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Review Article

Roles of prostaglandins in immunosuppression

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ABSTRACT

Prostaglandins (PGs) play a crucial and multifaceted role in various physiological processes such as intercellular signaling, inflammation regulation, neurotransmission, vasodilation, vasoconstriction, and reproductive functions. The diversity and biological significance of these effects are contingent upon the specific types or subtypes of PGs, with each PG playing a crucial role in distinct physiological and pathological processes. Particularly within the immune system, PGs are essential in modulating the function of immune cells and the magnitude and orientation of immune responses. Hence, a comprehensive comprehension of the functions PG signaling pathways in immunosuppressive regulation holds substantial clinical relevance for disease prevention and treatment strategies. The manuscript provides a review of recent developments in PG signaling in immunosuppressive regulation. Furthermore, the potential clinical applications of PGs in immunosuppression are also discussed. While research into the immunosuppressive effects of PGs required further exploration, targeted therapies against their immunosuppressive pathways might open new avenues for disease prevention and treatment.

1. Introduction

Prostaglandins (PGs) were first discovered and described by von Euler in 1935 as bioactive substances found in human prostate and seminal vesicle secretions, exhibiting significant vasodilatory and smooth muscle-stimulating effects [1]. PGs are a class of active lipid compounds, including prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin D_2 (PGD_2), prostaglandin I_2 (PGI_2), and thromboxane A_2 (TxA_2), which are biosynthesized from arachidonic acid (AA) (a 20-carbon polyunsaturated fatty acid) [2]. PG signaling regulates a variety of physiological and pathological processes, covering aspects such as body temperature, cardiovascular stability, reproduction, and inflammation [3]. (See Figs. 1–6.)

The immune system is composed of the innate immune system and the adaptive immune system [4]. The primary function of the immune system is to protect the host from the invasion of pathogens [5]. The immune system is a complex network of various organs, immune cells, and immunologically active substances (such as antibodies, lysozymes, complement factors, immunoglobulins, cytokines, etc.) distributed throughout the body, collaborating to perform immune surveillance, defense, and regulatory functions [6]. In this process, the transfer of metabolites and biological information between cells is crucial for the coordination and regulation of functions, with immune cells actively communicating through direct contact or the release of soluble cytokines [7,8].

PGs are essential bioactive lipids that play a crucial role in the regulation of inflammatory responses and immune system functions. Their ability to modulate the function and phenotype of T cells, thereby exerting both pro-inflammatory and anti-inflammatory effects, highlights the intricate mechanisms through which they operate, including their impact on immune cell activation and immune response regulation [9–12]. The immune system plays a vital role in maintaining internal equilibrium and protecting against external pathogens [13]. Nevertheless, dysregulation or hyperactivity of the immune response can result in autoimmune disorders, allergic responses, rejection of transplanted organs, and other complications [14]. Consequently, investigating the role of PGs in immunosuppression is essential for enhancing our comprehension of immune modulation and for the advancement of novel

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immunotherapeutic approaches [15,16].

The objective of this review is to comprehensively examine the diverse functions of PGs in immunosuppression, including their impact on immune cell regulation, maintenance of immune tolerance, treatment of autoimmune disorders, and potential utility in tumor immunotherapy. By conducting a thorough analysis of PGs, our aim is to enhance comprehension of their significance in immunosuppression and offer robust recommendations for future investigations, facilitating the development of more efficacious immunoregulatory approaches to enhance human health. This review offers a thorough examination with the aim of encouraging further detailed discussions and pioneering research.

2. Biochemical features

PGs are bioactive lipids that contribute to normal development, tissue homeostasis, inflammation, and cancer progression [17,18]. PGs synthesis is mediated through a cascade of three sequential enzymatic processes. Initially, AA is liberated from membrane phospholipids by the enzyme phospholipase A_2 (PLA_2) in response to diverse physiological and pathological stimuli. Following this, prostaglandin H synthase (PGHS), commonly referred to as cyclooxygenase (COX), catalyzes the conversion of the liberated AA into the intermediate prostaglandin metabolites prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2) [19–21]. Finally, PGH_2 is metabolized into five principal prostaglandins—PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TxA_2—by specific enzymes: prostaglandin D synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), prostaglandin I synthase (PGIS), and thromboxane A synthase (TxAS), each of which specifically catalyzes the transformation to regulate the type and function of the resulting PG [22–24]. After synthesis, PGs are rapidly transported to the extracellular microenvironment via prostaglandin transport protein (PGT), which belongs to the 12-transmembrane domain anion transport polypeptide superfamily [17,25,26]. This step is crucial for the regulation of PG levels and their signaling functions [27].

Physiological homeostasis depends on PG production and degradation remaining in balance [28]. PGs are primarily metabolized by the initial oxidation of the 15(*S*)-hydroxyl group catalyzed by 15-hydroxyprostaglandin dehydrogenases (15-PGDHs). 15-PGDHs are regarded as the principal enzymes responsible for the biological deactivation of PGs and related eicosanoids. This enzyme group includes two distinct types: Type I, which is NAD^+-dependent, and Type II, which is NADP-dependent. Type I is regarded as the principal enzyme responsible for regulating the biological functions of PGs and related eicosanoids [29,30]. Overall, the regulation of PG production and clearance is mediated by a complex interplay of enzymes. These enzymes govern the synthesis of PGs from arachidonic acid, their transport to target sites, and their subsequent degradation. This intricate regulatory mechanism ensures precise control over the physiological and pathological effects of PGs.

PGs are lipid mediators derived from arachidonic acid that mediate a variety of biological functions through their specific G-protein-coupled receptors (GPCRs) [31]. The PGD_2 receptors are comprised of two G protein-coupled receptors, the D-type prostanoid receptor (DP or DP1),

