Lipid mediators have long been considered as regulators of homeostasis. BIOSYNTHESIS AND FUNCTION OF PROSTANOIDS (Txs). The precursor molecule for prostanoids is Arachidonic acid. The prostanoid family, comprises prostaglandins (PGs) and thromboxanes (TXs). The precursor molecule for prostanooids is Arachidonic acid. Arachidonic 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. 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. Both COX-1 and COX-2 activation results in the generation of PGH2, which is then reduced to the intermediate PGH2 via a separate peroxidase site. Various specific isomerases and oxidoreductases convert PGH2 to the different types of PGs, such as PGE2, PGD2, PGI2, and TXA2.

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. However, some PGs may exert anti-inflammatory actions.

PGE2: SYNTHESIS, FUNCTION AND IMPORTANCE
The isomerization of PGH2 to PGE2 is catalyzed by three different PGE synthases, namely cytosolic PGE synthase and two membrane-bound PGE synthases, mPGE-1 and mPGE-2. Cytosolic PGE synthase and mPGE-1 are constitutive, whereas mPGE-1 is mainly induced. It is postulated that cytosolic PGE synthase uses PGH2 produced by COX-1, whereas mPGE-1 uses COX-2-derived PGH2. mPGE-2 can use both sources of PGH2. mPGE-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 lipopolysaccharide are defined as some of the inducers of m-PGES-1. 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, hence making it an innovative therapeutic target.

PGE2 is the most abundant prostanooid found in the human body. It has many important functions in physiology and is ubiquitously produced in pathophysiological conditions. This molecule stereo-specifically exerts potent tissue- and cell type-selective...
The biological functions of PGE2 range from effects on the reproductive, gastro-intestinal, immune, cardiovascular and nervous systems. PGE2 has been implicated in multiple physiological processes mainly because of its ability to induce vasodilation or vasoconstriction. 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, PGE2 has been shown to be a key player in regulating body temperature and sleep–wake mechanisms and gastrointestinal secretion along with mucosal barrier functions. In the field of tumor biology, COX-2 overexpression leads to increased levels of PGE2 and has been associated particularly with colorectal, pancreatic, lung and breast cancer. PGE2 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. Besides, PGE2 also has a role in metastasis, and promotes cell survival by inhibiting apoptosis via PGE2 and has been associated particularly with colorectal, pancreatic, tumor biology, COX-2 overexpression leads to increased levels of prostanoids exert both pro-inflammatory and anti-inflammatory actions. The biological functions of PGE2 range from effects on the reproductive, gastro-intestinal, immune, cardiovascular and nervous systems. Over the past decades, extensive research using COX-2, m-PGES1 and EP receptor knockout mice yielded novel and important findings proving that prostanoids act also as an inducer of matrix metallo-proteinases MMP-2 and MMP-9 secretion along with mucosal barrier functions. In the field of inflammation that PGE2's actions are most diverse. 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. 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 Gi in addition to Gi, and evokes CAMP production. Moreover, EP3 has been demonstrated to activate the small GTPase Rho in various cell types. 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. The long C-terminal of the EP4 receptor contributes to its susceptibility to rapid agonist-induced internalization and desensitization. However, the EP2 receptor undergoes neither rapid agonist-induced internalization nor desensitization owing to a shorter C-terminal sequence. 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

PGE2 RECEPTORS: THE EP RECEPTORS (1–4)

