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Scylla and Charybdis: growth inhibition via the S6K-TSC pathway in Drosophila

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1. ABSTRACT

The analyzed study examined two genes, named *scylla* and *charybdis*, in the fruit fly *Drosophila melanogaster*. The authors observed that these genes are induced under conditions of hypoxia—that is, reduced oxygen availability—and that their increased activity reduces growth. The signal associated with protein synthesis mediated by S6K decreases, while the activity of PKB/AKT remains unchanged in the available material.In section 4.6 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that insulin signaling passes through AKT, the TSC1/TSC2 complex, and mTORC1. Independent studies in mammalian cells confirm that AKT can phosphorylate and reduce the activity of TSC2, promoting downstream signals of mTORC1. However, genetic studies in the fruit fly indicate that this phosphorylation is not essential for normal growth. The confirmation is therefore primarily mechanistic and dependent on the experimental model.

ONLINE ARTICLE

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MISSION

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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 was how a developing organism can coordinate growth with oxygen availability. The hypothesis evaluated was that *scylla* and *charybdis*, two homologous genes in the fruit fly, act as growth brakes when oxygen is scarce.The relevance to section 4.6 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns the segment of the network connecting AKT, TSC, and the growth signal measured via S6K. S6K is a protein that promotes the production of cellular components and represents an indicator of mTORC1 pathway activity. The study places Scylla and Charybdis after PKB/AKT and before the TSC complex, which is a position compatible with controlling the brake exerted by TSC on growth.The publication does not directly demonstrate that insulin activates mTORC1 in humans, nor does it prove on its own that AKT inhibits TSC1/TSC2 in every tissue. Instead, it documents, in *Drosophila*, a segment of growth regulation: hypoxia induces two regulators that reduce the S6K signal without reducing PKB/AKT activity.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract is available; therefore, information not included in the abstract cannot be reconstructed. The authors initially identified *scylla* and *charybdis* through an EP overexpression screen, a genetic strategy that allows for increasing the activity of selected genes and observing the consequences on growth.The study compared flies with a simultaneous loss of both genes and flies in which the activity of one of the two genes was increased. Hypoxia conditions, gene expression, and the activity of proteins in the growth pathway, particularly S6K and PKB/AKT, were also evaluated. Genetic and biochemical analysis allowed for the placement of Scylla and Charybdis between PKB/AKT and TSC.The size of the groups, oxygen concentrations, duration of exposures, animal selection criteria, details of biochemical experiments, statistical procedures, and significance values are not reported in the available material.

4. RESULTS

In simple terms, when both genes were missing, the fruit flies tolerated oxygen reduction more poorly and showed a slight excess of growth. In the opposite direction, increasing the activity of *scylla* or *charybdis* reduced growth. These data indicate that the two genes normally act as growth limiters.The result most relevant to the book's paragraph concerns intracellular signaling. Growth inhibition was associated with a reduction in the activity of S6K, a protein located downstream of the mTOR network and involved in protein synthesis. The activity of PKB/AKT, however, was not reduced. The authors therefore placed Scylla and Charybdis downstream of PKB/AKT and upstream of TSC.This position means that, in the experimental model, Scylla and Charybdis can decrease a growth signal without turning off PKB/AKT. The abstract does not report absolute values, percentage changes, sample sizes, confidence intervals, or P-values. Furthermore, the abstract does not report a direct measurement of mTORC1 activity.

5. INTERPRETATION

The biological significance is that the cell can reduce growth programs when oxygen is limited. In a useful simplification, AKT transmits growth-promoting signals; the TSC1/TSC2 complex can act as a brake; mTORC1 then coordinates processes such as protein synthesis, including through S6K. The analyzed study suggests that Scylla and Charybdis intervene in the area of the network between AKT and TSC, helping to reduce the signal to S6K.The segment of the chain that is most directly documented is therefore: hypoxia induction of *scylla*/*charybdis* reduction of S6K activity reduced growth. The genetic placement downstream of PKB/AKT and upstream of TSC makes the study consistent with the book's narrative, but it does not equate to direct proof that AKT inactivates TSC1/TSC2 through insulin.Independent studies on mammalian cells have provided a more direct basis for this part of the network: AKT phosphorylates TSC2 and reduces its inhibitory function on mTOR signaling; mutations of TSC2 phosphorylation sites can limit S6K1 activation induced by the PI3K-AKT pathway [1,2]. However, this step remains sensitive to the cell type, species, and experimental conditions.

