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REVIEW

Prostaglandin E_2 and T cells: friends or foes?

Vinatha Sreeramkumar, Manuel Fresno and Natalia Cuesta

Our understanding of the key players involved in the differential regulation of T-cell responses during inflammation, infection and auto-immunity is fundamental for designing efficient therapeutic strategies against immune diseases. With respect to this, the inhibitory role of the lipid mediator prostaglandin E_2 (PGE_2) in T-cell immunity has been documented since the 1970s. Studies that ensued investigating the underlying mechanisms substantiated the suppressive function of micromolar concentrations of PGE_2 in T-cell activation, proliferation, differentiation and migration. However, the past decade has seen a revolution in this perspective, since nanomolar concentrations of PGE_2 have been shown to potentiate Th1 and Th17 responses and aid in T-cell proliferation. The understanding of concentration-specific effects of PGE_2 in other cell types, the development of mice deficient in each subtype of the PGE_2 receptors (EP receptors) and the delineation of signalling pathways mediated by the EP receptors have enhanced our understanding of PGE_2 as an immune-stimulator. PGE_2 regulates a multitude of functions in T-cell activation and differentiation and these effects vary depending on the micro-environment of the cell, maturation and activation state of the cell, type of EP receptor involved, local concentration of PGE_2 and whether it is a homeostatic or inflammatory scenario. In this review, we compartmentalize the various aspects of this complex relationship of PGE_2 with T lymphocytes. Given the importance of this molecule in T-cell activation, we also address the possibility of using EP receptor antagonism as a potential therapeutic approach for some immune disorders.
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BIOSYNTHESIS AND FUNCTION OF PROSTANOIDS

Lipid mediators have long been considered as regulators of homeostasis and inflammation. These molecules are usually produced by a conserved biosynthetic pathway controlled by specific enzymes that exert their sequential action on lipid precursors that are released from the plasma membrane. One of the most important families of lipid mediators is the prostanoid family, comprises prostaglandins (PGs) and thromboxanes (Txs).[1] The precursor molecule for prostanoids is Arachadonic acid. Arachadonic acid is released from the plasma membrane phospholipids by the action of phospholipase A2, and is further processed by cyclooxygenase (COX) enzymes COX-1 and COX-2.[2] COX-1 is constitutive and has a role in the maintenance of homeostasis and normal physiology. COX-1 is expressed in most tissues and is responsible for the production of 'housekeeping' PGs that control normal physiological processes. On the other hand, COX-2 is inducible and can be activated by a variety of pro-inflammatory stimuli, especially during infection and inflammation.[3,4] Both COX-1 and COX-2 activation results in the generation of PGG_2, which is then reduced to the intermediate PGH_2 via a separate peroxidase site. Various specific isomerases and oxidoreductases convert PGH_2 to the different types of PGs, such as PGE_2, PGI_2, PGD_2 and $PGF_{2\alpha}$ and additionally TXA_2.[5]

Most PGs act as potent pro-inflammatory mediators, thereby making it a desirable therapeutic goal for the treatment of cancer, rheumatoid arthritis, intestinal inflammation, Alzheimer's disease and chronic musculoskeletal pain.[6] However, some PGs may exert anti-inflammatory actions.[7]

PGE_2: SYNTHESIS, FUNCTION AND IMPORTANCE

The isomerization of PGH_2 to PGE_2 is catalyzed by three different PGE synthases, namely cytosolic PGE synthase and two membrane-bound PGE synthases, mPGES-1 and mPGES-2. Cytosolic PGE synthase and mPGES-2 are constitutive, whereas mPGES-1 is mainly induced. It is postulated that cytosolic PGE synthase uses PGH_2 produced by COX-1, whereas mPGES-1 uses COX-2-derived PGH_2. mPGES-2 can use both sources of PGH_2.[8,9] mPGES-1 is upregulated in response to various pro-inflammatory and mitogenic stimuli with a concomitantly increased expression of COX-2. Cytokines such as interleukin (IL)-1β and tumor necrosis factor-α and Toll-like receptor 4 signalling activated by lipopolysaccahride are defined as some of the inducers of m-PGES-1.[10,11] Results obtained from m-PGES-1 knockout mice suggest that this enzyme has key roles in normal physiology and pathological conditions such as inflammation, pain, fever, arthritis, stroke, atherosclerosis and cancer,[9] hence making it an innovative therapeutic target.

