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Prostaglandin E2 regulates cell migration through intracellular activation of the epidermal growth factor receptor - Evidence review

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1. ABSTRACT

The analyzed study examined how prostaglandin E2 (PGE2), a lipid mediator produced during inflammation, can increase the motility of colorectal carcinoma cells. In cell cultures, PGE2 rapidly induced the phosphorylation—that is, the functional activation—of the epidermal growth factor receptor (EGFR) and the AKT protein, which is involved in survival and motility signaling. Selective EGFR inhibitors abolished the PGE2-induced AKT activation and the migratory response.In sections 5.6 and 5.7 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that PGE2 can activate EGFR and link to PI3K–AKT signaling. Independent evidence confirms that PGE2 can transactivate EGFR in gastrointestinal cells, that EP4 may participate in this connection, and that the axis can activate growth programs. However, the mechanism varies between tissues and experimental models; it does not, by itself, demonstrate a clinical effect in humans or a universal PGE2–EP4–EGFR–AKT–mTOR sequence.

ONLINE ARTICLE

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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 how PGE2 could activate the PI3K–AKT pathway (phosphoinositide 3-kinase–AKT, a network that transmits signals for cell growth, survival, and movement) in colorectal carcinoma cells. The authors evaluated the hypothesis that this activation depended on EGFR transactivation: in simple terms, a signal received by a PGE2 receptor would indirectly switch on a second receptor, EGFR.The relevance to the book's sections is precise. The publication documents the segment PGE2 EGFR activation AKT activation increased cell migration. It does not directly demonstrate that PGE2 necessarily acts through EP4 in this specific experiment, nor does it demonstrate the entire progression up to mTOR. Furthermore, as this is primarily cellular research, it cannot establish that the same circuit determines the clinical progression of human tumors.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The study used colorectal carcinoma cells and examined the effects of PGE2 exposure on EGFR phosphorylation and AKT activation. Selective EGFR tyrosine kinase inhibitors were used, which are experimental drugs capable of preventing the receptor's enzymatic activity.The authors also evaluated cell migration and invasion, two behaviors that, in culture, indicate an increased ability of cells to move and cross an artificial barrier. They studied the involvement of Src, a protein that transmits intracellular signals, and compared normal and malignant human colon samples to observe EGFR transactivation in vivo. The number of cultures, the number of human samples, selection criteria, complete concentrations, detailed experimental timelines, operational endpoints, and statistical analyses are not reported in the available material.

4. RESULTS

The main finding is that PGE2 activated EGFR within minutes in colorectal carcinoma cells. This activation was detected as receptor phosphorylation, a chemical modification that generally indicates the switching on of its signaling activity.Immediately following exposure to PGE2, AKT activation also increased. Specific EGFR inhibitors completely abolished the PGE2-induced activation of AKT. In practical terms, when EGFR was blocked, PGE2 was no longer able to switch on AKT in the available experimental model.The authors also report that PGE2 increased cell migration and invasion, and that these effects depended on EGFR transactivation. The rapid transactivation was found to be associated with an intracellular event mediated by Src, rather than the external release of an epidermal growth factor-like ligand. Differences consistent with EGFR transactivation were also observed when comparing samples of normal and malignant colon tissue. Numerical values, effect sizes, P-values, and confidence intervals are not reported in the available material.

5. INTERPRETATION

The biological significance is that a molecule produced during inflammation can rapidly modify the behavior of a tumor cell without necessarily having to enter the nucleus or immediately change gene expression. PGE2 can activate a membrane receptor for growth factors, EGFR, which in turn can transmit the signal to AKT. AKT represents a hub that can promote survival, movement, and, in other contexts, cell growth.The pathway demonstrated by the publication subject to the Evidence Review is PGE2 Src EGFR AKT migration/invasion in colorectal carcinoma cells. The most robust conclusion is therefore mechanistic and limited to the model studied: EGFR activity was necessary for the response to AKT and for the migration induced by PGE2.The result is consistent with the narrative in paragraphs 5.6 and 5.7, but requires some distinctions. The study does not identify EP4 as a necessary receptor in its model. It does not measure mTOR, the regulator of protein synthesis and cell growth located further downstream of the PI3K–AKT pathway. Furthermore, it does not demonstrate that hyperinsulinemia is the cause of PGE2 production in people with tumors or metabolic diseases.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the initial part of the chain comes from normal gastric epithelial cells and multiple colon carcinoma cell lines. In this study,

