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Eicosanoids in cancer: the prostaglandin E2 receptor 4 in oncology and immunotherapy - A review of the evidence

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1. ABSTRACT

The study analyzed is a narrative review examining the role of prostaglandin E2 (PGE2), a lipid mediator produced during inflammation, and its EP4 receptor in tumor progression. The authors synthesize experimental findings suggesting that EP4 activation can support proliferation, migration, invasion, metastasis, cancer stem-like cell properties, treatment resistance, and a reduction in the immune response against the tumor. For this reason, pharmacological blockade of EP4 is proposed as a potential strategy to be studied in combination with chemotherapy or immunotherapy.In section 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 the COX-2/PGE2/EP4 inflammatory pathway can converge on cellular growth signals, including PI3K/AKT and MAPK-ERK, and can influence the tumor immune microenvironment. Independent studies show that EP4 antagonists have increased sensitivity to docetaxel in cell models, attenuated myeloid immunosuppression in animal models, and reached initial human trials. However, there are results that depend on the tumor type: in some gastric carcinoma cell lines, EP4 activation reduced, rather than increased, proliferation. Overall, the therapeutic hypothesis is supported primarily at the mechanistic and preclinical level; the clinical efficacy of these combinations requires more robust comparative confirmation.

ONLINE ARTICLE

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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 the PGE2 EP4 receptor could represent a useful target against cancer. In simple terms, the authors evaluated whether interrupting one of the signals through which inflammation can help a tumor grow, spread, and evade immune control might be of therapeutic interest.The central hypothesis is that increased activity of cyclooxygenase-2, or COX-2 (an enzyme that converts arachidonic acid into prostaglandins), increases PGE2. The latter can bind to EP4, a receptor located on the membrane of tumor cells and immune cells. The activation of EP4 can involve PI3K/AKT and MAPK-ERK, which are pathways that help the cell receive survival and growth signals.The relevance to the book's paragraph is therefore specific: the study was used to argue that PGE2-EP4 signaling can link inflammation, proliferative pathways, and a reduction in antitumor defenses, making it rational to investigate EP4 antagonist drugs in combination with chemotherapy or immunotherapy. As it is a narrative review, however, it does not produce new experimental data nor does it demonstrate that an EP4 antagonist improves clinical outcomes in patients.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the literature, not an original clinical, animal, or cellular study. The authors described studies concerning the expression of COX-2, PGE2, and EP4 in different epithelial tumors and experimental studies on EP4 antagonists.The full text available does not report a systematic bibliographic search strategy, databases consulted, search period, inclusion or exclusion criteria, article selection procedure, or a formal risk of bias assessment. Therefore, there is no overall number of participants or experiments, a single control group, predefined endpoints, or a quantitative meta-analysis available.The review integrates results obtained from cell lines, mouse models, human samples, and early clinical trials available at the time. This approach is useful for outlining biological plausibility and identifying research directions, but it does not allow for an accurate estimation of the clinical efficacy or safety of a therapeutic strategy based on EP4 blockade.

4. RESULTS

The main result of the publication is a summary: in numerous experimental models, PGE2 acting through EP4 is associated with an increase in signals favorable to tumor growth and spread. The authors report that EP4 can activate ERK, cAMP/PKA, PI3K/AKT, and NF-kB. Simply put, these circuits can help some tumor cells multiply, move through tissues, resist cell death, and adapt to unfavorable conditions.Particularly relevant to this section of the book is the description of the activation of PI3K/AKT and MAPK-ERK by the PGE2/EP4 axis. The review also reports that EP4 antagonists or the reduction of receptor expression decreased migration, invasion, and metastasis in various preclinical models of breast, prostate, colon, and lung cancer. Quantitative values comparable across all studies are not reported in the available material, because the publication does not perform an aggregated analysis.A second relevant result concerns antitumor immunity. PGE2, through EP4, can reduce the activity of natural killer or NK cells (lymphocytes capable of recognizing and killing abnormal cells) and promote myeloid-derived suppressor cells, known as MDSCs. The authors describe that blocking EP4 countered these effects in experimental models. Finally, the review reports that some EP4 antagonists improved the response to chemotherapeutic agents in cells or animals and that drugs of this class had entered early clinical trials.

