BEHAVIOR OF PROSTAGLANDIN E2 IN THE TUMOR MICROENVIRONMENT AND ITS IMPACT ON DENDRITIC CELLS: AN INTEGRATIVE REVIEW

COMPORTAMENTO DA PROSTAGLANDINA E2 NO MICROAMBIENTE TUMORAL E SEU IMPACTO NAS CÉLULAS DENDRÍTICAS: UMA REVISÃO INTEGRATIVA

Fernando Araújo Espanhol, Julia Hailer Vieira, Márcia Antoniazi Michelin*

Instituto de Pesquisa em Oncologia - IPON, Universidade Federal do Triângulo Mineiro, Uberaba, Minas Gerais, Rua Vigário Carlos, 100, Nossa Senhora da Abadia. CEP 38025-350. marcia.michelin@uftm.edu.br

ABSTRACT

This integrative review provides an in-depth analysis of the influence of prostaglandin E2 on the intratumoral environment, highlighting its association with forms of immune evasion. The studies reviewed reveal that the presence, behavior, and overexpression of PGE2 are crucial in shaping the tumor microenvironment, emphasizing the need for a more detailed understanding of these interactions. Several studies have emphasized the importance of investigating agents capable of modulating cytokines and chemokines in the tumor microenvironment and using immunotherapy as a promising approach to treat specific immunometabolic conditions. These alternatives aim to strengthen the host immune system against tumor cells, representing a hopeful strategy to overcome the immunosuppression barriers associated with molecules such as prostaglandin E2. Therefore, this review highlights the complexity of the interactions between PGE2, dendritic cells, and cancer, indicating promising avenues for future research and more targeted and effective therapeutic interventions.

KEYWORDS: Prostaglandin E2, Cancer, Dendritic cells

RESUMO

Esta revisão integrativa fornece uma análise aprofundada da influência da prostaglandina E2 no ambiente intratumoral, destacando sua associação com formas de evasão imunológica. Os estudos revistos revelam que a presença, o comportamento e a sobre-expressão da PGE2 são cruciais na formação do microambiente tumoral, enfatizando a necessidade de uma compreensão mais detalhada destas interações. Vários estudos têm enfatizado a importância da investigação de agentes capazes de modular citocinas e quimiocinas no microambiente tumoral, bem como o uso da imunoterapia como abordagens promissoras para o tratamento de condições imunometabólicas específicas. Essas alternativas visam fortalecer o sistema imunológico do hospedeiro contra as células tumorais, representando uma estratégia esperançosa para superar as barreiras de imunossupressão associadas a moléculas como a prostaglandina E2. Portanto, esta revisão destaca a complexidade das interações entre PGE2, células dendríticas e câncer, indicando caminhos promissores para futuras investigações e intervenções terapêuticas mais direcionadas e eficazes.

PALAVRAS-CHAVE: Prostaglandina E2, Câncer, Células dendríticas

INTRODUCTION

The inflammatory process, a natural immune system response to injury, occurs in subsequent phases of transient local vasodilation, increased capillary permeability, leukocyte infiltration, and tissue degeneration, with consequent fibrosis. In this last stage, called the chronic proliferative phase, the enzyme phospholipase A2, present in the cell membrane, can be activated and release arachidonic acid from the- phospholipid membrane, which is converted into eicosanoids, such as prostaglandins, which are synthesized from a complex of enzymes known as cyclooxygenases (COX)[1,2].

Chronic inflammation, a significant player in establishing a tumor-promoting environment, is mediated by Prostaglandin E2 (PGE2). This key mediator alters the immune response, a fascinating aspect of its function[3–5].

The interference of PGE2 on immune system cells is a critical factor that triggers immunosuppressive processes. This interference hampers the triggering of an adequate anti-tumor immune response, mediated primarily by antigen-presenting cells and cytotoxic cells. This creates a microenvironment that supports neoplastic development, with greater survival of tumor cells, expression of angiogenic factors, and the establishment of immunosuppression[4,5].