PGE_2 is the most abundant prostanoid found in the human body. It has many important functions in physiology and is ubiquitously produced in pathophysiological conditions.[3,12,13] This molecule stereo-specifically exerts potent tissue- and cell type-selective

Centro de Biología Molecular Severo Ochoa, UAM-CSIC, Madrid, Spain
Correspondence: Dr V Sreeramkumar, Department of Molecular Biology, Centro de Biología Molecular Severo Ochoa, UAM-CSIC, Nicolás Cabrera 1, Campus de la Universidad Autónoma de Madrid, Madrid 28049, Spain.
E-mail: vinatha56@gmail.com
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actions.[14,15] The biological functions of PGE_2 range from effects on the reproductive, gastro-intestinal, immune, cardiovascular and nervous systems. PGE_2 has been implicated in multiple physiological processes mainly because of its ability to induce vasodilation or vasoconstriction.[16] This is especially important in processes such as embryo implantation, modulation of hemodynamics in kidney, blood pressure control, childbirth and gastro-intestinal motility. Apart from these functions, PGE_2 has been shown to be a key player in regulating body temperature and sleep–wake mechanisms and gastrointestinal secretion along with mucosal barrier functions.[16,17] In the field of tumor biology, COX-2 overexpression leads to increased levels of PGE_2 and has been associated particularly with colorectal, pancreatic, lung and breast cancer.[18] PGE_2 has been implicated in tumor progression through stimulation of angiogenesis, cell invasion and metastasis, and promotes cell survival by inhibiting apoptosis via numerous signalling pathways.[19,20] Besides, PGE_2 also has a role in tumor evasion of immunosurveillance and has been known to alter cytokine expression profiles of dendritic cells (DCs) in order to suppress antitumor cytotoxic T cells.[21,22] PGE_2-secreting cancer cells have been shown to induce human Treg cell formation and increase their inhibitory activity against Th cells that are specific for tumors.[23]

It is in the area of inflammation that PGE_2's actions are most diverse. Over the past decades, extensive research using COX-2, m-PGES1 and EP receptor knockout mice yielded novel and important findings proving that prostanoids exert both pro-inflammatory and anti-inflammatory effects, and that these actions are often produced through directed regulation of gene expression in relevant tissues.

PGE_2 usually serves as an important pro-inflammatory mediator that is involved in the production of all cardinal signs of inflammation: edema, redness, swelling and pain.[3,24] This is produced as a result of the effect of PGE_2 on increased microvascular permeability, increase in blood flow to the inflamed site, hyperalgesia and action on peripheral sensory neurons within the affected area.[25] The effect of PGE_2 on immune cell types is much more complex. Apart from favoring the production of inflammation, PGE_2 has been proved to favor DC maturation, antigen uptake and homing to lymph nodes.[26,27] In addition, it has been also demonstrated that PGE_2 can induce the expression of co-stimulatory molecules on DCs, thus augmenting T-cell activation.[28] In macrophages, PGE_2 acts as a positive aid in macrophage activation by interferon (IFN)-γ and tumor necrosis factor-α via its capacity to modulate intracellular cyclic adenosine monophosphate (cAMP) levels.[29] It has also been shown to be an inducer of matrix metallo-proteinases MMP-2 and MMP-9 in macrophages.[30]

However, there have been a large number of reports that compile evidence supporting the notion that PGE_2 acts also as an anti-inflammatory molecule that dampens the immune response (reviewed in Smyth *et al.*[4]). PGE_2 has been demonstrated to suppress Th1 differentiation, B-cell functions, T-cell activation and allergic reactions.[3,31] Furthermore, PGE_2 can exert anti-inflammatory actions on innate immune cells like neutrophils, monocytes and natural killer cells.[3,31] However, the past decade has seen a revolution in the outlook of PGE_2 as a T-cell immunosuppressor, owing to different reports that substantiate a beneficial role of PGE_2 in T-cell differentiation and immune functions, as discussed in the later sections of this review.

