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

ORIGINAL RESEARCH
ISSN 2845-7501

Prostaglandin E receptor 4 (EP4) promotes colon tumorigenesis - Evidence review

Dott. A. Colonnese[1]

1 Nutritional Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether the EP4 receptor for prostaglandin E2 (PGE2, a lipid molecule produced during inflammation and tissue repair) present in myeloid cells contributes to the formation of intestinal adenomas. In ApcMin/+ mice, which are predisposed to developing intestinal polyps, the selective removal of EP4 in myeloid cells reduced the average number of adenomas from 83.6 to 27.3 per animal and reduced their size. This reduction was associated with lower activation of ERK and mTOR, two signaling systems that promote cell growth and the synthesis of new cellular components.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 PGE2-EP4 inflammatory signal can converge on PI3K-AKT-mTOR in the tumor microenvironment. Independent studies confirm that PGE2 and EP4 can activate PI3K/ERK, promote cell proliferation, and maintain immunosuppressive myeloid cells in experimental models. However, direct evidence of a PGE2-EP4-mTOR chain in people with colorectal cancer remains limited; the clinical significance requires further study.

ONLINE ARTICLE

ARTICLE INFORMATION

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

DOI 10.5281/zenodo.24494454

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 EP4, one of the receptors through which PGE2 transmits signals to cells, promotes the development of intestinal tumors when expressed by myeloid cells. Myeloid cells include, among others, macrophage-like cells and dendritic cells: components of the immune system that, within a tumor, can take on functions that are either favorable or unfavorable to neoplastic growth.The authors' hypothesis was that selectively removing EP4 from these cells would reduce intestinal adenomas and attenuate the molecular signals that support proliferation. This is the precise reason why the study is relevant to section 5.7 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi: it documents, in a model of intestinal tumorigenesis, the PGE2-EP4 segment in myeloid cells lower observed activation of PI3K/AKT/mTOR and ERK when EP4 is deleted lower adenoma burden.The study can demonstrate a causal effect of the genetic deletion of EP4 in the mouse model used. However, it cannot establish that the same intervention prevents or cures colorectal cancer in humans. Furthermore, since ERK and mTOR were measured in adenoma tissues after EP4 deletion, the design shows a strong biological association in the mouse tumor, but it does not by itself identify all the intermediate cellular steps that link myeloid cells to the epithelial cells of the adenoma.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

An experimental study was conducted on ApcMin/+ mice, a mouse model genetically predisposed to developing intestinal adenomas. The authors crossed these animals with mice carrying a conditional deletion of the EP4 gene in CD11b-positive cells, i.e., myeloid cells. The comparison group consisted of ApcMin/+ mice with EP4 not deleted in myeloid cells.The animals were sacrificed at 20 weeks of age. The intestine was examined in a blinded manner, meaning the person counting the polyps was unaware of the experimental group, and the number and diameter of the adenomas were measured. For the main comparison, 15 control mice and 14 mice with myeloid EP4 deletion were included. Since the CD11b-Cre transgene was inserted into the Y chromosome, the EP4 deletion in myeloid cells only affected males.The authors used immunohistochemistry and immunofluorescence, techniques that allow for the localization of proteins in tissues, as well as immunoblotting to measure proteins extracted from the adenomas. They evaluated the phosphorylated, i.e., activated, form of ERK, PI3K, PDK1, AKT, mTOR, and proteins located downstream of mTOR. Markers associated with myeloid cells with an M2 phenotype, such as arginase-1 and the interleukin-4 receptor alpha, and a marker associated with the M1 phenotype, iNOS, were also measured.In a second experiment, 16-week-old ApcMin/+ mice received the selective EP4 antagonist L-161,982, 10 mg/kg per day intraperitoneally, or saline solution for one week. The total number of animals in this part is not reported uniformly for each analysis; for some molecular markers, n=5 is indicated. Finally, the murine cell model RAW264.7 was used to evaluate the effect of PGE2 and the EP4 antagonist on iNOS expression.Data were expressed as means with standard error. The authors report the use of Fisher's exact test, analysis of variance, and Bonferroni test. Formal criteria for animal exclusion, prior calculation of sample size, or randomization of treatment assignment are not reported in the available material.