PGE2 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. Some of the signalling pathways that are generated by PGE2 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 tuned signalling. 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. Another level of control of signalling by PGs is attributed to Ca2+, which is a highly versatile intracellular signal that modifies various cellular processes through spatial and temporal dynamic remodelling of a variety of signalling constituents. Activation of EP receptors leads to changes in the production of cAMP and/or phosphoinositide turnover and intracellular Ca2+ mobilization. EP1 was first described as involved in constriction of smooth muscle. The C-terminal domain of the EP1 receptor binds to Gαq heterotrimeric guanine nucleotide-binding protein. Activation of EP1 by ligand binding results in increased phosphatidylinositol hydrolysis and elevation of the intracellular Ca2+ through activation of phospholipase-C (Figure 1). In contrast, EP2 was originally believed to have a role in smooth muscle relaxation. Both EP2 and EP4 are coupled to Gs-proteins, leading to increased production of cAMP and activation of protein kinase A (PKA) (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. The distinguishing feature of EP4 is, however, the ability to activate phosphatidylinositol 3 kinase signalling pathways following phosphorylation by G-protein coupled receptor kinases or by virtue of the ability to bind Gi proteins (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. 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. 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 Gi in addition to Gi, and evokes CAMP production. Moreover, EP3 has been demonstrated to activate the small GTPase Rho in various cell types (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. The long C-terminal of the EP4 receptor contributes to its susceptibility to rapid agonist-induced internalization and desensitization. However, the EP2 receptor undergoes neither rapid agonist-induced internalization nor desensitization owing to a shorter C-terminal sequence. 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
restricted expression pattern within each organ system. Interestingly, this precise cellular localization of EP receptors is found in mice, humans and rabbits. A detailed summary of described physiological functions of each subtype of the four EP receptors are enlisted in supplementary Table 1.

EFFECT OF PGE2 ON T-CELL ACTIVATION AND DIFFERENTIATION

Although most of the PGE2 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.

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. Recent studies have confirmed that EP2 and EP4 are the main receptor subtypes to mediate the actions of PGE2 in human and murine CD4+ T cells.

Immunosuppressive role of PGE2 on T-cell function

PGE2-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. Starting from the early 1980s, it has been strongly believed that PGE2 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 PGE2 in T-cell activation was documented >30 years ago, when it was postulated that PGE2 concentration, as well as the state of differentiation of the target cell, and length of PGE2–target cell interaction were important factors controlling the process (reviewed in Goodwin and Ceuppens).

Initial findings reported a role of PGE2 in mediating induction of nonspecific T lymphocyte suppressor activity and a drastic inhibition of T-cell proliferation, hence modifying T-cell blastogenic responses in mice lymphoid organ and suppressing proliferation of lymphoma in mice. Later studies suggested that PGE2 primarily exerts its inhibitory effect on lymphocyte proliferation through an inhibition of IL-2 production. This was followed by reports that stated that inhibition of lymphocyte response was brought about by PGE2-producing macrophages, which were found to inhibit IL-1-dependent T-lymphocyte differentiation. Subsequent research substantiated the suppressive function of PGE2 in T-cell responses.

However, it was not until the late 1980s that research began to delineate the underlying inhibitory pathways of PGE2 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. cAMP was also shown to downregulate transferrin receptor expression in an IL-2-dependent manner and abrogate TCR-mediated cytosolic increases in Ca2+ later confirmed by studies in sepsis. 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. Increases in cAMP were also found to inhibit expression of IL-2 receptors. 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.

The suggestion that PGE₂ might alter polarization of T helper cells to Th1 and Th2 subtypes was demonstrated first in a study by Betz and Fox, where they showed that PGE₂ 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 PGE₂ upregulates IL-5 production in T cells. It was later demonstrated that while PGE₂ primed Th cells to produce higher amounts of IL-4, IL-10 and IL-13, it was found to inhibit IL-12 production and IL-12 receptor responsiveness, consolidating its role in the Th1/Th2 balance.

On the other hand, there are various reports that suggest that PGE₂ enhances induction and differentiation of FOXP₃⁺ CD₄⁺ CD₂₅⁺ adaptive regulatory T cells that thereby suppress effector T-cell stimulation pathways. In addition, PGE₂ has been shown to induce T-cell anergy to maintain the survival of CD₄5RO⁺ T cells and to inhibit γδ T-cell cytotoxicity triggered by the TCR through cAMP-mediated PKA type I-dependent signalling.

With respect to transcription factors and nuclear proteins, it was found that cAMP signalling interfered with the activation pathway for NF-κB and counteracted calcineurin-dependent pathways. Yet, decreased IL-2 production in the presence of PGE₂ was shown to be due to targeting of AP-1 and NF-AT transcription factors in human T cells. Therefore, qualitative differences in the concentration of cAMP and PKA activity can be considered as important elements in modulating T-cell proliferative responses.

