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cPLA2 is phosphorylated and activated by MAP kinase - Evidence review

D.ssa M. Mondini[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study examined whether MAP kinase, a family of proteins that transmits signals from the outside to the inside of the cell, can activate cytosolic phospholipase A2 (cPLA2), an enzyme that releases arachidonic acid from membrane phospholipids. The authors observed that phosphorylation of the enzyme at serine 505 increases its activity and that a mutation preventing this modification almost completely reduces the release of arachidonic acid following cellular stimulation.In "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the passage stating that the activation of the MAPK/ERK pathway can promote the activation of cPLA2a and the mobilization of arachidonic acid. Independent studies support the functional role of serine 505, the membrane, and intracellular calcium, but also show that the control of the enzyme depends on the stimulus and the cell type. The most prudent conclusion is therefore mechanistic: the MAP kinase–cPLA2–arachidonic acid link is well-documented in experimental models, while it does not, on its own, demonstrate an effect of chronic insulin or an inflammatory outcome in humans.

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MISSION

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2. ANALYZED STUDY

The research question was whether MAP kinase could directly modify cPLA2 and whether this modification was important for the release of arachidonic acid. The hypothesis was biologically relevant because cPLA2 acts as an enzyme that makes arachidonic acid contained in cell membranes available; this lipid can then be used to produce various biologically active mediators, including some mediators of inflammation.The relevance to the book's paragraph concerns a specific segment of the proposed chain: activation of a MAP kinase phosphorylation of cPLA2 increased enzyme activity increased release of arachidonic acid. The publication did not directly evaluate insulin, chronic insulin exposure, systemic inflammation, or clinical outcomes in humans. It can therefore document a cellular mechanism, not the entire pathophysiological chain described in the paragraph.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract is available. The study combined biochemical and cellular experiments. The authors evaluated whether cPLA2 was a substrate for MAP kinase, meaning a protein that can be modified by this enzyme through phosphorylation—the addition of a phosphate group capable of altering its behavior. They then measured the enzymatic activity following phosphorylation and identified the main site of the modification: serine 505.A mutated form of cPLA2 was also produced in which serine 505 was replaced with alanine, denoted as Ser-505 Ala. This substitution prevented phosphorylation of the site by MAP kinase. The authors then compared the release of arachidonate—the ionized form of arachidonic acid—in intact cells after stimulation with extracellular agonists. The number of experiments, the exact cell type, selection criteria, concentrations used, duration of incubations, specific statistical tests, and significance values are not reported in the available material.

4. RESULTS

The key finding is that cPLA2 was identified as a substrate for MAP kinase. In simple terms, MAP kinase could add a phosphate group to cPLA2, and this modification increased the enzyme's catalytic activity—that is, its ability to facilitate the release of arachidonic acid from membrane phospholipids.The identified site was serine 505. The authors noted that this site coincided with the main phosphorylation point observed in cells treated with phorbol ester, an experimental stimulant of cell signaling. When serine 505 was replaced with alanine, the mutated protein was no longer a substrate for MAP kinase. In intact cells, this mutation resulted in an absent or minimal increase in arachidonate release in response to agonists, compared to the enhancement observed with the non-mutated enzyme.The abstract does not report absolute values, percentage reductions, sample sizes, confidence intervals, or P-values. It is therefore not possible to precisely quantify the magnitude of the effect. The data directly supporting the book's paragraph is directional and clear: preventing the phosphorylation of serine 505 strongly reduced the release of arachidonic acid induced by extracellular stimuli.

5. INTERPRETATION

The biological significance of the result is that cPLA2 does not act simply because it is present in the cell: it can be made more efficient by intracellular signals. Phosphorylation of serine 505 represents one such regulation. Simply put, the MAP kinase signal can make cPLA2 better suited to reach or act on the membrane, where phospholipids containing arachidonic acid are present.The pathway documented by the publication is therefore MAP kinase phosphorylation of cPLA2 at serine 505 increased enzyme activity and release of arachidonic acid. This is a causal demonstration in experimental models, because the mutation of the site altered the biological outcome. However, it does not prove that ERK is the only MAP kinase involved, that cPLA2 is regulated solely by phosphorylation, nor that chronic insulin signaling is the primary activator of the enzyme in all tissues.The narrative of the paragraph indeed requires other steps: intracellular calcium promotes the transfer of cPLA2 to suitable membranes, and the overall response varies depending on the stimulus. For this reason, the original work precisely supports the link between phosphorylation and the mobilization of arachidonic acid, but it does not exhaust the regulation of cPLA2