PGE_2 RECEPTORS: THE EP RECEPTORS (1–4)

PGE_2 binds to four specific G-protein-coupled receptors termed EP receptors (EP1–4). EP receptors are distinguished by the signal transduction pathway that is activated upon ligand binding.[32] Some of the signalling pathways that are generated by PGE_2 are under the control of the secondary messenger cAMP. cAMP is derived from adenosine triphosphate by 1 of at least 10 currently identified isoforms of the adenylyl cyclase (AC) enzymes (AC 1–9 and soluble AC), which differ in cell-specific expression, regulation and effects, providing an intracellular system suited for finely targeted signalling.[33] The phosphatidylinositol and its phosphorylated products have been shown to be the precursors for messengers generated by phospholipases, although they have been directly implicated in signalling.[34,35] Another level of control of signalling by PGs is attributed to Ca^{2+}, which is a highly versatile intracellular signal that modifies various cellular processes through spatial and temporal dynamic remodelling of a variety of signalling constituents.[36] Activation of EP receptors leads to changes in the production of cAMP and/or phosphoinositol turnover and intracellular Ca^{2+} mobilization.[32]

EP1 was first described as involved in constriction of smooth muscle.[37] The C-terminal domain of the EP1 receptor binds to Gα-q heterotrimeric guanine nucleotide-binding protein. Activation of EP1 by ligand binding results in increased phosphatidylinositol hydrolysis and elevation of the intracellular Ca^{2+} through activation of phospholipase-C (Figure 1).

In contrast, EP2 was originally believed to have a role in smooth muscle relaxation.[38] Both EP2 and EP4 are coupled to Gs-proteins, leading to increased production of cAMP and activation of protein kinase A (PKA)[32,39] (Figure 1). Although both receptors share the same signalling pathway, they differ in the length of their C-terminal sequence and hence have differing sensitivities to phosphorylation and desensitization.[40] The distinguishing feature of EP4 is, however, the ability to activate phosphatidylinositol 3 kinase signalling pathways following phosphorylation by G-protein coupled receptor kinases[41] or by virtue of the ability to bind Gi proteins[42,43] (Figure 1). Both EP2 and EP4 are capable of stimulating the T-cell factor/lymphoid enhancer factor and inhibiting glycogen synthase kinase-3 through the PKA and phosphatidylinositol 3 kinase-dependent signalling pathways, respectively.[44]

The major signalling pathway activated by EP3 receptor-ligand binding goes through the pertussis toxin-sensitive Gi protein, resulting in inhibition of AC and decrease in cAMP levels.[45] However, EP3 receptors have different C-terminal splice variants that exhibit varied specificities for downstream G-proteins. In this context, EP3α and EP3β couple to Gi and inhibit AC, whereas EP3γ couples to Gs in addition to Gi, and evokes cAMP production.[46,47] Moreover, EP3 has been demonstrated to activate the small GTPase Rho in various cell types[48] (Figure 1).

A difference in the structure of the C-terminal domain of EP receptors determines the differential nature of agonist-induced desensitization and internalization. Till date, knowledge of EP1 receptor trafficking has been limited. But with respect to EP3, the existence of different variants generated by alternative splicing of the C-terminal tail reflects on the variations observed in signal transduction and intracellular trafficking. EP3α undergoes rapid agonist-induced desensitization and sequestration followed by long-term downregulation, whereas no such changes were observed in EP3β trafficking.[49] The long C-terminal of the EP4 receptor contributes to its susceptibility to rapid agonist-induced internalization and desensitization.[50,51] However, the EP2 receptor undergoes neither rapid agonist-induced internalization nor desensitization owing to a shorter C-terminal sequence.[40,51]

With respect to their tissue distribution and cellular localization, it has been demonstrated that EP2-4 are widely distributed in almost all mouse tissues, whereas EP1 mRNA expression is restricted to distinct organs such as the kidney, lung and stomach. EP2 is the least abundant of all the receptors. As each EP receptor is committed to a defined signalling pathway and its associated function, they follow a