Several molecular mechanisms have been proposed for the inhibition of T-cell activation by PGE₂. PGE₂ signalling has been proved to attenuate p59(fyn) protein tyrosine kinase activity and interfere with the protein-kinase C pathway. The enzyme Csk has been shown to negatively regulate Lck, a kinase responsible for TCR signalling following antigen recognition. PGE₂-mediated cAMP was also shown to regulate raft-associated Csk in a spatial and enzymatic manner. 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. 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. The inhibition of the kinase Lck was also proposed as a mechanism of suppression of T-cell activation triggered by PGE₂. Stimulation of prolactin expression (a negative regulator of T-cell proliferation) was also shown to be mediated through Ca²⁺ and cAMP signalling through EP₃ and EP₄ receptors by PGE₂ in T cells.

The immunosuppressive role of PGE₂ in T-cell responses has been summarized in Figure 2.
Pro-inflammatory role of PGE2 in T-cell function

An indirect pro-inflammatory role for PGE2 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 PGE2 came into view when it was shown that nanomolar concentrations of PGE2 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 PGE2 in Th17 expansion was also reported by Boniface et al.,56 who showed that PGE2 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 PGE2 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 PGE2 in regulation of Th17 responses.56 PGE2 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 PGE2-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 PGE2-EP2/EP4 signalling in T-cell preservation 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 PGE2 to differentially modulate Th1 and Th17 differentiation at different concentrations, could bring a new dimension to the PGE2-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 PGE2 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 PGE2 enhanced the differentiation of naive T cells toward the Th1 type.113 This was further emphasized in another report where the addition of PGE2 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, PGE2 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 PGE2-matured DCs upregulate the expression of OX-40L, CD40 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 PGE2 in T-cell response is shown in Figure 3.

PGE2-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](image-url)
immunodeficiency virus and parasitic infections. Given the importance of PGE₂ signalling in the modulation of T-cell responses, several reports have focused on the development of PGE₂-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 non-specific 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. This has resulted in the shift of focus of therapeutic interventions from COX enzymes to PGE₂ synthases such as m-PGES-1.

The past decade has experienced a major change in the outlook of treatment regimens that aim to inhibit the actions of PGE₂. Extensive work on the tissue, organ and cell-specific functions of PGE₂ 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. EP receptor antagonists have been employed for the inhibition of inflammatory pain hypersensitivity, paw edema and cancer.

The ‘classical’ perspective of the role of PGE₂ as only an immune modulator 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 PGE₂ 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 PGE₂ from a T-cell immunosuppressor to a T-cell immunomodulator, such as local concentration of PGE₂ during diverse phases of inflammation, differential use of EP receptors and signalling pathway involved in T-cell subsets and 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.

**CONCLUSION AND REMARKS**

The ‘classical’ perspective of the role of PGE₂ 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 PGE₂ 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 PGE₂ from a T-cell immunosuppressor to a T-cell immunomodulator, such as (1) local concentration of PGE₂ 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.