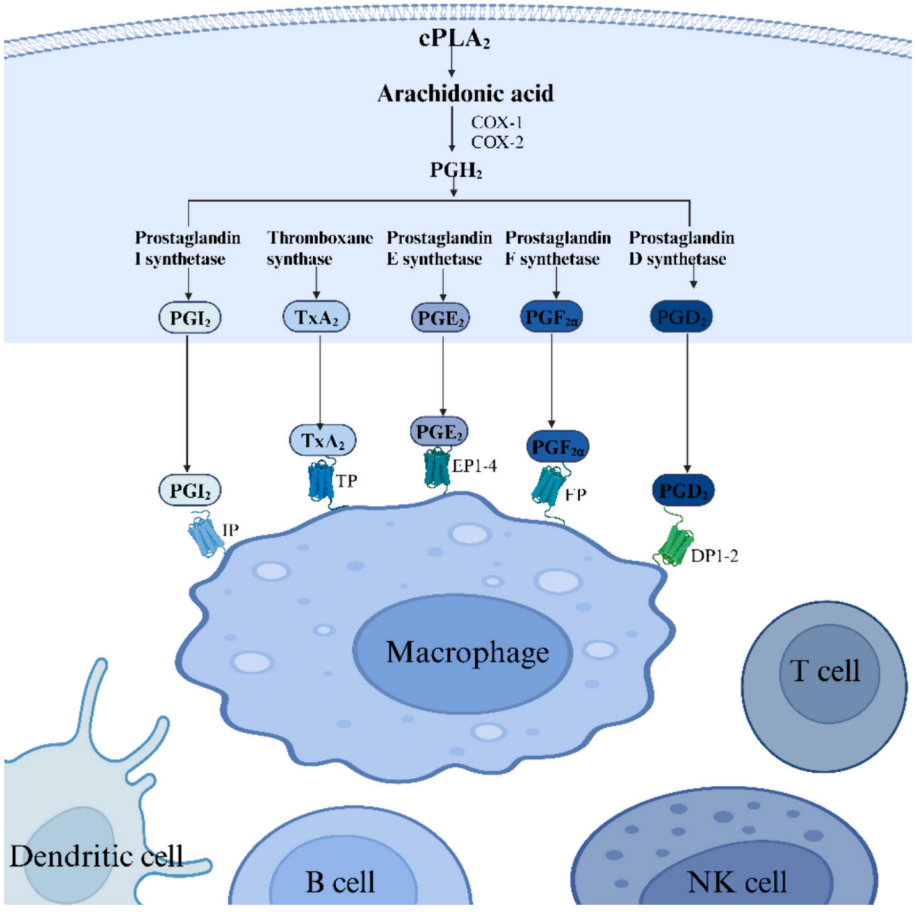

Fig. 1. The biosynthesis, transport, and functional activation of PGs. Beginning with AA, released by PLA_2, AA is then converted into PGH_2 by the action of cyclooxygenase enzymes (COX-1 and COX-2). PGH_2 is subsequently metabolized to the five primary PGs (PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, TxA_2) and is expelled from the cell through PGT. These PGs execute their biological functions by interacting with specific GPCR, thereby initiating a multitude of signaling pathways that regulate immune functions and various other physiological processes.

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and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2 or DP2) [32,33]. PGE_2 has four receptors, prostaglandin E receptor 1–4 (EP1–4) [34].There are also prostaglandin F receptors (FP), prostacyclin receptors (IP), and thromboxane A_2 receptors (TxA_2R), classified according to their specific ligands [35–37]. The binding of PGs to specific receptors leads to the activation of these receptors and the subsequent dissociation of the heterotrimeric G protein complex [38]. This activation initiates a cascade of downstream signaling pathways that are pivotal in a multitude of (patho)physiological processes. These pathways regulate immune functions, including the differentiation, activation, proliferation, migration, and cytokine secretion of immune cells [27,39,40]. The effects of these pathways on immune functions can be either synergistic or antagonistic, underscoring the complex interplay between PGs and the immune system.

3. Prostaglandins and immune cells

Over a century ago, researchers established the immune system as a pivotal defense against infectious diseases, a revelation that continues to significantly shape our comprehension of immunology and its portrayal in academic texts [41–43]. While traditionally regarded as a defense mechanism, this perspective only partially encompasses the immune system's role in sustaining tissue homeostasis and systemic integrity [44]. Immunosuppressive cells play a crucial role in mitigating overactivation of the immune system and preserving its homeostasis [45]. The tumor microenvironment not only supports tumor growth, progression, and dissemination through angiogenesis but also allows tumor cells to evade host immune surveillance. This tumor-associated immunosuppression is characterized by enhanced immunosuppressive cells, defective antigen-presenting cell function, a shift from T-helper 1 (Th1) to T-helper 2 (Th2) and T-helper 17 (Th17) immune responses, and impaired cytotoxic activity of $CD8^+$ T and natural killer (NK) cells [46–48]. Immune cells infiltrating the tumor, activated stromal cells within the tumor microenvironment (TME), and the tumor cells themselves generate and release various functional mediators, including PGs, believed to instigate inflammation and contribute to immunosuppression [49,50].

4. PGE_2

PGE_2 plays an important role in chronic and acute inflammatory responses [51,52]. PGE_2 is produced by a diversity of cell types including epithelial cells, fibroblasts, and infiltrating inflammatory cells. It plays a pivotal role in mediating numerous physiological and pathological responses, encompassing vascular homeostasis, inflammatory processes, nociception, and renal functionality [53–55]. The production of PGE_2 involves specific synthases, and to date, three types have been identified: microsomal PGE synthase-1 (mPGES-1), microsomal PGE synthase-2 (mPGES-2), and cytosolic PGE synthase (cPGES). A major function of mPGES-1 is to increase production of PGE_2, especially under conditions of inflammation. However, mPGES-2 and cPGES expression are constitutive rather than regulated [56]. As a result of degradation by 15-PGDH, PGE_2 has a faster turnover rate in vivo. [57]. PGE_2 exerts its effects through four GPCRs, EP1, EP2, EP3, and EP4 [58]. PGE_2 signaling is dependent on the expression of each EP receptor and the strength of each EP signal [59]. Calcium mobilization by PGE_2 is mediated by EP1 (couple to Gq) and EP3 (couple to Gi). EP2 and EP4 can increase intracellular cyclic AMP (cAMP) and phosphorylation of protein kinase A (PKA) in response to PGE_2, which is closely related to cancer development and suppression of anti-tumor immune responses [60,61].

Natural killer (NK) cells are cytotoxic innate lymphocytes that are important for killing virus-infected cells and tumor cells [62,63]. Specifically, PGE_2 impairs NK cell function through several mechanisms: (i) downregulation of NK cell receptors via the cAMP/PKA pathway; (ii) inhibition of NK cell production of interferon-γ (IFN-γ) through the EP2 receptor; and (iii) suppression of NK cell proliferation and induction of apoptosis [48]. Research has demonstrated that tumor cell-secreted

