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ORIGINAL RESEARCH

Nuclear S6K1 regulates cyclic AMP response element-dependent gene transcription through the activation of the mTOR signaling pathway - Evidence review

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ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 17, 2026
Updated: November 17, 2026

DOI 10.5281/zenodo.24305630

1. ABSTRACT

The analyzed study examined whether S6K1, a protein activated downstream of the mTORC1 complex, also performs functions within the cell nucleus in addition to its well-known role in protein synthesis. In cervical cancer cells, the authors observed that the phosphorylation of S6K1 at the Thr389 position, promoted by the presence of serum, was associated with its nuclear localization. Under these conditions, S6K1 interacted with CREB, a factor that contributes to activating specific genes, and increased the activity of a promoter regulated by CRE elements. Experimental reduction of S6K1 decreased the expression of c-JUN, a gene involved in the proliferative response.In paragraph 4.7, “mTORC1 - S6K1”, “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi uses this research to support a specific point: after activation, S6K1 can reach the nucleus and participate in the regulation of gene expression. Independent studies confirm that mTORC1 can be active in the nucleus and that S6 kinase activity contributes to transcriptional programs linked to growth. However, there is no direct independent replication of the S6K1-CREB interaction and the regulation of c-JUN described in the analyzed study. Furthermore, a study on HeLa cells did not detect nuclear S6K1 using their specific methods. The most prudent conclusion is therefore that the narrative is supported primarily at a mechanistic and cellular level.

MISSION

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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 S6K1, a kinase (an enzyme that modifies other proteins by adding phosphate groups) known primarily for acting in the cytoplasm, can enter the nucleus and contribute directly to gene control. The hypothesis was that the activation of the mTOR pathway, which is important for translating the availability of nutrients and growth factors into cell growth signals, does not only produce effects on protein synthesis but also on gene transcription.This question is relevant to the passage in the book because the paragraph does not attribute the entire genetic regulation of the cell to S6K1. Instead, it argues that, once phosphorylated, S6K1 can translocate into the nucleus and participate in the regulation of gene expression. The study analyzed addresses precisely this segment of the chain: mTORC1 activation, S6K1 phosphorylation, nuclear distribution, and association with elements that regulate transcription.As this is experimental research conducted on tumor cell lines, it can document molecular phenomena in the studied model. However, it cannot establish that the same mechanism occurs with identical intensity in healthy tissues, in all tumors, or in the human body.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract of the publication. The study used human cervical cancer cells and HeLa cells, a cell line derived from cervical carcinoma. The authors compared conditions with serum, which provides growth factors to the cells, and serum-deprivation conditions. They also used rapamycin, a drug that selectively inhibits a portion of mTORC1 signaling.The main variables reported in the abstract were the phosphorylation of S6K1 at Thr389, its distribution between the cytoplasm and the nucleus, its interaction with CREB, and the activity of a CRE promoter via a luciferase assay. This test uses a light signal to estimate how active a promoter is. The level of S6K1 was also experimentally reduced via knockdown to evaluate the effect on c-JUN expression. In HeLa cells, 891 promoter regions to which S6K1 bound directly were identified.The number of independent biological experiments, the selection criteria for the cell lines, the concentrations and duration of the treatments, the details of the cell fractionation techniques, the statistical tests, the significance values, and the quantitative measurements are not reported in the available material.

4. RESULTS

The main result indicates that S6K1 was not statically confined to the cytoplasm. In cervical tumor cells, its presence in the nucleus was serum-dependent. When serum was removed or cells were treated with rapamycin, S6K1 phosphorylation at Thr389 decreased, and S6K1 was retained in the cytoplasm. In simple terms, growth signals and the mTOR pathway were associated with both the activation of S6K1 and its ability to reach the nucleus.The authors also detected an interaction between endogenous S6K1, i.e., produced naturally by the cells, and CREB. S6K1 increased the activity of a promoter containing CRE elements, which are short DNA sequences recognized by CREB. When S6K1 was reduced via knockdown, c-JUN expression decreased. The direction of the effect is therefore clear: less S6K1 in the cells corresponded to lower c-JUN expression in the experimental model.The study also reported that the binding of CREB and S6K1 to the c-JUN promoter changed after serum restimulation and was associated with active epigenetic markers. Epigenetics includes modifications that influence gene accessibility without changing the DNA sequence. Finally, 891 promoter regions directly bound by S6K1 were identified in HeLa cells. The abstract does not provide the complete list of genes, the intensity of the binding, quantitative variations, or P-values.

5. INTERPRETATION

The biological significance of the results is that S6K1 may expand the function of the mTORC1 signal. Instead of being limited to modifying proteins in the cytoplasm and promoting the production of new proteins, a portion of activated S6K1 could contribute in the nucleus to making certain genes more or less usable by the cell.The segment documented by the publication subject to the Evidence Review is: growth signals and mTORC1 activity associated with the phosphorylation of S6K1 at Thr389 increased nuclear localization of S6K1 association with CREB, CRE promoter activity, and regulation of c-JUN. This is

consistent with the statement in the book that S6K1 can participate directly in the regulation of gene expression after being phosphorylated.However, it is necessary to distinguish between observation and interpretation. The observation concerns the cellular distribution of S6K1, the interaction with CREB, the variation in promoter activity, and the reduction of c-JUN after knockdown. The authors' hypothesis is that S6K1 may act on DNA through epigenetic mechanisms or by recruiting transcription factors. The study does not prove that S6K1 directly regulates all 891 identified promoters, nor does it prove that this nuclear activity is necessary for human physiology or for a specific disease.