1. Tiley SL, Coffman TM, Kallier BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest* 2001; 108: 15–23.
2. Smith WL, Dewitt DL. Prostaglandin endoperoxide H synthases-1 and -2. *Adv Immunol* 1996; 62: 167–219.
3. Harris SG, Padilla J, Kounnas L, Ray D, Phipps RP. Prostaglandins as modulators of immunity. *Trends Immunol* 2002; 23: 144–150.
4. Smyth MF, Grosser T, Wang M, Yu T, FitzGerald GA. Prostaglandins in health and disease. *J Lipid Res* 2009; 50(Suppl): S23-S428.
5. Samuelsson B, Goldyne M, Granström E, Hamberg M, Hammarström S, Malmström C. Prostaglandins and thromboxanes. *Ann Rev Biochem* 1978; 47: 997–1029.
6. Yedgar S, Krnisky M, Cohen Y, Flower RJ. Treatment of inflammatory diseases by selective eicosanoid inhibition: a double-edged sword? *Trends Pharmacol Sci* 2007; 28: 459–464.
7. Goodwin JS. Are prostaglandins proinflammatory, antiinflammatory, both or neither? *J Rheumatol Suppl* 1991; 28: 26–29.
8. Radmark O, Samuelsson B. Microsomal prostaglandin E synthase-1 and 5-lipoxygenase: potential drug targets in cancer. *J Intern Med* 2010; 268: 5–14.
9. Samuelsson B, Morgenstern R, Jakobsson PJ. Membrane prostaglandin E synthase-1: a novel therapeutic target. *Pharmacol Rev* 2007; 59: 207–224.
10. Jakobsson PJ, Thoren S, Morgenstern R, Samuelsson B. Activating prostaglandins: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. *Proc Natl Acad Sci USA* 1999; 96: 7220–7225.
11. Sampey AI, Monrad S, Crofford LJ. Microsomal prostaglandin E synthase-1: the inducible synthase for prostaglandin E2. *Arthritis Res Ther* 2005; 7: 114–117.
12. Sugimoto Y, Narumiya S. Prostaglandin E receptors. *J Biol Chem* 2007; 282: 11613–11617.
13. Ushikubi F, Sugimoto Y, Ichikawa A, Narumiya S. Roles of prostaglandins revealed from studies using mice lacking specific prostaglandin receptors. *Jpn J Pharmacol* 2000; 83: 279–285.
14. Lawrence T, Willoughby DA. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. *Nat Rev Immunol* 2003; 2: 787–795.
15. Samuelsson B, Dahlein SE, Lindgren JA, Rouzer CA, Sethan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. *Science* 1987; 237: 1171–1176.
16. Fortier MA, Krishnaswamy K, Danyod G, Boucher-Kovalik S, Chapdalaine P. A postgenomic integrated view of prostaglandins in reproduction: implications for other body systems. *J Physiol Pharmacol* 2008; 59(Suppl 1): 65–89.
17. Dey I, Lejeune M, Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. *Br J Pharmacol* 2006; 149: 611–623.
18. Wang MT, Honn KV, Nie D. Cyclooxygenases, prostanooids, and tumor progression. *Cancer Metastasis Rev* 2007; 26: 529–534.
19. Greenough A, Smartt HJ, Moore AE, Roberts HR, Williams AC, Parakawa C et al. The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. *Carcinogenesis* 2009; 30: 377–386.
20. Iniguez MA, Rodriguez A, Volpert OV, Fresno M, Redondo JM. Prostaglandin synthase: a microsomal, glutathione-dependent, inducible enzyme, a therapeutic target in angiogenesis. *Trends Mol Med* 2003; 9: 73–78.
21. Ahmadi M, Emery DC, Morgan DJ. Prevention of both direct and cross-priming of anti-TNFα CD8+ T-cell responses following overproduction of prostaglandin E2 by tumour cells in vivo. *Cancer Lett* 2005; 2520–7529.
22. Mullusawanny R, Urban J, Lee JJ, Reinhardt TA, Bartlett D, Kalinski P. Ability of mature dendritic cells to interact with regulatory T cells is imprinted during maturation. *Cancer Res* 2008; 68: 5972–5978.
23. Banatnev F, Lin Y, Zhu L, Yang SC, Heuze-Yourc'h N, Zeng G et al. Prostaglandin E2 induces FOXP3 gene expression and T regulatory cell function in human CD4+ T cells. *J Immunol* 2005; 175: 1483–1490.
24. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 2001; 294: 1871–1875.