Dendritic cells are considered to be the central antigen-presenting cells (APCs) and are influenced by PGE2 in tumor contexts, so we conducted an integrative literature review to understand the interactions between the altered metabolism of PGE2 in different types of tumors. This work aimed to identify the behavior of PGE2 and its influence on dendritic cells to guide investigations into the regulation and development of immunosuppressive tumor microenvironments.

METHODS

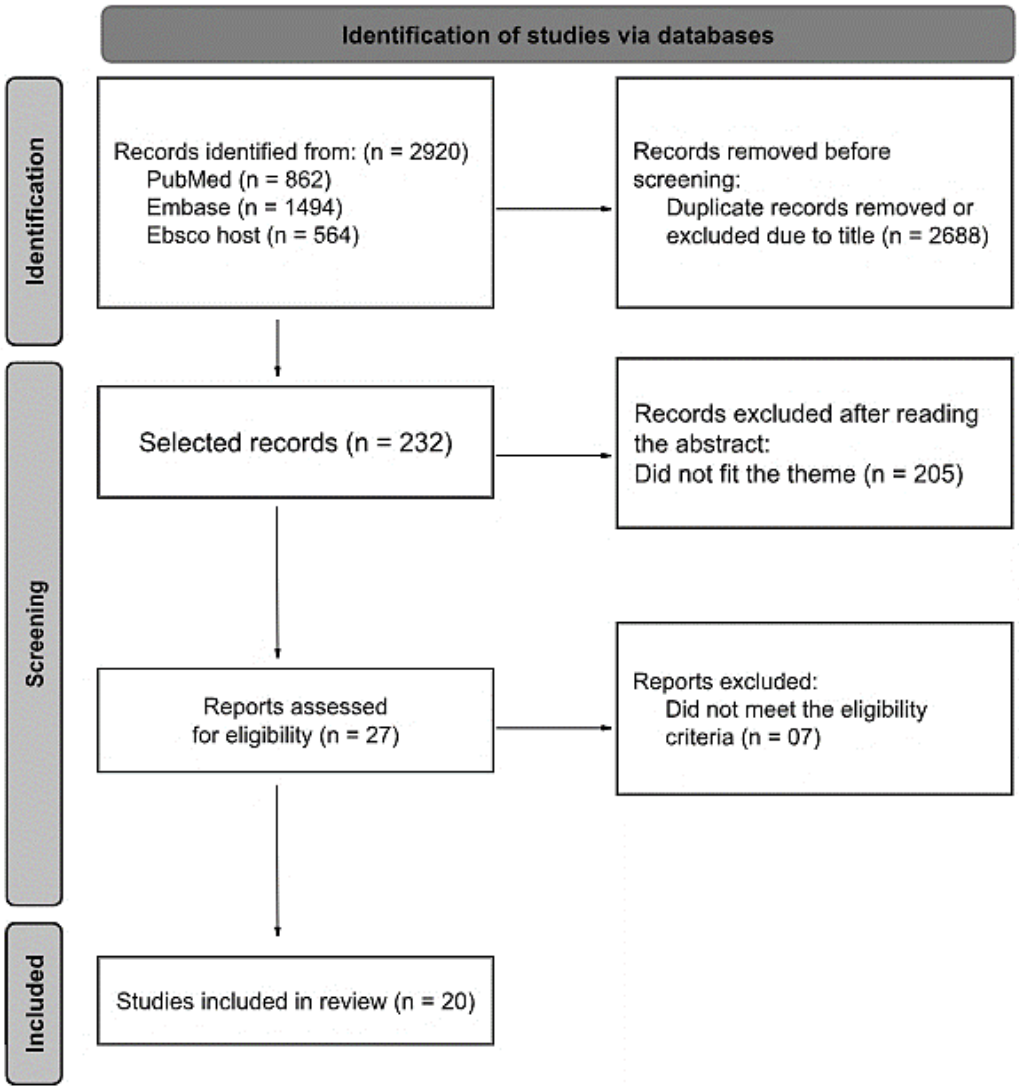
This integrative review had five stages: identifying the topic, determining the inclusion and exclusion criteria, surveying the databases, removing duplicates, analyzing the abstracts, including the articles for full reading, interpreting and organizing the results, and presenting the review.

