Review Article

The Signaling Pathway of PGE₂ and Its Regulatory Role in T Cell Differentiation

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Prostaglandin E2 (PGE₂) is a lipid mediator derived from arachidonic acid. As an essential inflammatory factor, PGE₂ has a critical impact on immune regulation through the prostanoid E (EP) receptor pathway. T cells, including CD4⁺ and CD8⁺ T cell subsets, play crucial roles in the adaptive immune response. Previous studies have shown that PGE₂ is involved in regulating CD4⁺ T cell differentiation and inflammatory cytokine production via the EP receptor pathway, thereby affecting the development of diseases mediated by CD4⁺ T cells. In this review, we summarize the signaling pathway of PGE₂ and describe the relationship between PGE₂ and T cell differentiation. Hence, this review may provide important evidence for immune therapies and may even promote the development of biomedicines.

1. Introduction

Prostaglandin (PG) is a lipid mediator family derived from the fatty acid arachidonic acid (AA). Due to differences in their molecular structures, PGs were classified into nine groups, including PGA, PGB, PGD, PGE, PGF, PGG, PGH, PGI, and PGJ. Among these molecules, PGE₂ is a kind of an inflammatory factor that has been intensively studied. Although PGE₂ has a short half-life and a 90% degradation rate in pulmonary circulation [1], it plays a significant role in mediating inflammation and multiple physiological processes [2]. PGE₂ functions by prostanoid E (EP) receptors, which include four types of membrane-bound G protein-coupled receptors named EP1 to EP4 mediating the multiple signaling pathway. To date, a series of studies has demonstrated that PGE₂ regulates the differentiation, maturation, and activation of immune cells, especially T cells [3, 4].

As essential components in the adaptive immune system, T cells are mainly divided into CD4⁺ helper T (Th) cells and CD8⁺ cytotoxic T lymphocytes (CTLs) [5]. After stimulation, CD4⁺ T cells can differentiate into a variety of effector subsets, including classical Th1 cells and Th2 cells, the subsequently defined Th17 cells, follicular helper T (Tfh) cells, and induced regulatory T (iTreg) cells. Th1 cells are characterized by their secretion of IFN-γ and are involved in cellular immunity, while Th2 cells produce IL-4, IL-5, IL-10, and IL-13 and are required for humoral immunity and allergic reactions. Th17 cells mainly secrete IL-17A, IL-17F, IL-21, and IL-22 and mediate inflammatory response. Tfh cells are a new subset of helper T cells that produce IL-21 and regulate the maturation of B cell responses. Treg cells are characterized by the expression of the forkhead transcription factor (Foxp3) and have essential roles in the maintenance of immune homeostasis by suppressing these effector T cell responses [6]. CTLs play their roles by directly killing infected cells and cancer cells. In this review, we provide a general overview of the metabolism of PGE₂, the signaling pathways of EPs, and the regulatory role of PGE₂ in T cell differentiation.

2. PGE₂ Synthesis and Metabolism

Prostaglandins are derived from AA and synthesized mainly through the cyclooxygenase (COX) pathway (Figure 1). When cells are damaged or stimulated, AA is released from plasma membrane phospholipids [7]. Free AA can be
modified into prostaglandin or leukotrienes [8]. For prostaglandin synthesis, AA released from membranes is oxidized by the cyclooxygenase enzymes COX-1 and COX-2 [9, 10]. The enzymatic effect of COX enzymes on AA involves two steps, one is the oxidation of AA to form prostaglandin G2 (PGG2), and the other is the reduction of PGG2 to form prostaglandin H2 (PGH2). Depending on the specific enzymes, PGH2 can be modified to five different prostaglandins, including PGI2, PGE2, PGF2α, PGE2, and thromboxane A2 (TXA2) [2, 7]. PGE2 synthesis through COX is mediated by three distinct enzymes, cytosolic PGE synthase (cPGES), microsomal PGE synthase-1 (mPGES-1), and mPGES-2 [2].

