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Akt signaling through GSK-3b, mTOR, and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy - A review of the evidence

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1. ABSTRACT

The analyzed study examined quadriceps muscle biopsies taken before and after eight weeks of resistance training, followed by eight weeks of detraining. The objective was to verify whether changes in muscle mass in humans were accompanied by variations in the intracellular signals AKT, GSK-3b, mTOR, and Foxo1. After training, quadriceps mass increased by approximately 10%; in parallel, the phosphorylated forms of AKT, GSK-3b, and mTOR increased. After detraining, muscle mass decreased by 5% compared to the value reached after training, and phosphorylated AKT and GSK-3b decreased.In section 4.12 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that AKT participates in coordinating signals associated with muscle growth and maintenance. Independent studies in humans confirm that resistance training is accompanied by the activation of components of the AKT-mTOR pathway and an increase in the synthesis of contractile proteins; animal models also indicate that AKT activation can cause hypertrophy. However, acute results obtained under Fasting conditions show that AKT phosphorylation can decrease immediately after a single intense exercise session. The confirmation is therefore biologically solid, but it does not prove that a single signal alone determines muscle mass in humans.

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2. ANALYZED STUDY

The research question was whether the growth or reduction of human skeletal muscle mass was associated with coordinated changes in the intracellular signals that regulate protein synthesis and degradation. In simple terms, the authors sought to understand whether muscle adapting to training also shows changes in the molecular signals that promote the building of its structural components.The hypothesis concerned AKT, a protein that transmits growth signals; GSK-3b, a kinase that can inhibit certain processes related to protein synthesis; mTOR, a central regulator of protein production; and Foxo1, a factor that, within the nucleus, can promote the expression of genes associated with muscle loss. Phosphorylation is the addition of a small chemical group to a protein: it often modifies its activity, but its significance depends on the protein and the precise site where it occurs.The relevance to the book's section is limited: the study documents that, during training and detraining, variations in muscle mass are accompanied by concordant variations in the phosphorylation of AKT, GSK-3b, and mTOR. However, it does not demonstrate that AKT acts as a single causal "switch" for anabolism or catabolism, nor does it establish that every change in phosphorylation directly produces a variation in muscle mass.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study analyzed human quadriceps biopsies obtained after eight weeks of resistance training, designed to stimulate hypertrophy, and after a subsequent eight-week period of detraining, designed to promote atrophy. The number of participants, age, sex, inclusion and exclusion criteria, precise characteristics of the training program, and exact timing of the biopsies are not reported in the available material.The authors measured the amount of phosphorylated AKT and several downstream targets: GSK-3b, mTOR, p70S6K, and 4E-BP1, which are proteins involved in the regulation of protein synthesis. They also evaluated Foxo1, Foxo3, atrogin-1, and MuRF1, markers linked to cellular programs that promote muscle protein degradation. The laboratory techniques, details of experimental controls, statistical procedures, and predefined endpoints are not reported in the available material.

4. RESULTS

After eight weeks of resistance training, quadriceps size increased by approximately 10%. This data indicates a measurable increase in muscle mass in the examined area. During the same period, the amounts of phosphorylated AKT, GSK-3b, and mTOR increased. The amount of Foxo1 in the nucleus—the cellular site where this protein can help regulate gene expression—also decreased.After eight weeks of detraining, muscle mass decreased by 5% compared to the level reached at the end of the training period. In parallel, phosphorylated AKT and GSK-3b decreased, and Foxo1 increased. According to the abstract, mTOR phosphorylation was increased after training; its trend during detraining is not reported in the available material.Atrogin-1 and MuRF1, two proteins frequently considered indicators of cellular programs associated with protein degradation, increased after the hypertrophy phase and decreased after the atrophy phase. This trend does not simply coincide with the idea that these markers alone represent muscle loss. Therefore, the result should be read as an observed biological variation, not as proof that atrogin-1 and MuRF1 caused the growth or subsequent reduction in mass.The result most directly relevant to the book's paragraph is the concordant direction between training, increased muscle mass, and increased phosphorylation of AKT, GSK-3b, and mTOR; conversely, during detraining, phosphorylated AKT and GSK-3b decrease along with muscle mass. The abstract does not report P-values, confidence intervals, sample size, or the quantitative magnitude of the protein changes.

5. INTERPRETATION

The primary biological significance is that human muscle does not change only in size: when repeatedly subjected to resistance exercise, cellular signals compatible with an increased capacity to synthesize and organize muscle proteins also change. AKT, GSK-3b, and mTOR move in the same direction as the increase in mass observed in the study.In more technical terms, the work associates hypertrophy with increased phosphorylation of AKT, GSK-3b, and mTOR, and associates detraining with a decrease in the phosphorylation of AKT and GSK-3b. Since AKT

can phosphorylate GSK-3b at sites that reduce its activity and can contribute to the regulation of mTOR, the sequence is biologically consistent with a reduction in the brakes on protein synthesis and with the activation of anabolic mechanisms.The essential limitation is temporal and causal. The measurements were obtained in a training and detraining design, not through an intervention that selectively blocks AKT, GSK-3b, or mTOR in humans. Consequently, the work shows a coordinated association between muscle adaptation and molecular signals; it does not prove that AKT, GSK-3b, or mTOR are alone necessary or sufficient to produce hypertrophy in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