The bibliographic searches were conducted between January and April 2021, using the PubMed®, EMBASE®, and EBSCO host® platforms. The following keywords were used as

descriptors: prostaglandin E2 (all fields), cancer (all fields), and dendritic cells (all fields).

This study adhered to the protocols pre-established by the PRISMA statement, ensuring a high standard of research. The review had specific criteria for article selection, including a publication year between 2016 and 2020, language (English, Spanish and Portuguese), and publication in peer-reviewed journals. The articles included were original, experimental, available from the university or free of charge, in their entirety, and in line with the given theme. The selection flowchart is described in Figure 1.

Figure 1. Flowchart based on the PRISMA protocol, showing search strategies and study selection. Source: Prepared by the authors, based on the 2020 PRISMA Protocol.



RESULTS

We initially retrieved 2,920 articles from the selected databases, of which 862 were obtained from PubMed®, 1494 from EMBASE®, and 564 from EBSCO Host®.

All these articles were initially selected based on their titles, which aligned with the theme and keyword system. At the end of this stage, 232 articles went on to read the abstracts in the screening phase.

After the screening stage, only 27 articles remained to be read, which were then selected based on the eligibility criteria to be included in the review. In the end, 20 articles were selected as eligible for this review. Their general characteristics, in terms of the name of the first author, journal, year of publication, the title of the article, types of tumors, PGE2 and its mechanism in tumorigenesis, and the animal models used, are shown in Table 1.

The pre-clinical studies included in the review were diverse, investigating one or more types of cancer. Approximately 30% of the studies focused on experimental models of colorectal carcinogenesis (6 studies), while 25% addressed breast cancer models (5 studies), and 10% dealt with melanoma. A further 55% encompassed various other types of experimental models, including a specimen of each of the following: epithelial cancer, gastrointestinal cancer, bladder cancer, oral cavity cancer, lymphoma, fibrosarcoma, Ehrlich carcinoma, prostate cancer and gastric cancer. This comprehensive approach underscores the connection between the immunoregulatory potential of PGE2 and its influence on various cellular and biomolecular processes that affect the microenvironment of different tumors, suggesting that PGE2 may play a crucial role in triggering, promoting, and predisposing to tumor formation[6–12].

Moreover, the findings of the research review have significant implications. There are reports of metastasis via tumor-specific PGE2-EPs signaling, immune suppression by changes in the differentiation and maturation of immune system cells, such as Natural Killer (NK) cells and dendritic cells (DC), resistance to chemotherapy, among other mechanisms[7,9–11,13–20]. These findings underscore the potential of PGE2 in cancer treatment and the need for further research in this area.

Table 1. General data for each article selected and included in the integrative review.