25. Simmons DL, Bolting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol Rev* 2004; 56: 387–437.
26. Legler DF, Krause P, Scandella E, Singer E, Goetzmann M. Prostaglandin E2 is generally required for human dendritic cell migration and exerts its effect via EP2 and EP4 receptors. *J Immunol* 2006; 176: 966–973.
27. van Helden SF, Krooshoff DJ, Broers KC, Raymakers RA, Figdor CG, van Leeuwen FF. A critical role for prostaglandin E2 in podosome dissolution and induction of high-speed migration during dendritic cell maturation. *J Immunol* 2006; 177: 1567–1574.
28. Krause P, Bruckner M, Uremis M, Singer E, Goetzmann M, Legler DF. Prostaglandin E2 (PGE2) enhances T-cell proliferation by inducing the cytostatimulatory molecules 40K0L, CD70, and 4-1BBL on dendritic cells. *Blood* 2009; 113: 2451–2460.
29. Mael J, Ransijn A, Corradin SB, Buchmuller-Rouiller Y. Effect of PGE2 and of agents that raise cAMP levels on macrophage activation induced by IFN-gamma and TNF-alpha. *J Leukoc Biol* 1995; 59: 217–224.
30. Cipollone F, Prontera C, Pini B, Marini M, Fazia M, De Cesaie D et al. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E2-dependent plaque instability. *Circulation* 2001; 104: 921–927.
31. Kunikata T, Yamane H, Segi E, Matsuoka T, Sugimoto Y, Tanaka S et al. Suppression of allergic inflammation by the prostaglandin E receptor subtype EP3. *Nat Immunol* 2005; 6: 524–531.
32 Alfranca A, Iniguez MA, Freso M, Rodondo J M. Prostanoid signal transduction and gene expression in the endothelium: role in cardiovascular diseases. Cardiovasc Res 2006; 70: 446-456.
33 Berridge MJ, Irvine RF. Inositol phosphates and cell signalling. Nature 1989; 341: 197-205.
34 Berridge MJ, Rootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and modelling. Nat Rev Mol Cell Biol 2003; 4: 517-529.
35 Breyer RM, Bajtova CK, Myers SA, Breyer EM. Prostanoid receptors: subtypes and signaling. Annu Rev Pharmacol Toxicol 2001; 41: 661-690.
36 Gardiner PJ. Characterization of prostaglandin relaxant/inhibitory receptors (psi) using a highly selective agonist, TRAP797. Br J Pharmacol 1986; 87: 45-56.
37 Narumiya S, Sugimoto Y, Ishikawa I. Prostanoid receptors: structures, properties, and functions. Physiol Rev 1999; 79: 1193-1226.
38 Barty S, Weil R, Mertelsmann R, Dupont B. Prostaglandin EP2 acts at two distinct pathways of T lymphocyte activation: inhibition of interleukin 2 production and down-regulation of transferrin receptor expression. J Immunol 1985; 135: 1172-1177.
39 Choudhry MA, Ahmad S, Saseen MM. Role of Ca2+ in prostaglandin EP2-induced T lymphocyte proliferative suppression in sepis. Infect Immun 1995; 63: 3101-3105.
40 Sonnenburg WK, Zhu JH, Smith WL. A prostaglandin E receptor coupled to a pertussis toxin-sensitive small GTPase Rho. J Biol Chem 2006; 281: 2614-2619.
41 Fujino H, Regan JW. Phosphorylation of glycogen synthase kinase-3 and down-regulation of the prostaglandin-E-receptor EP3 subtype with different C-terminal tail coupling in human peripheral blood T cells. J Exp Med 2006; 203: 265-276.
42 Fujino H, West KA, Regan JW. Phosphorylation of glycogen synthase kinase-3 and stimulation of T-cell factor signaling following activation of EP2 and EP4 prostaglandin receptors by PGE2. J Biol Chem 2002; 277: 2614-2619.
43 Rojo JM, Hispanic M, Ichikawa A. Two Gs-coupled prostaglandin E receptor subtypes, EP2 and EP4, differ in desensitization and sensitivity to the metabolic inactivation of the agonist. Mol Pharmacol 1996; 50: 1031-1037.
44 Fujino H, West KA, Regan JW. Phosphorylation of glycogen synthase kinase-3 and stimulation of T-cell factor signaling following activation of EP2 and EP4 prostaglandin receptors by PGE2. J Biol Chem 2002; 277: 2614-2619.
