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Invited review

Regulation of T helper cell subsets by cyclooxygenases and their metabolites

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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 by 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 PGE_2 generally exacerbate Th2 and Th17 phenotypes, while suppressing Th1 differentiation. Thus, cycloxygenases 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.

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Contents

1. Introduction

Cyclooxygenases (COXs) metabolize arachidonic acid (AA) to prostaglandin (PG) H_2, which is further metabolized by specific synthases to biologically active lipids including PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2) and thromboxane (TXA_2). 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 (Fig. 1). Prostanoids also play an important role in modulating the inflammatory response, especially in conditions such as allergic airway inflammation, chronic infection 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 (Fig. 1). COX-2 is generally expressed at low levels under basal conditions but becomes induced by various stimuli such as bacterial endotoxins, pro-inflammatory 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].

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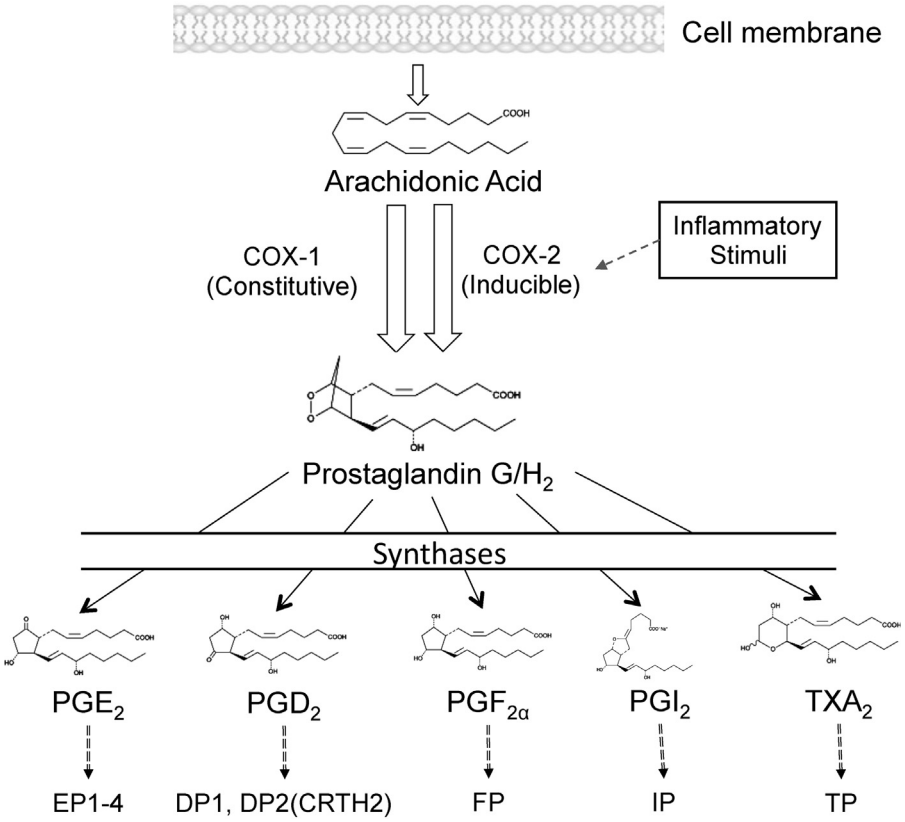

Fig. 1. Arachidonic acid metabolism by COX-1 and COX-2. COX1 and COX-2 convert arachidonic acid to PGH_2. PGH_2 is a substrate for terminal synthases which generate PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 and TXA_2, which activate cell signaling through their cognate receptors, EP1-4, DP1-2, FP, IP and TP.

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 RORγt. DC-derived IL-21 and IL-23 then regulate the establishment and clonal expansion of Th17 cells, while RORγt 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