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Regulation of Immune Responses by Prostaglandin E_2

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Abstract

Prostaglandin E_2 (PGE_2), an essential homeostatic factor, is also a key mediator of immunopathology in chronic infections and cancer. The impact of PGE_2 reflects the balance between its COX2-regulated synthesis and 15-PGDH-driven degradation, and the pattern of expression of PGE_2 receptors. PGE_2 enhances its own production, but suppresses acute-inflammatory mediators, resulting in its predominance at late/chronic stages of immunity. PGE_2 supports activation of dendritic cells, but suppresses their ability to attract naïve, memory- and effector T cells. PGE_2 selectively suppresses effector functions of macrophages and neutrophils and the Th1-, CTL- and NK cell-mediated type-1 immunity, but promotes Th2, Th17, and T_{reg} responses. PGE_2 modulates chemokine production, inhibiting the attraction of pro-inflammatory cells, while enhancing local accumulation of T_{reg} cells and myeloid-derived suppressor cells. Targeting the production, degradation and responsiveness to PGE_2, provides tools to modulate the patterns of immunity in a wide range of diseases, from autoimmunity to cancer.

Keywords

PGE_2; prostaglandins; cytokines; chemokines; interferons; macrophages; dendritic cells; T cells; CTLs; Tregs; myeloid-derived suppressor cells; Treg cells; inflammation; cancer; immunopathology; immunotherapy

Introduction

Prostaglandins (PGs) are small-molecule derivatives of arachidonic acid, produced by cyclooxygenases (constitutively active COX1 and inducible COX2) and prostaglandin synthases (1), with a relatively minor contribution of the isoprostane pathway (2). Local levels of prostaglandin E_2 (PGE_2), the main product of cyclooxygenases in myeloid and stromal cells, are regulated by the local balance between the COX2-driven synthesis and 15-PGDH-mediated degradation of PGE_2(1, 3). The receptors for PGE_2 (EP1-EP4) are present on multiple cell types (4), reflecting the ubiquitous functions of PGE_2, 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 current review focuses on the role of PGE_2 and its receptors in the regulation of different stages of immune responses and different effector mechanisms of immunity.

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Long-known and yet unknown: Paradoxes of PGE_2 function

PGE_2 (m. w. of 352), 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). While 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 pro-inflammatory cytokines allows it to limit nonspecific inflammation, promoting the immune suppression associated with chronic inflammation and cancer (1, 14). While PGE_2 can promote the activation, maturation and migration of dendritic cells (DC; see below), the central cells during the development of antigen-specific immunity, it has been widely demonstrated to suppress both innate and antigen-specific immunity at multiple molecular and cellular levels (1, 15), earning PGE_2 the paradoxical status of a pro-inflammatory factor with immunosuppressive activity.

While PGE_2 inhibitors, such as steroids (inhibitors of AA release) and non-steroid anti-inflammatory drugs (NSAIDs; blockers of COX 1/2 or COX2 function) represent some of the most-common and effective pharmaceutical agents, realizing the full potential of PGE_2 targeting in the treatment of chronic infections, inflammation and cancer, is restricted by the complex pattern of PGE_2-mediated immunoregulation and our still-incomplete understanding of the key mechanisms and targets of PGE_2-mediated immunoregulation.

Regulation of PGE_2 Production, Degradation, and Responsiveness to PGE_2

Regulation of PGE_2 production

PGE_2 can be produced by all cell types of the body, with epithelia, fibroblasts, and infiltrating inflammatory cells representing the major sources of PGE_2 in the course of an immune response. The process of PGE_2 synthesis involves phospholipase A2 (PLA2) family members, that mobilize arachidonic acid from cellular membranes (16), cyclooxygenases (constitutively-active COX1 and inducible COX2) that convert arachidonic acid into prostaglandin H_2 (PGH_2), and prostaglandin E synthase (PGES), needed for the final formulation of PGE_2 (17) (Fig 1).While the rate of PGE_2 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 PGE_2 synthesis is controlled by local expression and activity of COX2.

Regulation of PGE_2 degradation

PGE_2 is relatively stable *in vitro* although its decay is accelerated by albumin (18). In contrast, PGE_2 has a very rapid turnover rate *in vivo* and is rapidly eliminated from tissues and circulation (19). The rate of PGE_2 degradation *in vivo* in individual tissues is controlled by 15-hydroxyprostaglandin dehydrogenase (15-PGDH) (3). The suppression of 15-PGDH activity is observed in many forms of cancer (20–24) or UV-irradiated skin (25), the PGE_2-rich and immunosuppressive environments. Apoptotic cancer cells can modulate the prostanoid production by enhancing the macrophage expression of COX2 and microsomal prostaglandin E synthase-1 (mPGES1), 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 PGE_2 synthesis, also the rate of PGE_2 decay may contribute to immune pathology and constitute a potential target for immunomodulation (21).