4. RESULTS

The main result was a marked reduction in the intestinal adenoma burden when EP4 was deleted in myeloid cells. Mice with myeloid EP4 deletion developed an average of 27.3 ± 4.1 adenomas per animal, compared to 83.6 ± 7.0 in the control group; the difference was statistically significant ($P<0.0001$). Adenoma size was also smaller in the deletion group. In the colon, however, the average number of adenomas was similar: 1.44 ± 0.34 in controls and 1.67 ± 0.37 in mice with the deletion.In simple terms, removing EP4 from myeloid cells coincided with fewer and smaller intestinal tumors. At the molecular level, phosphorylation of ERK—a protein that transmits growth signals—was decreased in the adenomas of the mice with the deletion. There was also a decrease in the expression of cyclin D1, Ki67, and c-Myc, which are indicators consistent with reduced cell proliferation. For ERK, cyclin D1, Ki67, and mTOR, histological analyses reported $P<0.001$ in samples from four animals per group.The finding most relevant to the

book's narrative concerns the PI3K/AKT/mTOR axis. In the adenomas of mice lacking EP4 in myeloid cells, the authors observed reduced phosphorylation of PI3K, PDK1, AKT, raptor, and mTOR. Proteins located downstream of mTOR also decreased, including p70 S6K, eIF-4B, and rpS6. Immunoblotting confirmed lower levels of p-AKT, p-mTOR, and p-p70 S6K. These results indicate that, in this murine tumor tissue, the loss of EP4 in myeloid cells is associated with reduced activity of the axis that supports growth and protein production.The genetic deletion also reduced markers of M2 myeloid cells, an experimental classification used to describe cells often associated with tissue repair and immunosuppression. Arginase-1 positive cells decreased from 57.96 ± 5.5 to 5.7 ± 1.6 per high-power microscopic field (P<0.001; six animals per group). IL-4Ra positive cells decreased from 113.2 ± 10.7 to 22.2 ± 4.8 per field (P<0.001; six animals per group).The pharmacological antagonist of EP4 produced consistent but shorter-term results: after one week, it reduced ERK and mTOR phosphorylation, decreased arginase-1, and increased iNOS. In RAW264.7 cells, PGE2 reduced iNOS messenger RNA; pretreatment with L-161,982 prevented this reduction. The experiments therefore support a role for EP4 in maintaining a myeloid environment less oriented toward antitumor functions, but they do not demonstrate that M1 and M2 markers fully represent all the functions of the immune cells present in tumors.

5. INTERPRETATION

The biological significance of the study is that an inflammatory signal does not necessarily have to act only on the tumor cell to promote the growth of an adenoma. It can also act on the immune cells surrounding the lesion, modifying the tumor microenvironment, which is the set of cells and signals present around the tumor.In the studied model, the documented pathway is as follows: PGE2 signaling through EP4 in myeloid cells promotes a context associated with greater activation of ERK and the PI3K/AKT/mTOR axis in adenomas. When EP4 is deleted, the phosphorylation of these proteins, markers of proliferation, and the number of adenomas decrease. Phosphorylation is a chemical change that often acts as a molecular switch; in this case, lower values of p-AKT or p-mTOR indicate less detectable activity of those signals in the tissue.This corresponds to the passage in paragraph 5.7 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, according to which PGE2-EP4 can act upstream of mTOR activation in inflammatory contexts. However, the most faithful formulation regarding the data is cautious: the study demonstrates that the deletion of myeloid EP4 simultaneously reduces adenomas and the activation of PI3K/AKT/mTOR and ERK in ApcMin/+ mice; it does not prove that EP4 is the sole driver of mTOR, nor that all chronic inflammation conditions in humans follow the same sequence.A further limitation is that the ApcMin/+ model primarily develops small intestine adenomas, whereas human colorectal cancer has more heterogeneous locations, evolution times, genetic alterations, and immune interactions. The results are therefore particularly solid as mechanistic and preclinical evidence, not as clinical proof of therapeutic efficacy.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Initial independent confirmation of the link between PGE2, EP4, and proliferative signals comes from a study on murine CT26 colon adenocarcinoma cells and experiments in tumor-bearing mice. Inhibition of cyclooxygenase reduced cell proliferation, and these effects were rescued by PGE2 or a selective EP4 agonist. The authors linked the recovery of proliferation to the activation of PI3K and ERK. In mice, COX-2 inhibition reduced the number and size of CT26 tumors, along with tumor levels of PGE2. This study supports the upstream chain: PGE2 EP4 PI3K/ERK proliferation. This is an experimental causal confirmation, but it does not measure mTOR and uses a transplanted tumor model, which differs from the spontaneous adenomas of the ApcMin/+ model [1].A second study, conducted on human HCA-7 colon carcinoma cells, showed that PGE2 increases ERK phosphorylation and cell proliferation. The EP4 antagonist L-161,982 completely blocked both the increase in phosphorylated ERK and the increase in proliferation induced by PGE2. At 60 minutes, PGE2 increased the phosphorylation of ERK1 and ERK2 by approximately 3.5 and 5 times, respectively; pretreatment with the antagonist abolished this response. This evidence confirms the PGE2 EP4 ERK