PGE2 rapidly induced EGFR phosphorylation and the activation of ERK2, a protein in the MAPK pathway involved in the transmission of growth signals. EGFR inhibitors reduced the PGE2-induced activation of ERK2, c-fos expression, and proliferation. However, the proposed mechanism differed from that of the original study: here, transactivation depended on metalloproteinases, TGF-alpha, and Src, suggesting the release of an external ligand for EGFR [1]. This difference indicates that PGE2 can reach EGFR through alternative biological pathways.A second study verified the PGE2–EP4–EGFR axis in neonatal rat ventricular myocytes. The EP4 antagonist partially reduced the increase in protein synthesis induced by PGE2 and prevented the increase in cell area; furthermore, it blocked the rapid phosphorylation of EGFR. The EGFR inhibitor AG-1478 abolished the protein synthesis induced by PGE2. The result confirms that, in non-tumor tissue, EP4 can be upstream of EGFR, but the outcome was cardiac cell hypertrophy rather than tumor cell migration [2].A mouse model of gastric tumorigenesis provided a step closer to the book's narrative. In mouse gastric tumors, pharmacological blockade of EGFR reduced tumor growth, and inhibition of the PGE2 pathway reduced the phosphorylation of AKT and ERK1/2. The authors observed that EP4 was the most highly expressed PGE2 receptor in their model and concluded that the PGE2–EP4 signal promoted EGFR activation through the induction of EGFR ligands and ADAM proteases. This is an in vivo confirmation of the PGE2–EP4–EGFR convergence, but obtained in mice and in the context of gastric tumorigenesis [3].A further cellular study showed that stimulation of EP4, but not EP2, could activate PI3K and ERK and induce EGR-1, an early regulator of gene activity associated with the growth response. Blocking PI3K eliminated ERK activation. This evidence confirms the functional link between EP4 and PI3K, but it does not measure EGFR or AKT and uses HEK-293 cells modified to express human receptors [4]. Overall, the publications converge on the fact that PGE2 can activate EGFR and downstream signals, while the molecular details depend on the cell and tissue examined.

7. CONFLICTING EVIDENCE

A conflicting element concerns the idea that EP4 activation always leads to cell growth. In four human gastric carcinoma cell lines, selective EP2 and EP4 agonists reduced proliferation and increased cAMP, a molecule that transmits intracellular signals. Therefore, EP4 activation does not necessarily have a proliferative effect in all tumors or under all experimental conditions [5].This evidence does not refute the original study's observation regarding PGE2-induced migration via EGFR in colorectal cells. However, it scales back the scope of the narrative: the receptor involved, the downstream signal, and the final effect can change depending on the cell type, the availability of EGFR ligands, and other active intracellular circuits. No sufficiently relevant directly conflicting evidence has been identified regarding the rapid activation of EGFR by PGE2; this does not prove the absence of contradictory results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study subject to the Evidence Review from independent research. The strength of the evidence refers to the specific PGE2–EP4/EGFR–downstream signaling chain, not to the efficacy of treatments in humans.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular with human sample comparison	Colorectal carcinoma cells; normal and malignant colon samples	PGE2 activated EGFR and AKT; EGFR blockade abolished AKT activation and PGE2-induced migration.	direct confirmation	moderate
[1]	Cellular	Normal gastric epithelial cells and colon carcinoma lines	PGE2 increased EGFR and ERK2 phosphorylation; EGFR inhibitors reduced PGE2-induced signaling and proliferation.	direct confirmation	moderate
[2]	Cellular	Neonatal rat ventricular myocytes	EP4 blockade prevented EGFR phosphorylation; EGFR inhibition abolished PGE2-induced protein synthesis.	indirect confirmation	moderate
[3]	Animal and cellular	Murine models of gastric tumorigenesis	PGE2–EP4 signaling promoted EGFR activation; inhibition of PGE2 or EGFR pathways reduced downstream signaling and tumor growth.	indirect confirmation	moderate
[4]	Cellular	HEK-293 cells with stably expressed human EP2 or EP4 receptors	EP4, but not EP2, activated PI3K–ERK and EGR-1 expression; PI3K inhibition eliminated ERK activation.	biologically consistent evidence	preliminary
[5]	Cellular	Four human gastric carcinoma lines	Selective EP2 and EP4 agonists reduced cell proliferation.	discordant evidence	low

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the idea that PGE2 can rapidly activate EGFR and AKT, promoting migration and invasion in colorectal carcinoma cells. Blocking EGFR eliminated these responses in the experimental model. Independent literature confirms that PGE2 can converge on EGFR and that EP4 may participate in linking to growth pathways in certain tissues.The narrative is therefore supported primarily at a mechanistic level. It is incorrect to automatically extend these results to all tumors, all tissues, or people with hyperinsulinemia. In particular, EP4 does not always produce a proliferative effect, and the progression to mTOR requires specific validation in the models and populations of interest.

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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