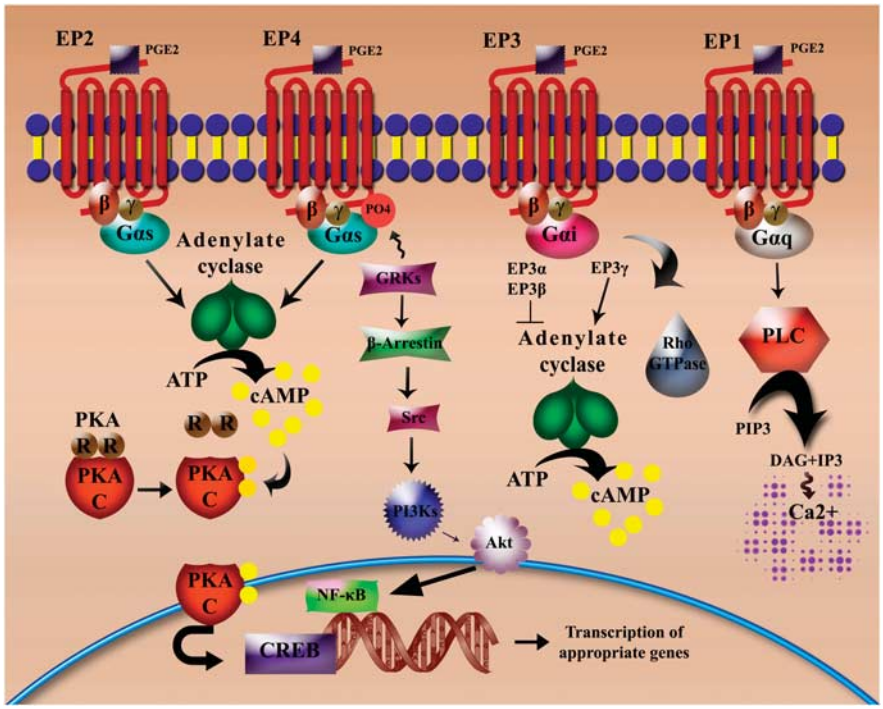

Figure 1 EP receptors: types and signalling. The four different EP receptors are high-affinity G-protein coupled receptors characterized by the activation of different signalling pathways. EP2 and EP4 are linked to Gαs proteins and function by inducing the adenylate cyclase (AC) system and concomitant increases in the secondary messenger cAMP. cAMP acts by activating PKA, resulting in the dissociation of the regulatory and catalytic subunits of the kinase. The catalytic subunits initiate the corresponding transactivation of the transcription factor CREB. EP4 is also capable of activating the phosphatidylinositol 3 kinase (PI3K) signalling pathway by phosphorylation induced by G-protein-coupled receptor kinases. This ultimately results in the triggering of NF-κB-mediated transcription programs. EP3 isoforms differ in their ability to modulate signal transduction. EP3α and EP3β are capable of blocking induction of AC while EP3γ potentiates AC and cAMP production. EP1, on the other hand, couples to Gαq protein and signals through the phospholipase C (PLC)/inositol-1,4,5-trisphosphate (IP3) pathway resulting in the formation of the second messengers diacylglycerol (DAG) and IP3, with the latter rapidly liberating Ca^{2+} ions from intracellular stores.

restricted expression pattern within each organ system. Interestingly, this precise cellular localization of EP receptors is found in mice, humans and rabbits.[52,53] A detailed summary of described physiological functions of each subtype of the four EP receptors are enlisted in supplementary Table 1.

EFFECT OF PGE_2 ON T-CELL ACTIVATION AND DIFFERENTIATION

Although most of the PGE_2 secreted in the body comes from professional APCs and stromal cells, *in vitro* findings have shown that *PTGS2* (gene for COX2) is transcriptionally upregulated in human T cells during T cell receptor (TCR)/CD3 triggering and that it behaves as an early inducible gene in the T-cell activation process.[54]

With respect to EP receptor expression, while mRNA for all types of EP receptors were detected in murine T cells, expression of EP1 and EP3 has not been fully documented.[55] Recent studies have confirmed that EP2 and EP4 are the main receptor subtypes to mediate the actions of PGE_2 in human and murine $CD4^+$ T cells.[56]

Immunosuppressive role of PGE_2 on T-cell function

PGE_2-induced activation of AC and production of cAMP and its role in producing an inhibitory effect on T-cell activation was documented in the early 1970s.[57,58] Starting from the early 1980s, it has been strongly believed that PGE_2 has a largely immunosuppressive role to have in T-cell activation and proliferation. Many attempts were made to describe the working mechanism of this process. The immunomodulatory role of PGE_2 in T-cell activation was documented >30 years ago, when it was postulated that PGE_2 concentration, as well as the state of differentiation of the target cell, and length of PGE_2–target cell interaction were important factors controlling the process (reviewed in Goodwin and Ceuppens[59]).

Initial findings reported a role of PGE_2 in mediating induction of nonspecific T lymphocyte suppressor activity,[60] and a drastic inhibition of T-cell proliferation, hence modifying T-cell blastogenic responses in mice lymphoid organs[61,62] and suppressing proliferation of lymphoma in mice.[63] Later studies suggested that PGE_2 primarily exerts its inhibitory effect on lymphocyte proliferation through an inhibition of IL-2 production.[64,65] This was followed by reports that stated that inhibition of lymphocyte response was brought about by PGE_2-producing macrophages,[66] which were found to inhibit IL-1-dependent T-lymphocyte differentiation.[67] Subsequent research substantiated the suppressive function of PGE_2 in T-cell responses.