5. INTERPRETATION

The biological significance of this review is that an inflammatory signal does not necessarily remain confined to inflammation. When PGE2 activates EP4, it can contribute to converging messages from the tumor environment onto pathways that regulate growth, cellular resource utilization, movement, and survival.Within the scope of the book's paragraph, the segment actually documented by the publication is: increased COX-2 activity and PGE2 production activation of EP4 involvement of PI3K/AKT and MAPK-ERK, with potential proliferative and immunosuppressive consequences. The mTOR complex, a regulator of cellular component synthesis and growth, is consistent with this chain because it is located downstream of AKT, but this review does not provide a unique and direct demonstration of the

entire PGE2/EP4/PI3K/AKT/mTOR sequence in every tumor.Therapeutic interpretation must therefore be cautious. The results make it biologically plausible to test EP4 antagonists, particularly in combination with chemotherapy or immunotherapy. However, they do not demonstrate that such drugs are already effective, safe, or superior to standard treatments in a defined oncological population.

6. INDEPENDENT SUPPORTING EVIDENCE

Confirmation regarding the chemotherapy component comes from a study on uterine smooth muscle tumors. Researchers examined tumor samples and cell lines, treating two tumor lines with docetaxel, either alone or following EP4 antagonists. In cells with characteristics of taxane resistance and higher EP4 expression, pretreatment with AH23848 or RQ15986 increased sensitivity to docetaxel approximately twofold. The result confirms that, at least in this cellular model, blocking EP4 can enhance the effect of chemotherapy; however, it does not demonstrate a benefit in patients or across all tumors [1].A second piece of evidence concerns the immune component of the narrative. In mouse tumor models, the selective antagonist E7046 reduced the differentiation and activation of myeloid cells with immunosuppressive activity and showed a greater antitumor effect when combined with a treatment that reduced regulatory T cells. Regulatory T cells are immune cells that, in some contexts, restrain responses against the tumor. This research supports the rationale for immunotherapeutic combinations, but it remains preclinical evidence [2].A transition to humans was provided by a phase 1 study with E7046 in 30 people with advanced, heavily pretreated tumors. The drug was administered alone at increasing doses. No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. The best radiological result was stable disease in 23% of participants; three of the fifteen patients evaluated with PET had a metabolic response. The study also detected signals consistent with immune modulation. These data confirm feasibility and biological activity in humans, but they do not evaluate the efficacy of combinations nor do they demonstrate a survival advantage [3].Taken together, these independent publications support three distinct steps of the same narrative: EP4 may participate in drug resistance; its blockade can modify an unfavorable immune microenvironment; and EP4 antagonists can be administered to humans in an experimental setting. However, the chain remains incomplete on a clinical level, as definitive randomized studies comparing combinations containing EP4 antagonists with standard therapies are still lacking.

7. CONFLICTING EVIDENCE

The direction of the EP4 effect is not identical in all cancers. In four human gastric carcinoma cell lines, pharmacological activation of EP2 and EP4 induced a reduction in cell proliferation, accompanied by an increase in cAMP, a molecule that transmits signals within the cell. In this specific model, therefore, stimulating EP4 produced an antiproliferative rather than a pro-proliferative effect [4].This result does not directly contradict the observation that EP4 may promote progression, metastasis, or immunosuppression in other tumors. However, it shows that the receptor's function depends on the cell type, the available intracellular signals, the experimental context, and likely the tumor microenvironment. No sufficiently relevant directly conflicting evidence has been identified regarding the overall proposal to combine EP4 antagonists with chemotherapy and immunotherapy; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from independent research that confirms or delimits the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on cells, animals, human samples, and early clinical trials	Synthesizes that PGE2/EP4 may support proliferative signaling, metastasis, resistance, and immunosuppression; proposes EP4 blockade in combination	biologically consistent evidence	moderate
[1]	Cellular and observational	Uterine samples and SK-UT-1 and SK-UT-1B lines	EP4 antagonists increased sensitivity to docetaxel by approximately two-fold in resistant cell lines	direct confirmation	moderate
[2]	Animal and cellular	Tumor mouse models and myeloid cells	E7046 reduced myeloid immunosuppression and showed synergy with a reduction in regulatory T cells	direct confirmation	moderate
[3]	Phase 1 clinical trial	30 patients with advanced tumors	E7046 showed manageable tolerability, signs of immune modulation, and stable disease as the best response in 23%	indirect confirmation	preliminary
[4]	Cellular	Four human gastric carcinoma lines	Activation of EP2 and EP4 reduced cell proliferation	discordant evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the idea that the COX-2/PGE2/EP4 axis may contribute to tumor progression through proliferative and immunosuppressive signals. Independent evidence confirms that blocking EP4 can increase sensitivity to chemotherapy in cell models and can modify immune mechanisms in animal models. The possibility of using it in combination with chemotherapy or immunotherapy is therefore supported at a mechanistic and preclinical level. Available clinical data are preliminary and do not allow EP4 antagonists to be considered standard treatments or to predict individual benefit.

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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