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Prostaglandins are small-molecule derivatives of arachidonic acid (AA), produced by cyclooxygenases (COX; constitutively active cyclooxygenase COX1 and inducible COX2) and PG synthases (1), with a relatively minor contribution of the isoprostane pathway (2). Local levels of PGE₂, the main product of cyclooxygenases in myeloid and stromal cells, are regulated by the local balance between the COX2-driven synthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-mediated degradation of PGE₂ (1, 3). The receptors for PGE₂ (EP₁–EP₄) are present on multiple cell types (4), reflecting the ubiquitous functions of PGE₂, which span nociception and other aspects of neuronal signaling, hematopoiesis, regulation of blood flow, renal filtration and blood pressure, regulation of mucosal integrity, vascular permeability, and smooth muscle function (5–9). The present review focuses on the role of PGE₂ and its receptors in the regulation of different stages of immune responses and different effector mechanisms of immunity.

Long known and yet unknown: paradoxes of PGE₂ function

PGE₂ (molecular mass of 352 Da), recognized as a biologically active factor in the 1960s, has been shown to regulate multiple aspects of inflammation and multiple functions of different immune cells (1). Although generally recognized as a mediator of active inflammation, promoting local vasodilatation and local attraction and activation of neutrophils, macrophages, and mast cells at early stages of inflammation (10–13), its ability to promote the induction of suppressive IL-10 and to directly suppress the production of multiple proinflammatory cytokines allow it to limit nonspecific inflammation, promoting the immune suppression associated with chronic inflammation and cancer (1, 14). Although PGE₂ can promote the activation, maturation, and migration of dendritic cells (DCs) (see below), the central cells during the development of Ag-specific immunity, it has been widely demonstrated to suppress both innate and Ag-specific immunity at multiple molecular and cellular levels (1, 15), earning PGE₂ the paradoxical status of a proinflammatory factor with immunosuppressive activity.

Although PGE₂ inhibitors, such as steroids (inhibitors of AA release) and nonsteroid anti-inflammatory drugs (blockers of COX1/2 or COX2 function), represent some of the most common and effective pharmaceutical agents, realizing the full potential of PGE₂ targeting in the treatment of chronic infections, inflammation, and cancer is restricted by the complex pattern of PGE₂-mediated immunoregulation and our still incomplete understanding of the key mechanisms and targets of PGE₂-mediated immunoregulation.

Regulation of PGE₂ production, degradation, and responsiveness to PGE₂

Regulation of PGE₂ production. PGE₂ can be produced by all cell types of the body, with epithelia, fibroblasts, and infiltrating inflammatory cells representing the major sources of PGE₂ in the course of an immune response. The process of PGE₂ synthesis involves phospholipase A₂ family members that mobilize AA from cellular membranes (16), cyclo-

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Abbreviations used in this article: AA, arachidonic acid; COX, cyclooxygenase; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; Treg, regulatory T cell.

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oxygenases (constitutively active COX1 and inducible COX2) that convert AA into PGH2, and PGE synthases, needed for the final formulation of PGE2 (17) (Fig. 1). Although the rate of PGE2 synthesis and the resulting inflammatory process can be affected by additional factors, such as local availability of AA, in most physiologic conditions the rate of PGE2 synthesis is controlled by local expression and activity of COX2.

**Regulation of PGE2 degradation.** PGE2 is relatively stable in vitro although its decay is accelerated by albumin (18). In contrast, PGE2 has a very rapid turnover rate in vivo and is rapidly eliminated from tissues and circulation (19). The rate of PGE2 degradation in individual tissues is controlled by 15-PGDH (3). The suppression of 15-PGDH activity is observed in many forms of cancer (20–24) or UV-irradiated skin (25), the PGE2-rich and immunosuppressive environments. Apoptotic cancer cells can modulate the prostanoid production by enhancing the macrophage expression of COX2 and microsomal PGE synthase-1 while suppressing 15-PGDH (26). Moreover, the deactivation of 15-PGDH has been shown responsible for the resistance of premalignant colon lesions to celecoxib (24). These observations suggest that in addition to the rate of PGE2 synthesis, the rate of PGE2 decay may contribute to immune pathology and constitute a potential target for immunomodulation (21).