45 Irie A, Sugimoto Y, Namba T, Harazono A, Honda A, Watabe A. Two isoforms of the prostaglandin-E-receptor EP3 subtype with different C-terminal tail coupling to both stimulation and inhibition of adenylyl cyclase. Eur J Biochem 1993; 217: 313-318.
46 Mary D, Aussel C, Ferrua B, Fehlmann M. Regulation of interleukin 2 synthesis by prostaglandin EP2/EP4 receptor signaling in human peripheral blood T cells. J Immunol 1993; 150: 2790-2798.
47 Nishigaki N, Negishi M, Ichikawa A. Two Gs-coupled prostaglandin E receptor subtypes, EP2 and EP4, differ in desensitization and sensitivity to the metabolic inactivation of the agonist. Mol Pharmacol 1996; 50: 1031-1037.
48 Sakata D, Yao C, Narumiya S. Prostaglandin EP2, an immunomodulator. J Pharmacol Sci 2010; 112: 1-5.
49 Fujino H, Regan JW. EP4 receptor prostaglandin receptor coupling to a pertussis toxin-sensitive inhibitory G protein. Mol Pharmacol 2006; 69: 9-15.
50 Sonneberg WK, Zhu JH, Smith WL. A prostaglandin E receptor coupled to a pertussis toxin-sensitive guanine nucleotide regulatory protein in rabbit cortical collecting tubule cells. J Biol Chem 1990; 265: 8479-8483.
51 Desai S, Aprile H, Nwaneshiudu C, Ashby B. Comparison of agonist-induced intracellular calcium mobilization, neurite retraction via small GTPase Rho. J Immunol 2001; 167: 1193-1226.
52 Walker C, Kristensen F, Bettens F, DeNeck AL. Lympophagin regulation of activated (G1) lymphocytes. J Immunol 1993; 150: 936-940.
53 Lian D, Seder L, Goodwin JS. Phospholipid inositol hydrolysis after CD3 binding in human peripheral blood T cells. Inhibition by prostaglandin EP2. Int Immunopharmacol 2000; 10: 829-836.
54 Anastasiou ED, Palagianni F, Balow JP, Yamada H, Bourpas DT. Prostaglandin E2 enhances both cytokine production and nuclear translocation of NF-kappaB in peripheral blood mononuclear cells. Immunol Lett 2001; 77: 3526-3531.
55 Breyer MD, Davis L, Jacobson HR, Breyer RM. Differential localization of prostanoid EP2 receptor subtypes in human kidney. Am J Physiol 1999; 276: F912-F918.
56 Iniguez MA, Punzon C, Fresno M. Induction of cyclooxygenase-2 on activated T lymphocytes: regulation of T cell activation by cyclooxygenase-2 inhibitors. J Immunol 1999; 163: 111-119.
57 Nataraj C, Thomas DW, Tilley SL, Nguyen MT, Mannon R, Koller BH et al. Receptors for prostaglandin E2 that regulate cellular immune responses in the mouse. J Clin Invest 2001; 108: 1229-1235.
58 Nataraj C, Thomas DW, Tilley SL, Nguyen MT, Mannon R, Koller BH et al. Receptors for prostaglandin E2 that regulate cellular immune responses in the mouse. J Clin Invest 2001; 108: 1229-1235.
59 Smith JW, Steiner AL, Newberry JR WM, Parker CW. Cycloadenosine 3';5'-monophosphate in human peripheral blood mononuclear cells: Alterations after phagophagocytosis stimulation. J Clin Invest 1971; 50: 432-441.
60 Smith JW, Steiner AL, Parker CW. Human lymphocytic metabolism. Effects of cyclic and noncyclic nucleotides on stimulation by phagohagmatin. J Clin Invest 1971; 50: 442-448.
61 Goodwin JS, Ceppaglia JS. Regulation of the immune response by prostaglandins. J Clin Immunol 1983; 3: 295-315.
62 Fischer A, Durandy A, Griscelli C. Role of prostaglandin E2 in the induction of noncyclic TPX-L tumor promoter 12.0 tetradecanoyl phorbol-13 acetate. J Exp Med 1994; 179: 1245-1247.
63 Rojo JM, Portoles MP, Barasaan I, Portoles A. Exogenous additions of prostaglandins variably alter the blastogenic response of B and T lymphocytes from different mouse lymphoid organs. Immunopharmacology 1982; 4: 95-104.
Prostaglandin E2 (PGE2) induces the nuclear transcription of the human interleukin 2, but not the IL-4, gene in human T cells by targeting transcription factors AP-1 and NF-AT. Cell Immunol 1996; 171: 95–101.

