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Signal transduction pathways (MAPK, NF-kB, and C/EBP) regulating COX-2 expression in nasal fibroblasts of asthmatic patients with aspirin intolerance - A review of the evidence

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1. ABSTRACT

The analyzed study evaluated how certain intracellular pathways of the MAPK family (proteins that transmit signals from the outside to the inside of the cell) participate in the increase of COX-2, an enzyme necessary for producing prostaglandins from arachidonic acid. The researchers studied fibroblasts obtained from nasal mucosa and nasal polyps of five patients per group, subjecting them to the inflammatory stimulus of interleukin-1b.The publication found that the p38 MAPK inhibitor reduced COX-2 expression in nasal mucosa cells, while ERK and JNK inhibitors did not produce a significant reduction. This detail is important for interpreting the reference found in “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi: the study contributes to the general narrative that MAPK pathways can regulate COX-2, but it does not demonstrate that ERK is the decisive functional node in the model studied. Independent research confirms that p38 or ERK can contribute to the induction of COX-2 in different cells; however, the relative contribution of individual pathways depends on the tissue, species, and stimulus. The confirmation of the insulin chain proposed in the book therefore remains indirect and predominantly mechanistic.

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 the reduced COX-2 expression observed in aspirin-induced asthma could depend on differences in MAPK pathway activation or on the translocation of transcription factors—proteins that regulate gene activation—into the nucleus. The hypothesis was that alterations in ERK, JNK, p38 MAPK, NF-kB, or C/EBP could explain a lower induction of the enzyme.The reason for the reference in paragraph 5.5 is clear: the publication experimentally verifies whether the pharmacological inhibition of certain MAPKs modifies the increase of COX-2 in human fibroblasts. However, the specific data does not fully align with the book's statement regarding MAPK-ERK. In the model examined, ERK inhibition did not significantly reduce COX-2; the statistically significant effect was observed with p38 MAPK inhibition. The study can therefore document a segment of the narrative, namely MAPK COX-2 regulation, but it cannot demonstrate the complete sequence insulin ERK COX-2 PGE2, nor establish that it operates in all human tissues.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract. This is a cellular experiment conducted on fibroblasts, connective tissue cells that can participate in local inflammatory responses. The cultures were derived from nasal mucosa samples, referred to as NM, and from nasal polyps of patients with aspirin-induced asthma, referred to as NP-AIA; for each sample type, the abstract reports N=5.The cells were exposed to interleukin-1b, a cytokine that signals inflammation. COX-2 and the phosphorylated, i.e., activated, forms of ERK, JNK, and p38 MAPK were measured using Western blot, a technique that detects proteins in a cellular sample. To verify the causal role of the three pathways, pharmacological inhibitors of ERK, JNK, and p38 MAPK were used at concentrations ranging from 0.1 to 10 µM before exposure to interleukin-1b.The abstract also reports the evaluation of the nuclear translocation of NF-kB and C/EBP using Western blot and TransAM®, a test that measures the activity of transcription factors. The inclusion and exclusion criteria for participants, the recruitment period, age, sex, clinical characteristics of the patients, the number of biological replicates for each experiment, and the detailed statistical plan are not reported in the available material.

4. RESULTS

In simple terms, the cells of both tissue types activated the main MAPKs with a similar temporal dynamic following the inflammatory stimulus. No differences were observed in the course of ERK, JNK, and p38 phosphorylation between nasal mucosa fibroblasts and nasal polyp fibroblasts associated with aspirin-induced asthma.The most relevant functional result emerged with the inhibition of p38 MAPK. In nasal mucosa cultures, 10 µM of the p38 inhibitor reduced interleukin-1b-induced COX-2 expression by 85%. In nasal polyp fibroblasts, COX-2 inhibition was 65% at 1 and 10 µM, but this reduction was not statistically significant compared to untreated cells.Conversely, ERK and JNK inhibitors did not significantly modify COX-2 expression in either nasal mucosa cultures or those derived from polyps. The effect of interleukin-1b on the nuclear translocation of NF-kB and C/EBP subunits was also similar in the two cell groups. The observed data therefore primarily support p38 MAPK as a regulator of interleukin-1b-induced COX-2 in the studied nasal mucosa model.