However, it was not until the late 1980s that research began to delineate the underlying inhibitory pathways of PGE_2 in T cells, mainly through the production of cAMP. It was found that cAMP exerts its anti-proliferative effects through interference with IL-2-mediated gene-expression.[68,69] cAMP was also shown to downregulate transferrin receptor expression in an IL-2-dependent manner[70] and abrogate TCR-mediated cytosolic increases in Ca^{2+},[71] later confirmed by studies in sepsis.[72] cAMP was also found to negatively regulate the phosphoinositide cycle-related transduction pathway including inhibition of phosphatidylinositol hydrolysis and diacylglycerol and

inositol phosphate (IP) production.[73,74] Increases in cAMP were also found to inhibit expression of IL-2 receptors.[75,76] Increasing intracellular concentrations of cAMP may result in a reduction of K^+ movements and in negative modulation of signal transduction via G-proteins, impairing T-cell activation further.[77]

The suggestion that PGE_2 might alter polarization of T helper cells to Th1 and Th2 subtypes was demonstrated first in a study by Betz and Fox,[78] where they showed that PGE_2 inhibits IL-2 and IFN-γ production (Th1) but not IL-4 and IL-5 production (Th2). This was further re-confirmed by the demonstration that PGE_2 upregulates IL-5 production in T cells.[79] It was later demonstrated that while PGE_2 primed Th cells to produce higher amounts of IL-4, IL-10 and IL-13,[80] it was found to inhibit IL-12 production and IL-12 receptor responsiveness,[81] consolidating its role in the Th1/Th2 balance.

On the other hand, there are various reports that suggest that PGE_2 enhances induction and differentiation of $FOXP3^+CD4^+CD25^+$ adaptive regulatory T cells that thereby suppress effector T-cell stimulation pathways.[82–84] In addition, PGE_2 has been shown to induce T-cell anergy[85] to maintain the survival of $CD45RO^+$ T cells[86] and to inhibit γδ T-cell cytotoxicity triggered by the TCR through cAMP-mediated PKA type I-dependent signalling.[87]

With respect to transcription factors and nuclear proteins, it was found that cAMP signalling interfered with the activation pathway for NF-κB,[88] and counteracted calcineurin-dependent pathways.[89] Yet, decreased IL-2 production in the presence of PGE_2 was shown to be due to targeting of AP-1 and NF-AT transcription factors in human T cells.[90] Therefore, qualitative differences in the concentration of cAMP and PKA activity can be considered as important elements in modulating T-cell proliferative responses.[91]

Several molecular mechanisms have been proposed for the inhibition of T-cell activation by PGE_2. PGE_2 signalling has been proved to attenuate p59(fyn) protein tyrosine kinase activity[92,93] and interfere with the protein-kinase C pathway.[94,95] The enzyme Csk has been shown to negatively regulate Lck, a kinase responsible for TCR signalling following antigen recognition.[96–99] PGE_2-mediated cAMP was also shown to regulate raft-associated Csk in a spatial and enzymatic manner.[100] It is well known that TCR ligation results in the activation of mitogen-activated protein kinase cascades involving different members such as ERK and p38 mitogen-activated protein kinases. These kinases are important for regulating transcription factors that control growth, survival and differentiation of T cells.[101,102] Hematopoietic protein tyrosine phosphatase phosphorylation by PKA in T cells and its negative regulation of extracellular signal-regulated protein kinase and mitogen-activated protein kinase pathways has also been reported.[103] The inhibition of the kinase Lck was also proposed as a mechanism of suppression of T-cell activation triggered by PGE_2.[104] Stimulation of prolactin expression (a negative regulator of T-cell proliferation) was also shown to be mediated through Ca^{2+} and cAMP signalling through EP3 and EP4 receptors by PGE_2 in T cells.[105]

The immunosuppressive role of PGE_2 in T-cell responses has been summarized in Figure 2.

