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Regulation of T Helper Cell Subsets by Cyclooxygenases and Their Metabolites

Hong Li, Matthew L. Edin, Artiom Gruzdev, Jennifer Cheng, J. Alyce Bradbury, Joan P. Graves, Laura M. DeGraff, and Darryl C. Zeldin*

Laboratory of Respiratory Biology, Division of Intramural Research, NIEHS/NIH, Research Triangle Park, North Carolina 27709

Abstract

Cyclooxygenases and their metabolites are important regulators of inflammatory responses and play critical roles in regulating the differentiation of T helper cell subsets in inflammatory diseases. In this review, we highlight new information on regulation of T helper cell subsets by cyclooxygenases and their metabolites. Prostanoids influence cytokine production on both antigen presenting cells and T cells to regulate the differentiation of naïve CD4⁺ T cells to Th1, Th2 and Th17 cell phenotypes. Cyclooxygenases and PGE₂ generally exacerbate Th2 and Th17 phenotypes, while suppressing Th1 differentiation. Thus, cyclooxygenases may play a critical role in diseases that involve immune cell dysfunction. Targeting of cyclooxygenases and their eicosanoid products may represent a new approach for treatment of inflammatory diseases, tumors and autoimmune disorders.

Keywords

Cyclooxygenases; T helper cells; Prostanoids; PGE2

1. Introduction

Cyclooxygenases (COXs) metabolize arachidonic acid (AA) to prostaglandin (PG) H₂, which is further metabolized by specific synthases to biologically active lipids including PGD₂, PGE₂, PGF_{2α}, prostacyclin (PGI₂) and thromboxane (TXA₂). These AA-derived signaling molecules are collectively known as prostanoids, and elicit various effects through their respective cognate receptors, named DP, EP, FP, IP and TP. These receptors are widely expressed in the immune system, including on T cells, B cells, dendritic cells (DCs) and macrophages (Figure 1). Prostanoids also play an important role in modulating the inflammatory response, especially in conditions such as allergic airway inflammation, chronic infections and cancer [1].

There are two COX isoforms: COX-1 and COX-2. COX-1 is the constitutive isoform, with relatively stable expression, and plays important roles in many physiologic “housekeeping” functions (Figure 1). COX-2 is generally expressed at low levels under basal conditions but becomes induced by various stimuli such as bacterial endotoxins, pro-inflammatory

*Correspondence to: Darryl C. Zeldin, M.D., Division of Intramural Research, NIH/NIEHS, 111 T.W. Alexander Drive, Building 101, Room A214, Research Triangle Park, NC 27709.

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cytokines and growth factors. COX-2-dependent prostanoid production plays an essential role in inflammation and cell proliferation [2]. COX-2 and downstream synthases represent important targets for the treatment of a wide range of diseases from autoimmunity to cancer [3].

Both COX isoforms play critical, but distinct roles in T cell maturation and lymphocyte development [4]. In this review, we highlight recent developments in the regulation of T-cell subsets (e.g., Th1, Th2 and Th17 cells) by COXs and PGs. We also summarize the current understanding of the role of COXs and PGs in regulating the function of T cells in immune diseases, which may provide guidance for future basic, translational and clinical research.

2. T helper cell differentiation and function

During inflammatory and immune responses to pathogens and tumors, naïve, CD4⁺ T cells differentiate into different effector/helper T cells after activation by antigen-presenting cells (APCs). Two lineages of effector/helper CD4⁺ T cells, named Th1 and Th2, were first described by Coffman and Mosman over two decades ago [5]. Subsequent studies showed that different stimuli could direct T cells preferentially toward Th1 or Th2 lineages. These lineages are involved in immunity against intracellular and extracellular pathogens, as well as immunopathologies such as autoimmunity and allergy. In general, Th1 cells mediate a more aggressive response by promoting the inflammatory/cytotoxic form of immunity, while Th2 cells mediate less tissue-destructive forms of immunity [6, 7]. Th1 cells are implicated in the pathogenesis of many diseases such as autoimmune disorders, Crohn's disease, *Helicobacter pylori*-induced peptic ulcer and acute kidney allograft rejection [8]. Allergic atopic disorders, such as allergic rhinitis, asthma and atopic dermatitis, are the result of systemic inflammatory reactions triggered by enhanced Th2-type responses to allergens [9].

The field of immune regulation was dominated by the Th1/Th2 dichotomy until 2005, when IL-17-expressing T helper cells (Th17) were identified as a third lineage of CD4⁺ effector/helper T cells distinct from the Th1 and Th2 lineages. In addition to Th17 cells, other T-cell subsets were recently discovered, such as Foxp3⁺ regulatory T (Treg) cells, T follicular helper (Tfh) cells and IL-9-expressing Th9 cells [10, 11].

