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Induction of cyclooxygenase-2 by the MEKK1 SEK1/MKK4 p38 mitogen-activated protein kinase pathway - Evidence review

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1. ABSTRACT

The analyzed publication investigated whether a specific intracellular signaling cascade, MEKK1 → SEK1/MKK4 → p38, can increase the expression of COX-2 (cyclooxygenase-2, an enzyme that contributes to the production of prostaglandins) and the synthesis of PGE2 (prostaglandin E2, a lipid mediator involved in many inflammatory responses). The authors used genetically modified cells to keep certain nodes of the cascade active and observed an increase in COX-2 and PGE2, which was reduced by a p38 inhibitor.In “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that MAPK family signals can induce COX-2 and promote the production of prostaglandins. Independent evidence confirms the involvement of p38 in the regulation of COX-2 and PGE2 in cellular models; in some models, ERK also contributes to the same result. However, the dependence on ERK is not universal, and the original study does not directly demonstrate an insulin → ERK → COX-2 chain in humans.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether the artificial activation of an intracellular signaling protein cascade could induce the production of COX-2 and, consequently, increase PGE2. In simple terms, the authors verified whether certain molecular switches, activated upstream, were capable of making the cell more capable of producing prostaglandins.The hypothesis was that MEKK1, through SEK1/MKK4 and p38 MAPK (p38 mitogen-activated protein kinase, an enzyme that modifies other proteins via phosphorylation), promoted the expression of COX-2. The relevance to section 5.5 of the book stems from this point: the publication documents a segment of the MAPK COX-2 PGE2 relationship. However, the segment actually studied primarily concerns MEKK1 and SEK1/MKK4; it does not directly demonstrate that insulin is the initial signal, nor does it prove that ERK is the pathway responsible for the observed effect.The study can therefore support the general concept that the activation of specific MAPK pathways can increase COX-2 and PGE2 in a cellular model. It cannot, on its own, establish that the same mechanism operates in all tissues, in people, during chronic insulin exposure, or in an inflammatory disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study used a cell model with overexpression of engineered forms of MEKK1 and SEK1/MKK4. The ΔMEKK1 form was a constitutively active variant, meaning it was designed to continuously send its signal. The authors also compared an active form of SEK1, called SEK1-ED, with a dominant-negative form, SEK1-AL, designed to hinder the SEK1 signal.COX-2 expression, PGE2 production, and the phosphorylation of p38 and JNK/SAPK (c-Jun N-terminal kinase/stress-activated protein kinase, another family of stress-activated kinases) were measured. SC68376, described in the abstract as a pharmacological inhibitor of p38 MAPK, was also used. The activities of SEK1/MKK4, MKK3, and MKK6—proteins that can be located upstream of various MAPK pathways—were evaluated.The number of experiments, the number of biological replicates, exclusion criteria, the detailed analytical method, complete cell characteristics, reagent concentrations, duration of exposures, and statistical analyses are not reported in the available material. Complete quantitative values, including P-values and variability ranges, are also not reported in the available material.

4. RESULTS

The main result was a concordant increase in COX-2 and PGE2 when the studied cascade was artificially activated. The overexpression of ΔMEKK1 increased COX-2 expression and PGE2 production. This increase was reported as completely blocked by SC68376, the pharmacological inhibitor of p38 MAPK. In plain language, when the p38 signal was hindered, both the increase in the COX-2 enzyme and the increase in the prostaglandin PGE2 were absent in the experimental model.The activation of ΔMEKK1 increased the activity of SEK1/MKK4, but not that of MKK3 or MKK6. It also activated p38 MAPK and JNK/SAPK. The constitutively active form of SEK1, SEK1-ED, increased the phosphorylation of p38 and JNK/SAPK, as well as COX-2 and PGE2. Conversely, the dominant-negative form SEK1-AL reduced the phosphorylation of p38 and JNK/SAPK and reduced COX-2 expression.The finding most relevant to the book is therefore the direction of the effect: the activation of the MEKK1 SEK1/MKK4 p38 sequence was accompanied by an increase in COX-2 and PGE2; the pharmacological inhibition of p38 abolished the increase induced by ΔMEKK1 in the cell model. The abstract does not report absolute values, percentages, sample sizes, P-values, or confidence intervals; it is therefore not possible to precisely quantify the magnitude of the effects.