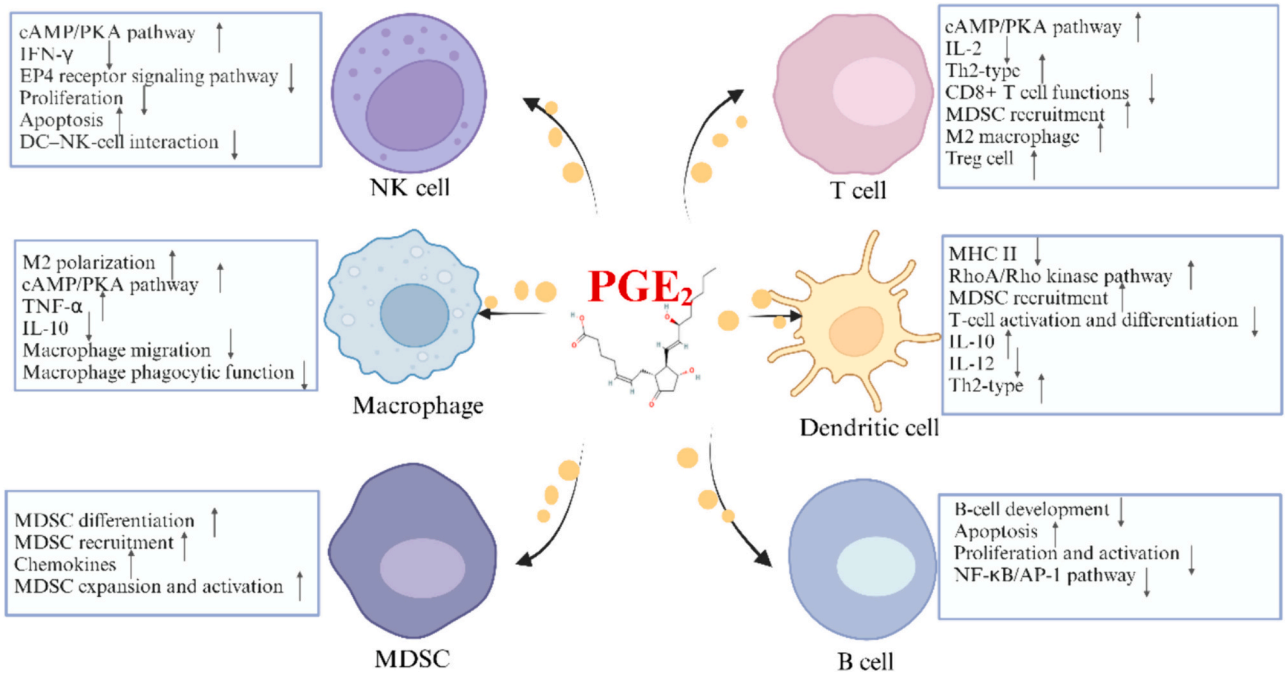

Fig. 2. The mechanism of PGE_2-mediated immunosuppression. PGE_2 exerts its immunosuppressive effects by influencing a variety of immune cells, including NK cells, T cells, macrophages, DCs, MDSCs, and B cells. It mediates these effects through downregulating NK cell receptors, inhibiting the production of IFN-γ, hindering NK cell proliferation and apoptosis, suppressing T cell activation and proliferation, promoting macrophage polarization towards an M2 phenotype, reducing DCs maturity, enhancing the immunosuppressive function of MDSCs, and both directly and indirectly inhibiting the development and activation of B cells. These actions are achieved through impacts on cell surface receptor expression, cytokine production, cell signaling pathways, and intercellular interactions, highlighting the complexity and diversity of PGE_2 in regulating immune responses.

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PGE_2 hampers NK cells activation and IFN-γ production through both EP2 and EP4 receptors, consequently diminishing NK cells cytotoxicity and their capacity to recruit subsequent adaptive immune responses [64]. PGE_2 exerts its effects not only by directly inhibiting NK cells activation and cytotoxic functions but also by indirectly hampering NK-dendritic cell (DC) interactions through the modulation of chemokine and cytokine secretion by mature DCs. This results in a decreased NK cell-mediated Th1 polarization and tumor cell elimination [65]. Furthermore, a recently identified function of NK cells is their ability to engage in reciprocal communication with T cells and DCs. The secretion of cytokines and chemokines, along with the regulation of T cell polarization, migration, and the activation of DCs, are intricately regulated by activated NK cells. The interaction between NK cells and activated DCs, crucial for NK cells function, involves both membrane-bound molecules and soluble mediators, such as cytokines and PGs. This bidirectional communication is often compromised by PGE_2 [66].

Within the immune system, the influence of PGE_2 on T cell function has been established, serving as a pivotal mechanism in immunosuppression [67]. Initially, PGE_2 was found to impede T cell receptor (TCR) signaling and T cell activation by elevating intracellular cAMP levels, thereby activating PKA and facilitating the inhibition of Lck by Csk [68]. Moreover, PGE_2 was shown to suppress the transcription of the IL-2 gene during T cell activation, leading to diminished IL-2 secretion and, consequently, reduced T cell proliferation [69]. Research has indicated that PGE_2 significantly reduces T cell proliferation in a dose-dependent manner and encourages the differentiation of $CD4^+$ T cells towards a Th2 phenotype by enhancing the IL-4/IFN-γ ratio in $CD4^+$ T cell cultures. This effect is primarily mediated through the overexpression of indoleamine 2,3-dioxygenase (IDO), thereby promoting the formation and proliferation of regulatory T cells (Tregs) [70]. Additionally, PGE_2 signaling was found to disrupt T cell receptor signaling in $CD4^+$ T cells via the EP2 receptor and compromise $CD8^+$ T cell function by inducing a tolerant phenotype in DCs, thus inhibiting inflammatory T cell responses [71,72]. In the tumor microenvironment, PGE_2 facilitates inflammation and immunosuppression via the EP2/EP4 signaling pathways, by activating the regulatory DC-Treg axis, which leads to the recruitment and activation of Tregs, thereby supporting tumor progression [73]. PGE_2 enables tumor cells to evade T cell-mediated cytotoxicity and induces the recruitment of myeloid-derived suppressor cells (MDSCs) and the polarization of M2-type macrophages, thereby promoting lung metastasis through both endogenous and exogenous pathways [74]. In vitro studies have demonstrated that PGE_2 inhibits the survival, Type I interferon production, and cytotoxic activity of $CD8^+$ cytotoxic T lymphocytes (CTLs) [75]. Lastly, PGE_2 exerts immunosuppressive effects on peripheral Tregs by inhibiting their proliferation through the blockade of the IL-2 pathway and preventing Th1 induction, thereby obstructing the initiation of inflammation [76].

PGE_2 exerts a complex and pivotal role in modulating the immune responses of macrophages [77,78]. Due to their significant plasticity, macrophages can respond to various stimuli (such as IFN-γ, LPS, IL-4) and polarize into either M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes in inflamed tissues or cancer environments [79,80]. It has been revealed that PGE_2 facilitates macrophage polarization towards the M2 phenotype by activating hypoxia-inducible factor 1 alpha (HIF-1α) and the EP2/EP4 receptors. This process not only enhances their migratory capacity and pro-tumorigenic actions but also amplifies their suppressive effects on T cell function, thereby playing an immunosuppressive role in the tumor microenvironment [81]. Moreover, PGE_2 regulates the expression of $cPLA_2$ and COX-2 through epigenetic mechanisms, thereby increasing the production of inflammatory factors while simultaneously diminishing macrophage phagocytosis and bactericidal capabilities via the EP2 receptor, leading to impaired wound healing in diabetic patients [82]. PGE_2 activates the cAMP-CREB/CRTC pathway and upregulates krüppel-like factor 4 (KLF4) expression, encouraging M2 macrophage polarization and diminishing inflammatory responses, which aids in maintaining insulin sensitivity [83]. Studies have shown that PGE_2 reduces TNF-α production and enhances IL-10 production by increasing intracellular cAMP levels and activating the EP2 and EP4 receptors, thus modulating macrophage responses to inflammation [84]. Endogenous PGE_2 was thought to suppress the production of macrophage-derived chemokines via the EP4 receptor [85]. Furthermore, PGE_2 influenced macrophage migration to tumors, evidenced by the upregulation of CCL2, a crucial chemokine involved in macrophage recruitment to tumors [86]. PGE_2 suppressed macrophage anti-tumor immune functions by reducing 15-PGDH expression, increasing IL-10 and IL-13 secretion, suppressing CD11c and major histocompatibility complex class II (MHC II) expression, and enhancing arginase activity [87]. By activating the cAMP-PKA signaling pathway and inhibiting salt-inducible kinase 2 (SIK2) activity, PGE_2 facilitated the nuclear translocation of cAMP-regulated transcriptional co-activator 3 (CRTC3), which associated with CREB to enhance the transcription of IL-10 and other suppressive factors, rendering macrophages a regulatory phenotype [88]. The activation of the EP4 also shifted the polarization of adipose tissue macrophages towards an anti-inflammatory M2 phenotype, thus mitigating chronic inflammation [89].