10 Bauman GP, Bartik MM, Brooks WH, Roszman TL. Induction of cAMP-dependent protein kinase (PKA) activity in T cells after stimulation of the prostaglandin E2 or the beta-adrenergic receptors: relationship between PKA activity and inhibition of anti-CD3 monoclonal antibody-induced T cell proliferation. Cell Immunol 1994; 158: 182–194.

11 Choudhry MA, Ahmed Z, Sayeed MM. PGE(2)-mediated inhibition of T cell p59(fyn) is independent of cAMP. Am J Physiol 1995; 277: C302–C309.

12 Choudhry MA, Uddin S, Sayeed MM. Prostaglandin E2 modulation of p59fyn tyrosine kinase in T lymphocytes during sepsis. J Immunol 1998; 160: 929–935.

13 Naito Y, Endo H, Arii K, Coffman RL, Arii N. Signal transduction in Th clones: target of differential modulation by PGE2 may reside downstream of the PKC-dependent pathway. Cytokine 1996; 8: 346–356.

14 Schwach MG, Ayala A, Cioffi WG, Bland KI, Chaudry IH. Role of protein kinase C in cyclic AMP-mediated suppression of T lymphocyte activation following burn injury. Biochim Biophys Acta 1999; 1455: 45–53.

15 Bredica T, Pavlištová D, Leo A, Breyna E, Korínek V, Angelova P et al. Phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG), a novel ubiquitously expressed transmembrane adapter protein, binds the protein tyrosine kinase csk and is involved in regulation of T cell activation. J Exp Med 2000; 191: 1591–1604.

16 Hermiston ML, Xu Z, Majeti R, Weiss A. Reciprocal regulation of lymphocyte activation signaling promotes immune inflammation through Th1 cell differentiation and Th17 lymphocytes. J Immunol 2005; 175: 1561–1572.

17 Chakraborti AK, Gang SK, Kumar R, Motiwa H, Jadhavar PS. Progress in COX-2 inhibitors: a journey so far. Curr Med Chem 2010; 17: 1563–1593.

18 Abdal-Tawab M, Zettl H, Schubert-Zsilavecz M. Nonsteroidal anti-inflammatory drugs: a critical review on current concepts applied to reduce gastrointestinal toxicity. Curr Med Chem 2009; 16: 2042–2063.

19 Lai LH, Chan FK. Nonsteroid anti-inflammatory drug-induced gastroduodenal injury. Curr Opin Gastroenterol 2009; 25: 544–548.

20 Koeberle A, Werz O. Inhibitors of the microsomal prostaglandin E(2) synthase-1 as antagonists of prostaglandin E2 (PGE2)-induced prolactin expression in human T cells: cooperation of PGE2 and T cells. J Biol Chem 2003; 278: 17597–17600.

21 Cobb MH, Xu S, Hepler JE, Hutchison M, Frost J, Robbins DJ. Regulation of the MAP kinase cascade. Cell Mol Biol Rev 1994; 40: 253–256.

22 Whithurst CE, Geppert TD. MEK1 and the extracellular signal-regulated kinase-activated protein kinases are required for the stimulation of IL-2 gene transcription in T cells. J Immunol 1996; 156: 1020–1029.

23 Nika K, Hyun H, Williams S, Paul S, Botlini N, Tasken K et al. Haematopoietic protein tyrosine phosphatase (HePTP) phosphorylation by cAMP-dependent protein kinase in T-cells: dynamics and subcellular location. Biochem J 2004; 378: 335–342.

24 Chenmkit JM, Driesen J, Classen S, Riley JL, Deby S, Beyer M et al. Prostaglandin E2 impairs CD4+ T cell activation by inhibition of Iκκ: implications in Hodgkin’s lymphoma. Cancer Res 2006; 66: 1114–1122.

25 Gerlo S, Verdoorn P, Gellersen B, Hooghe-Peters EL, Kooijman R. Mechanism of prostaglandin (PGE2)-induced prolactin expression in human T cells: cooperation of two PGE2 receptor subtypes, E-prostaoid (EP) 3 and EP4, via calcium- and cyclic adenosine 5′-monophosphate-mediated signaling pathways. J Immunol 2004; 173: 5952–5962.

26 Carlisi S, Piraino G, Cucinotta M, Valenti A, Loddo S, Teli D. Prostaglandin E2 induces interleukin-8 gene transcription by activating C/EBP homologous protein in human T lymphocytes. J Biol Chem 2005; 280: 14433–14442.

