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

ORIGINAL RESEARCH
ISSN 2845-7501

PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent p42/44 MAPK activation and EGFR transactivation - Review of the evidence

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study examined whether prostaglandin E2 (PGE2), a lipid mediator produced during inflammation, induces cardiac myocyte growth through the EP4 receptor and the epidermal growth factor receptor (EGFR). In primary cultures of neonatal rat ventricular myocytes, PGE2 increased protein synthesis, cell area, and the activity of a hypertrophy marker. Blocking EP4 only partially reduced protein synthesis, while EGFR inhibition abolished it in the available experimental model.The publication contributes to the section of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi dedicated to the PGE2 → EP4 → EGFR sequence. Independent evidence confirms that PGE2 can promote hypertrophic characteristics in cardiomyocytes and that EP4 signaling can increase EGFR network activation in murine gastric tumors. However, the role of EP4 in the heart is not uniquely pro-growth: in ischemia-reperfusion models, its signaling has been shown to be protective. The confirmation is therefore primarily mechanistic and dependent on the biological context.

ONLINE ARTICLE

ARTICLE INFORMATION

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

DOI 10.5281/zenodo.24495661

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 PGE2 could induce cardiac myocyte growth through the EP4 receptor, a membrane receptor that receives the prostaglandin signal, and through EGFR, a surface protein capable of initiating cell growth programs. The authors initially hypothesized an EP4 cyclic AMP protein kinase A (PKA) pathway, which is the most well-known pathway linked to EP4. The results, however, indicated a different pathway: PGE2 activated EP4, promoted the phosphorylation of EGFR and the p42/44 MAPK pathway (proteins that transmit growth signals), and increased protein synthesis.The relevance to section 5.6 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is precise: the publication documents, in cultured cardiac myocytes, the PGE2 EP4 EGFR transactivation MAPK segment increase in hypertrophy indicators. Transactivation means that one receptor, in this case EP4, indirectly activates a second receptor, EGFR, without the latter necessarily having to bind its usual ligand.This experiment can demonstrate a pharmacologically consistent sequence in neonatal rat cells. It cannot demonstrate that the same process occurs with identical intensity in the human heart, nor that PGE2 produced during hyperinsulinemia alone causes chronic inflammation, tumors, metastases, or activation of the PI3K-AKT-mTOR pathway in living people.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is experimental, conducted *in vitro* on primary cultures of neonatal rat ventricular myocytes. The number of animals, the number of independent cultures, and the inclusion or exclusion criteria are not reported in the available material, which consists only of the abstract.Cell growth was primarily assessed by measuring the incorporation of tritium-labeled leucine into the total protein fraction: an increase in this signal indicates higher protein synthesis. The authors also measured the surface area of the cells and the activity of the atrial natriuretic factor promoter, a gene frequently used as an indicator of hypertrophic response in myocytes.To reconstruct the signaling pathway, an EP4 antagonist, a PKA inhibitor, the selective EGFR inhibitor AG-1478, and the p42/44 MAPK pathway inhibitor PD-98053 were used at a concentration of 25 micromoles per liter. The phosphorylation of EGFR and p42/44 MAPK was evaluated using cellular protein analysis; for EGFR, immunoprecipitation is reported, a technique that isolates a specific protein to verify its modifications. Exposure durations, PGE2 concentrations, statistical details, P-values, and the number of replicates are not reported in the available material.

4. RESULTS

PGE2 increased three indicators consistent with hypertrophic myocyte growth: leucine incorporation into proteins, cell surface area, and atrial natriuretic factor promoter activity. In simple terms, the treated cells produced more protein and displayed characteristics associated with an increase in their size. Absolute values, percentage changes, and P-values are not reported in the available material.The EP4 antagonist partially reduced the increase in protein synthesis induced by PGE2 and prevented the increase in cell area and atrial natriuretic factor promoter activity. This distinction is essential: the available abstract does not report that blocking EP4 completely abolished protein synthesis. The PKA inhibitor did not modify the increase in protein synthesis, making it unlikely that the classic cyclic AMP-PKA pathway was the primary mediator of the observed effect.PGE2 rapidly induced EGFR phosphorylation, a molecular modification consistent with receptor activation. The EP4 antagonist blocked this phosphorylation. Conversely, the EGFR inhibitor AG-1478 completely abolished the increase in protein synthesis induced by PGE2. Phosphorylation of p42/44 MAPK also increased rapidly following PGE2 and was inhibited by both EP4 blockade and EGFR inhibition. Finally, PD-98053 blocked the increase in protein synthesis. Overall, the data support the PGE2 EP4 EGFR p42/44 MAPK protein synthesis pathway in the cell model studied.