Dendritic cells (DCs) play a key role in the immune system, acting as sentinels of immune surveillance by continuously monitoring changes in the immune microenvironment [90]. In peripheral tissues, PGE_2 activated DCs, enhancing their immunogenic activity. However, as these cells migrated to secondary lymphoid organs, PGE_2 began to exhibit its immunosuppressive effects, primarily by reducing the maturity of DCs and the expression of MHC II, thereby weakening their ability to activate T cells [91,92]. Furthermore, PGE_2, by activating COX-2 and EP2/EP4

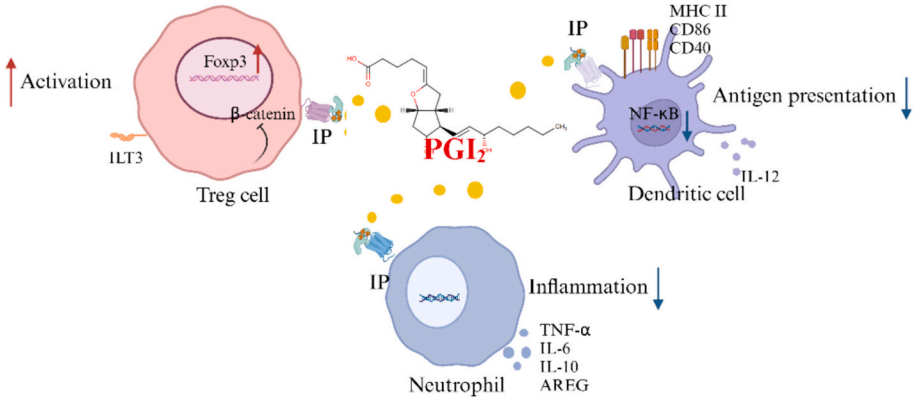

Fig. 3. The mechanism of PGI_2-mediated immunosuppression. PGI_2 interacts with the IP receptor to broadly inhibit the immune response. This includes suppressing B and T cells activity, enhancing Tregs stability, diminishing ILC2 function, modulating cytokine profiles to reduce pro-inflammatory and increase anti-inflammatory IL-10 levels, and inhibiting DCs maturation and function.

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receptors, not only impeded the differentiation of monocytes into functional dendritic cells but also induced their transformation into MDSCs with immunosuppressive functions [93]. PGE_2 increases cAMP levels and activates EP2 and EP4 receptors, thereby stimulating the RhoA-Rho-kinase pathway. This activation promotes actin contraction, which results in the loss of podosomes on the surface of DCs. Consequently, the migratory and antigen-presenting capabilities of DCs are diminished [94]. Furthermore, PGE_2 was found to increase both the expression and activity of metalloproteinase-9(MMP-9) through the EP2 and EP4 receptors, as well as the cAMP-PKA signaling pathway. This enhancement in MMP-9 activity facilitated the migration and maturation of DCs, which in turn, indirectly influenced the activation and differentiation of T cells [95]. PGE_2 induces DCs to secrete IL-10, a cytokine that regulates the production of inflammatory mediators, thereby influencing the phenotype and function of DCs and highlighting its immunoregulatory properties [96]. Concurrently, PGE_2 induces DCs to express IDO and CD25, processes that further suppress T cell proliferation and the secretion of IFN-γ and TNF-α by decreasing tryptophan concentration and inhibiting the action of IL-2 [97]. By promoting the production of IL-10, PGE_2 inhibited the secretion of IL-12, reducing the antigen-presenting function and T cell activation capacity of DCs [98], and regulated the maturation and function of DCs via the COX-2 pathway, promoting Th2 cell differentiation and inhibiting Th1 cell immune responses [99].

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells that accumulate in cancer and play a crucial role in maintaining the immunosuppressive microenvironment [100]. Sinha et al. were the first to clarify the key role of PGE_2 in MDSCs, demonstrating how PGE_2 controls the differentiation of MDSCs in preclinical models of breast cancer. Their study indicated that PGE_2 could enhance the levels of suppressive $Gr1^+CD11b^+$ cells by threefold in vitro, thereby supporting the hypothesis that PGE_2 is involved in the differentiation process from bone marrow progenitor cells to MDSCs [101]. Existing research has shown that PGE_2 plays a key role in the recruitment of MDSCs to tumor sites. The CXCR4-CXCL12 axis is widely considered a critical pathway for the recruitment of MDSCs to tumors [102]. Obermajer et al. identified a significant association between the expression levels of COX-2 and CXCL12 and the production of PGE_2 in ovarian cancer. Their results demonstrated that COX-2 inhibitors suppressed CXCL12 secretion in ovarian cancer ascites, while PGE_2 promoted the synthesis of CXCL12 in the ovarian cancer environment and the upregulation of CXCR4 on MDSCs precursors. This mechanism facilitates the recruitment and retention of MDSCs in the tumor microenvironment [93]. In a murine glioma model, administration of COX-2 inhibitors resulted in decreased PGE_2 production, subsequently reducing the expression of the chemokine CCL2 responsible for attracting MDSCs to tumor sites. These findings suggest that COX-2 blockade hinders the generation and infiltration of MDSCs within tumors via a CCL2-mediated pathway [103]. PGE_2 promoted the nuclear translocation of p50 nuclear factor-κB (NF-κB) in monocytic MDSCs (M-MDSCs) via the EP2 receptor, further facilitating the binding of STAT1 to regulatory regions of IFN-γ-dependent genes such as nitric oxide synthase 2 (NOS2), triggering excessive production of NO and downregulation of TNF-α, thereby inhibiting T cell proliferation and function [104]. PGE_2 also enhanced the NF-κB/COX-2 signaling pathway in MDSCs by suppressing the expression of receptor-interacting protein

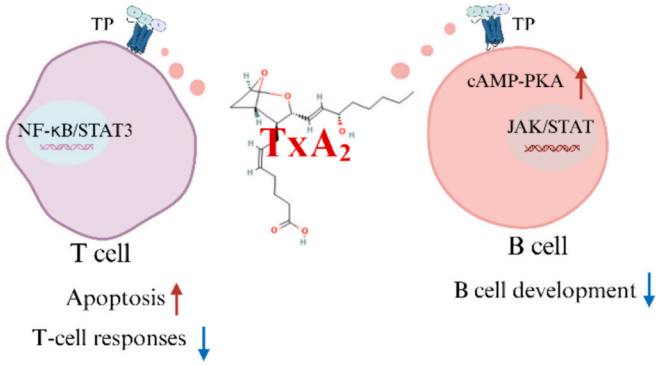

Fig. 5. The immunomodulatory mechanism of TxA_2. TxA_2 exerts multifaceted regulatory effects on the immune system through its interaction with the TP receptor. Initially, it can inhibit the interaction between low-affinity $CD4^+$ T cells and DCs, enhancing the quality of the immune response, thereby preventing autoimmune reactions. Moreover, TxA_2 regulates the adaptive immune response to exogenous antigens by inhibiting the adhesion and proliferation of T cells and DCs. It also induces apoptosis or functional incapacity in autoreactive T cells in the thymus, generating tolerance to transplants. Finally, TxA_2 promotes the early development of B cells by activating the cAMP-PKA signaling pathway and regulating the JAK/STAT5 signaling pathway.