growth pathway in human cells, but the system is a cell culture exposed to experimental concentrations and does not reproduce the entire tumor microenvironment [2].The immune component of the original study is supported by independent research in murine models of colorectal cancer. The authors identified EP4 as a regulator of immunosuppressive myeloid cells and observed that the selective antagonist TP-16 reduced markers associated with suppressive myeloid cells, promoted the activation of cytotoxic T lymphocytes, and increased the response to anti-PD-1 treatment. In the murine model of colorectal cancer associated with chronic inflammation, EP4 blockade therefore shifted the microenvironment toward a more active immune response. The study does not directly demonstrate mTOR activation, but it independently confirms the role of EP4 in pro-tumorigenic myeloid cells highlighted by the analyzed publication [3].Overall, the independent evidence outlines a coherent network: PGE2 can activate EP4; EP4 can stimulate PI3K/ERK and proliferation in tumor cells; EP4 can also support immunosuppressive myeloid cells in the microenvironment. The original study adds to this network the observation, in the ApcMin/+ model, of the concomitant reduction of AKT, mTOR, and downstream mTOR proteins when EP4 is deleted in myeloid cells.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified that shows an increase in tumorigenesis following the loss of EP4 in myeloid cells within the same type of intestinal adenoma model. However, there are significant limitations to the generalizability of this narrative.A comparative study on murine and human immune models showed that the simultaneous inhibition of EP2 and EP4 was more effective than the selective inhibition of just one of the two receptors in restoring immune activation and reducing tumor burden, including in an ApcMin/+ model. This result does not contradict the role of EP4 observed in the original study, but it indicates that PGE2 may use partially redundant pathways: in some contexts, blocking only EP4 may not be sufficient to achieve the maximum biological effect [4].The responses of epithelial cells to PGE2 also depend on the relative expression of the different EP receptors, the concentration of the ligand, and the cell model. For this reason, the PGE2-EP4-PI3K/AKT/mTOR pathway is biologically plausible and experimentally supported, but it should not be considered identical in all colon cancers or in all stages of the disease.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the Evidence Review from the independent publications used to confirm or define the scope of the same scientific narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal, genetic, and pharmacological	ApcMin/+ mice with myeloid EP4 deletion; RAW264.7 cells	Myeloid EP4 deletion reduced adenomas, p-ERK, p-AKT, p-mTOR, and M2 markers.	direct confirmation	moderate
[1]	Cellular and animal	Murine CT26 cells and mice with transplanted CT26 tumors	PGE2 or EP4 agonist restored proliferation after COX inhibition via PI3K/ERK; COX-2 inhibition reduced tumors.	direct confirmation	moderate
[2]	Cellular	Human HCA-7 colon carcinoma cells	EP4 antagonist blocked the increase in phosphorylated ERK and proliferation induced by PGE2.	direct confirmation	low
[3]	Cellular and animal	Murine colorectal tumor models and CD11b-positive myeloid cells	EP4 blockade reduced myeloid immunosuppressive features and improved antitumor activity.	indirect confirmation	moderate
[4]	Cellular and animal	Murine and human immune cells; ApcMin/+ mouse model	Combined EP2/EP4 blockade was more effective than individual antagonists in some models.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study convincingly supports, in the ApcMin/+ mouse model, that EP4 expressed by myeloid cells contributes to intestinal tumorigenesis. The deletion of this receptor reduced the number and size of adenomas and was associated with lower activity of ERK and the PI3K/AKT/mTOR pathway.Independent research confirms that PGE2-EP4 can promote proliferation and ERK/PI3K signaling in colon cancer cells and can maintain immunosuppressive functions in the tumor microenvironment. The narrative is therefore well-supported at the mechanistic and preclinical levels. It remains necessary to verify how reproducible this chain is in human tissues and whether blocking EP4 can offer safe and effective clinical benefits.

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] **The EP4 receptor antagonist, L-161,982, blocks prostaglandin E2-induced signal transduction and cell proliferation in HCA-7 colon cancer cells**
CHERUKURI et al., 2007
Experimental Cell Research
DOI: https://doi.org/10.1016/j.yexcr.2007.06.004

[2] **Reprogramming immunosuppressive myeloid cells facilitates immunotherapy for colorectal cancer**
Lu et al., 2021
EMBO Molecular Medicine
DOI: https://doi.org/10.15252/emmm.202012798

[3] **Dual Blockade of EP2 and EP4 Signaling is Required for Optimal Immune Activation and Antitumor Activity Against Prostaglandin-Expressing Tumors**
Francica et al., 2023
Cancer Research Communications
DOI: https://doi.org/10.1158/2767-9764.CRC-23-0249

[4] **Colon Carcinoma Cell Growth Is Associated with Prostaglandin E2/EP4 Receptor-evoked ERK Activation**
Pozzi et al., 2004
Journal of Biological Chemistry
DOI: https://doi.org/10.1074/jbc.M313989200