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MAPK/ERK signaling regulates insulin sensitivity to control glucose metabolism in Drosophila - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether the MAPK-ERK pathway can influence cell sensitivity to insulin in the *Drosophila* fruit fly. The authors identified components of this cascade as regulators of the insulin response: persistent inhibition of MAPK-ERK reduced insulin receptor gene expression and was associated with insulin resistance. The proposed mechanism involves Pointed, a transcription factor functionally corresponding to the ETS-1 family.The research contributes to the section "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which states that proper MAPK-ERK activity participates in the regulation of insulin sensitivity. Independent evidence shows that a reduction in insulin receptor availability can decrease signaling to AKT and that, in contexts of cellular stress or experimental obesity, persistent ERK activation may instead promote insulin resistance. The overall picture therefore indicates regulation dependent on intensity, duration, tissue, and the model studied. Direct demonstration in humans of the mechanism observed in the fruit fly is not available.

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 whether there were genetic regulators capable of modifying, in a living organism, how a cell responds to insulin. The hypothesis evaluated was that the MAPK-ERK cascade, a sequence of proteins that transmits signals from the outside to the cell nucleus, contributes to determining insulin sensitivity in addition to the AKT pathway, which is involved in the classic metabolic effects of insulin.The relevance to section 5.4 is precise: the publication is not intended to demonstrate every consequence attributed in the book to MAPK-ERK signaling, nor does it demonstrate a clinical effect in humans. Instead, it documents a specific segment of the narrative: MAPK-ERK activity can modulate cellular sensitivity to insulin through control of insulin receptor expression. In simple terms, the MAPK-ERK signal can contribute to establishing how well-equipped a cell is to receive the insulin signal.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

According to the available abstract, the authors performed an *in vivo* genetic screen in *Drosophila*, which is a systematic search for genes and signaling pathways capable of modifying the cellular response to insulin in the living animal. The MAPK-ERK cascade emerged as a modifier of insulin responsiveness.The available material reports that the authors examined the effect of persistent MAPK-ERK inhibition on the expression of the insulin receptor gene similar to that of mammals and attributed the transcriptional control to Pointed, a transcription factor of the ETS family. The number of animals, selection criteria, details of genetic manipulations, specific analytical techniques, statistical analyses, significance values, and quantitative endpoints are not reported in the available material.

4. RESULTS

The main finding is that components of the MAPK-ERK pathway modified the cellular response to insulin in the *Drosophila* model. When inhibition of the MAPK-ERK pathway was persistent, the authors observed a reduction in insulin receptor gene expression and insulin resistance. Insulin resistance refers to a reduced cellular response to an insulin signal that, under normal conditions, promotes the use and management of glucose.The abstract attributes this effect to Pointed. The proposed biological significance is that MAPK-ERK does not act solely as a parallel pathway activated by growth signals, but contributes to the transcriptional regulation of the insulin receptor and, therefore, to the cell's ability to respond to the hormone. The authors also report that this mechanism helps maintain appropriate levels of circulating glucose in the animal model. Absolute values, percentages, effect sizes, P-values, and confidence intervals are not reported in the available material.

5. INTERPRETATION

The biological message is that insulin sensitivity does not depend solely on what happens after the hormone binds to its receptor. It also depends on the amount of receptor available and its regulation over time. In the studied model, a prolonged reduction in MAPK-ERK activity decreased insulin receptor expression and reduced the response to insulin.This is the segment of the chain supported by the publication that is the subject of the Evidence Review: MAPK-ERK Pointed-mediated transcriptional regulation insulin receptor expression insulin sensitivity. It does not demonstrate that every increase in MAPK-ERK is favorable. On the contrary, studies in other systems indicate that chronic activation or activation linked to metabolic stress can contribute to insulin resistance. The data must therefore be interpreted as evidence of a contextual regulatory function, not as an indication that MAPK-ERK should simply be increased or reduced.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Independent confirmation of the link between receptor availability and insulin response comes from cellular experiments conducted on murine muscle cells, human liver cells, and other cell lines. Brown and colleagues showed that endoplasmic reticulum stress, a cellular compartment that contributes to protein maturation, reduced the presence of the mature insulin receptor on the membrane. The experimental reduction of the insulin receptor by approximately 50% was accompanied by a similar decrease in insulin-induced AKT phosphorylation, a