5. INTERPRETATION

Biologically, COX-2 allows the cell to convert arachidonic acid into prostanoids, a family of lipid mediators that includes PGE2. The study suggests that a portion of the MAPK pathways not only regulates the release of a lipid substrate but can also increase the amount of the enzyme necessary to transform it into PGE2.The pathway specifically documented by the publication is MEKK1 SEK1/MKK4 p38 MAPK increase in COX-2 and PGE2. The most robust conclusion therefore concerns an experimental cellular mechanism. The use of constitutively active

and dominant-negative forms makes the design useful for evaluating the causal direction within the model: increasing the signal was associated with an increase in COX-2 and PGE2, while hindering SEK1 or p38 reduced this response.However, the section in "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi discusses MAPK-ERK and insulin signaling. This formulation requires an important clarification: in the analyzed study, the inhibitor that abolished the effect was directed against p38, not ERK. JNK/SAPK and p38 were activated, while ERK is not identified in the abstract as the necessary node for the increase in COX-2 and PGE2. The work is therefore consistent with the general idea of MAPK COX-2 PGE2, but it directly supports, above all, the p38 branch of the MAPK family.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the p38 COX-2 PGE2 pathway comes from HeLa cells stimulated with interleukin-1. Ridley and colleagues observed that the p38 inhibitor SB203580, at concentrations of 0.1–1 micromolar, reduced interleukin-1-induced PGE2 release without reducing arachidonic acid release. The reduction in PGE2 was associated with lower induction of COX-2 protein and messenger RNA. The authors also indicated that p38 contributed to stabilizing COX-2 messenger RNA, effectively prolonging the availability of the cellular instructions needed to produce the enzyme [1]. This study provides mechanistic and independent confirmation that p38 can promote COX-2 and PGE2, but it involves a human cell line and an inflammatory stimulus, not insulin.A second study evaluated immortalized human cartilage cells exposed to interleukin-1b. In this model, the inflammatory signal rapidly activated ERK1/2, p38, and JNK, followed by an increase in COX-2 and PGE2. Inhibition of p38 with SB203580 reduced COX-2 protein and messenger RNA expression and decreased PGE2 production; at 1 micromolar, COX-2 expression was reduced by 40%. Inhibition of ERK1/2 with PD98059 also reduced COX-2 and PGE2 in a concentration-dependent manner [2]. This result is particularly relevant to the book's formulation because it shows, in a human cell model, that multiple MAPK branches can contribute to the same inflammatory response. The limitation is that the model involves cartilage and interleukin-1b, not insulin signaling.Taken together, these independent studies make the idea that the activation of certain MAPKs can increase COX-2 and PGE2 production biologically consistent. However, the chain should not be simplified as if a single branch were identical and indispensable in every cell: p38, ERK, and JNK can have different roles depending on the stimulus, the duration of the signal, and the cell type.

7. CONFLICTING EVIDENCE

Directly relevant evidence shows that the role of ERK is not universal. In human cells similar to follicular dendritic cells, Cho and Choe studied the induction of COX-2 by PGE2. Stimulation with PGE2 rapidly increased the phosphorylation of p38, but not that of ERK. Furthermore, silencing p38 markedly reduced the induction of COX-2, whereas silencing ERK did not significantly reduce the induction of COX-2 caused by PGE2 or interleukin-1b. The same results were reproduced with pharmacological inhibitors [3].This study does not contradict the general involvement of MAPKs in the regulation of COX-2. Instead, it indicates that the necessary pathway may change depending on the biological context: in the cells studied, p38 was decisive while ERK was not. Consequently, the claim that MAPK-ERK inhibition would entirely abolish COX-2 and PGE2 cannot be generalized to all tissues or stimuli. No directly conflicting evidence sufficiently relevant to the involvement of p38 in the regulation of COX-2 has been identified; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent research and shows the level at which each piece of evidence supports the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Cellular model with active or dominant-negative forms of MEKK1 and SEK1/MKK4	Activation of MEKK1 or SEK1 increased COX-2 and PGE2; p38 inhibition blocked the increase induced by ΔMEKK1.	biologically consistent evidence	preliminary
[1]	Experimental cellular	Human HeLa cells stimulated with interleukin-1	p38 inhibition reduced COX-2, its messenger RNA stability, and PGE2 release.	direct confirmation	moderate
[2]	Experimental cellular	Immortalized human T/C28a2 chondrocytes stimulated with interleukin-1b	p38 and ERK1/2 inhibition reduced COX-2 and PGE2; p38 also reduced COX-2 messenger RNA.	direct confirmation	moderate
[3]	Experimental cellular	Human follicular dendritic-like cells	p38, but not ERK, was required for the induction of COX-2 by PGE2 and interleukin-1b.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports a cellular mechanism in which the activation of the MEKK1 SEK1/MKK4 p38 cascade increases COX-2 and PGE2. Independent evidence confirms that p38 can promote the production of COX-2 and PGE2 and indicates that ERK may contribute in some human models. The general narrative that MAPK pathways regulate the cellular capacity to produce prostaglandins is therefore well-supported at a mechanistic level.It remains necessary to distinguish this result from the broader formulation regarding insulin and ERK. The original study does not directly demonstrate an effect of insulin, does not study people, and does not establish that ERK is always indispensable. The proposed chain therefore requires validation in appropriate physiological and clinical models.

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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