**PGE2 receptors and signaling pathways: regulation of PGE2 responsiveness.** The heterogeneous effects of PGE2 are reflected by the existence of four different PGE2 receptors, designated EP1, EP2, EP3 and EP4, with an additional level of functional diversity resulting from multiple splice variants of EP3 that exists in at least eight forms in humans and three forms in mice (reviewed in Ref. 4).

**FIGURE 1.** Regulation of PGE2 synthesis, degradation, and responsiveness to PGE2. PGE2 synthesis is initiated by the (glucocorticosteroids sensitive) phospholipase A2-driven release of AA from cell membranes. AA becomes the substrate for COX1 (constitutive activity) and COX2 (inducible) that convert AA to PGH2 (process that can be suppressed by nonsteroid anti-inflammatory drugs), which is then converted to biologically active PGE2 by PGE synthases. PGE2 signals via four known receptors (EP1–EP4), with the cAMP/PKA/CREB signaling pathway responsible for major suppressive and regulatory functions of PGE2. Local PGE2 degradation is regulated by 15-PGDH. Dark-green arrows indicate currently applied inhibitory drugs; light green arrows indicate potential targets for prospective drugs. (+), activating; (−), inhibitory.

EP3 and EP4 represent high-affinity receptors, whereas EP1 and EP2 require significantly higher concentrations of PGE2 for effective signaling. The signaling through the two Gs-coupled receptors, EP2 and EP4, is mediated by the adenylate cyclase-triggered cAMP/PKA/CREB pathway (27–29), mediating the dominant aspects of the anti-inflammatory and suppressive activity of PGE2 (Fig. 1). Despite their similar nominal functions, the signaling by EP2 and EP4 is triggered by different concentrations of PGE2 and differs in duration. EP4 signaling is rapidly desensitized following its PGE2 interaction, whereas EP2 is resistant to ligand-induced desensitization, implicating its ability to mediate PGE2 functions over prolonged periods of time and at later time points of inflammation (30). Although EP2 is thought to signal in a largely cAMP-dependent fashion, EP4 also activates the PI3K-dependent ERK1/2 pathway (31). However, both EP2 and EP4 have been shown to activate the GSK3/β-catenin pathway (32).

In contrast to EP2 and EP4, low-affinity EP1 and high-affinity EP3 are not coupled to Gs and lack cAMP-activating functions. Most of the splice variants of EP3 represent Gi-coupled PGE2 receptors that inhibit adenylate cyclase (33), although at least some are Gs-coupled and show different sensitivity to ligand-induced desensitization (4). Signaling via EP1 involves calcium release (4).

The differences in sensitivity, susceptibility to desensitization, and ability to activate different signaling pathways between the different PGE2 receptor systems allow for adaptable patterns of responses of different cell types at different stages of immune responses. Additional flexibility of the PGE2 receptor system results from different sensitivity of the individual receptors to regulation by additional factors. The expression of EP2 and the resulting responsiveness to PGE2 can be suppressed by hypermethylation, as observed in patients with idiopathic lung fibrosis (34). These observations raise the possibility that, in addition to the regulation of PGE2 production and its degradation, the regulation of PGE2 responsiveness at the level of expression of individual PGE2 receptors can also contribute to the pathogenesis of human disease and be exploited in their therapy. In support of this possibility, the use of synthetic inhibitors, preferentially affecting EP2, EP3, or EP4 signaling, allows for differential suppression of different aspects of PGE2 activity (reviewed in Ref. 4).

**PGE2 and the activity of innate immune cells**

Although PGE2 can promote the tissue influx of neutrophils (10), macrophages (11), and mast cells (13), it differentially affects the functions of different innate effector cells.

**NK cells.** PGE2 suppresses the cytolytic effector functions of NK cells (35, 36), in a mechanism involving suppression of IL-12 and IL-15 responsiveness (37, 38), and most likely IL-2. It also inhibits NK cell production of IFN-γ, abrogating NK cell “helper” function in the DC-mediated induction of Th1 and CTL responses (39). PGE2-mediated suppression of NK cell function during surgery has been shown to facilitate the establishment of metastases in experimental animals (40).

