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Mitotic regulators and the SHP2-MAPK pathway promote insulin receptor endocytosis and feedback regulation of insulin signaling - Evidence review

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1. ABSTRACT

The analyzed publication investigated how the cell terminates or reduces the insulin-activated signal over time. The authors propose that ERK1/2 and SHP2 participate in a feedback loop: following the activation of the insulin receptor, they promote its endocytosis, i.e., the transfer of the receptor from the outside to the inside of the cell. This process would primarily limit the component of the signal associated with cell growth, while leaving the metabolic component more prolonged.In paragraph 5.4 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the statement that mediators of the MAPK-ERK cascade participate in feedback loops that modulate the activation of the insulin receptor on the plasma membrane. Independent evidence shows that insulin can promote ERK activation through networks involving IRS and SHP2, and that the reduction of hepatic SHP2 increases insulin sensitivity in mice. However, other data indicate that the way in which the receptor is internalized varies between cell types. The narrative is therefore moderately supported: the principle of regulatory feedback is consistent, while the precise mechanism is not uniformly demonstrated across different human tissues.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether insulin receptor activation is regulated not only by signals originating from the receptor itself, but also by a feedback mechanism capable of controlling its presence on the cell surface. The hypothesis evaluated was that the IRS1 and IRS2 proteins, normally involved in insulin signaling, collaborate with ERK1/2 and SHP2 to promote insulin receptor endocytosis.The topic is relevant to the book's section because it distinguishes between the two major branches of insulin signaling. The PI3K-AKT pathway is primarily linked to metabolic effects, such as glucose utilization. The MAPK-ERK pathway is more closely associated with changes in gene expression and mitogenic signals, which promote cell proliferation. The study analyzed proposes that MAPK-ERK is not only a pathway activated by insulin, but also contributes to controlling the duration of receptor activation.The publication can document an experimental mechanism of receptor regulation and observe metabolic consequences in mice. However, it cannot demonstrate that the same circuit operates with identical intensity in all organs, nor can it establish on its own what its role is in the development of insulin resistance in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The material presents a mechanistic experimental study, supplemented by observations in mice. The authors examined the relationship between IRS1/2, the AP2 adaptor complex involved in clathrin-mediated endocytosis, ERK1/2, and SHP2. They also evaluated the consequences of SHP2 inhibition on insulin signaling regulation and insulin sensitivity in mice.The abstract reports that insulin receptor endocytosis depends on the recruitment of AP2 and a coordinated change in the phosphorylation of IRS1/2. Phosphorylation is the addition of phosphate groups to a protein, which can alter its interactions and function. This information does not specify which cell lines were used, how many animals were studied, the sex or age of the animals, the dosages of the inhibitor, the duration of the treatments, the inclusion and exclusion criteria, the quantitative endpoints, the statistical analyses, or the significance values. This information is not provided in the available material.

4. RESULTS

The key finding is that IRS1 and IRS2 cooperate with mitotic control proteins to promote insulin receptor endocytosis. In simple terms, after the receptor receives the insulin signal, certain proteins help selectively remove a portion of it from the cell membrane. According to the authors, this helps prevent the signal from remaining active for too long.The proposed molecular step is a phosphorylation switch on IRS1/2. ERK1/2, terminal components of the MAPK cascade, modify IRS1/2; SHP2, a phosphatase—an enzyme that removes phosphate groups—completes the modification necessary to enable interaction with AP2. AP2 then facilitates the transfer of the receptor into intracellular vesicles through a clathrin-mediated process.The abstract also reports that SHP2 inhibition blocked this feedback regulation and the cell growth-associated component of the receptor signal. At the same time, it prolonged the metabolic action of insulin and improved insulin sensitivity in mice. The practical significance is that the same regulatory network could influence the metabolic and mitogenic functions of insulin in different ways. Absolute values, percentages, effect sizes, confidence intervals, and P-values are not reported in the available material.

