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Role of mTOR in glucose and lipid metabolism - Review of the evidence

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1. ABSTRACT

The analyzed publication is a narrative review dedicated to the role of mTOR, a protein that integrates nutritional, hormonal, and energy signals in the control of glucose and lipid metabolism. The authors describe two complexes, mTORC1 and mTORC2, and synthesize results obtained primarily in cells, animal models, and human tissues. The relevant passage for “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi concerns the observation that persistent mTOR activation can reduce insulin sensitivity and contribute to the biological context of obesity and type 2 diabetes.Independent evidence supports a plausible chain: excessive activity of the mTORC1-S6K1 pathway can modify IRS-1, a protein necessary for transmitting the insulin signal, reducing glucose entry into muscle cells. In mice, the absence of S6K1 protects against diet-induced obesity and maintains greater insulin sensitivity. Furthermore, increased mTORC1 activity has been observed in the pancreatic islets of people with type 2 diabetes. However, the relationship is not linear: even prolonged pharmacological inhibition of mTOR can compromise metabolism if it interferes with mTORC2. The narrative is therefore well-supported at a mechanistic level, but it does not authorize considering every increase or reduction of mTOR as automatically beneficial or harmful.

ONLINE ARTICLE

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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 of the publication was to understand how mTOR participates in the control of glucose and lipid metabolism in the main metabolic organs: adipose tissue, liver, skeletal muscle, pancreas, and brain. The hypothesis synthesized by the authors is that mTOR acts as an integration hub: it receives information about nutrients, insulin, growth factors, and the cell's energy status, then coordinates cell growth, protein and fat synthesis, glucose utilization, and the recycling of cellular components.The relevance to paragraph 4.6 is specific. The publication was used to support the claim that the hyperactivation of mTOR, especially mTORC1, can contribute to a reduced response to insulin and to metabolic dysfunctions associated with obesity and type 2 diabetes. The work is not a clinical study demonstrating that mTOR activity alone causes these diseases in humans. It is a review that brings together experimental and observational findings, which are useful for describing the biological mechanism and its limitations.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the scientific literature and not a new experiment on participants, animals, or cells. The authors discussed previous studies on mTOR signaling in the various tissues involved in energy balance and metabolism.The available text does not report a structured bibliographic search strategy, databases consulted, time ranges for the searches, inclusion or exclusion criteria for the publications, formal assessment of the risk of bias, or quantitative meta-analysis. This information is not provided in the available material. Consequently, the work is useful as an interpretive framework, but it lacks the methodological strength of a systematic review.The review distinguishes between mTORC1, the complex associated with protein synthesis, lipid production, and the inhibition of autophagy, and mTORC2, which is involved, among other things, in the full activation of AKT, a protein important for the insulin response. In the segment most relevant to the book, the authors describe the mTORC1-S6K1-IRS-1 circuit: S6K1 is a protein activated downstream of mTORC1; IRS-1 is a protein that helps the insulin receptor transmit the signal inside the cell.

4. RESULTS

The publication reports that when nutrients and growth signals are abundant, mTORC1 promotes protein synthesis, glycolysis, and lipid production. Under physiological conditions, these functions are necessary: they allow the cell to grow, build molecules, and adapt to energy availability.However, the central finding for the book's section concerns excessive or prolonged activation. In skeletal muscle, the review describes that mTORC1 activation can increase S6K1 activity. S6K1 can phosphorylate IRS-1, meaning it adds phosphate groups to sites that promote the loss or inhibition of this protein. The described consequence is reduced activation of the PI3K-AKT sequence and a decrease in insulin-stimulated glucose uptake.The authors also report that persistent mTORC1 activation can have different effects in various organs. In the liver, it can promote lipid production; in the pancreas, it may initially increase the mass of insulin-producing beta cells, while over time it can be associated with cellular stress and loss of function; in adipose tissue, it can participate in the regulation of fat formation and accumulation. The review does not provide a single overall quantitative value, a total number, or a unique statistical estimate, because it summarizes heterogeneous studies.The text also highlights an essential element: prolonged inhibition of mTOR with rapamycin can compromise insulin sensitivity, partly because it can disrupt mTORC2. This means that metabolic function depends on the balance between the two complexes, the tissue being considered, and the duration of the alteration.