Nearly all types of cells and tissues can secrete PGs. When PGs are secreted, however, they are quickly degraded by the lung or liver. The lung is the primary organ involved in PGE2 metabolism [11, 12]. PGE2 metabolism mainly occurs via three mechanisms, leading to the inactive metabolite: (i) 15-hydroxyprostaglandin dehydrogenase (15-PGDH) converts a 15-hydroxy group to a keto group for metabolism; (ii) 9-ketoreductase reduces 9-ketone to hydroxyl; and (iii) a side chain is inactivated by \( \beta \)-oxidation and/or \( \omega \)-hydroxylation. The final metabolites of PGE2 are eliminated from the body in the urine. The effects of PGE2 are regulated by the balance between its COX-2-regulated synthesis and 15-PGDH-driven degradation [13].

2.1. PGE2 Signaling and EP Receptors. After PGE2 is synthesized in the cytoplasm, it diffuses out of the cell through facilitated diffusion. Since PGE2 is quickly degraded, it is distinct from typical hormones that act on distant target tissues but can only be produced and released locally. After being secreted from cells, the lipid mediator binds to membrane receptors, activates downstream signaling pathways, and exerts biological effects [14].

PGE2 signals through four morphologically distinct G-protein-coupled receptors, namely, EP1, EP2, EP3, and EP4, and triggers divergent signaling pathways (Figure 2), thereby mediating its various biological functions. The mRNAs of the EP receptors also exhibit different expression patterns in a number of tissues, and activating each receptor subtype leads to distinct functional consequences [15]. EP3 and EP4 are high-affinity receptors and are expressed in all human tissues, whereas the activation of EP1 and EP2 occurs in only a few organs and requires significantly higher levels of PGE2 [16]. EP receptors are also expressed on various immune cell membranes. EP2 and EP4 are the main receptors of PGE2 involved in regulating the differentiation of CD4+ T cells [17]. By coupling with the activated G protein, it stimulates adenylyl cyclase (AC) to activate the cAMP/protein kinase A (PKA)/cAMP-responsive element-binding protein (CREB) signaling pathway and downstream molecules to participate in mediating proinflammatory responses and inhibiting PGE2 activity [18]. It is well known that clear signal transduction of EPs is beneficial for therapeutic strategies against diseases related to the immune system.

2.2. EP1 Receptor. In humans, the EP1 receptor has the lowest affinity for PGE2 [19] and couples to a Gq alpha subunit (Gaq). PGE2 can result in smooth muscle contraction through this complex. The human single EP1 receptor consists of 402 amino acid residues, whereas the rat single EP1 receptor consists of 405 amino acid residues. The EP1 receptor has 7 hydrophilic transmembrane domains. An arginine residue exists in the 7th domain, and this residue is an important PGE2 binding site. The phosphorylation of EP1 depends on cAMP-dependent protein kinase (cAMP-). The Gaq subunit activates phosphoinositide-phospholipase C (PLC) and finally leads to an elevation in intracellular \( \text{Ca}^{2+} \) and the activation of PKC, mediating gene transcription through the activation of the nuclear factor of activated T cells (NFAT), nuclear factor-kappaB (NF-κB), and the mitogen-activated protein kinase (MAPK) pathways [16].

EP1 receptor mRNA is highly expressed in the kidney, lung, and stomach [15]. EP1 has not been demonstrated to play a significant role in innate immunity but participates in controlling T cell differentiation [2, 4].

2.3. EP2 Receptor. The human EP2 receptor consists of 358 amino acids [20]. This receptor is coupled to a Gs alpha subunit (Gsα). The long C-terminal tail of the EP2 receptor contains serine and threonine, the phosphorylation of which depends on cAMP-dependent protein kinase [15, 21]. Gs proteins lead to an increase in cAMP and activation of PKA. A high concentration of intracellular cAMP can also activate both PKA and the exchange protein directly activated by cAMP (EPAC). Then, EPAC phosphorylates the
transcription factor CREB [22]. In addition, EP2 receptor signaling leads to the inhibition of glycogen synthase kinase-3 (GSK-3), which inhibits the translocation of β-catenin into the nucleus [21].