PGE_2 receptors and signaling pathways: Regulation of PGE_2 responsiveness

The heterogeneous effects of PGE_2 are reflected by the existence of four different PGE_2 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 8 forms in humans and 3 forms in mice (Reviewed in (4)).

EP3 and EP4 represent high affinity receptors, while EP1 and EP2 require significantly higher concentrations of PGE_2 for effective signaling. The signaling through the two G_s-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 PGE_2 (Fig 1). Despite their similar nominal functions, the signaling by EP2 and EP4 is triggered by different concentrations of PGE_2 and differs in duration. EP4 signaling is rapidly desensitized following its PGE_2 interaction, while EP2 is resistant to ligand-induced desensitization, implicating its ability to mediate PGE_2 functions over prolonged periods of time, and at later time-points of inflammation (30). While EP2 is believed 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 G_s and lack cAMP-activating functions. Most of the splice variants of EP3 represent G_i-coupled PGE_2 receptors inhibit adenylate cyclase (33), although at least some are G_s-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 PGE_2 receptors system allow for adaptable patterns of responses of different cell types at different stages of immune responses. Additional flexibility of the PGE_2 receptor system results from different sensitivity of the individual receptors to regulation by additional factors. The expression of EP2 and the resulting responsiveness to PGE_2 can be suppressed by hyper-methylation, as observed in patients with idiopathic lung fibrosis (34). These observations raise the possibility that, in addition to the regulation of PGE_2 production and its degradation, the regulation of PGE_2 responsiveness at the level of expression of individual PGE_2 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, allow for differential suppression of different aspects of PGE_2 activity (reviewed in (4)).

PGE_2 and the Activity of Innate Immune Cells

While PGE_2 can promote the tissue influx of neutrophils (10) and macrophages (11) and mast cells (13), it differentially affects the functions of different innate effector cells.

NK cells

PGE_2 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 IFNγ, abrogating NK cell “helper” function in s the DC-mediated induction of Th1 and CTL responses (39). PGE_2-mediated suppression of NK cell function during surgery has been shown to facilitate the establishment of metastases in experimental animals (40).

Granulocytes

PGE_2 has been shown to inhibit granulocyte functions (41), contributing to the defective innate host defense in patients after bone marrow transplantation or with cancer, and other conditions associated with overproduction of PGE_2 (42).

Macrophages

Acting in the EP2-dependent (43) and PTEN-dependent (44) manner, PGE_2 limits the phagocytosis by alveolar macrophages (43) and their pathogen-killing function (45). At least a part of the inhibitory impact of PGE_2 on the alveolar macrophage function is mediated by via the induction of IRAK-M which blocks the scavenger receptor mediated phagocytosis and the TLR-dependent activation of TNFα (46).

Mast Cells

PGE_2 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 pro-angiogenic and immunosuppressive VEGF and MCP-1 by mast cells (11, 49), which contributes to the overall disease-promoting activity of PGE_2 in cancer.

PGE_2 and the Induction of Antigen-Specific Immune Responses

PGE_2 affects several key phenomena relevant to the induction of immune responses. In addition to its multi-faceted regulation of DC functions during the priming of naïve T cells (*reviewed directly below*), it also directly inhibits T cell production of IL-2 (50) and IL-2 responsiveness (51), suppressing the activation and expansion of antigen-specific T cells.

DC development

PGE_2 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). While the ability of PGE_2 to suppress the differentiation of functionally-competent Th1-inducing DCs has been long recognized (52), it was recently shown that the resulting "PGE_2-DC" represent myeloid-derived suppressor cells (MDSC), 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, PGE_2 has a much more complex effect on the activation of fully-developed (although functionally immature) DCs. PGE_2 has been shown to support the induction of fully-mature DCs capable of homing to lymph nodes and highly-effective in priming naïve T cells. The addition of PGE_2 to the cocktail of proinflammatory cytokines involving IL-1β and TNFα, accelerates DC maturation and elevates their expression of costimulatory molecules (59–61).

PGE_2 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 proteinase (MMP)-9 (65), suggested the role for PGE_2 in DC migration to the lymph nodes. However, recent data demonstrate that the CCR7-enhancing effects of PGE_2 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 which can limit the *in vivo* migratory

potential of the PGE_2-matured DCs is the ability of PGE_2 to induce tissue inhibitor of proteinases (TIMP)-1 (67).

