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ORIGINAL RESEARCH

Role of the mTORC1-S6K1 signaling pathway in the regulation of hematopoietic stem cells and acute myeloid leukemia - Review of evidence

Dott. A. Colonnese[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed publication is a narrative review dedicated to the mTORC1-S6K1 pathway, a cellular system that links the availability of nutrients and growth factors to programs of protein synthesis, growth, metabolism, proliferation, and autophagy. The available text is only the abstract: it does not report a new experiment, a number of participants, or an original statistical analysis, but synthesizes previous studies on hematopoietic stem cells, leukemic stem cells, and acute myeloid leukemia.In paragraph 4.7, “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi uses this publication primarily to describe S6K1 as an important downstream effector of mTORC1: a protein that transforms the received signal into changes in protein synthesis, cell growth, and metabolism. Independent literature confirms this mechanistic role and also supports the existence of feedback from mTORC1-S6K1 to IRS-1, a protein essential for insulin signal transmission. However, the individual phosphorylation sites of IRS-1 and the final metabolic effects are not identical in all tissues and experimental models. The confirmation of the narrative is therefore strong on a biological and mechanistic level, but it does not allow S6K1 to be treated as the sole determinant of insulin resistance in humans.

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 the mTORC1-S6K1 pathway contributes to the functioning of hematopoietic stem cells—the cells from which blood elements are derived—and leukemic stem cells in acute myeloid leukemia. The general hypothesis is that this pathway regulates processes essential for cellular life, including proliferation, metabolism, and autophagy, which is the system by which the cell recycles damaged or unnecessary components.In section 4.7 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the relevance is more circumscribed: S6K1 is presented as one of the main targets of mTORC1 and as a mediator of cell growth, protein synthesis, and metabolic adaptation. The available abstract explicitly states that mTORC1-S6K1 regulates proliferation, metabolism, and autophagy; however, it does not directly describe experiments on IRS-1, nor does it provide quantitative data on the feedback linking the hyperactivation of the pathway to insulin resistance. This latter segment can therefore be linked to the publication only at the level of a general biological framework and must be evaluated with specific independent studies.As it is a review, the analyzed study does not by itself demonstrate a causal relationship in humans. Its value lies in placing mTORC1-S6K1 at the center of a cellular control network and in discussing the limitations of pathway inhibitors in acute myeloid leukemia.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists exclusively of the abstract. From this, it appears to be a literature review on the functions of the mTORC1-S6K1 pathway in normal hematopoietic stem cells, leukemic stem cells, and acute myeloid leukemia.The available material does not report a bibliographic search strategy, the databases consulted, search terms, inclusion or exclusion criteria for studies, the number of publications examined, a pre-registered protocol, a systematic risk of bias assessment, or a meta-analysis. Furthermore, no sample sizes, follow-ups, clinical endpoints, group comparisons, or original statistical analyses are reported, as the publication does not present a new clinical or laboratory experiment.The abstract notes that the authors also discuss possible therapeutic approaches and drugs directed against mTORC1-S6K1, including RapaLink-1. However, the available material does not report detailed experimental results on this compound; therefore, these aspects are not used to evaluate the book's narrative.

4. RESULTS

The main result reported in the abstract is that the dysregulation of the mTORC1-S6K1 pathway is frequent in patients with acute myeloid leukemia and that this pathway contributes to the functions of both normal hematopoietic stem cells and leukemic stem cells. In simple terms, the system helps cells decide when to build new proteins, increase their mass, use nutrients, and activate survival or internal recycling programs.The abstract identifies proliferation, metabolism, and autophagy as processes regulated by mTORC1. It also indicates that pathway inhibitors, used alone in clinical trials for acute myeloid leukemia, have produced heterogeneous results. No patient numbers, specific drugs, response rates, survival data, confidence intervals, or P-values are reported; this information is therefore not available in the provided material.Compared to the book passage, the most relevant data point is the attribution of a regulatory role in cell growth and metabolism to mTORC1-S6K1. The abstract does not quantify how much S6K1 contributes compared to other mTORC1 effectors, such as 4E-BP1, and does not directly demonstrate that S6K1 phosphorylation is a quantitative measure of protein synthesis in every tissue.

5. INTERPRETATION

The biological significance of the publication is that mTORC1 does not act as a single switch capable of directly producing all growth effects. Instead, it transmits the signal to effector proteins; S6K1 is one of these and contributes to implementing programs for protein synthesis, cell mass growth, and adaptation to nutrient abundance.This interpretation is consistent with the description proposed in "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi. The segment actually supported by the publication subject to the Evidence Review is: activation of mTORC1 regulation of S6K1 control of