Types of tumors and their characteristics	PGE2 and mechanism in tumorigenesis	Animal model
Colitis-associated colon cancer [8]	Shapes the tumor microenvironment (via the PGE2-EP2 axis), favoring tumorigenesis	Type mice wild and deficient in EP2
Epithelial tumors that express the EP2 receptor and produce PGE2[9]	PGE2 signaling via the EP2 receptor of the host, affected tumor progression genes	C57BL/6
Colon cancer[21]	In addition to stimulating the self-expansion of CICs, it drove several changes in the tumor microenvironment	Nude mouse xenograft model
4T1 breast cancer cells, CT26 colorectal cancer cells, or BRAF melanoma cells[10]	PGE2 damaged NK cells and cDC1, culminating in a state of immune evasion	C57BL/6, MMTV-PyMT transgenic C57BL/6, Batf3−/−, Rag1−/−, Rag2−/−Il2rg−/− and BALB/c
Gastrointestinal cancer[6]	Participation of PGE2/COX-2 and TLR/MyD88 signaling generate an inflammatory microenvironment	Apc Δ716 mice; Gan mice; K19-C2mE mice; Tnf−/− mice; Myd88−/− mice; Apc mutant mice; Tgfbr2−/− mice; Trp53R270H mice.
Bladder cancer[15]	PGE2 receptors (EPs) induce urothelial progression, cisplatin resistance, via modulation of PTEN expression	NOD-SCID
Colon cancer with PGE2; Colorectal tumorigenesis[22]	PGE2 increases the expression and transcriptional activity of YAP1, which feeds back into the increase in COX-2 and EP4	C57BL/6; 15-PGDH–knockout mice; YAP-knockout mice
Lymphangiogenesis associated with breast cancer[13]	Activation of EP4 by endogenous PGE2 promoted lymphangiogenesis and lymphatic metastasis, via +regulation of VEGF-C/D	Athymic Nude-Foxn1 nu/ Foxn1+)
Oral cavity cancer[7]	PGE2 promotes migration in oral cancer cells	BALB/c Slc-nu/nu mice
Murine lymphoma model[14]	PGE2 compromises DC differentiation (downregulates the Zbt46 factor) and the maturation process (IL-10 induction)	C57BL/6; BALB/c; NOD/NcrCrl-Prkdcscid
Murine fibrosarcoma and murine melanoma[23]	PGE2 promotes p50 NF-κB-dependent differentiation of monocytic MDSCs	p50 NF-κB-deficient mice on the C57BL/6J; NF-κB1flox/flox; Cg-Tg(Tek-Cre)1Ywa mice; Tie2Cre mice; OT-I mice
Breast with doxorubicin resistance[16]	It acts to generate chemotherapy-induced immune resistance, via the PGE2/miR-10a/AMPK axis	BALB/c
Ehrlich's ascitic carcinoma (EAC)	Alters the migration, phenotype and	Swiss albino mice; BALB/c

and Sarcoma 180[17]	immunosuppressive capacity of macrophages, by inducing PGE2-HIF-1α	
Sporadic mouse colon cancer[24]	PGE2 participates in increased CRTC1 activity in mouse colon tumors	C57BL/6; BALB/c
Colon and breast cancer[18]	Inhibits the recruitment of cDC to the tumor, by signaling via EP4; Furthermore, it activates suppressor cells and inhibits effector CD8+ T cells	K19-Wnt1/C2mE; Apcmin/+ mice;
Breast cancer[19]	Activation of EP4 can transactivate EGFR and form invadopodia (enable metastasis)	SCID
Experimental model of prostate cancer bone metastasis in nude mice[11]	The PGE2-EP4 axis is essential for metastasis and bone destruction in prostate cancer, via modulation of the tumor microenvironment	Nude mice, BALB/c nu/nu
Gastric cancer[2]	Investigation of the role of PGE2 in DNA methylation in gastric epithelium	COX-2 transgenic mice; C57BL/6; nude mice
Pancreatic adenocarcinoma[12]	Regulates VEGF expression and secretion via COX-2 activation	BALB/c-nu/nu mice
Kidney cancer (metastatic renal cell carcinoma)[20]	The PGE2-EP4 axis is associated with renal cell carcinoma xenograft tumor metastasis	Athymic Nude-Foxn1nu mice

DISCUSSION

Research into the intrinsic connection between inflammation and carcinogenesis dates back to the 19th century, but it was only in 1964 that the biosynthesis of the Prostaglandin E2 molecule was described. It participates as a mediator and regulator of inflammatory processes, acting in their initiation, propagation, and resolution[3,25]. Since then, scientific research has sought to understand the intricate relationship between establishing an inflammatory tumor microenvironment and its impact on the anti-tumor immune response, determining factors for progression and metastasis[1,2].

One of the key areas of focus in this research is the intricate PGE2 axis and its four distinct receptors (EP1-4). These receptors, each expressed in different cell types, play a significant role in transmitting cellular signals in response to PGE2 binding. The complexity of this system is underscored by the fact that each receptor subtype performs specific functions, triggering unique intracellular signaling pathways and resulting in specific responses[3–5,26,27].

The interactions between cancer cells and the immune system manifest themselves in

different ways in each organism, preventing the tumor from developing or supporting its progression[4,26].

The mechanisms involved in tumor eradication encompass innate and acquired immunity, forming a cohesive defense system in the body where various cells and molecular components operate in an integrated manner. Innate immunity acts as the first barrier against cancer cells, employing mechanisms that include natural killer (NK) cells, antigen-presenting cells (APCs), and phagocytes. Adaptive immunity works mainly through T lymphocytes (T CD4+ and T CD8+), which are highly specific for tumor antigens[4,5,26].

