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Activation of epidermal growth factor receptor signaling via the prostaglandin E2 EP4 receptor pathway during gastric tumorigenesis - Evidence review

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1. ABSTRACT

The analyzed study examined whether prostaglandin E2 (PGE2), a lipid mediator of inflammation, can indirectly activate the epidermal growth factor receptor (EGFR), a membrane protein that transmits cell growth and survival signals. In transgenic mouse models of gastric cancer, the PGE2 pathway increased the expression of EGFR ligands and ADAM proteases, enzymes that can release these ligands and make them available to activate the receptor. Blocking EP4 suppressed this induction; the combination of EGFR and COX-2 inhibitors significantly reduced tumorigenesis in mice.In Chapter 5 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the PGE2 → EP4 → EGFR activation pathway, included in the description of a circuit between inflammation and growth signals. Independent studies confirm that PGE2 can activate EGFR and downstream signals in gastric, intestinal, colon cancer, and cardiac cells. However, the effects of EP4 depend on the cell type: in some human gastric carcinoma lines, its stimulation reduced, rather than increased, proliferation. The confirmation is therefore primarily mechanistic.

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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.

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2. ANALYZED STUDY

The research question was whether PGE2 signaling could explain EGFR activation *in vivo* during the development of gastric tumors. The authors evaluated the hypothesis that the EP4 receptor, one of the four cellular receptors for PGE2, promotes EGFR activation by increasing the availability of its ligands and the enzymes that release them from the cell surface.The relevance to Chapter 5 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is specific. The book describes PGE2 as a signal that, through EP4, can reactivate EGFR and amplify cellular growth programs. The study analyzed documents precisely the PGE2/EP4 EGFR ligands and ADAM proteases EGFR activation segment in the context of murine gastric tumors. It does not, however, evaluate hyperinsulinemia, arachidonic acid production, nor does it directly demonstrate the entire PI3K–AKT–mTOR sequence in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors report using transgenic mice that developed gastric tumors following oncogenic activation and induction of the PGE2 pathway. They compared the expression of EGFR ligands, including amphiregulin and epiregulin, and ADAM proteases in gastric tumors. ADAMs are enzymes that can cleave and release portions of membrane proteins, including certain EGFR ligands.A selective EP4 inhibitor and treatments capable of inhibiting EGFR and COX-2 were also used. COX-2 is the enzyme that contributes to the production of PGE2. The abstract also reports on experiments involving activated macrophages and gastric epithelial cells to distinguish between potential direct effects of EP4 signaling and indirect effects associated with inflammation.The number of animals and cell cultures, inclusion and exclusion criteria, dosages, treatment duration, detailed analytical methods, predefined endpoints, and statistical procedures are not reported in the available material.

4. RESULTS

In murine gastric tumors, activation of the PGE2 pathway was associated with a significant increase in the expression of four EGFR ligands: epiregulin, amphiregulin, HB-EGF, and betacellulin. The expression of ADAM8, ADAM9, ADAM10, and ADAM17 was also increased. In simple terms, the tumor possessed more molecules capable of providing EGFR with the signal required for activation, as well as more enzymes potentially capable of making them available.Inhibition of the EP4 receptor suppressed the broad induction of EGFR ligands and ADAMs. In activated macrophages, EP4 signaling induced amphiregulin and epiregulin. In gastric epithelial cells, however, EP4 was necessary for the basal expression of epiregulin. ADAMs were not directly induced by PGE2 in these cells; the authors therefore proposed an indirect mechanism, likely mediated by the inflammatory response associated with PGE2.The combination of EGFR and COX-2 inhibitors significantly suppressed gastric tumorigenesis in transgenic mice. The abstract does not report absolute values, reduction percentages, P-values, confidence intervals, or experimental sample sizes. The result supports a functional link between the COX-2/PGE2, EP4, and EGFR pathways in the mouse model, but the available material does not quantify the precise magnitude of the effect nor demonstrate a clinical benefit in humans.

5. INTERPRETATION

The primary biological significance is that a molecule produced during inflammation can increase the signals that promote the activation of a receptor involved in cell growth. In the model studied, PGE2 does not appear to be merely an end product of inflammation: through EP4, it contributes to increasing EGFR ligands and ADAM proteases, creating favorable conditions for EGFR signaling.The technical detail is a form of transactivation: EP4, despite being a different receptor from EGFR, can indirectly promote the activation of EGFR. The authors indicate that this occurs through the induction of amphiregulin, epiregulin, and other ligands, not necessarily through a single rapid intracellular mechanism. The most directly documented segment is therefore PGE2 EP4 increase of EGFR and ADAM ligands EGFR activation in mouse gastric cancer.This finding is consistent with the passage in the book, but requires clarification: the study does not demonstrate that EP4 directly increases the expression of the EGFR receptor itself. It primarily demonstrates the increase of molecules that can activate it. Furthermore, the

PI3K–AKT–mTOR axis is only partially represented in the available abstract: it is not possible to attribute to the study a complete demonstration of the entire molecular circuit described in the book.