proliferation, metabolism, and biosynthetic processes. The formulation stating that S6K1 is the main effector must, however, be read as a popularizing simplification: mTORC1 has multiple downstream targets, and the effects vary based on cell type, nutritional status, and signal duration.The final link to IRS-1 is biologically plausible and documented by independent studies, but it is not described in the available abstract of the analyzed study. Furthermore, the phosphorylation of IRS-1 can be produced by multiple kinases, i.e., enzymes that add phosphate groups to proteins; not all phosphorylated sites of IRS-1 have the same functional significance.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial confirmation of the role of S6K1 in cell growth comes from experiments in mammalian cells. Fingar and colleagues showed that mTOR inhibition with rapamycin reduced cell size; the expression of S6K1 forms partially resistant to rapamycin attenuated this reduction. Furthermore, the experimental increase of S6K1 increased cell size. The study supports the passage in the book stating that mTOR transmits part of its effect on growth through S6K1, but it does not prove that S6K1 is the sole effector, nor does it directly measure insulin resistance [1].Holz and colleagues clarified a step closer to protein synthesis. In cell lines, stimulation by nutrients, energy, and growth factors promoted the association of mTOR/raptor with the eIF3 complex, which is involved in initiating the translation of RNA into proteins. Phosphorylation activated S6K1, which then modified targets such as eIF4B. In plain language, the signal of abundance makes the initiation of protein production more efficient. This is a direct mechanistic confirmation, but it was obtained in cells and not in a human organism [2].The link between S6K1 and the negative regulation of insulin signaling has also been observed in animals. In mice lacking the S6K1 gene, Um and colleagues detected greater insulin sensitivity compared to normal mice, despite the presence of some metabolic alterations. In normal mice fed a high-fat diet and in mouse models of obesity, S6K1 activity and the phosphorylation of IRS-1 at the Ser307 and Ser636/639 sites were increased. The authors interpreted these data as the loss of a negative feedback loop from S6K1 to IRS-1 in mice lacking the kinase [3].Particularly relevant evidence also includes human data. Tremblay and colleagues identified Ser1101 of IRS-1 as a site directly phosphorylatable by S6K1 in vitro. Mutation of this site reduced the ability of amino acids to suppress the tyrosine phosphorylation of IRS-1 and AKT, a protein that transmits the insulin signal. In obese mice, hepatic phosphorylation of Ser1101 increased; in humans, an infusion of amino acids was associated with S6K1 activation, increased phosphorylation of IRS-1 Ser1101, reduced IRS-1 function, and insulin resistance in skeletal muscle. The result strengthens the chain of nutrients S6K1 modification of IRS-1 reduction of the insulin response, but it concerns acute exposure and does not prove that every form of insulin resistance shares this same mechanism [4].A further study showed that S6K1 activation induced by the inflammatory factor TNF-alpha increased the phosphorylation of multiple serine sites of IRS-1 in adipocytes and hepatocytes. Experiments with interfering RNA—that is, targeted reduction of S6K1 expression—and with a dominant-negative form of the kinase attenuated the inhibition of IRS-1 and the deterioration of glucose uptake induced by insulin. The effect was also observed with purified proteins in vitro and in the adipose tissue of obese mice, but the mechanism is contextual to TNF-alpha-induced inflammation and does not equate to a general demonstration in humans [5].

7. CONFLICTING EVIDENCE

Independent evidence does not support the conclusion that every IRS-1 phosphorylation is a direct effect of S6K1. In primary human adipocytes isolated from six subjects, Rajan and colleagues studied the IRS-1 Ser307 site. Experimental reduction of S6K1 and the use of the selective inhibitor PF-4708671 decreased the phosphorylation of S6, a known target of S6K1, but did not reduce insulin-induced IRS-1 Ser307 phosphorylation. The authors therefore concluded that, in this specific human cell type, S6K1 is likely not the physiological kinase responsible for Ser307 [6].This result does not negate the overall mTORC1-S6K1-IRS-1 feedback loop, nor the data regarding other sites such as Ser1101. However, it demonstrates that molecular detail depends on the tissue and the specific IRS-1 site considered. In particular, it is incorrect to automatically extend a mechanism demonstrated in specific cell models,

animal models, or conditions of nutritional overload to all organs or all IRS-1 phosphorylation sites.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on hematopoietic stem cells, leukemic stem cells, and acute myeloid leukemia	Describes mTORC1-S6K1 as a regulator of proliferation, metabolism, and autophagy.	biologically consistent evidence	moderate
[1]	Cellular	Mammalian cells	S6K1 contributes to the effects of mTOR on cell size.	direct confirmation	moderate
[2]	Cellular	Cell lines	mTOR and S6K1 coordinate the initiation of protein synthesis through eIF3 and eIF4B.	direct confirmation	moderate
[3]	Animal	S6K1-deficient mice, high-fat diet, and mouse models of obesity	The absence of S6K1 increases insulin sensitivity and reduces feedback toward IRS-1.	indirect confirmation	moderate
[4]	Cellular, animal, and human	Purified proteins, obese mice, and human skeletal muscle	S6K1 phosphorylates IRS-1 Ser1101; amino acid infusion in humans is associated with reduced IRS-1 function and insulin resistance.	direct confirmation	moderate
[5]	Cellular and animal	Adipocytes, hepatocytes, and adipose tissue of obese mice	S6K1 increases inhibitory phosphorylations of IRS-1 and reduces insulin-stimulated glucose uptake.	direct confirmation	moderate
[6]	Human cellular	Primary human adipocytes from six subjects	S6K1 does not appear to be responsible for the insulin-stimulated phosphorylation of IRS-1 Ser307.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication pertinently supports the role of the mTORC1-S6K1 pathway in the regulation of essential cellular processes, including growth, metabolism, and proliferation. Independent research confirms that S6K1 participates in protein synthesis and cell mass growth. It also confirms, with significant limitations, that persistent activation of the pathway can attenuate insulin signaling through modifications of IRS-1.The relationship with insulin resistance is quite well supported at a mechanistic level and in some animal and human models, but it is not a unique pathway, nor is it identical in all tissues. In particular, not every insulin-regulated IRS-1 site depends directly on S6K1. The book's narrative is therefore well-supported if interpreted as a description of a regulatory network, rather than a universal and invariable sequence.

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.

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