International Journal of Inflammation, Cancer and Integrative Therapy

Perspective Open Access

Role of Prostaglandins in Chronic Inflammation

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Introduction

The innate immune system is immediately activated in response to molecules bearing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) upon the invasion of foreign pathogens or tissue damage, and it recruits granulocytes to the injured tissue to clear pathogens. It also produces inflammatory mediators, including pro-inflammatory cytokines like TNF, IL1 and IL6, as well as lipid mediators like PGs and leuko. When PAMPs, DAMPs, pathogens, and injured tissues are removed, chemokine up-regulation and scavenging stop granulocyte recruitment, and recruited granulocytes are subsequently eliminated via efferocytosis, the acute inflammation is ended and the tissue is healed. The underlying cause of many chronic conditions, including autoimmune, neurological, vascular and metabolic diseases, and cancer, is chronic inflammation, which can last for weeks, months, or even years. Recent research in a variety of experimental systems has started to reveal some of the potential processes by which chronic inflammation is sustained. They involve the development of positive feedback mechanisms that self-amplify inflammatory responses and the suppression of negative feedback mechanisms that obstruct resolution, which promotes the recruitment, activation, phenotypic transformation, and synergistic interaction of various cell types and maintains pro-inflammatory cytokine signalling at inflammatory sites.

The majority of tissues and cells create PGs, such as PGD2, PGE2, PGF2, PGI2, and TXA2, either constitutively in response to physiological stimuli or in reaction to unpleasant stimuli. In either scenario, cyclooxygenases (COXs, which include COX1 and COX2) liberate C20-unsaturated fatty acids like arachidonic acid from phospholipids in the cell membrane and transform them into PGH2. Then, through the appropriate PG synthases, PGH2 is transformed into each PG. The EP1, EP2, EP3, and EP4 subtypes of PGE receptor, PGF (FP) receptor, PGI (IP) receptor, TXA (TP) receptor, and another PGD receptor in a different GPCR family, formerly known as chemoattractant receptorhomologous molecule expressed on Th2 cells (CRTH2) and now known as DP2 receptor, are the GPCR types and subtypes through which PGs act.

These PG receptors cause the activation of diverse downstream signalling pathways, and as a result, they serve various physiological and pathological processes in a variety of ways that are sometimes additive and other times antagonistic. EP3 and DP2 receptors, for instance, suppress cAMP signalling whereas EP2, EP4, DP1, and IP receptors enhance it. The PKC and Ca2+ pathways are primarily activated by EP1, FP, and TP receptors. The small G protein Rho is also activated by TP and EP3 receptors, while the PI3K and arrestin pathways are also activated by EP2 and EP4 receptors. Non-steroidal anti-inflammatory, antipyretic, and analgesic medicines (NSAIDs) that resemble aspirin work by blocking PG production and targeting COX. The production of the inducible isoforms of COX and PGE synthase, COX2 and microsomal PGE synthase 1 (mPGES1), is induced by PAMPs/DAMPs such LPS and pro-inflammatory cytokines like IL-1 and TNF. As a result, PGs have historically been considered to be inflammatory mediators that connect innate immunity to acute inflammation. The kinds of PG and their receptors implicated in each of the acute inflammatory responses have been discovered in research utilising genetically engineered mice defective in each PG receptor [1]. The expression of COX2 and mPGES1 is widespread in tissues with chronic inflammation, such as the joints of people with rheumatoid arthritis (RA), the spinal cord of people with multiple sclerosis (MS), the colon of people with inflammatory bowel disease (IBD), the cerebral arterial wall of people with cerebral aneurysms, and tumours and their microenvironment in many cancers [2-4]. These results imply that PGs play significant roles in several chronic inflammatory illnesses in addition to their activities in acute inflammation. Recent studies have shown that PGs closely interact with cytokines, drive pathogenic conversion, recruit and activate inflammatory cells, and contribute to chronic inflammation through a variety of mechanisms. These studies used PG receptor knockout (KO) mice and PG receptor-type selective agonists and antagonists in various animal models of chronic diseases. Furthermore, gene signature analyses of disease tissues from patients and genome-wide association studies (GWASs) significantly support the applicability of these experimental findings to chronic inflammation in people. Here, we evaluate these results and talk about how PG-related medications could be used to treat chronic human disorders.

