aged between 2 and 65 years with tuberous sclerosis and drug-resistant focal seizures. The proportion of participants with at least a 50% reduction in seizures was 15.1% with placebo, 28.2% with low exposure to everolimus, and 40.0% with high exposure. The median reduction in seizure frequency was also greater with everolimus compared to placebo. These data confirm that, for a portion of patients, inhibiting mTOR can reduce a clinically relevant neurological manifestation of tuberous sclerosis. However, they do not demonstrate that the drug corrects all the disease's anomalies; furthermore, grade 3 or 4 serious adverse events were more frequent in the everolimus groups [3].

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.However, there are elements that require caution. The return of angiomyolipomas to their initial volume after the discontinuation of sirolimus indicates that reducing mTOR activity can control part of the lesion growth without necessarily eliminating the underlying genetic cause [2]. Furthermore, in the randomized study on epileptic seizures, a significant proportion of participants did not achieve a seizure reduction of 50% or more, and serious adverse events were more frequent with everolimus compared to placebo [3]. These results do not contradict the biological role of mTOR, but they show that the mechanism is dependent on the tissue, the clinical manifestation, and the therapeutic context.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent evidence 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	Review article	Mouse models of tuberous sclerosis and acquired epilepsy, described in the abstract	mTOR inhibitors prevented epilepsy and brain abnormalities in mouse models of tuberous sclerosis.	biologically consistent evidence	preliminary
[1]	Cellular	U2OS cells with experimental expression of TSC1/TSC2 and a TSC2 variant associated with tuberous sclerosis	TSC1/TSC2 reduced downstream mTOR signaling; the TSC2 variant did not adequately repress 4E-BP1.	direct confirmation	moderate
[2]	Prospective non-randomized interventional	25 people with tuberous sclerosis or sporadic lymphangioleiomyomatosis	Sirolimus reduced the mean volume of angiomyolipomas during treatment; volume increased after discontinuation.	indirect confirmation	moderate
[3]	Double-blind, placebo-controlled RCT	366 people with tuberous sclerosis and drug-resistant focal seizures	Everolimus increased the proportion of people with at least a 50% reduction in seizures compared to placebo.	indirect confirmation	high

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication is relevant to the passage in the book because it uses tuberous sclerosis as an example of the biological and clinical significance of mTOR regulation by the TSC1/TSC2 complex. The connection is well-supported at a mechanistic level and reinforced by clinical studies showing a reduction in certain manifestations of the disease with mTOR inhibitors.However, the evidence does not allow us to consider mTOR the sole cause of all consequences of tuberous sclerosis, nor to interpret the efficacy of the drugs as uniform or definitive. The control of lesion growth and the reduction of seizures appear to be dependent on the treatment, the location of the disease, and the individual response. The book's narrative is therefore strongly confirmed in its biological core, with significant limitations in its general clinical extension.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling**
Tee et al., 2002
Proceedings of the National Academy of Sciences
DOI: https://doi.org/10.1073/pnas.202476899

[2] **Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis**
Bissler et al., 2008
New England Journal of Medicine
DOI: https://doi.org/10.1056/NEJMoa063564

[3] **Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study**
French et al., 2016
The Lancet
DOI: https://doi.org/10.1016/S0140-6736(16)31419-2