The EP2 receptor participates in most of the immunoregulatory effects of PGE₂ in both the innate and adaptive immune responses. For example, PGE₂ in the supernatant of thyroid cancer cells inhibits the activity of NK cells through the EP2 and EP4 receptors [23]. In addition, PGE2 promotes neurite outgrowth and suppresses cell proliferation by activating the EP2 receptor subtype, and the cAMP signaling pathway is involved in the PGE₂-induced differentiation of NSC-34 cells [24].

2.4. EP3 Receptor. The EP3 receptor, which consists of 365 amino acid residues, is an abundantly and widely expressed EP receptor [15]. EP3 also contains two cAMP-dependent protein kinase phosphorylation sites. EP3 is the only EP receptor that includes multiple variants (α, β, and γ). During the transcription of the EP3 coding sequence, several types of mRNA spliceosomes are produced. The differentiation of these spliceosomes results in a change in the C-terminal tail [25]. It should be noted that these variants have a similar affinity for PGE₂, but they have different signal transduction pathways, relative expression patterns, and desensitization properties [2]. EP3α and EP3β are coupled to Gi and inhibit adenyl cyclase (AC) or cAMP, whereas EP3γ is coupled to Gs or Gi and stimulates cAMP production. Therefore, a high concentration of PGE₂ inhibits AC, while a low concentration of PGE₂ activates AC [26].

EP3 mRNA can be detected in almost all tissues. EP3 signaling participates in many metabolic processes. The selective inhibition of EP3 might be a potential approach for reducing chronic neuropathic pain [27]. Moreover, it has been reported that EP3 signaling is induced in placentas associated with unexplained recurrent pregnancy losses [28].

2.5. EP4 Receptor. The EP4 receptor signals through a pathway similar to that of the EP2 receptor. The EP4 receptor consists of 513 amino acids. Similar to EP2, EP4 couples to the Gαs protein and activates the cAMP/PKA pathway. cAMP is rapidly degraded by phosphodiesterase to limit the duration of the signal. PKA then phosphorylates target proteins in the cells [29]. EP2 exhibits higher sensitivity and can more effectively increase cAMP. However, the EP4 receptor has a higher affinity for PGE₂ than the EP2 receptor [21]. Compared to EP2, EP4 performs the remarkable function of activating the phosphatidylinositol 3 kinase (PI3K) signaling pathways. The subsequent phosphorylation is mediated via G-coupled receptor kinases or via the ability to bind Gi protein [30, 31]. In addition, EP4 also stimulates noncanonical activation of the PI3K-Akt (also known as protein kinase B) and extracellular regulated kinase (ERK) pathways [16, 29].

Among all four types of EP receptors, the maintenance of EP4 has received much attention [32]. PGE₂-EP4 interaction causes muscle-specific stem cell expansion by triggering a cAMP/pCREB pathway that activates the proliferation-inducing transcription factor Nurr1 [33]. Besides, activation of EP4 may mediate many cellular responses, such as the promotion of angiogenesis, proliferation, motility, and metastasis or the delay of tumor cell apoptosis [32].

2.6. Effects of PGE₂ on T Cell Subsets. PGE₂ exerts many complex immunoregulatory roles under physiological and pathophysiological conditions [34, 35]. PGE₂ influences the
that PGE2 can also decrease the production of IL-12 by mono-
cytes or dendritic cells, leading to an effect on the proliferation
differentiation and differentiation of Th1 cells [37, 38].

2.7. PGE2 and Th1 Cells. Th1 cells mainly secrete IFN-γ, IL-2,
and TNF-α, mediating cellular immune responses and playing a
key regulatory role in resistance to bacterial and viral infec-
tions. T-bet is the key transcription factor of this T cell subset.
Previous experiments indicated that both EP2- and EP4-
mediated Th1 differentiation are inhibited by PI3K inhibitors
[36]. This signaling pathway can decrease the cAMP level and
then reduce the cAMP-mediated inhibition of T cell, indicat-
ing that PGE2 could activate the differentiation of Th1 cells.
Other researches suggested that PGE2 selectively inhibits the
differentiation of naïve CD4+ T cells into Th1 cells and noted that
PGE2 can also decrease the production of IL-12 by mono-
cytes or dendritic cells, leading to an effect on the prolifera-
tion and differentiation of Th1 cells [37, 38].