Differentiation of Th cells is regulated by the inflammatory cytokines found within the local microenvironment. Naïve CD4⁺ T cell differentiation to Th1 or Th2 subsets often occurs after migration to secondary lymphoid organs. There, APCs, such as DCs, play an important role in the maturation of these naïve cells to distinct T cell lineages. DC-derived IL-12 is a potent inducer of Th1 differentiation. IL-12 induces Th1 differentiation via signal transducer and activator of transcription (Stat) 4 and T-bet signaling [12]. Thus, factors that lower IL-12 production will lead to reduced Th1-promoting capacity. Th1 cells secrete IL-2, IFN- γ , and TNF- α that activate tissue cells and macrophages which are responsible for cell-mediated immunity and phagocyte-dependent protective responses [13]. In contrast, IL-2 and IL-4 activate Stat6 and GATA3 signaling to induce Th2 cell differentiation [12]. Th2 cells secrete IL-4, -5, -6, -10, and -13, which control macrophage function as well as antibody production by B cells [2]. Mature DCs also secrete chemokines that induce the migration of Th1 and Th2 cells. The IFN- γ inducible protein-10 (IP-10) is a Th1-recruiting chemokine, while macrophage-derived chemokine is a Th2 chemoattractant [14–16].

Differentiation of Th17 cells in the mouse is promoted by TGF- β and IL-6, which induce the STAT3-dependent expression of IL-21, IL-23R and the transcription factor ROR γ t. DC-derived IL-21 and IL-23 then regulate the establishment and clonal expansion of Th17 cells, while ROR γ t induces secretion of IL-17A, IL-17F and IL-22. IL-17, IL-21, and IL-22 are all potent pro-inflammatory mediators, although IL-22 may also be involved in promoting

tissue protection and regeneration [13, 17]. In addition, these Th17-related cytokines can stimulate chemokine secretion by resident tissue cells, leading to the recruitment of neutrophils and macrophages to sites of inflammation. Recruited cells, in turn, produce additional cytokines and proteases that further exacerbate the immune response [13, 17].

In contrast to mouse Th17 differentiation, human Th17 polarization is dependent upon IL-1 β , IL-6, IL-21, and IL-23, but does not require TGF- β . Thus, the mechanisms of Th17 differentiation may vary by species. Another notable difference is that human Th17 cells can secrete IL-26, a member of the IL-10 family of cytokines, for which there is no known murine homologue [18, 19].

The cytokines produced by Th17 cells can have both beneficial and pathogenic effects. They play a central role in eliminating harmful microbes, but persistent secretion promotes characteristics of autoimmune diseases such as chronic inflammation and tissue destruction. For these reasons, factors involved in Th17 differentiation may serve as potential targets for preventing a variety of autoimmune conditions, including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disorders [11, 17, 18, 20–26]. The cytokines, signaling molecules and transcription factors involved in Th cell differentiation are summarized in Figure 2. Following activation by antigen-presenting cells such as dendritic cells (DCs), naïve CD4⁺ T cells can be polarized into different effector T cell subsets, including Th1, Th2, Th17 and Th9 cells, depending on the local cytokine environment (IL-12-Th1; IL-4-Th2; IL-6+TGF- β -Th17 and IL-4+TGF- β -Th9). The differentiation of each of these effector T cell subsets is controlled by distinct sets of transcription factors (Stat4/T-bet-Th1; Stat6/GATA3-Th2; Stat3/ROR γ t; and Stat6/PU.1/IRF4-Th9). Th1, Th2, Th17 and Th9 cell subsets produce their specific cytokines and have different function (Figure 2).

3. COX-derived PGs inhibit the differentiation and activation of Th1 cells

COX-1, via PGE₂ production and EP2 receptor signaling, is required for early T cell development (i.e. CD4/CD8 double negative (DN) to double positive (DP) transition). COX-2-derived PGs also stimulate T cell maturation [2]. After maturation to naïve CD4⁺ cells, differentiation of T helper cell lineages is driven by chemokine signaling and interaction with surface molecules on APCs [5, 27]. Recent studies indicate that several chemical mediators, hormones and neuropeptides are also important in modulating the Th1/Th2 balance and immune responses [28–31]. PGE₂ produced by APCs, such as macrophages and DCs, is one of the well-known factors that influence Th1 activation.

Numerous examples indicate that COX-2-derived prostaglandins, such as PGE₂, suppress Th1 cell differentiation, particularly in anti-tumor and anti-infection immune responses. Macrophages from BALB/c mice produce greater amounts of PGE₂ after LPS stimulation than those from any other strain of mice. This is associated with decreased macrophage-derived IL-12 synthesis, Th1 differentiation, and T cell-derived IFN- γ production [32]. COX-2 activation suppresses Th1 polarization in response to *Helicobacter pylori* [33]. Conversely, short-term therapy with the specific COX-2 inhibitor celecoxib increases the Th1 immune response in human gastric mucosa [34, 35]. COX-2 inhibition promotes IFN- γ -dependent enhancement of anti-tumor responses [36]. Deletion of COX-2 in mouse mammary epithelial cells delays breast cancer onset through augmentation of type 1 immune responses in tumors [37].