**Granulocytes.** PGE2 has been shown to inhibit granulocyte functions (41), contributing to the defective innate host defense in patients after bone marrow transplantation or with
cancer, as well as other conditions associated with overproduction of PGE₂ (42).

**Macrophages.** Acting in an EP2-dependent (43) and PTEN-dependent (44) manner, PGE₂ limits the phagocytosis by alveolar macrophages (43) and their pathogen-killing function (45). At least a part of the inhibitory impact of PGE₂ on the alveolar macrophage function is mediated via the induction of IL-1R-associated kinase-M, which blocks the scavenger receptor-mediated phagocytosis and the TLR-dependent activation of TNF-α (46).

**Mast cells.** PGE₂ promotes both the induction of mast cells (47) and their local attraction and degranulation in a mechanism involving EP1 and EP3 (11–13, 48). It also promotes the degranulation-independent production of the proangiogenic and immunosuppressive vascular endothelial growth factor and MCP-1 by mast cells (11, 49), which contributes to the overall disease-promoting activity of PGE₂ in cancer.

**PGE₂ and the induction of Ag-specific immune responses**

PGE₂ affects several key phenomena relevant to the induction of immune responses. In addition to its multifaceted regulation of DC functions during the priming of naive T cells (see below), it also directly inhibits T cell production of IL-2 (50) and IL-2 responsiveness (51), suppressing the activation and expansion of Ag-specific T cells.

**DC development.** PGE₂ has been shown to disrupt early stages of DC differentiation (52), contributing to local and systemic DC dysfunction in cancer (53–55) or following UV exposure (56, 57). Although the ability of PGE₂ to suppress the differentiation of functionally competent Th1-inducing DCs has been long recognized (52), it was recently shown that the resulting “PGE₂ DCs” represent myeloid-derived suppressor cells (MDSCs), capable of suppressing CTL responses (58).

**DC activation, migration, and stimulatory function.** In striking contrast to its uniform inhibitory impact on early stages of DC development, PGE₂ has a much more complex effect on the activation of fully developed (although functionally immature) DCs. PGE₂ has been shown to support the induction of fully mature DCs capable of homing to lymph nodes and to be highly effective in priming naive T cells. The addition of PGE₂ to the mixture of proinflammatory cytokines involving IL-1β and TNF-α accelerates DC maturation and elevates their expression of costimulatory molecules (59–61).

PGE₂ has been shown to promote high-level expression of CCR7 (the receptor for CCL19 and CCL21) and responsiveness to these lymph node-type chemokines in maturing monocyte-derived DCs (62, 63). This activity and its roles in podosome dissolution (64) and induction of matrix metalloproteinase-9 (65) suggested the role for PGE₂ in DC migration to the lymph nodes. However, recent data demonstrate that the CCR7-enhancing effects of PGE₂ are mediated by the suppression of CCL19 in maturing DCs (endogenous CCR7 ligand driving CCR7 internalization) and are rapidly compensated after DC removal from the maturation cultures (66). An additional factor that can limit the in vivo migratory potential of the PGE₂-matured DCs is the ability of PGE₂ to induce tissue inhibitor of proteinase-1 (67).

Although PGE₂-matured DCs indeed migrate to the lymph nodes faster than do immature DCs (68), two small clinical studies comparing the in vivo migratory capacity of differentially matured human DCs did not reveal any migratory advantage of DCs conferred by exogenous PGE₂ (66, 69). In line with the notion that DC maturation and effective lymph node migration can occur in the absence of PGE₂, a recent mouse study in PGE synthase-1–deficient animals showed an abrogation of PGE₂ synthesis by DCs and their altered cytokine profile, but it did not reveal any impact on their maturation status or migratory function (70). These data suggest that although PGE₂ can enhance the migratory function of DCs, it is not critically required in this regard and can be successfully replaced by alternative factors.

The elevated expression of the maturation-associated costimulatory factors on the surface of PGE₂-matured DCs translates into their enhanced ability to activate naive T cells, when compared with immature DCs (59–61). Although PGE₂ also enhances the DC production of several suppressive factors, such as IL-10 (52), thrombospondin-1, (71), and IDO (72), its most frequently observed net effect during DC maturation is the enhanced ability of DCs to promote T cell expansion (59–61).