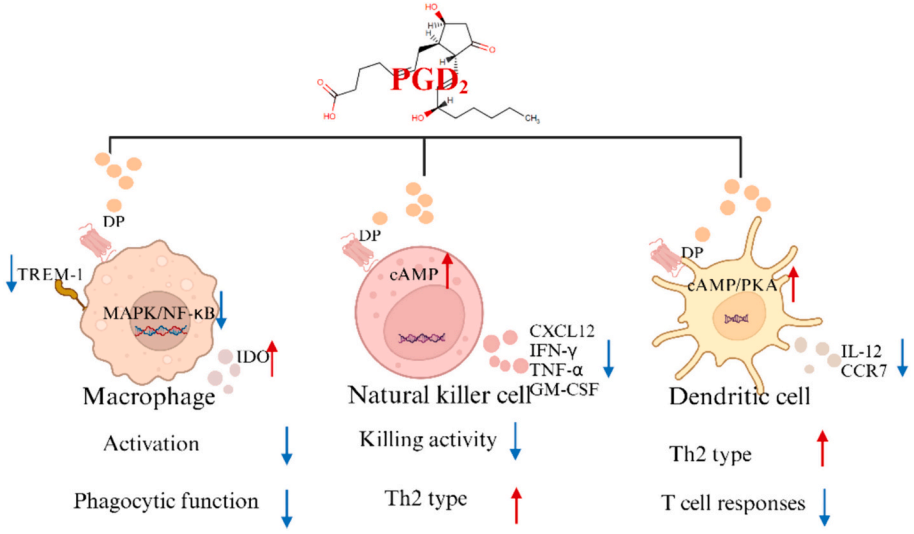

Fig. 4. The immunomodulatory mechanism of PGD_2. PGD_2 exerts complex regulatory effects on the immune system through the activation of specific receptors, such as DP1 and CRTH2. It inhibits the immune response of macrophages to pathogens by modulating the MAPK and NF-κB signaling pathways, as well as the secretion of cytokines and chemokines. PGD_2 also directly inhibits the activity of NK cells, reduces IFN-γ production by iNKT cells, and regulates the function of DCs, suppressing the development of Th1 cells while promoting the differentiation of Th2 cells. Furthermore, PGD_2 influences the activation of ILC2s and the expansion of M-MDSCs, further establishing an axis of immune suppression.

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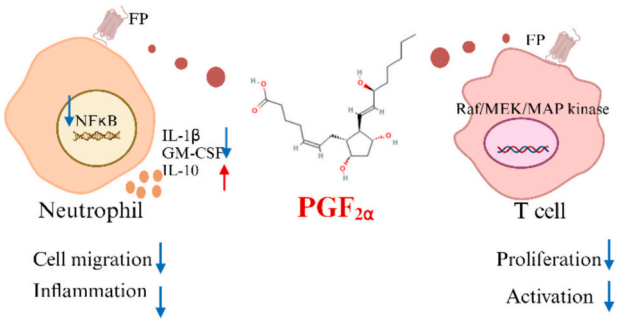

Fig. 6. The immunomodulatory mechanism of $PGF_{2\alpha}$. $PGF_{2\alpha}$ regulates the immune system by activating the FP receptor, leading to the activation of multiple signaling pathways. These include PKC and calcium signaling via the Gq protein subtype, small G protein Rho activation by G12/G13, and the Raf/MEK/MAP kinase pathway through Gi activation. These pathways collectively modulate immune functions, such as reducing IL-1β and GM-CSF production, increasing IL-10 secretion, and affecting chemokine expressions like CXCL1 and CCL2, thereby influencing the behavior of mesenchymal stem cells, neutrophils, and other immune cells.

kinase 3 (RIPK3), increasing the immunosuppressive activity of MDSCs and their pro-tumor effects [105]. As an inflammatory mediator synthesized by COX-2 catalysis, PGE_2 was able to promote the expansion and activation of MDSCs in the spleen, thereby inhibiting the proliferation, secretion, and delayed-type hypersensitivity of $CD4^+$ T cells, leading to post-sepsis immune dysfunction [106]. These studies highlighted the significant role of PGE_2 in the development and function of MDSCs, especially in creating an immunosuppressive environment that could promote tumor growth and hinder the effectiveness of immunotherapy [107].

Recent studies have elucidated the significant impact of PGE_2 in modulating B cell activity, particularly in immunosuppression. PGE_2 has been found to inhibit the development of B cells in vivo [108]. Further in vitro studies showed that PGE_2 promoted apoptosis of immature B cells induced by B cell receptor (BCR) and inhibited the proliferation [109] and activation of mature B cells activated by BCR through the EP4 receptor [110]. Specifically, PGE_2 acted on key molecules in the BCR signaling pathway through the EP4 receptor, reducing their transcriptional activity, including the inhibition of NF-κB and activator protein-1 (AP-1), while decreasing the expression of MHC molecules, thereby suppressing the proliferation and function of B cells [111]. Beyond its direct effects on B cells, PGE_2 exerts an indirect influence on these cells via its effects on mesenchymal stem cells (MSCs) and their immunoregulatory functions. MSCs exhibit substantial immunosuppressive properties, capable of inhibiting the proliferation and activation of various immune cells, including T cells and B cells. This inhibition is facilitated through the secretion of PGE_2 and other soluble factors, such as transforming growth factor-β (TGF-β) and IDO [112]. This mechanism underscores the pivotal role of PGE_2 in sustaining immune homeostasis, particularly through its direct and indirect pathways that modulate B cell function, thereby highlighting its intricate and multifaceted roles in immune suppression.

5. PGI_2

PGI_2 is produced by vascular endothelin and trophoblastic cells [113,114]. PGI_2 has a variety of pharmacological effects, including vasodilation, inhibition of smooth muscle cell proliferation, and platelet aggregation [115]. As an essential regulator of immunity, PGI_2 influences the functionality and differentiation of a diverse array of immune cells through interactions with its IP receptor [116].