2.8. PGE2 and Th2 Cells. Th2 cells, which mediate humoral
immunity, mainly secrete IL-4, IL-5, IL-10, and IL-13.
GATA-3 is considered the crucial transcription factor of
Th2 cells, autoactivating its expression and driving epige-
netic changes in the Th2 cytokine cluster (IL4, IL5, and
IL13 genes) while suppressing the factors critical for regulat-
ing the Th1 pathway, such as signal transducer and activator
of transcription factor 4 (STAT4) and the IL-12Rβ2 chain
[39]. PGE2 inhibits the production of both IL-4 and IL-5
by Th2 clones [40]. Later, Bao et al. discovered that PGE2
can enhance the IL-4/IFN-γ ratio in CD4+ T cell culture and polarize CD4+ T cells towards Th2 cells [41]. Hence,
the promotion effect of PGE2 mainly activates the differen-
tiation of Th2 cells via the inhibition of Th1 cells.

2.9. PGE2 and Th17 Cells. Th17 cell differentiation requires
RORγt, a transcription factor that is induced by TGF-β in
combination with the proinflammatory cytokines IL-6,
IL-21, and IL-23, all of which activate STAT3 phosphoryla-
tion. The differentiation of naïve CD4+ T cells into Th17 cells
is mediated by the EP2 or EP4 receptor leading to cAMP
production. Moreover, PGE2 increases the concentrations
of IL-23R and IL-1R. cAMP and other cytokines induce the
expression of IL-23R via the EP2 receptor [17, 42]. Klasen
et al. found that the expression level of EP4 is significantly
increased in Th17 cells from patients with ankylosing spond-
ylitis (AS) compared to those in healthy individuals or rhe-
umatoid arthritis (RA) patients and that the EP4 expression
level in Th17 cells from AS patients has a positive correlation
with disease activity [43]. Lee et al. declared that the T cell-
intrinsic EP2/EP4 signaling is critical in IL-23-driven gener-
ation of pathogenic Th17 cells and consequent pathogenesis
in psoriasis [44].

2.10. PGE2, and Tfh Cells. Tfh cells are defined as CD4+ T
helper cells that express CD40L, chemokine receptor 5
(CXCR5), programmed death 1 (PD-1), and inducible T cell
co-stimulator (ICOS). Bcl-6 is the characteristic transcription
factor of Tfh cells [45]. Tfh cells migrate into follicles and
interact with antigen-specific B cells to support their differ-
entiation into memory B cells or plasma cells [46]. Tfh cells
can secrete IL-21, which binds to IL-21R on the surface of B
cells, assists B cell activation and proliferation, and induces
self-antibody production. IL-21 is a potent differentiation
factor for B cells. Tfh cell defects or hyperactivity can cause
immune system dysfunction, leading to the occurrence of
autoimmune diseases [47]. A recent study has shown that
PGE2 can facilitate antibody class switching in B cells by
inducing Tfh cell differentiation [48]. We recently discov-
ered that the serum concentration of prostaglandin E metab-
olite (PGEM) and the proportion of Tfh cells are increased
in the collagen-induced arthritis mouse model compared with
those in wild-type mice. In addition, there is a positive
correlation between the concentration of serum PGEM and
the population of Tfh cells in RA patients, suggesting that
PGE2 acts as a positive regulator of the process of Tfh
differentiation [1]. However, the mechanism underlying
the regulation of Tfh differentiation by PGE2 still needs to be
explored.