However, DCs matured in the presence of PGE₂ develop a distinct “exhausted” phenotype, manifested by their impaired ability (compared with alternatively matured DCs) to induce the CTL-, Th1-, and NK cell-mediated type 1 immunity (61, 73, 74), while promoting Th2 responses (73). Such negative effects are mediated by the suppression of proinflammatory cytokines, including the bioactive IL-12p70 (61) (see below).

In accordance with the notion that exogenous PGE₂ may have a net inhibitory effect on the functional activity of maturing DCs, it was shown that the replacement of PGE₂ by other DC maturation-driving factors can enhance the immunogenic and anti-tumor effectiveness of DC vaccines (75, 76).

**Regulation of the attraction of naive T cells, DC–T cell interaction, and T cell activation.** CCR7 ligands (CCL19/MIP3β/ELC and CCL21/6Ckine/SLC) and CXCR4 ligand CXCL12/SDF-1 represent two groups of chemokines needed for effective T cell entry into lymph nodes (77). Although the role of PGE₂ in the local regulation of these two chemokines within the lymph nodes remains unclear, PGE₂ has been recently shown to suppress the ability of DCs to produce CCL19 (the only CCR7 ligand produced by human monocyte-derived DCs) and to block the ability of DCs to attract naive T cells (66). In contrast, PGE₂ was shown to enhance the production of CXCL12 by vascular endothelium (78), raising the possibility that a similar effect may also operate in the lymph nodes, resulting in an opposite impact of PGE₂ on the CCR7- versus CXCR4-driven events governing T cell accumulation in the lymph nodes and their interaction with different types of APCs.

The suppressive effects of PGE₂ on the activation and expansion of naive T cells also include the direct inhibitory effects of PGE₂ on IL-2 production (50) and the expression of IL-2 receptor and JAK3, which mediate the responsiveness of T cells to IL-2 (51, 79).

In accord with the overall suppressive, rather than stimulatory, impact of PGE₂ during the induction of immune responses, the suppression of COX2 activity during vaccination was shown to enhance the immune and therapeutic activity of cancer vaccines (80, 81).

**PGE₂ and the regulation of the character of the immune response**

PGE₂ suppress IL-2 production and IL-2 responsiveness in T cells, nonspecifically suppressing T cell activation and...
proliferation at high doses. Already much lower concentrations of PGE2 show profound modulatory effects shifting the pattern of CD4+ T cell responses from the aggressive Th1 cells (promoting the inflammatory/cytotoxic form of immunity) toward Th2 and Th17 cells that mediate less tissue-destructive forms of immunity.

Balance between Th1 and Th2 responses. The original evidence that PGE2 is involved in regulating the balance between different forms of Th cell responses came from in vitro studies showing its ability to selectively inhibit the production of the Th1 cytokine IFN-γ, but not the Th2 cytokines IL-4 and IL-5, in mouse (82) and human CD4+ T cells (83).

In addition to its direct impact on CD4+ T cells, the Th1-suppressive impact of PGE2 also relies on its ability to suppress the production of IL-12 (84) in monocytes (84) and DCs (52, 61). Additional mechanisms of the IL-12 antagonistic activity of PGE2 include its ability to suppress the expression of IL-12 receptor and the resulting responsiveness to IL-12 (85), and may include the induction of IL-12p40 homodimer (86, 87), a competitive inhibitor of the IL-12 receptor in mice (88). Thus, PGE2 shifts the balance away from Th1 responses toward other forms of immunity, such as Th2 responses. In support of its involvement in Th2-mediated human pathology, overproduction of PGE2 is observed in multiple Th2-associated diseases, most notably atopic dermatitis and asthma (89).

Th17 differentiation. EP2- and EP4-dependent signals from PGE2 have also been shown to promote the development of IL-17–producing T cells in multiple models of infection and autoimmunity (90–93). The Th17-promoting activity of PGE2 is related to its ability to suppress the production of (Th17-inhibitory) IL-12p70 while enhancing the Th17-supporting IL-23 (94).