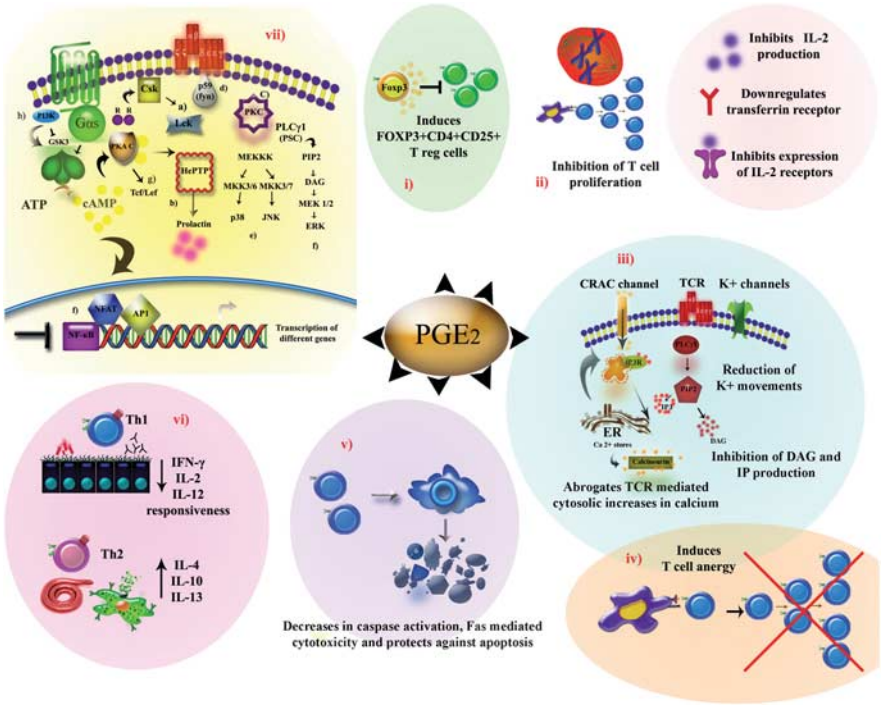

Figure 2 Negative regulation of T-cell responses by PGE_2. PGE_2 mediates its anti-inflammatory effects on T cells through different mechanisms: (i) PGE_2 has been shown to induce differentiation of $FOXP3^+CD4^+CD25^+$ adaptive regulatory T cells that were found to inhibit effector T-cell responses, (ii) PGE_2 has also been demonstrated to suppress T-cell proliferation through different mechanisms, (iii) PGE_2 is involved in the inhibition of secondary messenger generation including the abrogation of Ca^{2+}, K^+, diacylglycerol (DAG) and IP production, (iv) T-cell anergy has been known to be promoted by high concentrations of PGE_2, (v) PGE_2 favors cell survival by blocking activation-induced apoptosis, cellular cytotoxicity and caspase activation, (vi) PGE_2 at micromolar concentrations was found to be inhibitory for Th1 differentiation and beneficial for Th2 differentiation, (vii) modulation of TCR-mediated signal transduction pathways by PGE_2. (a) regulation of Csk, (b) hematopoietic protein tyrosine phosphatase (HePTP) phosphorylation by cAMP-dependent protein kinase and promotion of prolactin expression, (c) interference of PKC signalling, (d) attenuation of p59(fyn) protein tyrosine kinase activity, (e, f) negative regulation of extracellular signal-regulated protein kinase (ERK) and mitogen-activated protein kinase (MAPK) pathways (g) PKA-mediated signalling potentiates T-cell factor (Tcf)/lymphoid enhancer factor (Lef) signalling pathways, (h) while PI3K inhibits glycogen synthase kinase-3 (GSK3) signal-mediation.