signal that documents a reduced cellular response to the hormone [1]. This study does not verify the MAPK-ERK control of receptor transcription, but it confirms the essential downstream step of the narrative: less available insulin receptor can reduce insulin signaling.A second study examined L6 muscle cells subjected to endoplasmic reticulum stress and a mouse model of type 2 diabetes. Under these conditions, ERK was more phosphorylated, meaning it was activated. Pharmacological inhibition of ERK with U0126 or the experimental reduction of ERK improved AMPK and AKT signaling, also increasing the recovery of glucose uptake in muscle cells [2]. The publication therefore supports the part of the paragraph regarding the fact that a persistent alteration of the MAPK-ERK pathway can be associated with insulin resistance. However, it represents a context of cellular stress and does not demonstrate that the same transcriptional mechanism observed in *Drosophila* operates in human tissues.

7. CONFLICTING EVIDENCE

An important piece of context comes from a study on obese mice with a genetic deficiency of ERK1. Compared to obese mice with ERK1 present, animals lacking ERK1 did not develop hyperglycemia, showed better glucose tolerance, and had greater overall insulin sensitivity as measured by hyperinsulinemic-euglycemic clamp, despite having comparable weight and adiposity [3]. In this model, therefore, reduced ERK1 activity was associated with an improvement, rather than a worsening, of insulin sensitivity.This result does not eliminate the correspondence between the original study and the book's paragraph, but it prevents a linear interpretation of the MAPK-ERK pathway. In the fruit fly, persistent inhibition of MAPK-ERK reduced insulin receptor expression; in the mouse model of obesity, the loss of ERK1 attenuated insulin resistance in association with reduced adipose tissue inflammation and increased muscle glucose utilization. Differences in species, ERK isoform, tissue, duration of the alteration, and metabolic condition are significant limitations to generalizability.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to confirm or define the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	In vivo genetic screening	Drosophila	Persistent inhibition of MAPK-ERK reduced insulin receptor expression and insulin response.	biologically consistent evidence	preliminary
[1]	Experimental cellular	Murine muscle cells, human liver cells, and other cell lines	A reduction of approximately 50% in the insulin receptor similarly decreased insulin-induced AKT phosphorylation.	indirect confirmation	moderate
[2]	Cellular and animal	L6 myotubes and mice with experimental diabetes	Cellular stress increased ERK activation; inhibiting it improved insulin signaling and glucose uptake.	indirect confirmation	moderate
[3]	Genetic animal	ob/ob mice with or without ERK1 deficiency	ERK1 deficiency increased insulin sensitivity and improved glucose tolerance in obese mice.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication clearly supports the idea that, in *Drosophila*, MAPK-ERK contributes to maintaining insulin sensitivity by regulating insulin receptor expression. This step is consistent with the book section and with independent evidence linking receptor quantity to the strength of insulin signaling. However, the literature shows that the effect of ERK is not unidirectional: chronic activation can promote insulin resistance in some models, while the reduction of ERK1 can improve metabolism in others. The narrative is therefore supported at a mechanistic level and requires direct validation in human tissues.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Endoplasmic reticulum stress causes insulin resistance by inhibiting delivery of newly synthesized insulin receptors to the cell surface**
Brown et al., 2020
Molecular Biology of the Cell
DOI: https://doi.org/10.1091/mbc.E18-01-0013

[2] **Inhibitory cross talk between the AMPK and ERK pathways mediates endoplasmic reticulum stress induced insulin resistance in skeletal muscle**
Hwang et al., 2013
British Journal of Pharmacology
DOI: https://doi.org/10.1111/bph.12124

[3] **Deficiency in the extracellular signal-regulated kinase 1 (ERK1) protects leptin-deficient mice from insulin resistance without affecting obesity**
Jager et al., 2011
Diabetologia
DOI: https://doi.org/10.1007/s00125-010-1944-0