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Dynamic modeling and analysis of the crosstalk between insulin/AKT and MAPK/ERK signaling pathways - Evidence review

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1. ABSTRACT

The analyzed study constructed a mathematical model of the interactions between two main branches of insulin signaling: the PI3K-AKT pathway, primarily linked to metabolic effects, and the MAPK-ERK pathway, which is also involved in the regulation of gene expression and cell growth. The goal was to identify feedback circuits capable of influencing the duration, intensity, and dynamic behavior of the signal. Since only the abstract is available, the cell model, quantitative parameters, specific simulations, and the scale of any validation experiments are not reported in the available material.In section 5.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that insulin coordinately activates the AKT branch and the MAPK-ERK branch. Independent studies confirm that insulin can activate ERK and that ERK can participate in feedback on insulin receptor substrates. However, these effects depend on the cell type and experimental conditions. The confirmation is therefore indirect and primarily mechanistic.

ONLINE ARTICLE

ARTICLE INFORMATION

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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.

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2. ANALYZED STUDY

The research question was how insulin-activated signaling pathways influence each other over time. The hypothesis was that feedback loops—mechanisms in which a cellular response modifies the signal that generated it—contribute to determining both physiological behavior and disease-associated alterations.This work is relevant to section 5.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it analyzes the crosstalk between the insulin-AKT pathway and the MAPK-ERK pathway. The supported argument is therefore the general idea that the two branches are not isolated, but coordinated by regulatory and temporally overlapping interactions.The analyzed study can describe, through simulations, which interactions and parameters are compatible with different signaling profiles. However, based solely on the available abstract, it cannot directly demonstrate that the phosphorylation of IRS substrates is the initial step of the MAPK-ERK cascade in a specific human tissue, nor can it establish clinical consequences.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication describes the development of a dynamic mathematical model of the interactions between the insulin-AKT and MAPK-ERK pathways. A dynamic model uses equations to represent how multiple biological components change over time, allowing for the simulation of the effects of connections, feedback loops, and parameter variations.The abstract reports that both the steady-state behavior—that is, after reaching equilibrium—and the dynamic behavior of the two pathways were studied. Simulation cases were also created to identify interaction parameters and feedback circuits associated with normal or pathological phenotypes.The following information is not provided in the available material: the complete model architecture, the number of variables, the equations used, parameter values, experimental data sources, cell or animal models, sample sizes, selection criteria, laboratory techniques, statistical tests, quantitative endpoints, and numerical simulation results.

4. RESULTS

The central finding reported in the abstract is the identification of feedback loops considered key to the crosstalk between the insulin-AKT pathway and the MAPK-ERK pathway. In simple terms, the model indicates that the two branches of insulin signaling can mutually modify one another and that this regulation helps define the intensity and duration of the cellular response.The authors also report that the simulations identified interaction parameters capable of distinguishing behaviors compatible with normal phenotypes from those of disease phenotypes. However, the abstract does not specify what these parameters are, in which direction they vary, which feedback loops proved dominant, or what numerical values supported the conclusions.For the book excerpt, the most relevant data is therefore qualitative: AKT and MAPK-ERK are treated as connected networks subject to mutual regulation. The available material does not report a direct experimental measurement of the insulin receptor IRS MAPK-ERK sequence, nor a demonstration in humans.

5. INTERPRETATION

The biological significance of the model is that a cell does not interpret insulin through a single switch. The signal is distributed across multiple branches and is regulated by internal brakes and adjustments. The PI3K-AKT pathway is often associated with the management of glucose and nutrients; the MAPK-ERK pathway, on the other hand, also contributes to growth, adaptation, and gene transcription responses.In section 5.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication primarily supports the segment regarding the coordinated and temporally overlapping activation of the AKT and MAPK-ERK branches. The model makes it biologically plausible that feedback between these branches regulates the insulin signal.However, this is an interpretation at the network level. Independent experimental data are needed to establish which steps actually occur in each tissue, with what intensity, and in what context. In particular, the abstract alone does not directly prove that IRS is always the initial causal link to ERK, nor that prolonged activation of ERK alone produces insulin resistance in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