27 Yao C, Sakata D, Esaki Y, Li Y, Matsuoka T, Kuroiwa K et al. Prostaglandin E2 enhances Th17 responses via modulation of IL-17 and IFN-gamma production by memory CD4+ T cells. Eur J Immunol 2009; 39: 1301–1312.

28 Esaki Y, Li Y, Sakata D, Yao C, Segi-Nishida E, Matsuoka T et al. Dual roles of PGE2-EP4 signaling in mouse experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA 2010; 107: 12233–12238.

29 Khayruyllina T, Yen JH, Jing H, Ganesa D. In vitro differentiation of dendritic cells in the presence of prostaglandin E2 alters the IL-12/IL-23 balance and promotes differentiation of Th17 cells. J Immunol 2008; 181: 721–735.

30 Shebanie AF, Tadmoni I, Jing H, Vassiliou E, Ganea D. Prostaglandin E2 induces IL-23 production in bone marrow-derived dendritic cells. FASEB J 2004; 18: 1318–1320.

31 Lee JJ, Takei M, Hori S, Inoue Y, Harada Y, Tanosaki R et al. The role of PGE2 in the differentiation of dendritic cells: how do dendritic cells influence T cell polarization and chemokine receptor expression? Stem Cells 2002; 20: 448–459.

32 Rubio MT, Means TK, Chakraverty R, Shaffer J, Fusaba YA, Chittenden M et al. Maturation of human monocyte-derived dendritic cells (MoDCs) in the presence of prostaglandin E2 optimizes CD4 and CD8 T-cell-mediated responses to protein antigens: role of PGE2 in chemokine and cytokine expression by MoDCs. Int Immunol 2005; 17: 1561–1572.

33 Chakraborti AK, Gang SK, Kumar R, Motiwa H, Jadhavar PS. Progress in COX-2 inhibitors: a journey so far. Curr Med Chem 2010; 17: 1563–1593.

34 Abdal-Tawab M, Zettl H, Schubert-Zsilavecz M. Nonsteroidal anti-inflammatory drugs: a critical review on current concepts applied to reduce gastrointestinal toxicity. Curr Med Chem 2009; 16: 2042–2063.

35 Lai LH, Chan FK. Nonsteroid anti-inflammatory drug-induced gastroduodenal injury. Curr Opin Gastroenterol 2009; 25: 544–548.

36 Koeberle A, Werz O. Inhibitors of the microsomal prostaglandin E2 synthase-1 as alternative to non-steroidal anti-inflammatory drugs (NSAIDs)–a critical review. Curr Med Chem 2009; 16: 4274–4296.

37 Chen Q, Muramoto K, Masaaki N, Ding Y, Yang Y, Mackey M et al. A novel antagonist of the prostaglandin E2 (EP2) receptor inhibits Th1 differentiation and Th17 expansion and is orally active in arthritis models. Br J Pharmacol 2010; 160: 292–310.

38 Claudino RF, Kasuya CA, Ferreira J, Calixto JB. Pharmacological and molecular characterization of the mechanisms involved in prostaglandin E2-induced mouse paw edema. J Pharmacol Exp Ther 2006; 318: 611–618.

39 Kundu N, Ma X, Holt D, Goloubeva O, Ostrand-Rosenberg S, Fulton AM. Antagonism of the prostaglandin E receptor EP4 inhibits metastasis and enhances NK function. Breast Cancer Res Treat 2009; 117: 235–242.

40 Lin CR, Amaya F, Barrett L, Wang H, Takada J, Samad TA et al. Prostaglandin E2 receptor EP4 contributes to inflammatory pain hypersensitivity. J Pharmacol Exp Ther 2006; 319: 1096–1103.

41 Ma X, Kundu N, Rief S, Walser T, Fulton AM. Prostaglandin E receptor EP4 antagonism inhibits breast cancer metastasis. Cancer Res 2006; 66: 2923–2927.

42 Piazuelo E, Jimenez P, Strunk M, Santander S, Garcia A, Esteva F et al. Effects of selective PGE2 receptor antagonists in esophageal adenocarcinoma cells derived from Barrett’s esophagus. Prostaglandins Other Lipid Mediat 2006; 81: 150–161.