5. INTERPRETATION

In simple terms, mTOR is useful when it helps the cell use nutrients and insulin in a balanced way. It can become problematic when the signal remains constantly elevated: in this situation, a part of the pathway can trigger a feedback mechanism that weakens the insulin message.The segment most directly documented by the publication subject to the Evidence Review is: hyperactivation of mTORC1 increased S6K1 activity modification and functional reduction of IRS-1 reduced PI3K-AKT signaling

reduced insulin response. This is a plausible biological explanation for reduced insulin sensitivity, not a demonstration that this circuit is the sole cause of obesity or type 2 diabetes.The book's formulation is therefore consistent with the review, provided it is read with precision. mTOR hyperactivation can contribute to unfavorable metabolic conditions, but it does not equate to a simple and universal relationship. Obesity and type 2 diabetes depend on multiple factors, including genetic predisposition, adipose tissue distribution, inflammation, pancreatic function, physical activity, diet, and clinical context.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial direct confirmation of the molecular pathway comes from L6 muscle cells cultured in the laboratory. Exposure for one hour to a balanced mixture of amino acids reduced insulin-stimulated glucose transport by up to 55%. The authors also observed a 70% reduction in PI3K activity associated with IRS-1 after 30 minutes of insulin stimulation, along with increased S6K1 activity. Rapamycin prevented these effects. The study therefore supports the pathway of excess nutrients mTOR/S6K1 weakening of IRS-1 and insulin signaling, but it is limited to a cellular model and does not directly demonstrate the clinical risk of type 2 diabetes [1].A second study verified the relevance of the S6K1 axis in whole organisms. In mice lacking the S6k1 gene, the absence of this mTOR effector protected against age- and diet-related obesity and maintained greater insulin sensitivity. In normal mice fed a high-fat diet and in two genetic models of obesity, by contrast, S6K1 activity and inhibitory phosphorylation of IRS-1 were increased. This experiment reinforces the direction proposed in the book, but it remains a murine model, in which the genetic absence of S6K1 differs from the natural hyperactivation of mTOR in humans [2].A third piece of evidence adds a human and pancreatic level. In pancreatic islets obtained from people with type 2 diabetes, mTORC1 activity was increased, while mTORC2 activity was reduced. Inhibition of the mTORC1-S6K1 signal improved glucose-stimulated insulin secretion and restored signals attributed to mTORC2 in diabetic islets. This result is consistent with the idea that a persistent imbalance of the mTOR pathway contributes to metabolic dysfunction; however, as it is based on isolated tissues, it cannot establish the complete causal sequence in human diabetes on its own [3].Taken together, these studies build a convergent chain. The cellular model documents the braking mechanism on insulin signaling; the animal model shows a consequence for obesity and insulin sensitivity; the human islets show that an alteration of mTORC1 and mTORC2 is present in type 2 diabetes. No single publication demonstrates the entire chain in all people, but the results are biologically consistent.

7. CONFLICTING EVIDENCE

The main evidence calling for caution does not deny the potential harm of mTORC1 hyperactivation, but demonstrates that indiscriminately reducing mTOR signaling is not necessarily beneficial. In mice treated with rapamycin for two weeks, chronic inhibition reduced glucose tolerance and insulin action. The authors linked this effect primarily to the loss of mTORC2 function, which is necessary to suppress fasting-induced hepatic glucose production [4].This result clarifies that balance is more important than a simple logic of increase or decrease. Persistently elevated mTORC1 signaling can hinder the insulin response through S6K1 and IRS-1; however, prolonged inhibition capable of interfering with mTORC2 can also promote insulin resistance. The direction of the effect therefore depends on the complex involved, the tissue, the experimental model, and the duration of the intervention.No sufficiently relevant directly conflicting evidence has been identified that demonstrates that persistent mTORC1 hyperactivation stably improves insulin sensitivity; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to confirm or define the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on cells, animals, and human tissues	Describes mTORC1 and mTORC2 as metabolic regulators; persistent hyperactivation can reduce insulin signaling.	biologically consistent evidence	moderate
[1]	Cellular	L6 muscle cells	Amino acids reduced insulin-stimulated glucose transport and increased the mTOR-S6K1 circuit associated with IRS-1 inhibition.	direct confirmation	moderate
[2]	Animal	S6K1-deficient mice and mouse models of obesity	The absence of S6K1 protected against diet-induced obesity and maintained higher insulin sensitivity.	direct confirmation	moderate
[3]	Human and animal ex vivo study	Diabetic human pancreatic islets, beta cells, and diabetic mice	In type 2 diabetes, mTORC1 was increased and mTORC2 was reduced; mTORC1-S6K1 inhibition improved insulin secretion in the islets.	indirect confirmation	moderate
[4]	Animal	Mice treated chronically with rapamycin and mice with Rictor deletion	Chronic rapamycin worsened glucose tolerance and insulin action through the loss of mTORC2.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the section of the book regarding the metabolic consequences of mTOR hyperactivation. Independent evidence indicates that persistent activation of the mTORC1-S6K1 axis can impair insulin signaling through IRS-1, leading to a reduction in cellular glucose utilization. The link to obesity and type 2 diabetes is supported by animal models and observations in human pancreatic islets, but it does not identify mTOR as the sole cause of metabolic diseases. The body of evidence also requires considering the distinct role of mTORC2: prolonged and non-selective suppression of the pathway can be metabolically unfavorable.

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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