nor its clinical consequences.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation particularly close to the original result came from experiments with human cPLA2 modified in HEK293 cells. The Ser505Ala substitution reduced the enzyme's affinity for membranes containing phosphatidylcholine, especially at low calcium concentrations. After stimulation with ionomycin, cells expressing normal cPLA2 or a variant mimicking phosphorylation released arachidonic acid, whereas the Ser505Ala variant showed little release and did not adequately reach the perinuclear region. This study confirms that serine 505 phosphorylation promotes stable interaction with the membrane and supports the pathway: phosphorylation access to phospholipids arachidonic acid release. It is solid mechanistic evidence, but it was obtained in transfected cells and not in humans [1].A second study examined rabbit vascular smooth muscle cells stimulated with noradrenaline. Stimulation first increased cPLA2 phosphorylation at serine 515 and subsequently ERK1/2 activation and phosphorylation at serine 505. The ERK1/2 inhibitor reduced phosphorylation at serine 505; furthermore, the combined Ser515Ala/Ser505Ala mutation blocked both cPLA2 phosphorylation and arachidonic acid release. The work confirms that the ERK component can contribute to serine 505 phosphorylation, but it also shows that an upstream signal linked to calcium and CaMKII kinase participates in the sequence. The confirmation is direct for the vascular model studied, but not automatically transferable to other tissues [2].A third study, conducted in human HEK cells, showed that the Ser505Ala variant reached internal membranes more slowly after an increase in intracellular calcium or levels of phosphatidylinositol 4,5-bisphosphate, a regulatory membrane lipid. In four experiments, arachidonic acid release by the Ser505Ala variant was lower than that of the normal protein under various stimulation conditions, with differences reported as statistically significant. This confirms the paragraph's premise that calcium, membrane, and phosphorylation work together: calcium does not necessarily replace serine 505 phosphorylation, but acts in concert with it to allow for effective mobilization of arachidonic acid [3].

7. CONFLICTING EVIDENCE

A study on murine peritoneal macrophages confirmed that cPLA2 is necessary for the release of arachidonic acid and the production of eicosanoids, which are lipid mediators derived from arachidonic acid. However, it also showed that the relationship between ERK, serine 505 phosphorylation, and arachidonic acid release is not linear under all conditions. ERK and p38 contributed to serine 505 phosphorylation, but ERK inhibition reduced the release induced by certain stimuli even when serine 505 phosphorylation remained unchanged. Conversely, ERK inhibition did not reduce the release caused by the calcium ionophore alone [4].This evidence does not negate the results of the original study. Rather, it indicates that, in macrophages and for specific agonists, ERK can influence the release of arachidonic acid through additional mechanisms as well, likely including transcriptional regulation and new protein synthesis. The limitation of the chain proposed in the book is therefore the presentation of MAPK/ERK as the sole or universally primary activator: the regulation of cPLA2 depends on the cell type, the stimulus, calcium, and additional signaling pathways.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table summarizes the contribution of the original study and independent publications to the specific MAP kinase–cPLA2–arachidonic acid release chain.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and biochemical	cPLA2 protein, Ser-505 site mutagenesis, and intact cells; full details not available in the abstract	Phosphorylation by MAP kinase increases cPLA2 activity; the Ser-505→Ala mutation drastically reduces induced arachidonate release.	direct confirmation	moderate
[1]	Cellular, biochemical, and mutagenesis	Human cPLA2 and transfected HEK293 cells	Ser505Ala reduces interaction with the membrane, cellular translocation, and arachidonic acid release; Ser505Glu preserves function.	direct confirmation	moderate
[2]	Cellular and mutagenesis	Rabbit vascular smooth muscle cells	ERK1/2 phosphorylation at serine 505 contributes to arachidonic acid release; the double mutation Ser515Ala/Ser505Ala blocks it.	direct confirmation	moderate
[3]	Cellular and imaging	Stably transfected human HEK cells	Ser505Ala delays translocation to internal membranes and reduces arachidonic acid release following stimuli involving calcium or membrane lipids.	indirect confirmation	moderate
[4]	Cellular and genetic	Murine peritoneal macrophages, including cPLA2-deficient macrophages	ERK contributes to arachidonic acid release, but some effects persist without changes in Ser505 phosphorylation and are stimulus-dependent.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The original study directly supports that the phosphorylation of cPLA2 at serine 505 by a MAP kinase increases the enzyme's function and that the loss of this site reduces arachidonic acid release following cellular stimulation. Independent evidence confirms that this modification promotes interaction with membranes, translocation, and the release of arachidonic acid.

The narrative is therefore well-supported at a mechanistic level for the MAP kinase–cPLA2–lipid mobilization pathway. However, it remains to be validated, through appropriate human studies, whether this chain extends to chronic insulin signaling, the actual production of inflammatory mediators in specific tissues, and clinical outcomes. The regulation of cPLA2 is multifactorial and cannot be reduced to a single signaling pathway.

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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