Human confirmation particularly close to the narrative in this section comes from a study involving ten sedentary young men, in which each participant trained one leg with resistance exercises and the other with endurance exercise for ten weeks. Resistance training increased the resting phosphorylation of AKT, GSK-3b, and other components of the system that regulates the initiation of protein synthesis. After a resistance exercise session, myofibrillar protein synthesis—that is, the muscle's contractile proteins—increased by 36% in the trained muscle. This research confirms the resistance training AKT-mTOR signaling anabolic response pathway in humans, although it does not prove that this signal is the sole cause of growth [1].A second human study evaluated whether the response of p70S6K, a protein that operates downstream of mTOR, was linked to the increase in mass following a resistance training program. The increase in p70S6K phosphorylation after a single session was found to be correlated with the subsequent increase in muscle mass. The direction of the association is consistent with the chain described in the book: a greater response from a downstream effector of mTOR is accompanied by a greater increase in mass. However, this is a correlation and does not establish causality; furthermore, p70S6K does not represent the entire AKT-GSK-3b-mTOR pathway [2].An animal model provides causal support for the initial step of the chain. In genetically modified adult mice, the inducible activation of a constitutively active form of Akt in skeletal muscle caused rapid muscle hypertrophy and the activation of the Akt-p70S6K pathway. This experiment shows that an increase in the AKT signal can be sufficient to promote muscle growth in vivo in mice. Its strength lies in the causal design; its limitation is that an artificial genetic modification in an animal is not equivalent to the physiological adaptation to training in humans [3].Overall, independent evidence supports a convergent network: resistance training in humans is associated with greater anabolic signaling activity, the activation of components downstream of mTOR is associated with increases in mass, and the direct activation of Akt can induce hypertrophy in a mouse model. None of these studies, either individually or collectively, proves that GSK-3b is the only indispensable mediator of human muscle growth.

7. CONFLICTING EVIDENCE

An apparently conflicting result comes from an acute study on nine healthy young men who performed ten sets of ten leg extensions at 80% of their one-repetition maximum, in a fasting state. Within 30 seconds of finishing the exercise, AKT phosphorylation decreased by 60% to 90%, depending on the site measured, and remained reduced at the Thr308 site even after 24 hours. At the same time, p70S6K phosphorylation increased more than twenty-fold [4].This finding does not invalidate the result of the analyzed study, because it compares a single intense session with the adaptations to eight weeks of training. However, it shows that the AKT response depends on the context: nutritional status, intensity, timing of the sample, training level, and the protein measured can change the observed direction. In particular, it suggests that p70S6K activation after exercise does not necessarily require a simultaneous increase in AKT phosphorylation measured at that precise moment.Conflicting evidence therefore reduces the strength of a linear interpretation of the AKT mTOR growth chain. The mTOR pathway can also receive signals from mechanical stimuli and other intracellular pathways. No directly conflicting evidence sufficiently relevant to the chronic association between resistance training, increased basal phosphorylation of AKT-GSK-3b-mTOR, and muscle adaptation has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to confirm or define the scope of the paragraph's content.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Human intervention with training and detraining	Human quadriceps biopsies; sample size not reported in available material	After eight weeks of training, quadriceps mass increased by approximately +10% with greater phosphorylation of AKT, GSK-3b, and mTOR; after detraining, mass decreased by −5% compared to post-training, with lower phosphorylation of AKT and GSK-3b.	direct confirmation	moderate
[1]	Intra-subject controlled human intervention	10 healthy young men; one leg trained with resistance and the other with endurance for 10 weeks	Resistance training increased resting phosphorylation of AKT and GSK-3b; a single resistance session increased myofibrillar synthesis in the trained muscle.	direct confirmation	moderate
[2]	Prospective human intervention	Human subjects undergoing short-term resistance training	Increased p70S6K phosphorylation after a session was correlated with a greater subsequent increase in muscle mass.	indirect confirmation	moderate
[3]	Genetically modified animal	Adult mice with inducible Akt activation in skeletal muscle	Akt activation induced rapid muscle hypertrophy and activation of the Akt-p70S6K pathway.	biologically consistent evidence	moderate

[4]	Acute human intervention	9 healthy young men, intense resistance exercise while fasting	Immediately after exercise, phosphorylated AKT decreased, while phosphorylated p70S6K increased more than twenty-fold.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports that, in human muscle, eight weeks of resistance training are associated with both an increase in quadriceps mass and greater phosphorylation of AKT, GSK-3b, and mTOR. Subsequent detraining is associated with a partial loss of the acquired mass and a reduction in the phosphorylation of AKT and GSK-3b.This observation is consistent with the section of the book that presents AKT as a regulator of signals related to muscle growth and maintenance. Independent evidence moderately confirms this narrative: in humans, it links training to AKT-mTOR signaling and protein synthesis, while in mice, it shows that Akt can induce hypertrophy. However, the relationship is not linear under every experimental condition and requires further causal studies in humans.

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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