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MAPK signaling in cellular metabolism: stress or well-being? - A review of the evidence

Dott. A. Conte[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The publication analyzed is a scientific review describing MAPK pathways (proteins that transmit signals to the cell from the environment, hormones, and stress) as necessary tools for metabolic adaptation, but potentially involved in metabolic diseases when their activation is inappropriate or persistent. Since the available material contains only the abstract, the full details of the study selection, experimental models, and analyses performed by the authors are not included in the available material.In the chapter dedicated to the dialogue between metabolism and inflammation, "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi uses this publication for the passage stating that chronic insulin stimulation can cause the MAPK-ERK pathway to take on a role associated with metabolic stress and inflammation. Independent studies show that hyperinsulinemia can increase inflammatory genes in adipose tissue through ERK and that the alteration of ERK1 in obese mice is accompanied by changes in inflammation and insulin sensitivity. However, different results obtained in other genetic models indicate that the effects depend on the ERK isoform, the tissue, and the experimental context. The conclusion is therefore primarily mechanistic, not a definitive causal demonstration in humans.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 question addressed by the publication is how MAPKs, or mitogen-activated protein kinases, contribute to linking changes in cellular metabolism to the body's adaptive or pathological responses. The general hypothesis is that these signaling pathways are beneficial when activated in a controlled and temporary manner, but can contribute to metabolic alterations when the signal is inadequate in terms of intensity, duration, or context.The reason for its relevance to paragraph 5.4 is specific. “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi describes the MAPK-ERK pathway as a branch of the insulin response that, if repeatedly stimulated under conditions of hyperinsulinemia, can promote cellular programs of metabolic stress and inflammation. The analyzed publication contributes to this narrative at a conceptual and mechanistic level: it states that inappropriate MAPK signaling participates in pathological features of metabolism, including those associated with metabolic syndrome.As it is neither a clinical trial nor a single controlled experiment, the publication cannot establish that hyperinsulinemia causes inflammation in humans through ERK in every tissue. Furthermore, from the available abstract, it is not possible to determine which primary studies were included, nor to quantify the effect of specific insulin exposures on ERK or inflammatory markers.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is presented as a Review, meaning a summary article that discusses previously published studies rather than directly enrolling participants or conducting a single original experiment. The stated objective in the abstract is to provide an overview of the MAPK mechanisms that regulate cellular metabolism and their relationship with disease.Only the abstract is available. Therefore, the available material does not report the bibliographic research protocol, the databases consulted, the keywords, the inclusion and exclusion criteria for the studies, the number of publications considered, the characteristics of the participants or experimental models, the laboratory techniques examined, the quantitative endpoints, the statistical analyses, or any assessment of the risk of bias.This lack of detail does not necessarily mean that such information was absent from the full article, but it prevents us from verifying, based on the provided material, whether the review was systematic, narrative, or structured according to a predefined protocol.

4. RESULTS

The main result reported in the abstract is that MAPK signaling is activated in response to many changes in the external or internal environment that influence the metabolism of the cell, organ, or the entire organism. In simple terms, this network helps cells adapt their activities when nutrients, hormones, stress, or energy demands change.The authors indicate that MAPK-dependent signal transduction is necessary for physiological metabolic adaptation. At the same time, they report that inappropriate MAPK signaling contributes to the development of multiple interdependent pathological features collectively defined as metabolic syndrome, a condition also associated with type 2 diabetes.For the book passage, the relevant element is the general direction of the result: regulated activation of MAPK is described as adaptive, while inappropriate activation is linked to the development of pathological metabolic alterations. The abstract does not report numerical values, sample sizes, insulin concentrations, ERK phosphorylation levels, inflammation markers, P-values, or risk estimates. These data are therefore not reported in the available material.

5. INTERPRETATION

The biological significance is that the MAPK-ERK pathway is not automatically harmful. ERK, an acronym for extracellular signal-regulated kinase, is a protein that receives and transmits signals; its brief activation can help the cell adapt to a hormone or a change in nutrients. The problem can emerge when the stimulus repeats or persists and the signal is placed in a context of energy excess, obesity, elevated circulating lipids, or pre-existing inflammation.In the book's paragraph, the segment supported by the publication subject to the Evidence Review is: persistent or inappropriate metabolic stimulation non-physiologically regulated MAPK-ERK signaling cellular programs associated with metabolic stress and disease. This segment is consistent with the abstract,

but it does not by itself demonstrate the entire insulin chain described in the chapter, nor does it prove that ERK is the sole mediator of inflammation induced by hyperinsulinemia.The distinction is important. The analyzed publication proposes a general biological framework; independent studies must separately verify whether high and persistent levels of insulin increase inflammatory signals, whether ERK participates in such an increase, and whether this alteration has measurable metabolic consequences. The available evidence supports these steps primarily in adipocytes and murine models, with significant limitations regarding direct extension to humans.