While PGE_2-matured DCs indeed migrate to the lymph nodes faster than 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 PGE_2 (66, 69). In line with the notion that DC maturation and effective lymph node migration can occur in the absence of PGE_2, a recent mouse study in PGES-1-deficient animals showed an abrogation of PGE_2 synthesis by DCs and their altered cytokine profile, but did not reveal any impact on their maturation status or migratory function (70). These data suggest that while PGE_2 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 PGE_2-matured DCs translates into their enhanced ability to activate naïve T cells, when compared with immature DCs (59–61). While PGE_2 also enhances the DC production of several suppressive factors, such as IL-10 (52), trombospondin (TSP-1) (71), and IDO (72), its most frequently observed net effect is during DC maturation is the ability of DC to promote T cell expansion (59–61).

However, DCs matured in the presence of PGE_2 develop a distinct “exhausted” phenotype, manifested by their impaired ability (compared to 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 pro-inflammatory cytokines, including the bioactive IL-12p70 (61) (*see below*). In accordance with the notion that exogenous PGE_2 may have a net inhibitory effect on the functional activity of maturing DCs, it was shown that the replacement of PGE_2 by other DC maturation-driving factors can enhance the immunogenic and anti-tumor effectiveness of DC vaccines (75, 76).

Regulation of the attraction of naïve T cells, DC-T cell interaction and T cell activation

CCR7 ligands (CCL19/MIP3β/ELC & CCL21/6C-kine/SLC) and CXCR4 ligand CXCL12/SDF-1 represent two groups of chemokines needed for effective T cell entry into lymph nodes (77). While the role of PGE_2 in the local regulation of these two chemokines within the lymph nodes remains unclear, PGE_2 has been recently shown to suppress the ability of DCs to produce CCL19 (the only CCR7 ligand produced by human monocyte-derived DC), and to block the ability of DCs to attract naïve T cells (66). On the other hand, PGE_2 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 PGE_2 on the CCR7- versus CXCR4-driven events governing T cell accumulation in the lymph nodes and their interaction with different types of antigen-presenting cells.

The suppressive effects of PGE_2 on the activation and expansion of naive T cells also include the direct inhibitory effects of PGE_2 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 PGE_2 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).

PGE_2 and the Regulation of the Character of the Immune Response

PGE_2 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 PGE_2 show profound modulatory effects shifting the pattern of $CD4^+$ T cell responses from the aggressive Th1 cells (promoting the inflammatory/cytotoxic form of immunity) towards Th2 and Th17 cells that mediate less tissue-destructive forms of immunity.

Balance between Th1 and Th2 responses

The original evidence that PGE_2 is involved in regulating the balance between different forms of T helper cell responses came from *in vitro* studies showing its ability to selectively inhibit the production of the Th1 cytokine IFNγ, 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 PGE_2 also relies on its ability to suppress the production of IL-12 (84) in monocytes (84) and dendritic cells (52, 61). Additional mechanisms of the IL-12-antagonistic activity of PGE_2 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 PGE_2 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, over-production of PGE_2 is observed in multiple Th2-associated diseases, most notably atopic dermatitis and asthma (89).

Th17 differentiation

EP2 and EP4-dependent signals from PGE_2 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 PGE_2 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- and allo-antigens is highly sensitive to PGE_2 and cAMP elevation (95, 96). PGE_2-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, PGE_2 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, PGE_2 has also been shown to suppress the ability of maturing DCs to develop CTL-inducing function, by suppressing the ability of maturing DC to secrete IL-12 during the subsequent interaction with naïve $CD8^+$ T cells (101).

Interestingly, CTLs can produce PGE_2 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 remains unclear.

B cells

PGE_2 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 PGE_2 to promote IgE production, the phenomenon contributing to atopic diseases (104), jointly with the ability of PGE_2 to support the induction, attraction and degranulation of mast cells (11–13, 47, 48).

PGE_2 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 PGE_2, enhancing the development and activity of suppressive types of immune cells.

Treg activity

PGE_2 has been shown to promote the development of Treg cells, in human and in mouse (105–108). COX2 and PGE_2 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 naïve precursors, PGE_2 also promotes the interaction of DCs with Tregs (109), suggesting that it may also promote the expansion of pre-existing Treg cells, as observed in cancer patients vaccinated with PGE_2-matured DCs (110). Interestingly, PGE_2 is also involved in mediating the suppressive activity of Tregs (111).

Suppressive macrophages and myeloid-derived suppressor cells: Positive and negative feedback involving PGE_2

PGE_2 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 PGE_2-mediated signals, MDSCs express high levels of COX2 and are a major source of PGE_2 secretion in human cancer (58, 117). The resulting positive feedback loop between PGE_2 and COX2 is essential for the functional stability of MDSCs, their ability to produce the additional MDSC-associated suppressive mediators and to suppress $CD8^+$ T cell function (58). Since PGE_2 participates in the induction of HIF-1α (118), the HIF-1α-mediated development of MDSC (119) is likely to represent a central downstream signaling event in the PGE_2-mediated impact on MDSC development.