CTL differentiation and effector function. Mouse models demonstrated that the induction of CTL activity against viral Ags and alloantigens is highly sensitive to PGE2 and cAMP elevation (95, 96). PGE2-dependent inhibition of CTL activity contributes to local immune suppression in decidual tissues and tumors (97–99). Interestingly, apart from the interference with the de novo development of CTL activity, PGE2 can also suppress the ability of fully developed CTLs to interact with their targets and kill tumor cells (99, 100). In addition to its direct effects on CD8+ T cells, PGE2 has also been shown to suppress the ability of maturing DCs to develop CTL-inducing function by suppressing their ability to secrete IL-12 during the subsequent interaction with naive CD8+ T cells (101).

Interestingly, CTLs can produce PGE2 by themselves, resulting in the acquisition of their suppressive function (102), although the implications of this phenomenon to the overall regulation of CTL cell function remain unclear.

B cells. PGE2 has been shown to interfere with early stages of B cell activation and show profound cAMP-mediated regulation of the process of Ig class switch in activated B cells (1, 103). Perhaps the most striking of these effects is the ability of PGE2 to promote IgE production, the phenomenon contributing to atopic diseases (104), jointly with the ability of PGE2 to support the induction, attraction, and degranulation of mast cells (11–13, 47, 48).

PGE2 and suppressive cells

In addition to its long-recognized direct inhibitory effects on type 1 immune cells, more recent studies demonstrate indirect suppressive effects of PGE2, enhancing the development and activity of suppressive types of immune cells.

Regulatory T cell activity. PGE2 has been shown to promote the development of regulatory T cells (Tregs) in humans and in mice (105–108). COX2 and PGE2 have been shown to be essential for the EP2- and EP4-dependent induction of murine Tregs in cancer (106) and following skin UV irradiation (108), with an analogous role demonstrated in human tumor tissues (107). In addition to promoting de novo Treg differentiation from naive precursors, PGE2 also promotes the
interaction of DCs with Tregs (109), suggesting that it may also promote the expansion of pre-existing Tregs, as observed in cancer patients vaccinated with PGE2-matured DCs (110). Interestingly, PGE2 is also involved in mediating the suppressive activity of Tregs (111).

Suppressive macrophages and myeloid-derived suppressor cells: positive and negative feedback involving PGE2. PGE2 is needed for the development of tumor-associated suppressive macrophages (55, 112, 113) and myeloid-derived suppressor cells (58, 114–116). Interestingly, in addition to being the recipients of PGE2-mediated signals, MDSCs express high levels of COX2 and are a major source of PGE2 secretion in human cancer (58, 117). The resulting positive feedback loop between PGE2 and COX2 is essential for the functional stability of MDSCs, as well as their ability to produce the additional MDSC-associated suppressive mediators and to suppress CD8+ T cell function (58). Because PGE2 participates in the induction of hypoxia-inducible factor-1α (118), the hypoxia-inducible factor-1α–mediated development of MDSCs (119) is likely to represent a central downstream signaling event in the PGE2-mediated impact on MDSC development.

PGE2 has been shown to be critical for the development of the apoptotic body–induced suppressor function in macrophages, promoting the growth of intracellular parasites (120). Interestingly, PGE2 is a known inducer of another suppressive factor, IL-10, in tissue macrophages (112, 113). IL-10 acts as a controller of PGE2 secretion, resulting in the paradoxical role of IL-10 in the reversal of the PGE2-mediated macrophage dysfunction, facilitating effective control of the infection with pathogenic strain of Escherichia coli (121).

Trafficking of innate and Ag-specific immune cells to target tissues

In addition to its opposite impact on the development and function of the effector versus suppressive cells, PGE2 also differentially regulates their influx to affected tissues. PGE2 enhances the production of CXCL8/IL-8, the attractant for neutrophils (10) and macrophage-recruiting CCL2/MCP-1 (11). It is also a chemoattractant for mast cells (13), helping to recruit the three members of innate immune system specialized in fighting extracellular pathogens at early stages of immune responses.