Tumor antigens intended for recognition by T-cell receptors are presented through the MHC, which is present on the membranes of antigen-presenting cells. The central antigen-presenting cells are dendritic cells. MHC I and II expose antigens to CD8+ and CD4+ T lymphocytes, respectively, leading to the differentiation of these cells into effector forms[4,28].

In the context of immunosuppression, tumors can strategically compromise the functions of antigen-presenting cells, altering anti-tumor mechanisms and turning them pro-tumor. This can lead to a decrease in effective antigen presentation and, consequently, a failure to properly activate adaptive immune responses. The urgency of understanding these immunosuppressive mechanisms is underscored by the fact that it is crucial for the development of therapeutic strategies aimed at restoring or enhancing the effectiveness of anti-tumor immune responses [28].

Tumors appropriate immunoregulatory mechanisms via PGE2, which can promote immune evasion, increase tumor cell survival, and reduce immune cell responsiveness, aspects that have been the target of various immunotherapeutic strategies[14,20].

The biomolecule PGE2 has the potential to exert different results within the most distinct tumor microenvironments, thus favoring tumor multiplicity, promoting proliferation, and promoting the growth of neoplastic cells. Biosynthesis takes place in tumor cells and apoptotic processes in some cells, and its action can consolidate the development of an inflammatory environment via the PGE2 axis and its EP receptors, so it is capable of deregulating immunophysiological mechanisms and other signaling mechanisms, which would support carcinogenesis. The main findings of the studies covered by this review demonstrate the impact of PGE2 on dendritic cells, impairing the presentation of antigens via MHC class I to CD8+ T cells, which are crucial for the death of neoplastic cells[10].

In addition, some studies cite the attempt to repair the anti-tumor immune response as an

alternative through therapeutic strategies aimed at immunotherapy to increase and mature dendritic cells in the tumor microenvironment, strengthening the response against cancer[7,15]. NK cells would also be essential targets since they are significant in fighting and eliminating transformed cells, and their recruitment would also be compromised by the inflammatory mechanisms of PGE2[10,15].

PGE2 positively modulates myeloid-derived suppressor cells (MDSC) and can support the tumor by inhibiting anti-tumor T cells, resulting in poor prognosis in breast cancer patients[16,23].

Therefore, establishing an immunosuppressive microenvironment creates favorable conditions for carcinogenesis, altering the traffic of immune cells between the different tissue compartments. Studies highlight the importance of chemokines, critical molecules in the recruitment of dendritic cells to tumors, with emphasis on the chemokines XCL and CCL5, which are the main ones responsible for the migratory stimulus of DCs and suffer from the inhibitory action of PGE2. These studies also demonstrate the transition of the microenvironment from a Th1 profile, which is anti-tumor, to a Th2 profile, which is immunosuppressive, as a result of the inflammatory state[9,10].

As reported by different studies, the recruitment of dendritic cells and NK cells in the immune control of cancer is evident. However, the interference of PGE2 leads to the immune evasion of cancer, hindering the elimination of transformed cells and contributing to cancer progression[17].

Once synthesized, PGE2 exerts its biological effects, paracrine or autocrine, by binding to four possible receptors, forming the PGE2-EP1-4 axis[5]. Knowing this, knowledge of the level of receptor expression within the tumor microenvironment will make it possible to understand signaling and signal transduction mechanisms via the interaction between the PGE2 molecule and its receptor, thus contributing to different cellular responses and signals that mediate the effects of PGE2 on the proliferation, survival, and migration of neoplastic cells[8,29].

In the included studies, the participation of specific axes was noted for different types of tumors, emphasizing the PGE2-EP4 axis in renal cell carcinoma, oral cancer, lymphangiogenesis, and metastasis associated with breast cancer and bone metastasis in prostate cancer. The PGE2-EP2 axis is associated with epithelial tumors and colon tumorigenesis, the PGE2-EP3 axis in colorectal tumor cells, and EP3 expression in this type of tumor is prognostically poor[6,10]. Finally, the PGE2-EP1 axis is rarely reported in studies and is more characteristic of hepatocellular tumors[29].