Pro-inflammatory role of PGE$_2$ in T-cell function

An indirect pro-inflammatory role for PGE$_2$ in human T lymphocytes was shown to be mediated by the induction of IL-8 (CXCL8) gene transcription following activation of C/EBP homologous protein.[106] IL-8 (CXCL8) thus produced by T cells was then shown to mediate neutrophil recruitment and sustain inflammation.[106] However, a different perspective on the suppressive nature of PGE$_2$ came into view when it was shown that nanomolar concentrations of PGE$_2$ potentiated Th1 and Th17 differentiation through phosphatidylinositol 3 kinase and PKA signalling, respectively, in a process mediated by EP2 and EP4 receptors.[107] Interestingly, administration of an EP4 antagonist suppressed Th1 and Th17 expansion within draining lymph nodes in two disease models of inflammation: contact hypersensitivity and experimental autoimmune encephalomyelitis.[107] The role of PGE$_2$ in Th17 expansion was also reported by Boniface *et al.*,[56] who showed that PGE$_2$ in combination with IL-1β and IL-23 promoted differentiation of Th17 cells by upregulating the IL-1βR and IL-23R expression through the EP2/EP4–cAMP pathway. In this elegant report, investigators propose that PGE$_2$ promotes the development and maturation of Th17 cells through activation of the EP2 receptor, while inhibiting IL-10 and IFN-γ synthesis through the EP4 receptor in human and mouse T cells, substantiating a role for PGE$_2$ in regulation of Th17 responses.[56] PGE$_2$ was also found to synergize with IL-23 and increase the number of Th17 cells derived from human CD4$^+$CD45RO$^+$ (memory) T cells but not from CD4$^+$CD45RO$^-$ (naive) T cells.[108] The favoring of IL-17 production and down-modulation of IFN-γ production by memory CD4$^+$ T cells through PGE$_2$-mediated EP2/EP4 signalling, when present in micromolar concentrations, was also demonstrated in another study.[109] Esaki *et al.*[110] indicated an essential role of PGE$_2$-EP2/EP4 signalling in T-cell proliferation as well as IFN-γ and IL-17 cytokine production within the draining lymph nodes of mice during the course of experimental autoimmune encephalomyelitis. The unique ability of PGE$_2$ to differentially modulate Th1 and Th17 differentiation at different concentrations, could bring a new dimension to the PGE$_2$-mediated determination of the type of effector response and hence the outcome of the inflammatory reaction.

On the other hand, indirect control of T-cell differentiation through regulation of cytokine patterns produced by DCs has also been reported. Exogenous PGE$_2$ was found to enhance lipopolysaccharide-induced IL-23 production by DCs, which could therefore promote Th17 differentiation.[111,112] In addition, DCs cultured in the presence of PGE$_2$ enhanced the differentiation of naive T cells toward the Th1 type.[113] This was further emphasized in another report where the addition of PGE$_2$ and tumor necrosis factor-α for the maturation of human monocyte-derived DCs enhanced CD4$^+$ and CD8$^+$ T-cell proliferative responses, and favored Th1-type responses.[114] Interestingly, PGE$_2$ was found to enhance T-cell proliferation by inducing the co-stimulatory molecules OX40L, CD70 and 4-1BBL on DCs.[28] This study also shows that PGE$_2$-matured DCs upregulate the expression of OX-40L, OX-40 and CD70 on the surface of T cells, enlisting a possible role in T-cell–T-cell interactions and sustained antigen-specific immune responses.[28]

A comprehensive summary of the pro-inflammatory role of PGE$_2$ in T-cell response is shown in Figure 3.

PGE$_2$-based T-cell-targeted therapies for inflammatory disorders

Modulating T-cell effector functions is a promising therapeutic approach for various diseases, owing to the multi-faceted roles of T cells in immuno-pathogenesis of auto-immunity, allergy and human