PGI_2 plays a pivotal role in modulating the function and stability of Tregs. It accomplishes this by attenuating β-catenin signaling and suppressing the expression of immunoglobulin-like transcript 3 (ILT3), thereby enhancing the suppressive capacity of Tregs and their ability to mitigate Th2 cell reprogramming, ultimately reducing allergic inflammation [117]. Furthermore, PGI_2, through its IP receptor, diminishes the activity of type 2 innate lymphoid cells (ILC2s) in both mice and humans, mitigating allergic inflammatory responses [118]. Experimental findings have elucidated that PGI_2 regulates the development and functionality of $CD4^+$ T cell subsets, predominantly exerting inhibitory effects on the activation, differentiation, and cytokine production of Th1 and Th2 cells, while simultaneously promoting Th17 cell polarization and cytokine production [116]. The PGI_2/IP signaling axis contributes to immune regulation by obstructing STAT6-independent Th2 cell activation, reducing cytokine expression and allergic airway inflammation, curbing the production of inflammatory chemokines, and inhibiting $CD4^+$ T cell proliferation [119]. PGI_2, via its IP receptor, fosters the differentiation and functionality of Tregs, curtails Th2 cell-driven inflammatory responses, and prevents the conversion of Tregs into a pathogenic phenotype [120]. Research has highlighted the significance of PGI_2 and its IP receptor in establishing immune tolerance to ovalbumin (OVA) within the airways, where the PGI_2/IP pathway is instrumental in promoting immune tolerance, suppressing allergic inflammation, and Th2 immune reactions. Conversely, the blockade of COX or the deletion of the IP gene disrupts immune tolerance, exacerbating allergic responses [121]. Studies reported the impact of endogenous PGI_2 through its IP receptor on lipopolysaccharide-induced acute lung injury (ALI). PGI_2 was found to inhibit the infiltration and activation of neutrophils in the lungs, reduce the expression of inflammatory and chemotactic factors, increase the expression of the anti-inflammatory factor IL-10, thus alleviating lung inflammation and damage [122].

Studies have shown that PGI_2 and its analogues significantly reduce the production of various pro-inflammatory cytokines and chemokines by DCs through IP receptor signaling pathway, while increasing the production of anti-inflammatory cytokine IL-10. The observed effects are linked to increased levels of cAMP and decreased activity of NF-κB within the IP receptor signaling pathway [123]. Additionally, these analogs demonstrated inhibition of dendritic cell maturation and function, characterized by the decreased expression of CD86, CD40, and MHC II, as well as suppression of dendritic cell-induced T cell proliferation and cytokine production. These findings suggest that PGI_2 and its analogs play a critical role in regulating immune responses [124].

6. PGD_2

PGD_2 is produced by activated mast cells, macrophages, and Th2 cells [125]. The biological actions of PGD_2 are mediated through two G-protein-coupled receptors, DP and chemoattractant receptor homologous molecules expressed on Th2 cells (CRTH2) [126]. DP1 is predominantly expressed in cell types that mediate allergic and inflammatory reactions, including mast cells, basophils, eosinophils, Th2 lymphocytes, and dendritic cells in both humans and rodents [127,128]. DP1 is associated with allergic diseases like rhinitis and asthma and plays a crucial role in neurological diseases, reproductive development, digestive tract disorders, cardiovascular diseases, and maintaining hemodynamics in rodents and humans, including ischemia-reperfusion injury and niacin-induced vasodilation [129–132]. CRTH2 has been detected in humans on type 2 polarized lymphocytes, basophils, eosinophils, and monocytes [133]. PGD_2 signaling through DP and CRTH2 mediates different and often opposite effects in many cell types of the immune system [134]. Recent studies have identified PGD_2 as a key regulator of tumor and inflammation-related functions [135–137].

PGD_2 represents the most abundant prostanoid produced in central nervous system(CNS) of mammals [138], exerts anti-inflammatory effects by signaling through the DP1 receptor [139,140]. Specifically, the action of DP1 on macrophages inhibited their activation and phagocytic functions, while on microglial cells, it promoted the expression of inflammatory factors and the clearance of viruses. This indicates that the

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PGD_2/DP1 axis plays a complex regulatory role in viral infections of the central nervous system [141]. Additionally, PGD_2 was found to inhibit the increase in expression levels of IDO in macrophages. Previous studies have shown that IDO may exert immunosuppressive function through two different pathways, 'tryptophan depletion' and 'tryptophan metabolite accumulation' [142]. PGD_2 may play an immunosuppressive role by interfering with tryptophan metabolism [143]. Studies have shown that PGD_2 and its dehydration end product (such as 15-deoxy-Delta-prostaglandin J2, 15-dPGJ2) inhibit the expression of triggering receptor expressed on myeloid cells 1 (TREM-1) in macrophages through mechanisms independent of the PGD_2 receptor and peroxisome proliferator-activated receptor γ(PPARγ). This inhibitory effect is achieved by activating nuclear factor erythroid 2-related factor-2 (NRF2) and inhibiting NF-κB, demonstrating that PGD_2 and its metabolites modulate key transcription factors to exert immunosuppressive and anti-inflammatory effects [144]. These findings highlight the multifaceted roles of PGD_2 in regulating immune responses and inflammation processes.

PGD_2 directly inhibits the cytotoxic activity of NK cells by elevating the levels of cAMP within NK cells, without affecting the binding of NK cells to their target cells [145]. PGD_2 achieves this inhibitory effect by interacting with the D-prostaglandin receptor on the surface of NK cells, resulting in an increase in intracellular cAMP levels. Thus, this elevation would inhibit NK cell cytotoxicity, cytokine production, and chemotaxis, thereby promoting Th2-type immune responses [146]. Recent studies have shown that PGD_2, through the activation of the DP1, plays a pivotal role in modulating the immune response by inhibiting the production of IFN-γ by invariant natural killer T (iNKT) cells. IFN-γ is a key cytokine essential for combating tumors and pathogens [147]. Furthermore, the administration of PGD_2 and DP1 agonists has been found to reduce the effectiveness of iNKT cell-mediated responses against B16 melanoma, underscoring the significant role of PGD_2 in immune regulation [148].

PGD_2 influences DCs differentiation and function through the DP1, inhibiting Th1 cells development and facilitating Th2 cells differentiation, thus playing a role in immune response regulation [149]. PGD_2 suppresses IL-12 production by DCs, promoting a Th2 immune response [150]. Increased levels of PGD_2 in the lungs of aged mice result in reduced migration of respiratory dendritic cells (rDCs), with PGD_2 acting through the DP1 receptor and the cAMP/PKA signaling pathway to inhibit the expression of CCR7 on rDCs, affecting their chemotaxis, thereby diminishing virus-specific T cell responses and antiviral capabilities [151]. Studies have demonstrated that PGD_2, secreted by malignant cells in acute promyelocytic leukemia (APL), acts as an inflammatory mediator by binding to the CRTH2 receptor, activating ILC2s, and promoting the secretion of IL-13. This, in turn, leads to the expansion and activation of M-MDSCs, establishing an immunosuppressive axis that inhibits T cell antitumor function [152]. It has been shown that mesenchymal COX2-derived PGD_2 activates an ILC2-Treg axis to promote proliferation of normal and malignant hematopoietic stem and progenitor cells (HSPCs) [125].