6. INDEPENDENT CONFIRMING EVIDENCE

A first confirmation concerns the upstream step of the narrative: the existence of mTORC1 activity in the nucleus. Zhou and colleagues studied NIH3T3 cells, murine fibroblasts frequently used in cell signaling models, with fluorescent biosensors localized in the nucleus and with a form of S6K1 experimentally retained in the nucleus. Stimulation with PDGF, a growth factor, increased the phosphorylation of nuclear S6K1 by 34 ± 4 fold; rapamycin and Torin1 inhibited this response. The authors also observed a nuclear response to insulin signals in 3T3L1 adipose cells. The work does not demonstrate the spontaneous translocation of S6K1 or its interaction with CREB, but it directly confirms that the nuclear compartment can host mTORC1 signaling capable of phosphorylating S6K1 [1].A second independent line supports the link between the mTOR-S6K1 axis and transcriptional regulation. Hannan and colleagues studied the transcription of ribosomal genes in murine cells and nuclear extracts. Inhibition of mTOR with rapamycin reduced ribosomal RNA transcription, while active S6K1, but not an inactive form of the enzyme, restored transcriptional activity in extracts from rapamycin-treated cells. The final target examined was UBF, a factor that helps initiate the transcription of genes for ribosomal RNA. The result does not concern CREB or c-JUN, but it confirms that S6K1 can contribute to a transcriptional program regulated by mTOR [2].A third piece of evidence broadens the picture in a living organism. Chauvin and colleagues compared the livers of normal mice and mice lacking both S6K1 and S6K2 kinases after feeding. The absence of the kinases was associated with a defect in the transcriptional program of ribosome biogenesis, that is, the production of the components necessary to build ribosomes. Over 75% of the factors in this program were found to be controlled by S6Ks. Even mutations that prevented the phosphorylation of the ribosomal protein S6 reduced the activity of these promoters. This evidence does not prove a specific nuclear function of S6K1 in cervical cells, but it is biologically consistent with the idea that the activity of S6 kinases influences the expression of groups of genes linked to growth [3].Overall, independent research confirms three levels of the narrative: mTORC1 can be active in the nucleus; S6K activity can contribute to transcriptional processes; and the absence of S6K alters genetic programs in vivo. None of them autonomously and completely replicates the S6K1-CREB-c-JUN sequence observed in the analyzed study. For this reason, the confirmation of the book's general formulation is more solid than the confirmation of the specific mechanism proposed by the authors.

7. CONFLICTING EVIDENCE

Directly relevant evidence suggests caution. Iadevaia and colleagues studied HeLa cells and, while they detected mTORC1 and its component Raptor in the nucleus and nucleolus, they were unable to detect S6K1 in the nucleus or nucleolus using the fractionation and immunoblotting methods employed. The same authors observed that this finding conflicted with previous studies reporting nuclear S6K1 after phosphorylation at Thr389, proposing different cell lines or nuclear levels too low to be measured as possible explanations [4].This result does not eliminate the scientific correspondence between the analyzed study and the book paragraph. However, it shows that the nuclear localization of S6K1 is not necessarily identical in all cells, under all growth conditions, or with all experimental methods. The nuclear function of S6K1 therefore appears to be dependent on the biological context and the sensitivity of the techniques used. No directly conflicting evidence sufficiently relevant to the specific S6K1-CREB interaction or the reduction of c-JUN after knockdown has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study subject to the Evidence Review from the independent publications used to evaluate the same narrative in the book paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and molecular	Human cervical cancer cells and HeLa cells	Serum and mTOR activity associated with phosphorylation, nuclear localization of S6K1, and regulation of CRE promoters.	direct confirmation	moderate
[1]	Cellular with biosensors and targeted manipulations	NIH3T3 fibroblasts and 3T3L1 adipocytes	Growth factors and insulin increase nuclear mTORC1 activity; mTORC1 phosphorylates S6K1 localized in the nucleus.	direct confirmation	moderate
[2]	Cellular and biochemical	Murine NIH3T3 and FM3A cells, nuclear extracts	mTOR inhibition reduces ribosomal transcription; active S6K1 restores transcriptional activity in rapamycin-treated extracts.	indirect confirmation	moderate
[3]	Animal and transcriptomic	Liver of mice with S6K1 and S6K2 deletion	The absence of S6 kinases reduces the transcriptional program of ribosome biogenesis after feeding.	biologically consistent evidence	moderate
[4]	Cellular	HeLa cells	mTORC1 is detected in the nucleus and nucleolus, while nuclear S6K1 is not detected with the methods used.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, within its cellular model, the idea that activated S6K1 can localize to the nucleus and associate with gene regulation mechanisms. Independent literature confirms that mTORC1 possesses nuclear activity and that S6 kinases contribute to transcriptional growth programs. However, the specific evidence regarding CREB and c-JUN requires further independent validation. The book's narrative is therefore supported at a mechanistic level, without being automatically extendable to human physiology or disease.

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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