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# SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth - Evidence review

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## 1. ABSTRACT

The analyzed study evaluated whether the production of new lipids is necessary for AKT signaling—a protein that transmits growth signals—to increase cell mass. In engineered human epithelial cells and in Drosophila, AKT activation increased nutrient uptake, lipid synthesis, and cell size; these effects were diminished or blocked when mTORC1 or SREBP, a transcription factor that activates lipogenesis genes, were inhibited.In section 5.3 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the thesis that lipogenesis is not an accessory effect of insulin-anabolic signaling, but a functional component of it. Independent studies in rat hepatocytes, rodents, and cell models confirm that insulin, PI3K/AKT, mTORC1, and SREBP are linked to the lipogenic response. However, a mouse model shows that mTORC1 is necessary but, in the liver, not always sufficient on its own: a parallel AKT-dependent signal is also required. The confirmation is therefore primarily mechanistic and preclinical.

ONLINE ARTICLE

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## 2. ANALYZED STUDY

The research question was whether AKT-induced growth required only protein synthesis or also lipid production. The authors hypothesized that mTORC1, a protein complex that integrates nutrient and growth signals, activates SREBP and, consequently, the genes necessary to build fatty acids and other membrane lipids.This question is relevant to the passage from "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which describes lipogenesis as a structural component of the insulin anabolic program. The study did not examine people with chronic hyperinsulinemia, nor did it measure inflammation or clinical outcomes. Instead, it documents a segment of the biological chain: AKT activation mTORC1 and SREBP activity increased lipid synthesis increased cell mass.

## 3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The main experiments used immortalized human retinal pigment epithelial cells, equipped with a form of AKT1 that can be activated with 4-hydroxytamoxifen. The cells were cultured under low-lipoprotein conditions to reduce external lipid intake. U2OS cells, a human osteosarcoma cell line, Kc167 Drosophila cells, and transgenic fruit flies were also used.The authors measured cell volume using a Coulter counter and flow cytometry, nutrient consumption and certain metabolites using nuclear magnetic resonance spectroscopy, lipid synthesis via the incorporation of radiolabeled glucose, pyruvate, or acetate, and protein and RNA expression using immunoblotting and quantitative PCR. To block mTORC1, they used rapamycin; to reduce SREBP, mTOR, raptor, or rictor, they used RNA interference, a technique that selectively decreases the expression of a gene.In fruit flies, wing area, cell size, and wing compartment growth were analyzed following the reduction of dSREBP, the Drosophila version of SREBP. Cellular experiments were repeated at least three times for size measurements; for some metabolic analyses, at least six times. For the wings, at least 20 individuals per genotype were typically analyzed. The authors used two-tailed t-tests; exact P-values, inclusion and exclusion criteria, and complete sample sizes for each experiment are not reported in the available material.

## 4. RESULTS

In simple terms, the artificial activation of AKT increased cell mass, but the result required the ability to produce lipids. In human epithelial cells, AKT increased the median cell volume by 20-30%. Rapamycin abolished this increase and markedly reduced the increase in protein content induced by AKT.AKT nearly doubled glucose uptake and lactate production, signs of a more active metabolism; rapamycin blocked both effects. AKT activation also increased the incorporation of glucose into newly synthesized lipids. This increase was also completely blocked by rapamycin. Inhibition of the ACLY enzyme, which is necessary to provide starting materials for fatty acid synthesis, attenuated the AKT-dependent increase in cell volume.The central point for the book's paragraph concerns SREBP. Within two hours of AKT activation, the mature form of SREBP1—the form capable of activating genes—increased in the nucleus. Subsequently, FASN RNA and protein, an enzyme essential for synthesizing fatty acids, increased. Rapamycin prevented the nuclear accumulation of SREBP1 and the increase in FASN and ACLY. Silencing mTOR or raptor, a specific component of mTORC1, blocked the induction of SREBP1, FASN, and ACLY; silencing rictor, which is associated with mTORC2, did not produce the same effect.By reducing both SREBP1 and SREBP2, AKT-induced lipid synthesis was blocked, and the increase in cell size decreased in a dose-dependent manner using small interfering RNAs. In Drosophila, the reduction of dSREBP decreased the size of cells and specific areas of the wing. Furthermore, the reduction of dSREBP attenuated the 15-20% increase in wing area caused by the expression of the fly's PI3K. These results indicate that SREBP is functionally necessary for a significant portion of the growth induced by the PI3K/AKT pathway in the models studied.