7. TxA_2

TxA_2 was one of the first prostaglandins discovered in washed platelets in 1975, produced in large quantities when platelets come into contact with damaged blood vessels. Due to its potent platelet aggregation and vasoconstriction activities, the function of TxA_2 has been primarily studied in the cardiovascular system [153,154]. The TBXA2R gene, located at chromosome 19 p13.3, encodes the TxA_2 receptor, also known as thromboxane A_2 receptor, a member of the G protein-coupled receptor superfamily with two human subtypes, TPα and TPβ [155–157].

Neutrophil-derived TxA_2 can modulate the intensity and spread of T cell responses, thus regulating the immune response [158]. TxA_2 inhibits the interaction between low-affinity $CD4^+$ T cells and DCs through the TP receptor, thereby enhancing the quality of the immune response and preventing autoimmune reactions [159]. Kabashima et al. found that TxA_2, produced by activated DCs, inhibited the adhesion and proliferation of T cells with dendritic cells by binding to the thromboxane receptor on T cells, thus regulating the adaptive immune response to exogenous antigens [160]. TxA_2 induced apoptosis or functional incompetence of autoreactive T cells in the thymus by binding to receptors on T cells within the thymus, thereby generating tolerance to transplants in the body [161]. Yang et al. found that TxA_2, by binding to the TP receptor, activated the cAMP-PKA signaling pathway, which in turn modulated the JAK/STAT5 signaling pathway, thus promoting the early development of B cells. Therefore, low doses of aspirin inhibited B cell development by suppressing COX-1 and reducing levels of TxA_2, offering potential immunosuppressive effects [162].

8. $PGF_{2\alpha}$

$PGF_{2\alpha}$ is an endogenous metabolite of arachidonic acid that exerts its effects by binding to and activating the GPCR, specifically the $PGF_{2\alpha}$ receptor (FP). The FP receptor facilitates signal transduction through interactions with various G proteins, including Gαq/11, Gα12/13, and Gβγ (presumed to originate from Gαi), thereby regulating the physiological functions of multiple tissues and cell types [163]. $PGF_{2\alpha}$, a potent vasoconstrictor from the prostanoid family, is pivotal in female reproductive functions, including pregnancy physiology, labor initiation, and postpartum uterine contraction, and is also linked to hypertrophic growth in cardiomyocytes, vascular smooth muscle cells, and skeletal muscle cells [164,165].

Under agonist stimulation, the FP receptor primarily couples with the Gq subtype of G proteins, leading to its activation which subsequently activates Protein Kinase C (PKC) and triggers transient calcium signaling in response to the formation of inositol trisphosphate. Besides Gq, activation of FP also proceeds via G12/G13, inducing the activation of the small G protein Rho, and activates the Raf/MEK/MAP kinase pathway through Gi [23]. $PGF_{2\alpha}$ has been shown to modulate the proliferation, inflammation, and immunomodulatory properties of MSCs through its activation of the FP receptor and inhibition of the NF-κB signaling pathway. This mechanism results in decreased production of IL-1β and GM-CSF, while also promoting the secretion of IL-10 by lymphocytes [166]. Wallace et al. found that the $PGF_{2\alpha}$-FP signaling pathway could regulate the expression of the inflammatory chemokine CXCL1 in endometrial adenocarcinoma cells, thus modulating the influx of neutrophils within tumors [167]. $PGF_{2\alpha}$ inhibited the expression of inflammatory mediators, reduced neutrophil migration, decreased pulmonary edema, protected alveolar epithelial cells, and thus suppressed HCl-induced acute lung injury by activating the FP receptor [168]. Research has indicated that $PGF_{2\alpha}$ facilitates the systemic inflammatory response triggered by lipopolysaccharide (LPS) via activation of its receptor FP. Conversely, the FP receptor antagonist AL8810 attenuates LPS-induced tissue inflammation and injury by augmenting the secretion of the anti-inflammatory cytokine IL-10 by neutrophils and macrophages [169]. $PGF_{2\alpha}$, a luteolysis-promoting factor, has the ability to induce porcine luteal cells to secrete chemokines such as CCL2, which in turn attract and activate immune cells to contribute to the process of luteolysis [170].

9. Multiple prostaglandins

When multiple PGs coexist, their biological effects may be either diminished or enhanced, contingent upon the specific context and the varieties of PGs involved [171]. These PGs engage with their corresponding GPCRs, triggering a cascade of signaling pathways. Such interactions can result in either synergistic or antagonistic effects, thereby influencing the overall physiological outcome [172,173]. Under physiological conditions, PGI_2 and TxA_2 are expressed abundantly in the cerebral cortex and hippocampus. These metabolites play a critical role in

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the pathophysiological mechanisms of ischemic brain injury [174]. PGE_2 and PGI_2 not only sensitize nociceptors but also play crucial roles in the development of pulmonary fibrosis [175,176]. PGI_2 mitigates, while TxA_2 promotes, the initiation and progression of atherogenesis via their antagonistic effects on vasodilation, platelet aggregation, and leukocyte-endothelial cell interactions. Given the crucial roles of PGI_2 and TxA_2 in endothelial function regulation, maintaining a well-balanced PGI_2/TxA_2 homeostasis is essential for cardiovascular disease prevention [177,178].

PGD_2 and PGE_2 have opposite effects on alveolar macrophages infected with *Histoplasma capsulatum*. Although PGD_2 serves as an immunostimulatory mediator in controlling *H. capsulatum* infection, PGE_2 exerts immunosuppressive effects. The interplay between these two PGs may constrain collateral immune damage, potentially at the cost of microbial containment [179]. Recent studies have reported that following brain injury, the expression levels of the COX-2 and PGE_2 synthase are elevated, whereas PGD_2 synthase shows a decrease. This suggests that PGE_2 and PGD_2 may exert opposing effects on inflammation, with PGE_2 promoting inflammation and PGD_2 exerting anti-inflammatory effects [180].

In conclusion, the biological effects of various PGs are contingent upon their specific interactions and the contextual circumstances of their occurrence. These interactions can either amplify or mitigate the overall effects. Further investigation is essential to comprehensively understand these interactions and their ramifications across different physiological and pathological states.

10. Prostaglandins and immune-associated diseases

10.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systematic autoimmune disease characterized by synovial inflammation and joint damage [181]. PGs, found in elevated levels in both the synovial fluid and the synovial membrane, are believed to be crucial in causing vasodilation, fluid extravasation, and pain in synovial tissues. Additionally, there is growing evidence that PGs, particularly PGE_2, act as mediators in complex interactions that lead to erosions in articular cartilage and adjacent bone [182]. Knock-out mouse studies have demonstrated that PGE_2 can elicit both proinflammatory and anti-inflammatory effects. These effects are influenced by the type of receptor, the specific cell population involved, the context in which activation occurs, and the expression of receptor genes within the tissues [183].