However, the macrophage-attracting properties of PGE2 are limited by its ability to block the expression of CCR5 and Mac-1 on monocytes and macrophages, leading to interference with their extravasation and functions (122). The PGE2-driven suppression of CCL5, as well as all three CXCR3 ligands, CXCL9/MIG, CXCL10/IP10, and CXCL11/ITAC, results in its powerful inhibition of the attraction of not only the proinflammatory-type macrophages but also the CCR5+ and CXCR3+ type 1 effector cells (CTLs, NK cells, and Th1 cells) (74, 109, 123, 124). At the same time, PGE2 enhances the production of Th2-attracting chemokines (124) and promotes the production of CCL22/MDC and the resulting attraction of Tregs (109), as well as the CXCL12/SDF1-driven accumulation of MDSCs (125).

In addition to the differential regulation of the effector and Treg/MDSC-attracting chemokines, PGE2 also interferes with the expression of chemokine receptors. It blocks the induction of CCR5 on monocytes (122) and suppresses the DC and IL-12–driven induction of CCR5 and CXCR3 on CD8+ T cells (101), whereas it induces and stabilizes the expression of CXCR4 on cancer-associated MDSCs (125). Additionally, PGE2 is known to suppress the ability of gut-associated DCs to produce retinoic acid, needed for the ability of DCs to induce the CCR9 expression and gut-homing function in responding T cells (126).

PGE2 has also been shown to block the transendothelial migration of human and murine T lymphocytes, interfering with the expression and functions of relevant integrins (127, 128) and directly suppressing CTL motility (100).

Conclusions

In brief, PGE2 supports acute local inflammation and phagocyte-mediated immunity at the site of pathogen entry, but it has a specialized role in controlling the potentially harmful activation of CTL-, Th1-, and NK cell-mediated type 1 (cytotoxic) immunity, especially at later stages of immune responses (Fig. 2). Such PGE2-mediated suppression of type 1 immunity by PGE2 shifts the pattern of immune reactivity toward a less aggressive form of immunity mediated by Th2 and Th17 cells as well as B cells, as well as enhancement of the Treg- and MDSC-mediated suppressive events.

Although PGE2 can accelerate DC maturation and migratory function, the PGE2-dependent suppression of the naive T cell–attracting CCL19 in DCs (66) and its suppression of IL-2 and IL-12 production and functions result in the net inhibitory activity of PGE2 during the induction of Ag-specific immunity, reflected by the ability of COX2 inhibitors to enhance the immune and therapeutic activity of cancer vaccines (80, 81). In accordance with its selective functions in regulating the effector phase of immunity, PGE2 potently suppresses type 1 effector mechanisms, playing an important role of tissue preservation in such critical organs as the lung (34, 129) and reproductive system (6), while shifting the pattern of T cell responses toward Th2, Th17, and Treg activity, helping to contain the damage to tissues during prolonged immune responses.

Although this ability of PGE2 to limit type 1 immunity is crucial for the host self-preservation, it is counterproductive during infections with intracellular organisms (such as mycobacteria or HIV) and in cancer, which both depend on enhanced PGE2 production and/or reduced degradation of PGE2 for the establishment of immunosuppression and disease progression. Although the therapeutic antagonism with the PGE2 system has traditionally focused on the inhibition of PGE2 production using nonselective or COX2-selective blockers, the newly available agonists and antagonists of the individual PGE2 receptors, as well as the new understanding of the key role of 15-PGDH in controlling PGE2 degradation in the tissues, allow for new therapeutic approaches to control the PGE2-mediated immunopathology. Additionally, amplification of PGE2 production and responsiveness to this factor and antagonizing its rate of decay may be used to treat autoimmune phenomena. Recent advances and prospective identification of key mechanisms regulating the functions of 15-PGDH and individual PGE2 receptors in different organs and cell types (and the balance between their different signaling pathways) are likely to result in new therapeutic strategies with higher potency and improved selectivity of action.
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References
31. Judson, B. L., A. Miyaki, V. D. Kekatpure, B. Du, P. Gilleaudeau, M. Sullivan-
BRIEF REVIEWS: REGULATION OF IMMUNE RESPONSES BY PGE2