PGE₂ downregulates signaling primarily through the Th1-inducing IL-12 pathway. PGE₂ has been shown to suppresses LPS-induced IL-12 production by macrophages and DCs [38, 39], and down-regulates IL-12 receptor expression [40–42] to inhibit Th1 differentiation. APC-derived PGE₂ down-regulates IFN- γ production by T cells [43–45]. By suppressing Th1 differentiation, PGE₂ mediates a shift in the immune response from Th1 to Th2. For

example, Han et al. demonstrated that infection of Balb/c mice with low-level doses of *Mycobacterium bovis* led to Th1 immunity; however, high-dose infection increased levels of COX-2 and PGE₂-releasing macrophages, total serum immunoglobulin E (IgE), and serum IgG1 antibodies against heat shock protein 65 (Th2 responses). Cultures of spleen cells isolated from these mice expressed Th2 cytokines, IL-4 and IL-10, in recall responses. Treatment of these mice with the selective COX-2 inhibitor NS-398 reversed these effects. NS-398 increased IFN- γ levels, reduced IL-4 and IL-10 production in recall responses and decreased total serum IgE levels [46]. Thus, low doses of mycobacteria induced low levels of COX-2/PGE₂ and Th1 immunity, while high mycobacteria doses induced strong COX-2/PGE₂ and Th2 responses.

In vitro evidence indicates that PGs reduce the maturation and function of monocyte-derived dendritic cells (MDC). MDCs express COX-1 and COX-2 and produce prostaglandins that reduce MDC maturation and IL-12 production in an autocrine fashion. Whittaker et al. found that while monocytes express COX-1 constitutively and only express COX-2 when activated, immature MDCs (I-MDC) and mature MDCs constitutively express both COX-1 and COX-2. In I-MDCs, whether COX-1 or COX-2 catalyzes increases in PG production is dependent on several factors, such as IFN- γ and CD40 [47]. PGs produced through COX-2 are autocoids that inhibit IL-12 production and subsequent Th1 differentiation. Treatment of maturing MDCs with NS-398 yields MDCs that stimulate significantly more IFN- γ production (Th1 response). These studies demonstrate that MDCs express both COX isoforms constitutively and produce PGs that regulate Th1 maturation, differentiation and activation.

Another important mediator of Th1 cell differentiation is prostacyclin (PGI₂). *In vivo*, DCs are the primary producers of IL-12, which induces Th1 differentiation. PGI₂ analogs not only inhibit IL-12 production by BMDCs, but also directly decrease CD4⁺ Th1 cytokine production in a partially IP receptor-specific manner [48, 49]. Thus, like PGE₂, PGI₂ signaling also limits Th1 immune responses.

In summary, COXs metabolites, such as PGE₂ and PGI₂, inhibit Th1 cell activation in anti-tumor and anti-intracellular infection immune responses via down-regulation of IL-12 and IFN- γ production from APCs and Th2 cells. At high doses, PGE₂ can induce a switch from Th1- to Th2- dominated immune responses through downregulated activation of Th1-inducing IL-12 pathway (Figure 3). Thus, modulating PGE₂ and PGI₂ levels may be a viable therapeutic target for altering Th1 immune responses.

4. COX-derived PGE₂ promotes Th2 type responses

Prostaglandins play important roles in modulating Th2 immunity [45]. Regulation of Th2 cell responses by PGE₂ is well documented. In support of its involvement in Th2-mediated human pathology, overproduction of PGE₂ is observed in multiple Th2-associated diseases, most notably atopic dermatitis and asthma [50]. The variability in suppressive effects of PGE₂ in different mouse strains is determined largely by strain differences in the number of PGE₂ receptors [45]. An *in vivo* Th2-dominant immune response in BALB/c mice has been shown to be dependent on PGE₂, further confirming that PGE₂ can shift the balance of CD4⁺ helper T cells toward a Th2 type immune response [45]. In many cases, PGE₂ does not specifically upregulate cytokines or transcription factors that promote Th2 differentiation. Instead, PGE₂ strongly suppresses Th1-inducing factors generated by T lymphocytes, DCs, APCs and monocytes, and this can shift the balance toward more Th2 cell differentiation.

PGE₂ regulates CD4⁺ T cell differentiation by altering the local cytokine microenvironment through actions on APC. The balance of Th1 vs. Th2 differentiation is determined in large

part by relative levels of IL-12 and IL-4. High IL-12 levels direct naïve CD4⁺ T cells toward Th1 differentiation, while IL-4 directs them toward Th2 differentiation. The Th1-suppressive effect of PGE₂ also relies largely on its ability to lower the production of IL-12 in monocytes and DCs. In the absence of IL-12 signaling, IL-4 stimulates Th2 differentiation. Since Th2 cells secrete IL-4, these T cells participate in a positive feedback mechanism that drives Th2 differentiation. Thus, PGE₂ suppresses cytokine secretion which, in turn, leads to Th1 differentiation, rather than promotes Th2-inducing cytokines (Figure 3). While PGE₂ has been found to enhance IL-12 production from immature DCs stimulated by TNF- α or other signals, PGE₂ suppresses the capacity of mature DCs to secrete IL-12 during DC maturation and antigen presentation. Induction of CTL-, Th1-, and NK cell-mediated type 1 immune response is also diminished by PGE₂, lowering their Th1-promoting capacity, which results in Th2 responses [3]. In addition, PGE₂ also stimulates the production of Th2 chemoattractants from CD40-activated DCs. Similar to its effects on T cells, PGE₂ regulates the inflammatory phenotype and function of DCs through EP2 and EP4 receptor subtypes [51].