6. INDEPENDENT SUPPORTING EVIDENCE

The first independent confirmation concerns precisely the sentence in the book stating that AKT inhibits the brake represented by TSC1/TSC2. Inoki and colleagues studied mammalian cells and observed that TSC2 is directly phosphorylated by AKT. Phosphorylation reduced the stability of TSC2 and compromised its interaction with TSC1, leading to an increase in mTOR signaling. In simple terms, a growth signal can weaken the TSC brake and make it easier to activate the anabolic pathway. This is direct confirmation of the AKT functional inhibition of TSC2 increased mTOR signaling segment, but it comes from cellular experiments and not from a clinical intervention in humans [1].A second independent study identified TSC2 as a target of the PI3K-AKT pathway. The authors showed that AKT can phosphorylate TSC2 both in vitro and in cells, and that a form of TSC2 lacking the main sites regulated by the PI3K pathway prevented the activation of S6K1. This finding completes the link between AKT, TSC2, and S6K: when TSC2 cannot properly receive the regulatory signal, the signal to S6K decreases [2]. This is also mechanistic evidence, obtained in cellular systems and not proof that the entire sequence determines metabolic or clinical outcomes in the general population.Taken together, these independent studies support the direction of the chain described in the paragraph: the insulin signal can pass through PI3K and AKT, reduce the brake exerted by TSC2, and promote the downstream activity of mTORC1 and S6K. The original study adds to this network the theme of adaptation to hypoxia in the fruit fly, showing that a signal induced by low oxygen can reduce S6K without decreasing PKB/AKT.

7. CONFLICTING EVIDENCE

Directly relevant evidence suggests caution when applying the linear AKT TSC2 TORC1 model to every biological condition. In *Drosophila*, Dong and Pan genetically modified the Tsc2 sites normally phosphorylated by AKT. Both non-phosphorylatable variants and those mimicking phosphorylation still corrected the lethality and growth defects of animals lacking Tsc2. The authors therefore concluded that Tsc2 was not a critical target of AKT during normal fruit fly development [3].This result does not deny that AKT can phosphorylate TSC2, nor does it contradict cellular experiments in mammals. However, it indicates that the functional necessity of that step can change depending on the species, tissue, developmental stage, and the presence of parallel regulatory pathways. In the context of the book's section, the chain is biologically well-founded as a signaling mechanism, but it should not be interpreted as the sole, obligatory pathway for growth in all organisms.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent studies used to confirm or define the AKT–TSC–mTOR/S6K pathway.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Genetic and biochemical	Drosophila melanogaster	Hypoxia-induced Scylla and Charybdis reduce S6K and growth; they are located between PKB/AKT and TSC.	biologically consistent evidence	moderate
[1]	Cellular and molecular	Mammalian cells	AKT phosphorylates and reduces TSC2 activity, promoting mTOR signaling.	direct confirmation	moderate
[2]	Cellular and molecular	Mammalian cell lines	TSC2 is a target of PI3K-AKT; mutations in TSC2 regulatory sites reduce S6K1 activation.	direct confirmation	moderate
[3]	Animal genetic	Drosophila melanogaster	Phosphorylation of Tsc2 by AKT was not found to be critical for normal development and growth.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study pertinently supports the narrative segment regarding growth control in the region between AKT, TSC, and S6K. In fruit flies, hypoxia induces Scylla and Charybdis, which reduce S6K signaling and limit growth without reducing PKB/AKT.Independent research confirms at a mechanistic level that AKT can reduce TSC2 function and promote mTOR/S6K signaling. However, this step does not appear to be essential in every context of fruit fly development. The book's formulation is therefore well-supported as a general biological scheme, but requires caution when extended to all tissues, organisms, or clinical outcomes.

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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