LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Induction of COX-2-PGE2 synthesis via MAPK/ERK pathway activation contributes to neuronal death caused by TDP-43-deficient microglia - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether the experimental loss of TDP-43, a protein that regulates various cellular RNAs, can make microglia toxic to neurons. In rodent cell cultures, the reduction of TDP-43 in microglia increased the activation of the MAPK/ERK pathway, the expression of COX-2, and the release of PGE2. The culture medium produced by these microglia reduced the viability of cortical neurons and motor neurons; celecoxib attenuated this effect in the experimental model.In section 5.5.1 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication helps support the concept that the COX-2–PGE2 axis may act as an effector of the transition toward a pro-inflammatory context. Independent studies confirm that activated microglia can increase COX-2 and PGE2 and transmit signals to neurons; human data in ALS also show higher levels of COX-2 and PGE2. However, a clinical trial did not demonstrate a benefit of celecoxib in ALS. The confirmation is therefore primarily mechanistic, not therapeutic.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 24, 2026
Updated: November 24, 2026

DOI 10.5281/zenodo.24494129

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 reduction of TDP-43 in the resident immune cells of the nervous system, the microglia, could trigger an inflammatory signal capable of damaging neurons. The authors evaluated the hypothesis that the loss of TDP-43 would activate the MAPK/ERK cascade (a sequence of intracellular signals that can modify gene activity), inducing the COX-2 enzyme and increasing the production of PGE2, a prostaglandin derived from arachidonic acid.The relevance to paragraph 5.5.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is specific: the work documents that, in microglia with reduced TDP-43, the increase in COX-2 is accompanied by a functional increase in PGE2. Furthermore, it links this axis to a neurotoxic response in vitro. However, it does not evaluate insulin, phospholipase cPLA2a, the availability of arachidonic acid, or the systemic inflammation described more extensively in the book's chapter.The study can demonstrate a causal chain within the cell cultures used, because it experimentally reduces TDP-43 and selectively blocks certain pharmacological steps. However, it cannot establish that the same sequence occurs with identical intensity in people with amyotrophic lateral sclerosis (ALS), nor can it demonstrate that a COX-2 inhibitor is effective as a clinical treatment.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

This is an experimental in vitro study, meaning it was conducted on cells cultured outside of a living organism. The authors used primary microglia obtained from the cortex of newborn rats, primary astrocytes derived from the cortex of newborn mice, cortical neurons and motor neurons obtained from mouse embryos, as well as BV2 microglia cell lines and NSC-34 cells with motor neuron characteristics.TDP-43 was reduced using small interfering RNAs, known as siRNA (short sequences that decrease the expression of a target gene). The amounts of COX-2 and signaling pathway proteins were evaluated using immunoblotting, a technique that measures specific proteins. COX-2 messenger RNA was measured using quantitative PCR. The PGE2 released into the culture medium was measured using ELISA, a quantitative immunological test.To verify the role of intracellular signals, the cells were treated with U0126, a MEK1 inhibitor that reduces ERK activation, with JNK, p38, and GSK3b inhibitors, and with celecoxib, a selective COX-2 inhibitor. In the conditioned medium test, the liquid obtained from the treated microglia was transferred to the neurons: this procedure allows for the study of whether substances released by microglia influence neuronal survival. Cell viability was assessed by counting cells positive for propidium iodide, a dye that enters cells with a compromised membrane.U0126 was used at 20 micromolar, celecoxib at 50 micromolar, and lipopolysaccharide, a bacterial inflammatory stimulus, at 0.1 micrograms per milliliter. The authors report analyses using one-way ANOVA in several experiments. The overall biological sample size for each individual condition, exclusion criteria, and a predefined statistical plan are not reported in the available material.

4. RESULTS

The main finding is that the reduction of TDP-43 increased COX-2 in microglia, but not in astrocytes. This means that the response was not observed indiscriminately in all glial cells examined. According to the authors' discussion, COX-2 increased approximately threefold in microglia; the detailed numerical value and the corresponding P-value are not reported in the available text.The loss of TDP-43 increased the phosphorylated form of MEK and ERK. Phosphorylation is a chemical modification that often indicates the activation of a protein. Conversely, the phosphorylated forms of JNK and p38 did not increase, nor did the total amounts of MEK, ERK, or JNK. When MEK/ERK was inhibited with U0126, the increase in COX-2 RNA and protein was no longer observed. Inhibitors of JNK, p38, and GSK3b, however, did not block the increase of COX-2 in the model.The same sequence was linked to PGE2. Microglia deprived of TDP-43 released more PGE2 over time, while astrocytes did not show such an increase. The authors describe an approximate tenfold increase in microglia. Both U0126 and celecoxib blocked the increase in PGE2, consistent with a MEK/ERK COX-2 PGE2 pathway.The medium conditioned by microglia with reduced TDP-43 increased the death of cortical neurons and motor neurons, but not of mouse

embryonic fibroblasts. The medium from astrocytes with reduced TDP-43 did not reduce neuronal viability. Treating microglia with celecoxib before collecting the medium restored neuronal viability in the test. Celecoxib alone did not alter neuron viability. These data show protection in the culture system, but do not identify PGE2 with certainty as the sole toxic factor present in the conditioned medium.