5. INTERPRETATION

The most biologically relevant finding is that PGE2 did not act merely as a passive inflammatory signal. In cultured heart cells, it activated a network capable of increasing protein production, a characteristic trait of the hypertrophic response. Experimental details indicate that EP4 contributes to the signal and that

EGFR and p42/44 MAPK are necessary nodes for the observed increase in protein synthesis.The segment specifically documented for the book's paragraph is the EP4-dependent transactivation of EGFR. However, the statement that both EP4 antagonism and EGFR inhibition would completely abolish protein synthesis requires clarification: the available material reports a partial block of protein synthesis with the EP4 antagonist and a complete block with AG-1478, the EGFR inhibitor. This leaves open the possibility that PGE2 also utilizes additional receptors or mechanisms beyond EP4.The research did not measure AKT, PI3K, or mTOR. Therefore, it does not directly document the connection to the insulin-PI3K-AKT-mTOR axis described in the paragraph, nor does it establish that hyperinsulinemia increases PGE2 in this model. Its contribution is more circumscribed and solid: it demonstrates a PGE2-EP4-EGFR-MAPK cellular pathway associated with an increase in growth indicators in neonatal rat myocytes.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation in cardiac tissue comes from a study on neonatal rat cardiomyocytes. PGE2 increased protein synthesis, cell size, and the expression of hypertrophy markers in a dose-dependent manner. It also increased the phosphorylation of p42/44 MAPK and p38 MAPK; inhibition of the MEK1/2 kinase, located upstream of p42/44 MAPK, reduced PGE2-induced protein synthesis. The selective EP4 antagonist significantly inhibited the reduction of skeletal alpha-actin expression induced by PGE2. This study independently confirms the PGE2 MAPK hypertrophic characteristics pathway and supports a contribution from EP4, but does not directly verify EGFR transactivation [1].A second line of research, in a different biological context, strengthens the link between EP4 and EGFR. In transgenic mice with gastric tumors, activation of the PGE2 pathway was associated with an increase in EGFR ligands and ADAM proteases, enzymes that can release and make these ligands available. Inhibition of EP4 suppressed the increase of these molecules. The authors thus identified a mechanism through which the PGE2-EP4 signal can enhance EGFR activity in vivo, albeit through a slower regulation of gene expression and the tumor environment, rather than the rapid phosphorylation observed in myocytes [2].The two publications build a convergent but incomplete confirmation of the book's chain. The first replicates the growth and MAPK component in cardiomyocytes; the second shows that EP4 can support the EGFR network in an animal model of gastric cancer. Neither demonstrates that this sequence triggers the entirety of the inflammatory, proliferative, or metabolic programs discussed in the paragraph in humans.

7. CONFLICTING EVIDENCE

A relevant experimental result shows that EP4 activation is not necessarily harmful in the heart. In mice subjected to ischemia followed by reperfusion—that is, a temporary interruption and subsequent restoration of coronary blood flow—mice lacking EP4 developed more extensive heart attacks compared to controls. Furthermore, an EP4 agonist significantly reduced infarct size in normal mice. The EP4 signal therefore had a cardioprotective effect in that model [3].This evidence does not refute the fact that PGE2 can increase protein synthesis in cultured myocytes. However, it shows that the pathophysiological significance of EP4 varies according to cell type, duration of the stimulus, presence of ischemia, competing receptors, and tissue context. It is therefore not justified to transform the PGE2 EP4 EGFR cellular mechanism into a general rule that EP4 always promotes pathological remodeling or inflammation.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent research used to evaluate the PGE2 → EP4 → EGFR pathway and its cellular consequences.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Cultured neonatal rat ventricular myocytes	PGE2 increased protein synthesis; EP4 contributed to EGFR and MAPK phosphorylation; EGFR inhibition abolished the induced protein synthesis.	direct confirmation	moderate
[1]	Experimental cellular	Cultured neonatal rat cardiomyocytes	PGE2 increased protein synthesis, cell size, and MAPK phosphorylation; MEK1/2 inhibition reduced the induced protein synthesis.	indirect confirmation	moderate
[2]	Animal and cellular	Transgenic mice with gastric tumors, macrophages, and gastric epithelium	EP4 inhibition reduced the increase in EGFR ligands and ADAM proteases associated with the PGE2 pathway.	biologically consistent evidence	moderate
[3]	Animal	EP4-deficient mice and normal mice with cardiac ischemia-reperfusion	Loss of EP4 increased infarct size; an EP4 agonist reduced it in normal mice.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study convincingly supports, within its cellular model, that PGE2 can activate EP4, transactivate EGFR, activate p42/44 MAPK, and increase protein synthesis in neonatal rat ventricular myocytes. The narrative in the book chapter is therefore well-supported at a mechanistic level for this specific segment.However, a substantial clarification is necessary: the EP4 antagonist only partially, not completely, reduced the protein synthesis induced by PGE2; complete blockage was observed with the EGFR inhibitor. Independent studies confirm components of the chain but do not demonstrate the entire inflammation-metabolism-cell growth sequence in humans. The role of EP4 appears to be context-dependent and requires further clinical validation.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Prostaglandin E2 Induces Hypertrophic Changes and Suppresses a-Skeletal Actin Gene Expression in Rat Cardiomyocytes**
Miyatake et al., 2007
Journal of Cardiovascular Pharmacology
DOI: https://doi.org/10.1097/FJC.0b013e318145ae2e

[2] **Activation of epidermal growth factor receptor signaling by the prostaglandin E2 receptor EP4 pathway during gastric tumorigenesis**
Oshima et al., 2011
Cancer Science
DOI: https://doi.org/10.1111/j.1349-7006.2011.01847.x

[3] **Prostaglandin E 2 Protects the Heart From Ischemia-Reperfusion Injury via Its Receptor Subtype EP 4**
Xiao et al., 2004
Circulation
DOI: https://doi.org/10.1161/01.CIR.0000128046.54681.97