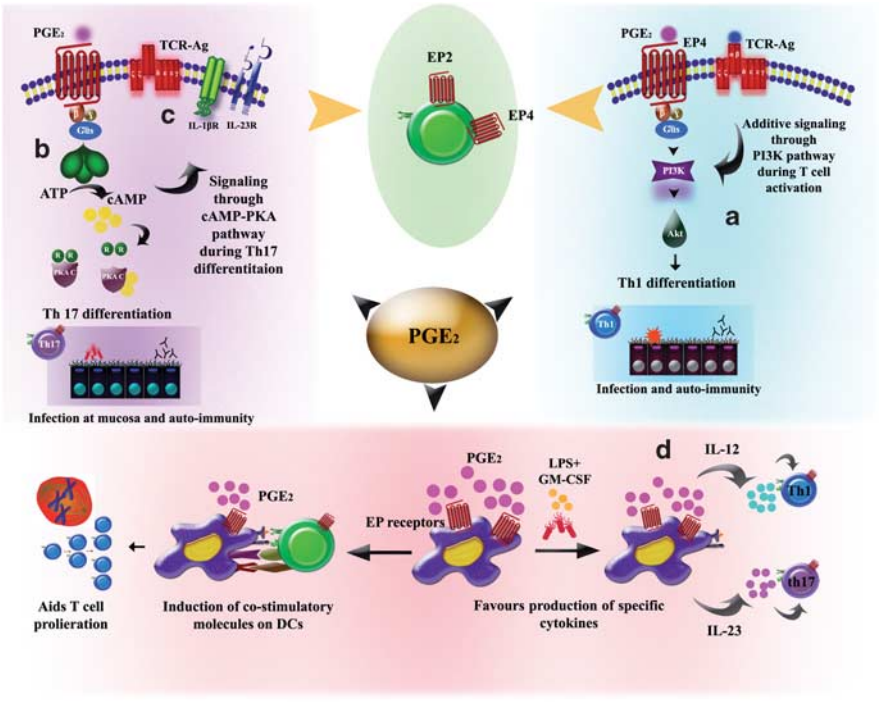

Figure 3 Positive regulation of T-cell responses by PGE$_2$. PGE$_2$ has diverse pro-inflammatory effects on T cells. (a) Nanomolar physiological concentrations of PGE$_2$ induce phosphatidylinositol 3 kinase (PI3K)/Akt signalling pathways through the EP4 receptor that serve to promote Th1 differentiation patterns. (b) PGE$_2$ has also been shown to potentiate Th17 differentiation through EP2-cAMP-PKA signalling pathways, primarily through (c) induction of IL-1β and IL-23 receptor (d) PGE$_2$ has been demonstrated to induce co-stimulatory molecules on the surface of DCs, thereby promoting T-cell proliferation. It has also been shown to promote secretion of specific cytokines by DCs, for example, IL-12, which further directs Th1 differentiation and IL-23, which enhances Th17 polarization.

immunodeficiency virus and parasitic infections. Given the importance of PGE_2 signalling in the modulation of T-cell responses, several reports have focused on the development of PGE_2-targeted therapies for immune disorders.

The non-steroidal anti-inflammatory drugs are a varied group of pharmacologic compounds used for the treatment of processes of inflammation, since the introduction of acetylsalicylic acid in 1899. The first-generation non-steroidal anti-inflammatory drugs exert anti-inflammatory, analgesic and antipyretic effects through the blockade of PG synthesis via nonspecific inhibition of COX-1 and COX-2. However, their employment as drugs over prolonged periods of time is not favored, since they cause pronounced side effects such as gastrointestinal and renal toxicity.[25,115–117] This has resulted in the shift of focus of therapeutic interventions from COX enzymes to PGE_2 synthases such as m-PGES-1.[118]

The past decade has experienced a major change in the outlook of treatment regimens that aim to inhibit the actions of PGE_2. Extensive work on the tissue, organ and cell-specific functions of PGE_2 has given place to the generation of EP receptor antagonists and agonists, which have already been applied in diverse experimental animal models. Interestingly, the antagonism of EP receptors has been proved to be efficient in ameliorating Th1 and Th17 responses, thereby proving to be a potential treatment option for arthritis, autoimmune encephalitis and contact hypersensitivity.[108,119] EP receptor antagonists have been employed for the inhibition of inflammatory pain hypersensitivity, paw edema and cancer.[120–124] The targeted modulation of T-cell function by blocking or potentiating specific EP receptor signalling pathways could thus be a revolutionary approach for the treatment of a variety of immune dysfunction-related diseases.

However, there have been various limitations to the use of receptor antagonists for therapy. One of them is the mild effectiveness of these compounds as compared with non-steroidal anti-inflammatory drugs: the reason being the inhibition of only one/two specific receptors as opposed to the robust inhibition of all downstream PGs by COX inhibitors. The antagonism/agonism of only one specific receptor would not be efficient enough to potentially curtail/cure a disease state. To complicate issues further, a lot of emphasis has been laid on the different additive, compensatory or opposing roles of EP receptors in a given disease setup or inflammatory condition. Therefore, it is not advisable to design treatments based solely on the blocking or triggering of individual prostanoid receptors. Extensive study of calculated combinations of specific agonists and antagonists will be required in order to design efficient therapies to treat inflammatory disorders.

CONCLUSION AND REMARKS

The 'classical' perspective of the role of PGE_2 as only an immunosuppressor of T-cell function has changed over the past decade. This has been due to the description of concentration-dependent and somewhat opposed effects in different scenarios of homeostasis and inflammation and the interplay of signalling events generated by the EP2 and EP4 receptors during the process of T-cell responses. The pro-inflammatory actions of PGE_2 in T cells and its promotion of the Th1 and Th17 differentiation have been well defined over the past few years. Determination of factors that cause the oscillation of PGE_2 from a T-cell immunosuppressor to a T-cell immunoactivator, such as (1) local concentration of PGE_2 during diverse phases of inflammation, (2) differential use of EP receptors and signalling pathway involved in T-cell subsets and (3) targeted effects of application of EP receptor antagonists in different disease scenarios, would be fundamental for the design of tailor-made therapies in infection, inflammatory disorders and autoimmunity.

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