6. INDEPENDENT CONFIRMING EVIDENCE

Initial confirmation of the general link between PGE2 and EGFR comes from experiments in normal gastric epithelial cells and colon carcinoma cell lines. Pai and colleagues observed that PGE2 rapidly induced EGFR phosphorylation—the biochemical activation of the receptor—and the ERK2 signal, which is involved in proliferation. Blocking EGFR reduced ERK2 activation, *c-fos* expression, and proliferation induced by PGE2. Blocking metalloproteases, TGF-alpha, or c-Src interrupted the transactivation, supporting a chain that includes ligand release and EGFR activation [1]. This study confirms the PGE2 EGFR pathway and the possible involvement of enzymes that release ligands, but it does not identify EP4 as the responsible receptor.In colorectal carcinoma lines, Buchanan and colleagues showed that PGE2 induced EGFR phosphorylation and the activation of AKT—a protein that transmits survival and cell movement signals—within minutes. EGFR tyrosine kinase inhibitors abolished the AKT activation induced by PGE2. Cell migration and invasion increased by PGE2 were therefore dependent on EGFR transactivation [2]. The work confirms the EGFR PI3K/AKT segment of the narrative, but in colon tumor cells and without demonstrating the involvement of EP4 or mTOR.More direct support for the EP4 EGFR segment comes from primary cultures of neonatal ventricular myocytes. Mendez and LaPointe observed that PGE2 rapidly phosphorylated EGFR; an EP4 antagonist blocked this phosphorylation. The EGFR inhibitor AG-1478 abolished PGE2-induced protein synthesis, while the EP4 antagonist only partially reduced it. The activation of p42/44 MAPK, a pathway that regulates cell growth, was also inhibited by blocking EP4 and EGFR [3]. The causal sequence is well demonstrated in these cells, but cardiac tissue is not a gastric tumor.Overall, independent research converges on the possibility that PGE2 activates EGFR and downstream signals involved in growth, migration, or protein synthesis. The originality of the analyzed study lies in having placed this relationship within the microenvironment of murine gastric tumors and in having linked EP4 to the induction of multiple EGFR and ADAM ligands.

7. CONFLICTING EVIDENCE

A relevant result, albeit in the opposite direction, was observed in four human gastric carcinoma cell lines. Okuyama and colleagues detected the expression of EP2 and EP4 in all examined lines and observed that selective EP2 or EP4 agonists induced a reduction in proliferation, accompanied by an increase in cyclic AMP, a cellular messenger [4].This study did not evaluate EGFR transactivation and does not directly refute the mechanism observed in the mouse model. However, it shows that EP4 activation does not necessarily produce a proliferative effect in every gastric context. The response may depend on the cell line, the presence of other receptors, dominant intracellular signals, and the inflammatory microenvironment—elements that a simplified cell culture does not fully reproduce.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the evidence obtained in the original study from independent verifications and the relevant conflicting result.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Transgenic mice with gastric tumors; macrophages and gastric epithelial cells	The PGE2/EP4 pathway increases EGFR and ADAM ligands; blocking EP4 suppresses induction.	direct confirmation	moderate
[1]	Cellular	Normal gastric epithelial cells and colon carcinoma lines	PGE2 rapidly increases EGFR phosphorylation and ERK signaling; EGFR inhibitors reduce proliferation and downstream signals.	indirect confirmation	moderate
[2]	Cellular and human samples	Colorectal carcinoma lines and comparison between normal and malignant colorectal tissues	PGE2 rapidly activates EGFR and AKT; blocking EGFR eliminates AKT activation and reduces migration and invasion.	biologically consistent evidence	moderate
[3]	Cellular	Primary cultured neonatal ventricular myocytes	Blocking EP4 prevents PGE2-induced EGFR phosphorylation; EGFR inhibition blocks protein synthesis.	direct confirmation	moderate
[4]	Cellular	Four human gastric carcinoma cell lines	Selective EP2 and EP4 agonists reduce proliferation and increase cyclic AMP.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports, in a murine model of gastric cancer, that PGE2 signaling through EP4 promotes EGFR activation by increasing ligands and proteases that facilitate its activation. Independent literature confirms that PGE2 can transactivate EGFR and activate downstream cellular signals, including AKT, and that EP4 can participate in this connection.The proposed narrative is therefore well-supported at a mechanistic level. However, important limitations remain: the models are primarily animal or cellular, effects can vary between tissues and tumor cell lines, and it has not been demonstrated that the entire PGE2–EP4–EGFR–PI3K–AKT–mTOR chain operates in the same way in human gastric tumors. Independent validation on human samples and clinically oriented studies are necessary.

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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 transactivates EGF receptor: A novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy**
Pai et al., 2002
Nature Medicine
DOI: https://doi.org/10.1038/nm0302-289

[2] **Prostaglandin E2 Regulates Cell Migration via the Intracellular Activation of the Epidermal Growth Factor Receptor**
Buchanan et al., 2003
Journal of Biological Chemistry
DOI: https://doi.org/10.1074/jbc.M302474200

[3] **PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent activation of p42/44 MAPK and EGFR transactivation**
Mendez et al., 2005
American Journal of Physiology-Heart and Circulatory Physiology
DOI: https://doi.org/10.1152/ajpheart.00838.2004

[4] **Activation of prostaglandin E2-receptor EP2 and EP4 pathways induces growth inhibition in human gastric carcinoma cell lines**
Okuyama et al., 2002
Journal of Laboratory and Clinical Medicine
DOI: https://doi.org/10.1067/mlc.2002.125784