Experimental confirmation of the feedback principle comes from a study on rat liver cells, HEK293 cells, and murine liver tissue. Following insulin stimulation, the phosphorylation of serine 907 of IRS-2, an adapter protein that transfers the signal from the receptor to other pathways, was found to be dependent on ERK1/2. Pharmacological inhibition and silencing of ERK1/2 reduced this phosphorylation. This finding confirms that the ERK branch can feed back to modulate IRS-2—a component located close to the insulin receptor—but it does not prove that this single site determines the entire insulin response [1].In primary rat adipocytes, insulin increased the phosphorylation of IRS-1 at serines 312 and 616 over time. Inhibition of PI3K and ERK1/2 reduced both modifications. This experiment supports the existence of a functional link between the insulin signal, ERK, and IRS-1. However, blocking ERK1/2 did not increase the tyrosine phosphorylation of IRS-1, whereas PI3K inhibition did. The authors therefore concluded that those two sites alone do not explain the negative feedback of PI3K on IRS-1 [2].A further study combined modeling and experiments in 3T3-L1 adipocytes to analyze rapid feedback in the AKT branch. Insulin-activated AKT phosphorylated IRS-1 and IRS-2, reducing their presence in the cell membrane and thus limiting the recruitment of PI3K. This result does not directly involve ERK, but it independently confirms the central idea of the analyzed study: insulin signaling branches include feedback loops that regulate the availability of IRS and prevent an excessive or overly prolonged response [3].Taken together, this research supports a cautious mechanistic chain: insulin activates multiple signaling branches; ERK and AKT can modify IRS through feedback circuits; and these circuits contribute to regulating the amplitude and duration of the signal. The available evidence is primarily cellular or animal-based and does not equate to the demonstration of the same mechanism in all human tissues.

7. CONFLICTING EVIDENCE

An analysis of human adipocytes shows how important context is. In cells obtained immediately after surgery or from fresh adipose tissue fragments, ERK1/2 was already strongly phosphorylated, and the addition of insulin did not further increase its phosphorylation. However, after an overnight recovery in culture, insulin increased ERK1/2 phosphorylation by approximately 2.3-fold. The authors interpreted the initial activation of ERK as a response to surgical stress, rather than an effect of insulin [4].This result does not deny that insulin can activate MAPK-ERK, but it indicates that the observed response depends on the initial state of the cell, the tissue, and the experimental preparation conditions. It therefore reduces the possibility of automatically extending data obtained in cell lines or animal models to human tissue under every physiological or pathological condition.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to verify the narrative passage of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Dynamic mathematical model	Insulin-AKT and MAPK-ERK networks; biological experimental model not reported in available material	Identifies feedback and parameters that can regulate the crosstalk between the two pathways	biologically consistent evidence	preliminary
[1]	Cellular and animal	Rat Fao liver cells, HEK293 cells, mouse liver	Insulin induces ERK1/2-dependent phosphorylation of IRS-2 at the Ser907 site	direct confirmation	moderate
[2]	Cellular and animal	Primary rat adipocytes	Insulin increases PI3K- and ERK1/2-dependent phosphorylations of IRS-1	direct confirmation	moderate
[3]	Cellular and modeling	3T3-L1 adipocytes and dynamic model of insulin signaling	AKT phosphorylates IRS-1/2 and limits a feedback that regulates signal intensity	indirect confirmation	moderate
[4]	Observational with ex vivo experiments	Adipocytes and adipose tissue from people with or without type 2 diabetes	The effect of insulin on ERK1/2 varies according to surgical stress and cellular recovery	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study consistently, albeit through modeling, supports the idea that the AKT and MAPK-ERK pathways can interact via feedback loops capable of modulating insulin signaling. Independent evidence confirms that ERK and AKT can act on IRS substrates, contributing to the regulation of the cellular response.The narrative of the paragraph is therefore mechanistically supported and indirectly confirmed. It remains necessary to distinguish results obtained in cells and animals from those demonstrated in human tissues. The MAPK-ERK response to insulin is not uniform but depends on the cell type, metabolic state, and experimental conditions.

Aggiornato al 25/11/2026. 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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