6. INDEPENDENT CONFIRMING EVIDENCE

A confirmation particularly close to the statement in the book comes from Pedersen and colleagues. The authors studied the relationship between insulin and inflammation of adipose tissue, which is the tissue that stores energy in the form of fat. In samples from 36 people with obesity, higher circulating insulin concentrations were associated with greater expression of inflammatory genes in adipose tissue; the association was observational and does not prove that insulin was the cause. In experiments on mice, however, reducing circulating insulin by approximately 50% decreased the macrophage content in adipose tissue and improved the insulin response. In lean mice maintained with normal glycemia, two hours of hyperinsulinemia increased the adipose expression of CCL2, IL6, and IL1B—genes involved in the recruitment and activation of immune cells—by 2–3 times. In 3T3-L1 adipocytes, insulin increased CCL2 messenger RNA by approximately tenfold within six hours; the ERK inhibitor PD98059 abolished this increase. This experiment directly supports the persistent insulin ERK inflammatory program pathway, but it remains limited to cells and mice; the drug used does not equate to demonstrating a useful treatment in people [1].Jager and colleagues evaluated the significance of ERK1 in obese mice lacking leptin. Compared to control obese mice with similar weight and fat mass, animals lacking ERK1 did not develop hyperglycemia and showed better glucose tolerance. The hyperinsulinemic-euglycemic clamp, a technique that measures how much glucose the body uses during a controlled level of insulin, indicated greater whole-body, muscle, and adipose tissue insulin sensitivity. These improvements were accompanied by a reduction in the expression of inflammatory cytokine markers and lymphocytes in adipose tissue. The work does not prove that hyperinsulinemia is the initial cause of ERK activation, but it strengthens the link between ERK1 alteration, adipose inflammation, and insulin resistance in an animal model of obesity [2].Hong and colleagues added a downstream metabolic step. In obese mice, ERK activation was found to be increased in adipose tissue; the authors linked this signal to greater lipolysis, that is, the release of fatty acids from fat cells. Genetic and pharmacological experiments showed that MEK-ERK inhibition reduced lipolysis in human, murine, and fruit fly adipose tissue. In obese mice, acute MEK-ERK inhibition reduced lipolysis and improved insulin sensitivity. The proposed mechanism involved the phosphorylation of the beta3-adrenergic receptor at serine 247 by ERK2. This study does not start from insulin and does not directly measure inflammation induced by hyperinsulinemia, but it confirms that ERK activation in obese adipose tissue can promote an alteration in lipid metabolism associated with poorer insulin sensitivity [3].

7. CONFLICTING EVIDENCE

There are relevant findings that suggest caution in attributing a uniform effect to ERK1. Khan and colleagues fed ERK1-deficient mice a high-fat diet. In this model, the animals lacking ERK1 became more obese than the controls, had higher concentrations of insulin, triglycerides, and cholesterol, and a higher HOMA-IR value, an indicator consistent with greater insulin resistance. In the livers of these same mice, ERK2 phosphorylation was increased, along with signs of greater fat synthesis and reduced fatty acid oxidation [4].This result does not negate the correspondence between the original publication and the passage in the book. However, it shows that genetically eliminating ERK1 can induce compensations, particularly through ERK2, and that the final effect depends on the tissue studied, the diet, the age of the animals, and the balance between the two isoforms. No sufficiently relevant directly conflicting evidence has been identified in humans that demonstrates the absence of an ERK contribution

to inflammatory programs associated with hyperinsulinemia; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to verify the specific passage in the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature synthesis on cellular metabolism and MAPK	Describes MAPK as necessary for metabolic adaptation and potentially involved in metabolic alterations when signaling is inappropriate.	biologically consistent evidence	moderate
[1]	Human, animal, and cellular observational	36 people with obesity; obese or lean mice; 3T3-L1 adipocytes	Hyperinsulinemia increased inflammatory genes in adipose tissue; in adipocytes, the increase in CCL2 was ERK-dependent.	direct confirmation	moderate
[2]	Genetic animal study	ob/ob mice with or without Erk1 deletion	The absence of ERK1 improved insulin sensitivity and reduced inflammatory markers in adipose tissue.	indirect confirmation	moderate
[3]	Animal, human tissue, and cellular	Human and murine adipose tissue, obese mice, modified cells, and fruit flies	ERK activation increased lipolysis; MEK-ERK inhibition reduced lipolysis and improved insulin sensitivity in obese mice.	biologically consistent evidence	moderate
[4]	Genetic animal study	Erk1-/- mice fed a high-fat diet	The absence of ERK1 was associated with greater obesity, higher HOMA-IR, and a compensatory increase in hepatic ERK2 phosphorylation.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the general idea that MAPKs are necessary for metabolic adaptation, but can contribute to disease when their activation is inappropriate. For the book section, the most well-supported point is that persistent excess insulin can activate ERK-dependent inflammatory programs in experimental adipose tissue.Independent evidence also shows that ERK1 modulation can alter adipose inflammation, lipid metabolism, and insulin sensitivity in mice. However, outcomes are not uniform across genetic models and tissues. The narrative is therefore confirmed at a mechanistic level and requires further validation in humans, especially through longitudinal and experimental studies capable of distinguishing between the different isoforms and sites of ERK activation.

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

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