PGE₂ can enhance Th2-type responses, in part through direct actions on T lymphocytes [52]. When added during the priming of naïve CD4⁺ T cells, PGE₂ selectively suppresses the production of Th1 cytokines, IL-2 and IFN- γ , which indirectly facilitates the development of a Th2-type immune response. IL-12 receptor expression and IL-12 responsiveness are also reduced by PGE₂ in peripheral blood lymphocytes stimulated by anti-CD3, which limits Th1 differentiation [41, 53]. PGE₂ leads to enhanced Th2 differentiation, but does so without promoting Th2-inducing cytokines. Bao et al. found that PGE₂ inhibits both Th1 and Th2-inducing cytokines in differentiating CD4⁺ T cells; however, Th1-inducing cytokines were inhibited to a much higher degree [54]. PGE₂ increases IL-5 secretion in Th2 clones, but has no effect on production of the key Th2-inducing cytokine IL-4 [2]. Thus, PGE₂ promotes the Th2 phenotype by strongly suppressing Th1 differentiation.

The PGE₂-dependent effects on naïve CD4⁺ T cells, Th1 cells and Th2 cells appear to be associated with increased intracellular cyclic AMP (cAMP), suggesting that the G α_s -linked EP2 and/or EP4 receptors may mediate these responses. The EP4 receptor is expressed in Jurkat T cells and responds to PGE₂ by raising cAMP levels [55]. COX-2 is upregulated upon T cell activation and may also promote T cell activation through as yet unidentified PGs [56].

PGE₂ may also interfere with feedback regulation of the Th1/Th2 balance. As the immune system skews toward the Th2 phenotype, production of the major Th2 cytokine, IL-4 will increase. However, IL-4 can suppress COX-2 expression and enhance Th1-promoting IL-12 production from DCs, which could return the immune system toward a more balanced Th1/Th2 response [52]. Since PGE₂ inhibits IL-12 production, it may interfere with this feedback mechanism and continue to drive the immune system toward a Th2 response. Similar to mature DCs, human monocyte production of IL-12 following LPS stimulation is also inhibited by PGE₂ in a dose-dependent manner. Macrophages are able to secrete both PGE₂ and IL-12 during antigen presentation, and the balance of these two factors may determine whether the T cells differentiate into Th1 or Th2 cells [39, 57].

By shifting the balance of the cellular immune response toward Th2-type cytokine production, PGE₂ ultimately potentiates the B cell-mediated humoral response. PGE₂ also attenuates Th2-mediated responses indirectly through actions on the effector B lymphocytes. PGE₂ inhibits several early events of LPS and IL-4 activation in normal mouse B cells such as lowering class II MHC molecule expression [58, 59]. This may indirectly blunt some of the T cell responses stimulated by B cells. In addition, B cells have an APC capacity and participate in the development of the Th2 subset. Stimulation of CD40 ligand on B cells is

necessary for the induction of Th2 responses. Th2 chemoattractant production is potentiated by PGE₂ in CD40 or LPS-stimulated B cells [58, 59].

Several studies also indicate a role of COX-1 in Th2 regulation. COX-1^{-/-} mice have exacerbated allergen-induced bronchoconstriction associated with increased numbers of CD4⁺ and CD8⁺ T cells. These effects are associated with exaggerated levels of the Th2 cytokines, IL-4, -5, and -13, and increased levels of eotaxin and thymus- and activation-regulated chemokines (TARC) in their airways. This data suggests a potential role of COX-1 in regulating T cell recruitment, Th2 cytokine secretion, and lung function in the allergic airway [4].

4.1 Regulation of Th2-type response by other PGs

PGD₂ also promotes the shift toward a Th2 response. PGD₂ is the major mast cell product released during the allergic response. Two G-protein-coupled receptors for PGD₂ are chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) and D-type prostanoid receptor (DP) [60]. PGD₂ stimulates the chemotaxis of eosinophils, basophils and Th2 lymphocytes [60]. In addition, most of the PGD synthase-expressing CD4⁺ lymphocytes show a typical Th2-type cytokine pattern [61]. Part of the Th2 cell population can also produce PGD₂ at sites of antigen presentation, and this may contribute to Th2-related immune responses [61]. PGD₂-DP signaling activates p38 MAPK, p44/42 MAPK, and protein kinase C pathways that lead to NF-κB activation and COX-2 gene expression. This positive feedback loop amplifies PGD₂ production and perpetuates the Th2 phenotype [62].