## 5. INTERPRETATION

Growing cells must produce not only proteins but also membranes. Lipids are, in fact, essential components of cell membranes; without their adequate production, the expansion of cell mass is limited. The study shows that, in the models used, AKT does not effectively

increase cell growth if the mTORC1-SREBP branch of lipogenesis is interrupted.The documented pathway is therefore: activated AKT  active mTORC1  greater nuclear presence of SREBP and greater expression of lipogenic genes  greater lipid synthesis  greater cell size. The result is consistent with the formulation of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, as it argues that lipogenesis can be a functional component of the anabolic program. However, the activation of AKT in these cells was experimental and is not equivalent to chronic exposure to insulin in a human organism.The work does not demonstrate that every increase in lipogenesis from insulin necessarily produces cell expansion in all tissues. It also does not demonstrate that this mechanism is, by itself, responsible for the inflammatory consequences attributed to hyperinsulinemia. Instead, it shows a causal mechanism in cells and fruit flies, with direct interventions on mTORC1 and SREBP.

## 6. INDEPENDENT CONFIRMING EVIDENCE

Particularly relevant confirmation concerns the link between insulin, PI3K/AKT, mTORC1, and SREBP-1c in the liver. In primary rat hepatocytes, insulin increased SREBP-1c messenger RNA by 25-fold and reduced that of PEPCK, a gene involved in hepatic glucose production, by 95%. PI3K and AKT inhibitors blocked both effects. Conversely, rapamycin blocked the insulin-induced increase in SREBP-1c without preventing the reduction of PEPCK. The same selective effect of rapamycin was observed in the livers of rats and mice after fasting and refeeding. This study directly confirms the insulin  PI3K/AKT  mTORC1  SREBP-1c/lipogenesis pathway, but it remains animal and cellular evidence [1].A second independent study examined murine cells lacking TSC1 or TSC2, genes that normally inhibit mTORC1. In these cells, mTORC1 was active even without growth factors and increased the expression of genes involved in lipid and sterol synthesis. Reducing SREBP1 and SREBP2 decreased de novo lipogenesis and blocked mTORC1-dependent proliferation. The result converges with the analyzed study: the program regulated by SREBP is not only associated with mTORC1 but also contributes to cell growth. The limitation is that these are cell lines and a genetic model of persistent mTORC1 activation, not normal insulin physiology [2].

## 7. CONFLICTING EVIDENCE

An important clarification comes from mice with selective deletion of TSC1 in the liver. In this model, mTORC1 is constitutively active, but the animals showed reduced activation of SREBP1c and lipogenesis, as well as protection against age- and diet-associated hepatic steatosis. The reason was a reduction in AKT signaling due to negative feedback. By restoring AKT, or by reducing INSIG2a, an inhibitor of SREBP1c, the response was recovered.This evidence does not contradict the fact that mTORC1 is necessary for the induction of SREBP1c by insulin. However, it shows that, in the liver, mTORC1 activation alone is not sufficient: a parallel AKT-dependent branch, which includes the reduction of INSIG2a, is also required. The biological chain is therefore context-dependent and cannot be simplified to "more mTORC1 always equals more lipogenesis" [3].

## 8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the Evidence Review from the independent publications selected to confirm or define the narrative progression of the book.

### Quadro comparativo

| Reference | Study type | Population or model | Main result | Direction of evidence | Strength of evidence |
|---|---|---|---|---|---|
| Original study | Cellular and animal | Human cells, Drosophila cells, and transgenic fruit flies | Blocking mTORC1 or SREBP reduces lipogenesis and limits AKT/PI3K-induced growth. | direct confirmation | moderate |
| [1] | Cellular and animal | Primary rat hepatocytes; rat and mouse liver | Insulin increases SREBP-1c via PI3K/AKT; rapamycin selectively blocks this induction. | direct confirmation | moderate |
| [2] | Cellular | Murine Tsc1-/- and Tsc2-/- cells; modified human lines | SREBP1/2 supports mTORC1-dependent lipogenesis and proliferation. | indirect confirmation | moderate |
| [3] | Animal and cellular | Mice with hepatic Tsc1 deletion and isolated hepatocytes | mTORC1 is necessary but not sufficient: a parallel AKT-dependent branch is also required. | discordant evidence | moderate |

## 9. SINTESI EDITORIALE E CONCLUSIONI

### CONCLUSIONS

The study analyzed directly supports, in cellular models and Drosophila, that lipid synthesis regulated by SREBP contributes to growth induced by the AKT-mTORC1 pathway. Independent evidence confirms that insulin can activate SREBP-1c through PI3K/AKT and mTORC1, and that SREBP contributes to lipogenesis and proliferation dependent on mTORC1.The most balanced conclusion is that lipogenesis is well-supported as a component of the cellular anabolic program in experimental models. However, it has not been demonstrated that the same chain, with identical intensity and consequences, operates in every human tissue during chronic hyperinsulinemia. Furthermore, the role of mTORC1 requires a contextual interpretation, because in the liver, the full response of SREBP1c also depends on parallel AKT signals.

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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