5. INTERPRETATION

The biological significance of this work is that insulin does not act as a simple on-off switch. The cell possesses systems that modulate how long the receptor remains available on the membrane and which signaling branches remain predominant. In the study analyzed, ERK1/2 and SHP2 are positioned within one of these feedback control systems.The segment of the book's narrative that is effectively documented is: activation of insulin signaling through MAPK-ERK and SHP2 modification of IRS1/2 recruitment of AP2 selective internalization of the activated insulin receptor. This is consistent with the statement that mediators of the MAPK-ERK cascade participate in circuits that modulate the activation of the insulin receptor on the plasma membrane.However, interpretation requires caution. Endocytosis does not automatically equate to complete signal termination: in some contexts, the

internalized receptor can continue to signal from within the cell. Furthermore, the effect attributed to SHP2 inhibition in mice does not demonstrate that a similar intervention would be effective or safe in humans, as SHP2 participates in many biological networks beyond insulin signaling.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the link between insulin, IRS, SHP2, and the activation of the MAPK-ERK pathway comes from an experimental study conducted in HEK293 cells, human cells commonly used for signaling analysis. The authors combined laboratory measurements and mathematical modeling to study the response to insulin and epidermal growth factor. Insulin alone activated ERK only slightly in that model, but together with low concentrations of epidermal growth factor, it increased ERK activation beyond the sum of the individual effects. At 1.5 minutes, the combined ERK signal was 2.57 ± 0.44 times higher than the predicted sum; at 15 minutes, it was 1.4 ± 0.1 times higher. The model and experiments indicated a role for IRS and SHP2 in the amplification of the Ras-ERK network. This confirms the upstream step of the narrative, namely that the insulin signal can integrate with SHP2 and MAPK-ERK. However, it does not demonstrate insulin receptor endocytosis nor the specific phosphorylation switch described in the original study [1].A second study, conducted in mice with selective deletion of Shp2 in the liver, confirms that SHP2 can act as a brake on the hepatic metabolic response to insulin. Both chronic and acute deletion of Shp2 increased insulin sensitivity and improved glucose tolerance compared to controls. These changes were associated with increased PI3K-AKT signaling downstream of IRS1/2. However, the study also observed a strong reduction in insulin-induced ERK activation. It therefore supports the functional part of the narrative according to which SHP2 contributes to the regulation of insulin sensitivity, but it does not directly replicate the AP2-mediated endocytosis mechanism. The model is animal-based and limited to the liver, therefore it does not allow for the results to be automatically extended to other organs or to humans [2].

7. CONFLICTING EVIDENCE

No sufficiently relevant directly conflicting evidence has been identified regarding whether MAPK-ERK and SHP2 can participate in insulin signaling regulatory circuits; this does not prove the absence of contrary results.However, there is significant evidence of context-dependency for the endocytosis step. In primary rat adipocytes, i.e., adipose tissue cells, the activated insulin receptor was rapidly internalized with a half-life of less than three minutes, together with phosphorylated caveolin-1. In this model, the inhibitor of clathrin-mediated endocytosis did not reduce receptor internalization, while it blocked the internalization of the transferrin receptor used as a control. The authors therefore attributed the process primarily to caveolae, small lipid-rich membrane invaginations, and not to the clathrin-mediated pathway [3].This result does not invalidate the mechanism proposed in the original study, which was obtained in a different experimental context, but it limits its generalizability. The fact that the insulin receptor can be internalized through different pathways suggests that modulation by MAPK-ERK, SHP2, and AP2 may depend on the cell type, the organ, and the metabolic state.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication that is the subject of the review from the independent research used to confirm or define the narrative passage of the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Mechanistic experimental with mouse observations	Cell models not specified in the abstract and mice	ERK1/2 and SHP2 regulate IRS1/2, AP2, and selective insulin receptor endocytosis; SHP2 inhibition improves insulin sensitivity in mice	direct confirmation	moderate
[1]	Cellular with systems modeling	HEK293 cells	Insulin and epidermal growth factor synergistically increase Ras-ERK activation; IRS and SHP2 contribute to the network	indirect confirmation	moderate
[2]	Genetic animal	Mice with chronic or acute hepatic Shp2 deletion	Loss of Shp2 increases insulin sensitivity, improves glucose tolerance, and increases hepatic PI3K-AKT signaling	biologically consistent evidence	moderate
[3]	Ex vivo cellular	Primary rat adipocytes	The insulin receptor is rapidly internalized via caveolae; blocking clathrin does not reduce its endocytosis	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the claim that the MAPK-ERK and SHP2 pathways participate in a feedback loop that promotes the endocytosis of the activated insulin receptor. This is the specific step for which the publication is consistent with the book's section. Independent research confirms that SHP2, IRS, and MAPK-ERK participate in the regulation of the insulin response and that SHP2 can influence insulin sensitivity in the liver of mice.The narrative is moderately supported, but the detail of the mechanism should not be considered identical in all tissues. In adipocytes, for example, receptor internalization may follow a caveolae-dependent pathway. Further validation in human tissues is needed to define the extent to which the MAPK-ERK/SHP2/AP2 circuit contributes to the physiological and pathological regulation of the insulin receptor.

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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