PGI₂ analogs also stimulate T cell proliferation and Th2 cytokine production in an antigen-specific fashion [48] through the IP receptor [49]. *In vivo* studies from several groups suggest that PGI₂ restrains allergen-induced lung inflammation [63–66]. Taken together, these results suggest that PGI₂ signaling modulates Th2 immune responses.

4.2 Discrepancies in reported COX-2/PGE₂ effects on Th2-type responses

Even though the majority of published studies suggest that PGE₂ enhances Th2 type responses [52], several lines of evidence also support an inhibitory effect of COX-2 on Th2 immune responses. Thus, Th2 regulation by COX-2 is much more complicated than previously thought. Jaffar et al. showed that selective COX-2 inhibition *in vivo* reduces PGE₂ biosynthesis and results in a marked increase in Th2-mediated, but not Th1-mediated, lung inflammation [67]. Carey et al. reported that acute pharmacologic inhibition of COX-1 or COX-2 during allergen sensitization and exposure leads to enhanced Th2 airway responses [4]. Laouini et al. reported a similar effect of COX-2 inhibition, in which it enhanced the Th2 immune response to percutaneous sensitization in a mouse model of atopic dermatitis [68]. Furthermore, using COX-2^{-/-} mice, Hamada et al. demonstrated that COX-2 deficiency enhances Th2 type responses and impairs neutrophil recruitment upon hepatic ischemia/reperfusion injury [69].

The observed differences in COX-2/PGE₂ effects may be due, at least in part, to alterations in various developmental phases of the immune response and may depend on the timing of COX-2 inhibitor application. For example, COX-2 inhibition during the immune response (late) phase, but not during the antigen priming (early) phase, can attenuate the development of experimental autoimmune myocarditis [70]. In contrast, in persistent post-infective enteric muscle hypercontractility, it is during the acute infection but not thereafter when increased expression of Th2 cytokines, IL -4, -5, and -13, is observed [71]. Moreover, levels of Th2 cytokines are significantly different between the acute infection phase and post-infection phase in a model of post-infective gut dysfunction [72]. A Th1 to Th2 cytokine

transition was observed in the progression of thyroid-associated ophthalmopathy from the early to late stages [46]. Furthermore, it was found that COX inhibition during immune sensitization, but not during the allergic challenge phase, is necessary and sufficient for increasing the Th2 response to OVA challenge after sensitization [73]. Other factors that may affect the direction of actual Th responses include the doses of infective agents and differences in the COX inhibitors used in the studies.

4.3 Regulation of COXs in immune cells

COX-2 expression and activity is regulated in T cells, DCs and monocytes. For instance, CD40 engagement on murine bone marrow-derived DCs upregulates COX-2, PGE₂ biosynthesis and EP2 receptor levels via activation of p38 and ERK1/2 MAPK signaling. These events contribute to the induction of Th2 immune responses [51]. T helper cell-derived chemokines can also induce COX-2 expression. Co-culture with monocytes exposed to Th2-inducing cytokines activates COX-2 function in human basal cell carcinoma cells and subsequently increases cellular invasion and angiogenesis [74]. Th2-cell-associated cytokines, particularly IL-4, have also been shown to suppress stimulation of PGE₂ biosynthesis and COX activity mainly through the downregulation of COX-2 in various cell lines, including circulating monocytes [75], alveolar macrophages [75], mature DCs [52] and fibroblasts [46]. In contrast, Th1-associated cytokines, such as IFN- γ , have varying effects on COX-2 expression depending on the cell type [7, 46, 76]. T cell-derived cytokines can activate both p38 MAPK and STAT signaling pathways, which are known to reduce COX-2 levels [46]. IL-13, which is secreted by Th2 cells, also decreases fibroblast PGE₂ release, and this is accompanied by a decrease in the expression of both COX-1 and COX-2 [77, 78].

4.4 Role of COXs in Th2-related pathological immunologic responses

Alterations in Th1 and Th2 responses exist in many immune disorders, such as immune tolerance, allograft rejection, atopy, cancer and HIV infection [79]. In many cases, both COXs and PGs are involved in this process [33]. In the gut mucosa, LPS induces COX-2-dependent PGE₂ production by mononuclear and/or stromal cells, creating a Th2-permissive local microenvironment. PGD₂ derived from the gastric mucosa and fibroblasts is protective against inflammatory changes in *H. pylori*-induced gastritis [80]. In addition, increased PGE₂ protects against allograft liver transplant rejection in rats [81].

Atopic disorders, such as allergic rhinitis, asthma and atopic dermatitis, are the result of a systemic inflammatory reaction triggered by a Th2-type immune response [9]. High levels of IL-4, IL-5 and IL-13, and diminished IL-12 and IFN- γ production from APCs appear to be central to the pathophysiology of these disorders [50, 82]. Inhibition of PGE₂ biosynthesis would increase IL-12 levels and promote a shift toward Th1 cytokine production.