5. INTERPRETATION

COX-2 is a protein that allows the cell to convert arachidonic acid into prostaglandins, including PGE2. For this reason, when COX-2 increases, the cell acquires a greater capacity to produce lipid mediators of inflammation. The study suggests that, in the nasal fibroblasts studied, p38 MAPK is an important component of the signal by which interleukin-1b increases COX-2.However, the result does not indicate that all MAPKs have the same role. In particular, it is not correct to extend the result to a demonstrated effect of ERK, because pharmacological blockade of ERK did not significantly reduce COX-2 in these cultures. The absence of significant differences may depend on an actual lack of involvement, the small sample size, or limitations of the inhibitors used, but it cannot be transformed into proof of an ERK function.Compared to the book chapter, the publication documents the cellular inflammation MAPK segment, especially p38 COX-2 induction. It

does not test insulin, does not measure the release of arachidonic acid, does not quantify PGE2, and does not evaluate clinical consequences. Its relevance is therefore mechanistic and limited to the nasal cell model.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the general relationship between MAPK and COX-2 induction comes from a study on immortalized human chondrocytes, which are cartilage cells. Following stimulation with interleukin-1b, the activation of ERK1/2, p38, and JNK was followed by an increase in COX-2 and PGE2. Inhibition of these three pathways reduced COX-2 and PGE2 production in a dose-dependent manner. This study confirms that ERK can contribute to the regulation of COX-2 in human cells, but it does not demonstrate that it is the predominant mechanism in nasal fibroblasts or during insulin stimulation [1].A second line of research concerns the link with insulin mentioned in the book's paragraph. In young rats, intracerebroventricular administration of insulin increased microglial activation and hippocampal levels of COX-2 and interleukin-1b. This effect was not observed in older rats. This work provides biologically consistent support for the idea that, under specific experimental conditions, insulin may be associated with an increase in COX-2; however, it does not identify ERK as a mediator, does not concern fibroblasts, and does not demonstrate a universal effect of insulin on human tissues [2].The relevance of p38 was also confirmed in primary cultures of human myometrial smooth muscle cells. Interleukin-1b induced COX-2 and tripled the release of PGE2; the p38 inhibitor SB203580 blocked COX-2 protein expression. This result converges with the analyzed study because it shows, in a different type of human cell, that p38 may be necessary to link an inflammatory stimulus to the increase of COX-2 and prostaglandins [3].Taken together, these studies support a signaling network in which MAPKs can increase COX-2 and, in some models, PGE2. The convergence is solid at the cellular level, but the relative position of ERK, p38, and JNK changes between tissues. For the specific passage in the book, clinical studies demonstrating a continuous causal chain in humans between chronic insulin, ERK, COX-2, and PGE2 are lacking.

7. CONFLICTING EVIDENCE

There is directly relevant evidence that necessitates caution in attributing a constant role to a single MAPK. In canine synovial fibroblasts stimulated with interleukin-1b, the inhibition or silencing of ERK1/2 reduced COX-2 expression and PGE2 release, whereas p38 and JNK inhibitors did not significantly alter COX-2 mRNA. This result is the opposite, regarding the relative role of ERK and p38, to the one predominant in the analyzed study [4].This divergence does not invalidate the scientific correspondence between the analyzed publication and the book section. Instead, it shows that COX-2 regulation is context-dependent: species, cell type, activation state, dose, and duration of the stimulus can alter which branch of the MAPK network is functionally more important. No sufficiently relevant directly conflicting evidence regarding the specific effect of insulin in human nasal fibroblasts has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from independent research and indicates the level at which each piece of evidence contributes to the narrative of the section.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Nasal mucosa fibroblasts and nasal polyps, N=5 per group	p38 inhibition reduced interleukin-1b-induced COX-2; ERK and JNK did not significantly reduce it.	biologically consistent evidence	preliminary
[1]	Experimental cellular	Immortalized human T/C28a2 chondrocytes	Inhibition of ERK, p38, or JNK reduced interleukin-1b-induced COX-2 and PGE2.	direct confirmation	moderate
[2]	Animal	Hippocampus of young and aged rats	Insulin increased activated microglia, COX-2, and interleukin-1b in young rats, but not in aged rats.	indirect confirmation	low
[3]	Experimental cellular	Primary human myometrial smooth muscle cells	p38 inhibition blocked interleukin-1b-induced COX-2, and the cytokine increased PGE2.	direct confirmation	moderate
[4]	Experimental cellular	Canine synovial fibroblasts	ERK1/2, but not p38 or JNK, supported interleukin-1b-induced COX-2 and PGE2.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed supports the idea at a cellular level that COX-2 induction by an inflammatory stimulus may depend on MAPK signaling. In this specific model, the most compelling result concerns p38 MAPK, not ERK. Independent evidence confirms that ERK, p38, and JNK can regulate COX-2 in different ways depending on the tissue and experimental model.The narrative that insulin could promote conditions that increase COX-2 is biologically consistent and has limited support from animal studies. However, based on this research, a universal causal chain of insulin ERK COX-2 PGE2 in humans has not been proven. The link is therefore supported primarily at a mechanistic level and requires targeted validation in relevant human cells and 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.

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