Most of the preclinical studies included in this review emphasize the need to identify new therapeutic targets to deal with the heterogeneity of carcinogenesis and fill existing therapeutic gaps in the treatment of neoplasms. Understanding signaling mechanisms and identifying alternative therapeutic targets are crucial to improving conventional treatments[7,20].

The idea that inflammation plays a role in carcinogenesis is supported by epidemiological studies, which indicate that the use of NSAIDs is correlated with a reduction in the incidence and progression of cancer. Preclinical studies have shown consistent evidence of immune evasion mediated by the participation of PGE2, highlighting prospects for identifying therapeutic targets for refractory and recurrent tumors based on the use of immunotherapies as a way of re-establishing and strengthening the appropriate anti-tumor immune response[3,27]. Non-steroidal anti-inflammatory drugs (NSAIDs) make up a diverse class of drugs and generally inhibit the production of prostaglandins in various cell types. They also have analgesic, antipyretic, and anti-inflammatory actions.

Furthermore, in recent years, studies have described the potential role of NSAIDs in cancer prevention and as antineoplastic agents. These properties may be related, among other things, to the role of prostaglandins in tumor development[4].

CONCLUSION

The studies analyzed provided a comprehensive understanding of prostaglandin's influence on the intratumoral environment, highlighting its association with forms of immune evasion. The presence, behavior, and overexpression of PGE2 emerged as crucial factors shaping the tumor microenvironment, indicating the need to delve deeper into the dynamics of these interactions.

It is evident that an urgent need for more research is required to consolidate our understanding of the complex relationship between PGE2 and the tumor microenvironment. The search for a clear delineation of the best therapeutic targets becomes imperative, demanding the development of more effective strategies to combat cancer.

In this context, several studies have underscored the importance of investigating agents capable of modulating cytokines and chemokines in the tumor microenvironment. Moreover, the exploration of standard receptor agonists and the use of immunotherapy have not just

emerged, but shone as promising approaches to treating specific immunometabolic conditions. These alternatives aim to fortify the host immune system against tumor cells, representing a hopeful and optimistic strategy to overcome the immunosuppression barriers associated with molecules such as prostaglandin E2.

Therefore, this review highlights the complexity of the interactions between PGE2, dendritic cells, and cancer, indicating promising avenues for future research and more targeted and effective therapeutic interventions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors wish to thank Fundação de Amparo à Pesquisa do Estado de Minas Gerais for the financial support.

REFERENCES

1. Palucka AK, Coussens LM. The Basis of Oncoimmunology. Cell. 2016; 164(6): 1233-1247. doi: 10.1016/j.cell.2016.01.049.

2. Wong CC, Kang W, Xu J, Qian Y, Luk STY, Chen H, Li W, Zhao L, Zhang X, Chiu PW, Ng EK, Yu J. Prostaglandin E $_2$ induces DNA hypermethylation in gastric cancer in vitro and in vivo. Theranostics. 2019;9(21):6256-6268. doi:10.7150/thno.35766.

3. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP. Prostaglandins as modulators of immunity. Trends Immunol. 2002;23(3):144-150. doi:10.1016/S1471-4906(01)02154-8.

4. Wang Q, Morris RJ, Bode AM, Zhang T. Prostaglandin Pathways: Opportunities for Cancer Prevention and Therapy. Cancer Res. 2022;82(6):949-965. doi:10.1158/0008-5472.CAN-21-2297/674402/AM/PROSTAGLANDIN-PATHWAYS-OPPORTUNITIES-FOR-CANCER.

5. Finetti F, Travelli C, Ercoli J, Colombo G, Buoso E, Trabalzini L. Prostaglandin E2 and Cancer: Insight into Tumor Progression and Immunity. Biology (Basel). 2020;9(12):434. doi:10.3390/biology9120434.