PGE₂ also modulates the actions of bacteria and viruses in evading and subverting the host immune response [83]. For example, *Francisella tularensis* alter host T cell responses by causing macrophages to release PGE₂ that blocks T cell proliferation and promotes a Th2-like responses [84]. A similar scenario is observed for lepromatous leprosy and *H. pylori* gastritis [85]. HIV infection induces a Th2-type immune response and defects in Th1 differentiation. High levels of PGE₂ released from monocytes/macrophages and reduced IL-12 production have also been observed in HIV [86]. Similar to bacteria or viruses, tumor cell growth increases when host immune responses are compromised. PGE₂-mediated mechanisms may contribute to an attenuated anti-tumor immune response in humans. Reduced IL-12 production by host MFGs and DCs could result in a lowered Th1 response that is known to contribute to the anti-tumor, cell-mediated immune response [87, 88].

An increase in COX-2 and PGE₂ release is associated with the susceptibility of smokers to cancer, infection, and allergy. Cigarette smoke extract (CSE) induces COX-2 protein levels and augments endogenous PGE₂ release [89]. This suppresses key DC functions and favors the development of Th2 immunity [89]. CSE inhibits the secretion of the Th1 cytokine IFN- γ and enhances production of the Th2 cytokine IL-4 in the mixed lymphocyte reaction (MLR).

4.5 Chemical regulation of COX-2 and Th2 immunity

Because of their essential roles in modulating immune responses, COX-2 and Th2 immune cells are promising targets for the treatment of many diseases. Several natural plant ingredients are active in various inflammatory diseases based on their effects on COX-2 and Th1–Th2 immunity. In mouse models of allergic diseases, suppression of Th2 differentiation leads to reduced inflammatory outcomes. Examples include curcumin for treatment of inflammatory bowel disease (IBD) [90], thymoquinone for allergic lung inflammation [1], anthocyanins for asthma [91], and 2-amino-3H-phenoxazin-3-one for treatment of T cell-mediated inflammatory autoimmune diseases and bacteria-induced chronic-inflammatory diseases [79].

In summary, Th2 regulation by COXs and PGs is complex and involves both positive/negative feedback loops and direct/indirect pathways (Figure 4). PGE₂ promotes IL-4 production in Th2 cells and inhibits IFN- γ and IL-2 secretion in Th1 cells. PGE₂ inhibits IL-12 and increases IL-4 production by DCs and macrophages, which in turn decreases Th1 cell and increases Th2 cell immune responses. PGE₂ triggers EP2 and EP4 receptor signaling to promote COX-2 transcription in macrophages and DCs, thus forming the COX-2 positive regulation loop. It also increases IL-4 production in Th2 cells, resulting in inhibition of COX-2 expression in dendritic cell and macrophages and forming a negative feedback loop in the Th2 cell immune response. Other PGs such as PGD₂ and PGI₂ directly promote Th2 cell immune responses. These results indicate that COXs and prostaglandins are critical regulatory mediators of the Th2 cell responses and are involved in the pathogenesis of a variety of inflammatory disorders.

5. COX-2 and PGs enhance Th17 responses

COX-2 and PGs promote Th17 cell development and function through both direct and indirect pathways. There are several examples whereby PGE₂ indirectly promotes Th17 differentiation by altering cytokine production of APCs. IL-23 and IL-12/IL-27 have opposite effects, supporting Th17 and Th1 phenotypes, respectively. PGE₂ actively shifts the IL-12/IL-23 balance in DCs in favor of IL-23. PGE₂ promotes IL-23 expression, and inhibits IL-12 and IL-27 release from stimulated DCs to enhance the pathogenic inflammatory Th17 phenotype [92, 93]. PGE₂ enhances the production of IL-23 and IL-1 β in macrophages and DCs while down-regulating IL-12 production [94]. PGE₂ promotes Th17 development by enhancing IL-6 production from macrophages and increasing IL-23 and IL-6 secretion by DCs. *B. bronchiseptica*-infected macrophages can induce IL-17 production from naïve CD4⁺ splenocytes and lung tissues from *B. bronchiseptica*-infected mice exhibit a strong Th17 immune response. PGE₂ enhances DC-derived IL-6 production and shifts the IL-23/IL-12 balance in favor of IL-23, resulting in increased IL-17 production [92]. In humans, peripheral blood mononuclear cells (PBMCs) produce PGE₂, which, together with IL-23, favors the expansion of human Th17 cells from and further enhances IL-17 production induced by IL-23 from memory CD4⁺ T cells [95].

COXs and PGs also directly regulate Th17 cells. PGE₂ can directly promote the differentiation and pro-inflammatory functions of human and murine Th17 cells. In human purified naïve T cells, PGE₂ acts via EP2- and EP4-mediated signaling and cyclic AMP

pathways to upregulate IL-23 and IL-1 receptor expression [96, 97]. In the presence of IL-1 β and IL-23, PGE₂ may favor the development and/or expansion of Th17 cells, while downregulating proliferation of non-Th17 cells. In addition, it may convert T cell lineages into IL-17 producers, resulting in an “apparent” increase in the number of Th17 cells. Moreover, PGE₂ promotes the selective enrichment of Th17 cells by differentially modulating the proliferation of memory T cell subsets *in vitro* [98].