2.11. PGE2 and Treg Cells. Tregs are immunosuppressive cells
that mainly participate in immune homeostasis by acting as a
major barrier to effective immunity against tumors and steril-
izing immunity against chronic viral infections [35]. The
membrane-bound IL-2 α-chain is a marker of Treg cells. There
are two critical cytokines, namely, IL-2 and TGF-β, that
drive the differentiation of Treg cells from naïve T cells. IL-2R
is required for both the thymic and peripheral generation of
Treg cells. TGF-β inhibits the recruitment of Dnmt1, the key
maintenance DNA methyltransferase whose activity likely
leads to silencing of the newly induced Foxp3 gene [49]. Foxp3
is a specific transcription factor that regulates the development
of Treg cells and is essential for the immunosuppressive func-
tion of Treg cells, which is initially considered a specific
marker of Treg cells. It has been reported that PGE2 promotes
the growth of Treg cells in both humans and mice via the EP2
or EP4 receptor [50]. Since PGE2 can effectively suppress the
EP4/cAMP/PKA pathway, it also inhibits the differentiation
of Treg cells. It is worth mentioning that PGE2 signaling via
EP2 expressed on human naïve CD4+ T cells suppresses Treg
differentiation in vitro via the cAMP-PKA signaling pathway
[3]. However, when UV was used to induce an immunosup-
pressive reaction, PGE2 facilitated an increase in Treg cell
numbers. Additionally, Kitipong et al. showed the impairment
of the immunosuppressive effect of UV with an EP4 antago-
nist and the reversal of the indomethacin-induced impairment
of immunosuppression by an EP4 agonist. Notably, treatment
with an EP4 agonist alone, without UV irradiation, does not
result in immunosuppression [50]. Additionally, PGE2
inhibits the expression and production of IL-27 by activating
conventional dendritic cells in vivo and in vitro, thus inhib-
iting the IL-27-induced differentiation and IL-10 production
of murine CD4+CD49b+LAG-3+Foxp3+Tr1 cells [51]. The
imbalance of Th17/Treg may play a role in the progression
of autoimmune diseases such as RA [52]; therefore, PGE2 is
expected to become one of the therapeutic directions.

2.12. PGE2 and CD8+ CTLs. CTLs, which originate from
naïve CD8+ T cells, can specifically recognize endogenous
antigen peptides (i.e., MHC I complex) and induce the
apoptosis of target cells. Li et al. showed that CD8+ T cell
mediated by PGE2, selective inhibition of the Th1 cell,
leads to an effect on the proliferation and differentiation of Th1 cells.

dysfunction correlates with PGE2 levels in chronic hepatitis B patients. Patients with high levels of PGE2 had more CD8+ T cells with remarkably low granzyme B expression and slightly low perforin expression; these proteins are two important effector molecules for the antiviral activity of CD8+ T cells in chronic hepatitis B patients [53]. Chen et al. showed that PGE2 suppresses exhausted antigen-specific CTL function and promotes CTL apoptosis. The comodulation of PGE2 and PD-1 signaling may represent a potent therapeutic avenue for the treatment of chronic viral infections [54]. Kim et al. demonstrated that the elevated mPGES1 expression is associated with low CD8+ T cell infiltration into melanomas and poor patient survival [55]. However, concrete results regarding the relationship between PGE2 and CTL differentiation are still lacking. Notably, CD4+ T cells with cytotoxic activity (CD4+ CTLs) have been observed in various immune responses. These cells are characterized by their ability to secrete granzyme B and perforin and to kill target cells in an MHC class II-restricted fashion. CD4+ CTLs seem to be derived from various types of CD4+ T cells, and several differences have been observed during their differentiation [56]. Most likely, the differentiation of CD4+ CTLs can be influenced by PGE2.

3. Conclusions and Future Perspectives

In this review, we highlight the immunoregulatory roles of the lipid mediator PGE2 in controlling the differentiation of T cells. The dysregulation of T cell differentiation leads to the occurrence of various diseases. Although PGE2 exerts effects on different CD4+ T cell subsets, its role in Tfh cells and CD8+ T cells is not well known. The sophisticated interactions between PGE2 and T cells still need to be further studied.

Various cells can secrete this lipid mediator, whereas all cells can generate responses to the signaling of PGE2 through the EP receptors. Importantly, studying the signaling pathways of PGE2 may contribute to further elucidating the pathogenesis of diseases, and targeting PGE2 may be used to develop personalized therapies for RA, AS, neuropathic pain, tumors, inflammation, and so on. PGE2 may be considered the point of intersection of different human systems. Thus, understanding the pathway of PGE2 would yield novel insights for designing more effective therapies for immune diseases.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

XN conceived and designed the manuscript. YA wrote the manuscript. JY helped with manuscript preparation and literature search. YA, JY, and XN edited and critically evaluated the manuscript.
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