6. Echizen K, Oshima H, Nakayama M, Oshima M. The inflammatory microenvironment that promotes gastrointestinal cancer development and invasion. Adv Biol Regul. 2018;68:39-45. doi:10.1016/j.jbior.2018.02.001.

7. Osawa K, Umemura M, Nakakaji R, Tanaka R, Islam RM, Nagasako A, Fujita T, Yokoyama U, Koizumi T, Mitsudo K, Ishikama Y. Prostaglandin E $_2$ receptor EP4 regulates cell migration through Orai1. Cancer Sci. 2020;111(1):160-174. doi:10.1111/cas.14247.

8. Aoki T, Narumiya S. Prostaglandin E2-EP2 signaling as a node of chronic inflammation in the colon tumor microenvironment. Inflamm Regen. 2017;37(1):4. doi:10.1186/s41232-017-0036-7.

9. Asting AG, Iresjö BM, Nilsberth C, Smedh U, Lundholm K. Host knockout of E-prostanoid 2 receptors reduces tumor growth and causes major alterations of gene expression in prostaglandin E2-producing tumors. Oncol Lett. 2017;13(1):476-482. doi:10.3892/ol.2016.5448.

10. Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, Rogers NC, Sahai E, Zelenay S, Reis e Sousa C. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell. 2018;172(5):1022-1037.e14. doi:10.1016/j.cell.2018.01.004.

11. Watanabe K, Tominari T, Hirata M, Matsumoto C, Maruyama T, Murphy G, Nagase H, Miyaura C, Inada M. Abrogation of prostaglandin E-EP4 signaling in osteoblasts prevents the bone destruction induced by human prostate cancer metastases. Biochem Biophys Res Commun. 2016;478(1):154-161. doi:10.1016/j.bbrc.2016.07.075.

12. Xie C, Xu X, Wang X, Wei S, Shao L, Chen J, Cai J, Jia L. Cyclooxygenase-2 induces angiogenesis in pancreatic cancer mediated by prostaglandin E2. Oncol Lett. Published online May 22, 2018. doi:10.3892/ol.2018.8786

13. Nandi P, Girish G V., Majumder M, Xin X, Tutunea-fatan E, Lala PK. PGE2 promotes breast cancer-associated lymphangiogenesis by activation of EP4 receptor on lymphatic endothelial cells. BMC Cancer. 2017;17(1):11. doi:10.1186/s12885-016-3018-2.

14. Pandey VK, Amin PJ, Shankar BS. COX-2 inhibitor prevents tumor induced down regulation of classical DC lineage specific transcription factor Zbtb46 resulting in immunocompetent DC and decreased tumor burden. Immunol Lett. 2017;184:23-33. doi:10.1016/j.imlet.2017.01.019.

15. Kashiwagi E, Inoue S, Mizushima T, Chen J, Ide H, Kawahara T, Reis LO, Baras AS, Netto GJ, Miyamoto H.Prostaglandin receptors induce urothelial tumourigenesis as well as bladder cancer progression and cisplatin resistance presumably via modulating PTEN expression. Br J Cancer. 2018;118(2):213-223. doi:10.1038/bjc.2017.393.

16. Rong Y, Yuan CH, Qu Z, Zhou H, Guan Q, Yang N, Leng XH, Bu L, Wu K, Wang FB. Doxorubicin resistant cancer cells activate myeloid-derived suppressor cells by releasing PGE2. Sci Rep. 2016;6(1):23824. doi:10.1038/srep23824.

17. Saha J, Sarkar D, Pramanik A, Mahanti K, Adhikary A, Bhattacharyya S. PGE2-HIF1α reciprocal induction regulates migration, phenotypic alteration and immunosuppressive capacity of macrophages in tumor microenvironment. Life Sci. 2020;253:117731. doi:10.1016/j.lfs.2020.117731.

18. Take Y, Koizumi S, Nagahisa A. Prostaglandin E Receptor 4 Antagonist in Cancer Immunotherapy: Mechanisms of Action. Front Immunol. 2020;11. doi:10.3389/fimmu.2020.00324.