In 2003, our lab reported that COX-1 and COX-2 regulate the Th1–Th2 balance in allergic and non-allergic lung diseases [4]. Recently, we found that COX-2-derived PGF_{2 α} and PGI₂ regulate Th17 cell differentiation during allergic lung inflammation through FP and IP receptors on T cells. Together, these data indicate that PGI₂, PGF_{2 α} and PGE₂ can promote Th17 cell differentiation via binding to FP, IP, EP2 and EP4 receptors (Figure 5) [99, 100].

In contrast, PGE₂ downregulates some functions of Th17 cells. Napolitani et al. demonstrated that PGE₂ inhibits IFN- γ and IL-10 production by Th17 cells, which attenuates their pathogenic potential. These opposing effects of PGE₂ are mediated by differential signaling through EP2 and EP4 receptors, leading to a rapid increase in levels of ROR γ t and a decrease in T cell-specific T-box transcription factor 21 (T-bet) expression [98].

Overall, COXs and PGs promote Th17 cell development via paracrine and autocrine regulation. In a paracrine manner, PGE₂ triggers EP2 and EP4 receptor signaling to increase IL-23 and IL-6 secretion, thus changing the IL-23/IL-12 balance of DCs and macrophages. IL-6 and TGF- β then drive naïve CD4⁺ T cells to Th17 cells, which proliferate under the influence of IL-23. In the autocrine pathway, PGI₂ and PGF_{2 α} promote Th17 differentiation via their respective FP and IP receptors, independent of DC interactions (Figure 5). Findings from these studies suggest possible therapies to treat Th17 cell-related inflammatory diseases.

6. Clinical consequences of COX inhibition in asthma and other T cell-mediated allergic diseases

Prostaglandins are critical mediators of inflammation and affect both humoral and T cell-mediated immune responses in humans. In experimental allergic diseases, COX-2 regulates the development of T helper cell subsets [101–103]. Examination of tissue sections from patients with chronic tonsillitis show that activated B and T cells express both COX-1 and COX-2 [101]. Further studies will be necessary to elucidate the role of COX expression and/or function in immunologic responses in chronic tonsillitis [23].

Pharmacologic manipulation of COX enzyme activity also affects allergic and inflammatory responses in humans. The COX-1 inhibitor aspirin induces a form of asthma termed aspirin-induced asthma (AIA), which is part of a syndrome that includes rhinitis and nasal polyposis. Aspirin suppresses PGE₂ levels in sensitive individuals, which leads to upregulation of lipid biosynthesis and respiratory distress. AIA can be at least partly reversed by treatment with PGE₂, which provides direct evidence that prostanoids can have direct effects on asthma pathogenesis [104].

Other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2, and offer relief from many inflammatory conditions; however, NSAIDs can induce serious side effects, including upper gastrointestinal injury. Selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib) avoid COX-1-dependent gastrointestinal effects. COX-2 produces prostaglandins almost exclusively responsible for pain, inflammation and fever. COX-2 inhibitors are often prescribed for the treatment of

osteoarthritis, rheumatoid arthritis and acute pain. Some studies suggest that selective COX-2 inhibitors reduce the incidence of gastrointestinal side effects compared with conventional NSAIDs. COX-2 selective inhibitors are used as alternative anti-inflammatory drugs in patients with ASA/NSAID intolerance [105, 106], asthma [107–120] and other allergic diseases [105, 106, 121, 122]. COX-2-selective inhibitors also have efficacy similar to NSAIDs in other inflammatory arthropathies including ankylosing spondylitis and gout [123]; however, recent concerns about prothrombotic cardiovascular effects in humans have limited widespread use of COX-2 inhibitors [124]. COX-2 regulates the development T helper cell subsets in experimental models of allergic diseases [101–103]. Thus, COX-2 inhibitors may suppress inflammation through attenuation of T cell differentiation. It is unclear to what degree suppression of immune responses contributes to the efficacy of COX-2 inhibitors in T cell-mediated allergic diseases in humans.

Not all COX-2 inhibitors alleviate inflammatory diseases. The ability of selective COX-2 inhibitors to exacerbate colonic injury in different models of experimental colitis suggests that PGs derived from COX-2 are anti-inflammatory and mucosal protective in this condition. Indeed, PGE₂ inhibits inflammatory cytokines and stimulates mucus secretion in the gastrointestinal mucosa through activation of (EP4) receptors. Pretreatment with intraluminal PGE₂ analogs (e.g. 16,16'-dimethyl PGE₂) reduces the severity of injury induced by trinitrobenzenesulfonic acid and acetic acid [125–127]. Together, these studies argue against the use of COX-2-selective inhibitors for the treatment of human or experimental colitis.