PG-cytokine crosstalk in immune and allergic inflammation

When acquired immunity is increased against pathogenic antigens produced at inflammatory sites and results in immunological inflammation, acute inflammation frequently progresses to chronic inflammation. Antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, which are activated as a result of this uptake, travel to draining lymph nodes, and present the antigens to T lymphocytes to activate the adaptive immune system, take up antigens produced in inflammatory areas. Additionally, activated APCs release a variety of cytokines that set antigen-activated T cells on the path to differentiating into distinct subsets of helper T (Th) cells, which then release the cytokines unique to that subset and cause inflammation. IFN is produced by the type 1 subset of T cells (Th1), type 2 cytokines including IL4, IL5, and IL13 are produced by Th2 cells, and type 17 cells generate IL17A, IL17F, and IL22. Invading pathogens are predominantly eliminated through the production of Th1, Th2, and Th17 cells; but, if their activation and differentiation are improperly managed, they might result in immunological disorders. In the onset of autoimmune inflammatory illnesses as MS, IBD, RA, and psoriasis, Th1 and Th17 cells

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Received: 20-May-2022, Manuscript No. ijm-22- 68170; **Editor assigned:** 23-May-2022, PreQC No. ijm-22-68170 (PQ); **Reviewed:** 06-Jun-2022, QC No. ijm-22-68170; **Revised:** 11-Jun-2022, Manuscript No. ijm-22-68170 (R); **Published:** 20-Jun-2022, DOI: 10.4172/2381-8727.1000194

Citation: Yu Z (2022) Role of Prostaglandins in Chronic Inflammation. Int J Inflam Cancer Integr Ther, 9: 194.

are crucial. Indeed, in the brain, synovial fluid, gut, and skin of patients with MS, RA, Crohn's disease, and psoriasis, respectively, the increase of Th1 and Th17 cells and rise of their characteristic cytokines have been discovered [5]. Additionally, treatment of several of these disorders with antibodies that target the cytokines they release has demonstrated therapeutic effectiveness [5,6]. Asthma and atopic dermatitis (AD) are examples of allergic inflammation that is mediated by Th2 cells. As previously mentioned, a growing body of research indicates that PGs, particularly PGE2, play a significant role in immune inflammation by promoting the differentiation and pathogenic conversion of Th1 and Th17 cells. PGs are also thought to play a role in various aspects of Th2-mediated allergic inflammation. Innate lymphoid cells (ILCs), a subset of lymphoid cells that resemble T cells but lack the T cell receptor, have also been shown in studies to be modulated by PGs [7-11].

Conclusion

By controlling both innate and adaptive immune cells, there is strong evidence that PGs play a key role in chronic inflammation. These experimental results are further supported by gene signature analyses of clinical samples and patient GWAS data. PGs and cytokines interact closely in the processes of chronic inflammation in a variety of ways. One is to increase or induce the expression of the cytokine receptor(s), as seen in the induction of IL-12, IFN-1, and IL-23 receptors in Th1 cells, IL-23 receptors in Th17 cells, ST2, and IL-17B receptors in ILC2 cells, and IL-1 receptor 1 in synoviocytes by PGE2EP2/EP4 receptor signalling and PGI2IP receptor signalling, respectively. Another is to work with cytokines, notably TNF, to improve NF-B activation and the production of COX-2 to self-amplify this signalling, which is found in inflammation driven by macrophages as in IA and neutrophil-driven inflammation such in colitis-associated cancer. It is probably not overdone to say that this COX2-mediated amplification mechanism operates in a number of chronic inflammatory illnesses that show high COX2 expression together with active NFB. However, it should be highlighted that, unlike in acute inflammation, the activities of PGs and their signalling in chronic inflammation are purely reliant on the environment, including the kinds of inflammation, cytokines, cells, and so on, the time of the disease process, and the locations of inflammation. For example, while PGE_2-EP_2/EP_4 receptor signalling facilitates Th1/Th17-mediated immune inflammation and sustains macrophage- or neutrophil-driven inflammation, the same signalling pathway dampens Th2-mediated allergic inflammation.

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