19. Tönisen F, Perrin L, Bayarmagnai B, Van den dries K, Cambi A, Gligorijevic B. EP4 receptor promotes invadopodia and invasion in human breast cancer. Eur J Cell Biol. 2017;96(2):218-226. doi:10.1016/j.ejcb.2016.12.005.

20. Zhang Y, Purayil HT, Black JB, Fetto F, Lynch LD, Masannat JN, Daaka Y. Prostaglandin E2 receptor 4 mediates renal cell carcinoma intravasation and metastasis. Cancer Lett. 2017;391:50-58. doi:10.1016/j.canlet.2017.01.007.

21. Bellamkonda K, Chandrashekar NK, Osman J, Selvanesan BC, Savari S, Sjölander A. The eicosanoids leukotriene D4 and prostaglandin E2 promote the tumorigenicity of colon cancer-initiating cells in a xenograft mouse model. BMC Cancer. 2016;16(1):425. doi:10.1186/s12885-016-2466-z.

22. Kim HB, Kim M, Park YS, Park I, Kim T, Yang SY, Cho CJ, Hwang D, Jung JH, Markowitz SD, Hwang SW, Yang SK, Lim DS, Myung SJ. Prostaglandin E2 Activates YAP and a Positive-Signaling Loop to Promote Colon Regeneration After Colitis but Also Carcinogenesis in Mice. Gastroenterology. 2017;152(3):616-630. doi:10.1053/j.gastro.2016.11.005.

23. Porta C, Consonni FM, Morlacchi S, Sangaletti S, Bleve A, Totaro MG, Larghi P, Rimoldi M, Tripodo C, Strauss L, Banfi S, Storto M, Pressiani T, Rimassa L, Tartari S, Ippolito A, Doni A, Soldà G, Duga S, Piccolo V, Ostuni R, Natoli G, Bronte V, Balzac F, Turco E, Hirsch E, Colombo MP, Sica A. . Tumor-Derived Prostaglandin E2 Promotes p50 NF-κB-Dependent Differentiation of Monocytic MDSCs. Cancer Res. 2020;80(13):2874-2888. doi:10.1158/0008-5472.CAN-19-2843.

24. Schumacher Y, Aparicio T, Ourabah S, Baraille F, Martin A, Wind P, Dentin R, Postic C, Guilmeau S. Dysregulated CRTC1 activity is a novel component of PGE2 signaling that contributes to colon cancer growth. Oncogene. 2016;35(20):2602-2614. doi:10.1038/onc.2015.283.

25. Calder PC. Eicosanoids. Essays Biochem. 2020;64(3):423-441. doi:10.1042/EBC20190083

26. Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10(3):181-193. doi:10.1038/nrc2809.

27. Ching MM, Reader J, Fulton AM. Eicosanoids in Cancer: Prostaglandin E2 Receptor 4 in Cancer Therapeutics and Immunotherapy. Front Pharmacol. 2020;11. doi:10.3389/fphar.2020.00819.

28. Bayerl F, Meiser P, Donakonda S, Hirschberger A, Lacher SB, Pedde AM, Hermann CD, Elewaut A, Knolle M, Ramsauer L, Rudolph TJ, Grassmann S, Öllinger R, Kirchhammer N, Trefny M, Anton M, Wohlleber D, Höchst B, Zaremba A, Krüger A, Rad R, Obenauf AC, Schadendorf D, Zippelius A, Buchholz VR, Schraml BU, Böttcher JP. Tumor-derived prostaglandin E2 programs cDC1 dysfunction to impair intratumoral orchestration of anti-cancer T cell responses. Immunity. 2023; 56(6):1341-1358.e11. doi:10.1016/j.immuni.2023.05.011.

29. Semmlinger A, von Schoenfeldt V, Wolf V, Meuter A, Kolben TM, Kolben T, Zeder-Goess C, Weis F, Gallwas J, Wuerstlein R, Hermelink K, Schmoeckel E, Harbeck N, Mayr D, Mahner S, Jeschke U, Ditsch N. EP3 (prostaglandin E2 receptor 3) expression is a prognostic factor for progression-free and overall survival in sporadic breast cancer. BMC Cancer. 2018;18(1):431. doi:10.1186/s12885-018-4286-9.