5. INTERPRETATION

In simple terms, the study describes a possible mechanism by which altered microglia can transform an internal molecular change into an inflammatory signal released externally. The reduction of TDP-43 activated MEK/ERK; this pathway increased COX-2; and COX-2 contributed to the increased production of PGE2. In the experimental model, the end result was an environment produced by the microglia that was less compatible with neuronal survival.The segment directly documented and relevant to the book is therefore: activation of a MAPK/ERK pathway in microglia increase in COX-2 increase in the synthesis and release of PGE2. The publication adds that, in this cellular context, the medium released by the microglia is associated with increased neuronal death and that the inhibition of COX-2 attenuates the phenomenon.This interpretation does not prove that every increase in COX-2 or PGE2 is necessarily harmful. Prostaglandins can have different effects depending on the tissue, the receptor involved, the duration of the stimulus, and the biological context. Furthermore, TDP-43 was artificially reduced in rodent cells: this only reproduces a part of the biology observed in human TDP-43 proteinopathies.

6. INDEPENDENT CONFIRMING EVIDENCE

Experimental confirmation particularly close to the proposed chain comes from a rat model of spinal cord injury. Zhao and colleagues localized activated ERK1/2 in microglia, observed that MEK/ERK inhibition reduced COX-2 in microglia, and measured a reduction in PGE2 following the blockade of microglia or the ERK pathway. Blocking the neuronal EP2 receptor, one of the PGE2 receptors, reduced the hyperactivity of dorsal horn neurons and partially improved nociceptive thresholds. While this is not a model of ALS or neuronal death, it confirms in vivo the biological coherence of the microglia ERK COX-2/PGE2 neuronal signaling segment [1].A second study added findings in humans with sporadic ALS. In post-mortem spinal cord samples from seven people with ALS, COX-2 was significantly more expressed compared to seven neurologically healthy controls and was also present in glial cells. In the cerebrospinal fluid, nine people with ALS had a mean PGE2 concentration of 45.8 ± 35.1 pg/mL, higher than the 15.8 ± 3.7 pg/mL found in nine controls without motor neuron disease. This data confirms an association with the human disease, but it does not define which cell produces the PGE2 nor does it prove that it causes motor neuron degeneration [2].In an independent cellular model, medium from murine macrophages activated with lipopolysaccharide and interferon-gamma induced the death of NSC-34 cells, a line with motor neuron characteristics. Celecoxib attenuated both the reduction in neuronal viability and the increase in PGE2 release, along with that of other inflammatory mediators. This research supports the idea that activated immune cells can create a harmful environment for motor cells and that COX-2 participates in the response; however, it studies peripheral macrophages, not microglia, and does not isolate PGE2 as the sole cause of toxicity [3].Taken together, these studies reinforce the narrow narrative of the paragraph: the COX-2–PGE2 axis is a biologically plausible effector of the pro-inflammatory response and may participate in communication between immune cells and neurons. The most direct demonstration of a causal role in a TDP-43 model, however, remains that of the original study.

7. CONFLICTING EVIDENCE

The most relevant evidence for defining the therapeutic interpretation comes from a randomized, double-blind, placebo-controlled trial on 300 people with ALS. Participants received 800 mg of celecoxib per day or a placebo for 12 months. Celecoxib did not slow the decline in muscle strength, vital capacity, the ALSFRS-R functional scale, or the estimated number of motor units, and it did not alter survival. In the subgroup evaluated, PGE2 in the cerebrospinal fluid was not elevated at baseline and did not decrease with treatment [4].This result does not disprove that COX-2 and PGE2 may increase in specific cellular models or in subgroups of people with ALS. However, it shows that inhibiting COX-2 with that dose of celecoxib did

not produce a demonstrable clinical benefit in the population studied. The reasons may include the biological heterogeneity of ALS, the timing of treatment, penetration into the nervous system, the absence of a baseline increase in PGE2 in the analyzed sample, or the fact that the COX-2–PGE2 pathway is not the dominant determinant of clinical progression.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the original study from independent publications and separates experimental evidence from observational and clinical evidence.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Rodent primary microglia, astrocytes, and neurons; BV2 and NSC-34 lines	Reducing TDP-43 in microglia increased MEK/ERK, COX-2, and PGE2; conditioned medium increased neuronal death.	direct confirmation	moderate
[1]	Experimental animal	Rats with spinal cord contusion injury	Microglial activation and ERK supported COX-2 and PGE2; blocking the pathway reduced painful neuronal signaling.	indirect confirmation	moderate
[2]	Human observational	Post-mortem spinal cord and cerebrospinal fluid from people with ALS and controls	COX-2 and PGE2 were higher in samples associated with ALS compared to controls.	biologically consistent evidence	moderate
[3] confirmation; [4] discordant	Experimental cellular; RCT	Murine macrophages and motor neuron-like cells; 300 people with ALS	Celecoxib attenuated toxicity and PGE2 in vitro, but did not improve clinical outcomes in ALS.	indirect confirmation; discordant evidence	low; high

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, within its cellular model, that the loss of TDP-43 in microglia can activate MAPK/ERK, increase COX-2 and PGE2, and make the medium produced by microglia harmful to neurons. This is the precise step that justifies its inclusion in the section of the book dedicated to the pro-inflammatory function of the COX-2–PGE2 axis.Independent evidence confirms that the axis can be activated in the immune cells of the nervous system and can influence neuronal signaling; in human ALS, COX-2 and PGE2 are found to be increased in small biological samples. The link is therefore supported at a mechanistic level and is biologically consistent. However, it remains to be validated how much this mechanism contributes to the disease in people and in which subgroups. The failure of celecoxib in the clinical trial indicates that a plausible mechanism does not automatically coincide with an effective treatment.

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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