PGE_2 has been also shown to be critical for the development of the apoptotic body-induced suppressor function in macrophages, promoting the growth of intracellular parasites (120). Interestingly, while PGE_2 is a known inducer of another suppressive factor, IL-10, in tissue macrophages (112, 113). IL-10 acts as a controller of PGE_2 secretion, resulting in the paradoxical role of IL-10 in the reversal of the PGE_2-mediated macrophage dysfunction, facilitating effective control of the infection with pathogenic strain of E. Coli (121).

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

In addition to its opposite impact on the development and function of the effector versus suppressive cells, PGE_2 also differentially regulates their influx to affected tissues. PGE_2 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 PGE_2 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 PGE_2-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 pro-inflammatory-type macrophages, but also the $CCR5^+$ and $CXCR3^+$ type-1 effector cells (CTLs, NK and Th1 cells) (74, 109, 123, 124). At the same time, PGE_2 enhances the production of Th2-attracting chemokines (124),

promotes the production of CCL22/MDC and the resulting attraction of Tregs (109), and the CXCL12/SDF1-driven accumulation of MDSCs (125).

In addition to the differential regulation of the effector- and regulatory T cell/MDSC-attracting chemokines, PGE_2 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), while it induces and stabilizes the expression of CXCR4 on cancer-associated MDSCs (125). In addition, PGE_2 is known to suppress the ability of gut-associated DCs to produce retinoic acid (RA), needed for the ability of DCs to induce the CCR9 expression and gut-homing function in responding T cells (126).

PGE_2 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, PGE_2 supports acute local inflammation and phagocyte-mediated immunity at the site of pathogen's entry, but 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 PGE_2-mediated suppression of type-1 immunity by PGE_2 shifts the pattern of immune reactivity toward less aggressive form of immunity mediated by Th2 and Th17 cell as well as B cells, and enhancement of the Treg- and MDSC-mediated suppressive events.

While PGE_2 can accelerate DC maturation and migratory function, the PGE_2-dependent suppression of the naïve T cell-attracting CCL19 in DCs (66) and its suppression of IL-2- and IL-12-production and functions, results in the net inhibitory activity of PGE_2 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, PGE_2 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 towards Th2, Th17 and Treg activity, helping to contain the damage to own tissues during prolonged immune responses.

While this ability of PGE_2 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 PGE_2 production and/or reduced degradation of PGE_2 for the establishment of immunosuppression and disease progression. While the therapeutic antagonism with the PGE_2 system has traditionally focused on the inhibition of PGE_2 production using non-selective or COX2-selective blockers, the newly available agonists and antagonists of the individual PGE_2 receptors, and the new understanding of the key role of 15-PGDH in controlling PGE_2 degradation in the tissues, allow for new therapeutic approaches to control the PGE_2-mediated immunopathology. On the other hand, amplification of PGE_2 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 PGE_2 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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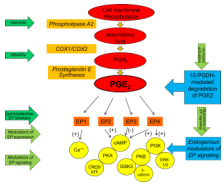

Figure 1. Regulation of PGE_2 synthesis, degradation, and responsiveness to PGE_2

PGE_2 synthesis is initiated by the (glucocorticosteroids sensitive) phospholipase A2-driven release of arachidonic acid (AA) from cell membranes. AA becomes the substrate for COX1 (constitutive activity) and COX2 (inducible) that convert AA to prostaglandin H2 (process that can be suppressed by NSAIDs), which is then converted to biologically-active PGE_2 by PGE synthases. PGE_2 signals via four known receptors (EP1-EP4), with the cAMP/PKA/CREB signaling pathway responsible for major suppressive and regulatory functions of PGE_2. Local PGE_2 degradation is regulated by 15-PGDH. Dark-green arrows: Currently-applied inhibitory drugs; Light green arrows: Potential targets for prospective drugs; (+) activating (−) inhibitory.

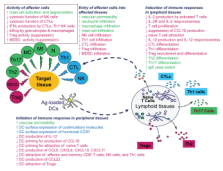

Figure 2. Regulation of the immune response by PGE_2

PGE_2 supports local acute inflammation and phagocyte-mediated immunity at the site of pathogen's entry, while selectively suppressing the CTL-, Th1- and NK cell-mediated type-1 (cytotoxic) forms of immunity, at the stage of their induction in lymphoid tissues and by differentially regulating the influx and activity of the effector- versus regulatory cells into affected tissues. ↑ Enhancement; ↓Suppression; Blue: Relevant to immunity against intracellular pathogens and cancer; Green: Relevant to immunity against extracellular pathogens; Purple: Relevant to immune suppression. MC: mast cells; Mf: macrophages; N: neutrophils.