7. Conclusions

In summary, COXs and their metabolites are important regulators of inflammatory responses and play critical roles in regulating the differentiation of T helper cell subsets in inflammatory diseases, tumor immunity and autoimmune diseases. PGs influence cytokine production on both APCs and T cells to regulate the differentiation of naïve CD4⁺ T cells to Th1, Th2 and Th17 phenotypes. COXs and PGE₂ generally exacerbate Th2 and Th17 phenotypes, while suppressing Th1 differentiation. Thus, they may play a critical role in diseases that involve immune cell dysfunction. COX-2 inhibitors are used in clinical treatment of asthma and T cell-mediated allergic diseases. These findings may provide new avenues of treating inflammatory diseases, tumors and autoimmune disorders.

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Highlights

- Prostanoids influence cytokine production on both antigen presenting cells and T cells to regulate the differentiation of naïve CD4⁺ T cells to Th1, Th2 and Th17 cell phenotypes
- COXs and PGE2 generally suppressing Th1 differentiation and exacerbate Th2 and Th17 phenotypes
- Targeting of cyclooxygenases and their eicosanoid products may represent a new approach for treatment of inflammatory diseases, tumors and autoimmune disorders.

Figure 1.

Arachidonic acid metabolism by COX-1 and COX-2. COX1 and COX-2 convert arachidonic acid to PGH₂. PGH₂ is a substrate for terminal synthases which generate PGE₂, PGD₂, PGF_{2α}, PGI₂ and TXA₂, which activate cell signaling through their cognate receptors, EP1-4, DP1-2, FP, IP and TP.

Figure 2.

Differentiation of Th cell subsets. Naïve $CD4^+$ T cells are activated by antigen-presenting cells (APCs) in the presence of co-stimulation through CD28 and/or inducible T-cell co-stimulator (ICOS). The cytokine microenvironment determines the terminal lineage commitment and cytokine expression profiles. IL-12, through STAT4, potentiates the production of IFN- γ and the expression of the transcription factor T-bet. T-bet increases IFN- γ which maintains Th1-cell-lineage commitment. IL-4, activates STAT6 to increase expression of GATA3. GATA3 potentiates IL-4 and IL-13 expression, which determines Th2-cell-lineage differentiation. TGF- β and IL-6 function through STAT6 to increase the expression of ROR γ t and promote $CD4^+$ T cells to Th17 effector cells that produce IL-17A and IL-17F. TGF- β can convert Th2 cells to Th9 cells that produce IL-9, IL-10 and IL-13 by increasing expression of PU.1 and IRF4 transcription factors. T-bet- T-box expressed in T cells; GATA3, GATA-binding protein 3; IFN γ , interferon- γ ; ROR γ t-retinoic acid receptor-related orphan receptor- γ t.

Figure 3.

Regulation of Th1 differentiation and activation by PGE₂. Differentiation to Th1 vs. Th2 cells is controlled by the balance of IL-12 and IL-4 cytokines. PGE₂ downregulates IL-12 production and Th1-inducing capacity of APCs. In the absence of IL-12 production, Th2 differentiation is enhanced. Th2 cells secrete IL-4 which augments Th2 cell development. Th2 cell-derived IL-4 also provides feedback inhibition on APCs to diminish COX-2 expression to restore Th1/Th2 balance.

Figure 4.

Regulation of Th2 cell immune response by COXs and PGs. Th2 cell differentiation is regulated by COXs and PGs in the inflammatory cytokine microenvironment. (A) PGE₂ inhibits IL-12 production by DCs and macrophages, which reduces Th1 differentiation. PGE₂ inhibits IL-12 receptor expression and IFN-γ and IL-2 secretion by Th1 cells. (B) PGE₂ indirectly promotes Th2 differentiation and autocrine signaling through increased IL-4 in Th2 cells. (C) PGE₂, via EP2 and EP4 receptors, promotes COX-2 transcription in macrophages and DCs, resulting in a COX-2 positive feedback loop. (D) Increased IL-4 production in Th2 cells inhibits COX-2 expression in DCs and macrophages, which forms a negative feedback loop in Th2 cell immune response. (E) PGD₂ and PGI₂ directly promote Th2 cell immune response.

Figure 5.

Regulation of Th17 cell differentiation by COX-2 and PGs. (A) Binding of PGE₂ to EP2 and EP4 on DCs leads to increased IL-23 and IL-1β expression. In addition, PGE₂ induces IL-23R and IL-1R expression on CD4⁺ T cells. The IL-23 and IL-1β signals activate Stat3 and upregulate RORγt, which in conjunction with TGF-β and IL-6, leads to IL-17 expression. (B) Autocrine effect of PGI₂ and PGF_{2α} on Th17 cell differentiation. CD4⁺ T cells generate PGI₂ and PGF_{2α}. Activation of IP and FP receptors on CD4⁺ T cells induces Stat3 signaling and upregulation of RORγt, which enhances TGF-β and IL-6 induction of IL-17 expression.