PGE_2 induces elevated levels of IL-6 and serum amyloid A (SAA) in arthritis patients through the activation of EP4 receptors, resulting in both systemic and localized inflammatory reactions that exacerbate the degradation of articular cartilage and bone. Consequently, targeting EP4 receptors with antagonists may present a novel therapeutic approach for RA [184]. In clinical, Nonsteroidal Antiinflammatory Drugs (NSAIDs) like Naprelan (naproxen sodium), Mobic (meloxicam), and Duexis (ibuprofen and famotidine) inhibit COX activity, thereby inhibiting PGs synthesis and producing antipyretic and analgesic effects used for relief of the symptoms and pain of rheumatoid arthritis [185]. PGE_2 exerts immunosuppressive effects in RA by modulating NF-κB activity through ERK-dependent and -independent pathways in synovial fibroblasts, key mediators of RA inflammation and cartilage erosion. This process can inhibit the action of inflammatory cytokines and may contribute to the resolution phase of inflammation to prevent cartilage degradation in arthritis [186].

10.2. Multiple sclerosis

Multiple sclerosis (MS) is a debilitating chronic inflammatory condition affecting the CNS, characterized by persistent inflammation, demyelination, gliosis, varying levels of axonal and oligodendrocyte damage, progressive neurological impairment, and significant infiltration by a diverse array of immune system cellular and soluble mediators [187]. In MS patients, increased PG levels in cerebrospinal fluid (CSF) can indicate the involvement of PGs in pathogenesis [188,189]. The prostaglandin synthesis enzymes PLA_2 and COX, particularly COX-2 and mPGES-1, exhibit elevated expression levels in the lesion sites associated with MS, thereby facilitating the generation of PGE_2 and subsequently contributing to neuroinflammation and demyelination. Consequently, pharmacological agents targeting COX-2 and mPGES-1 may offer promising therapeutic avenues for the management of MS [187,190,191]. PGE_2 increases Th1 cell differentiation and Th17 cell expansion through EP2/EP4 receptor signaling pathway, thereby exacerbating neuroinflammation. Therefore, the use of EP2/EP4 receptor antagonists may help to inhibit the development of MS [192].

Experimental autoimmune encephalomyelitis (EAE) is widely regarded as an effective MS model [193]. Xu et al. demonstrated that the cooperation between PGE_2 and adenosine can suppress the progression of EAE. Additionally, they observed that the combination of PGE_2 and adenosine significantly reduced the production of INF-γ and IL-17 from T cells. This inhibitory effect is mediated through EP4 and A_{2A} receptors. These findings indicate that the combination of PGE_2 and adenosine may protect against immune-mediated destruction in EAE by inhibiting T cell function [194]. These findings underscore the dual role of PGE_2 in immune responses, further illustrating how prostaglandins can function in both pro-inflammatory and immunoregulatory capacities depending on the context and interactions with other mediators.

10.3. Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the digestive system. The most common types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) [195]. PGs are a class of significant lipid mediators involved in regulating the defense and repair mechanisms of the gastrointestinal (GI) mucosa [196]. It has been reported that PGE_2 can inhibit lesion formation in DSS-induced colitis in rats and reduce the levels of mucosal inflammatory cytokines [197]. Zhou et al. demonstrated the immunomodulatory effects of urine-derived stem cells (USC) on chemically-induced colitis by inhibition of Th1/Th17 immune responses in a PGE_2-dependent manner [198].The synthesis of PGs is mainly dependent on the activity of COX, which can be inhibited by NSAIDs, leading to gastrointestinal injury and the exacerbation of IBD [199]. COX has two isoforms, COX-1 and COX-2, which play different roles in the defense and inflammation of the GI mucosa. COX-1 is primarily responsible for maintaining normal PG levels, whereas COX-2 is mainly induced to be expressed in situations of inflammation and injury, producing PGs with anti-inflammatory and pro-healing effects [200].The role of PGs in the treatment of IBD is complex and varied, depending on the subtype of prostaglandins, the type and expression level of their receptors and synthesizing enzymes.

10.4. Atopic dermatitis

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a complex and heterogeneous pathogenesis, encompassing allergic/immune dysregulation, skin barrier dysfunction, and pruritus [201]. It has been reported that the skin of AD patients can produce various prostaglandin species, including PGE_2 and PGD_2, both of which play significant roles in the pathogenesis of atopic dermatitis [202]. PGD_2 exerts different effects through two receptors, DP1 and CRTH2. DP1 has anti-inflammatory effects and maintains barrier function, while CRTH2 promotes chemotaxis of white blood cells and inflammatory responses. This demonstrates that prostaglandins can have both pro-inflammatory and regulatory effects depending on the receptor type involved. PGE_2 regulates the functions of various cells, including keratinocytes, immune cells, and neurons, through four receptors, EP1-EP4, affecting the skin's barrier, inflammation, and itchiness [203]. PGE_2 exacerbates the development of allergic contact dermatitis and atopic

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dermatitis by promoting T-cell production of IL-22 through EP2 and EP4 receptors, suggesting that inhibiting prostaglandin synthesis or receptor signaling could be a potential strategy for treating these skin inflammations [204]. In an OVA-induced AD model, the DP agonist BW245c inhibits OVA sensitization by suppressing the migration of skin DCs [205,206]. The dual roles of PGs in AD underscore their complex function within the immune system. These molecules are shown to exert both inflammatory and regulatory effects, illustrating that PGs are not merely inflammatory mediators. Their contribution to immune regulation and the maintenance of skin homeostasis is dependent on the specific receptors and pathways involved, highlighting the multifaceted nature of prostaglandin functions in dermatological contexts.

10.5. Allergic asthma

PGD_2 is the principal prostaglandin produced by mast cells and eosinophils, acting through DP1 and DP2 receptors. It can induce bronchoconstriction, vasodilation, exudation, and chemotaxis of effector cells, thereby playing a role in the pathogenesis of allergic asthma [207,208]. PGD_2 also enhances the activation of ILC2 and Th2 cells and the secretion of Th2-type cytokines, such as IL-5 and IL-13. Levels of PGD_2 are elevated in aspirin-exacerbated respiratory disease (AERD) and correlate with the severity and control of asthma. DP2 receptor antagonists have shown effects in improving asthma symptoms and lung function in some clinical trials, though some trials have not confirmed this [125]. Therefore, the DP2 receptor may be an effective target for asthma treatment, but further research and optimization are needed. PGE_2 primarily exerts anti-inflammatory effects in allergic asthma by inhibiting the differentiation and function of Th2 cells through EP2 and EP4 receptors, reducing IgE production, decreasing eosinophil infiltration, inhibiting mast cell release, and dilating bronchial smooth muscle [209]. Prostaglandin receptor antagonists, such as DP2 and EP2 antagonists, can specifically block prostaglandin signaling, thereby alleviating symptoms and inflammation in allergic asthma. Some clinical trials have already indicated their potential efficacy in asthma treatment [210].

10.6. Cancer

In numerous studies, PGs have been shown to play a key role in cancer progression [211]. PG pathways facilitate oncogenesis through their roles in regulating cellular proliferation, growth, apoptosis, invasion, migration, metastasis, and angiogenesis. The PGE_2/EPs, TxA_2/TBXA2R, and $PGF_{2\alpha}$/FP pathways are primarily involved in promoting cancer, while the PGI_2/IP and PGD_2/DP axes are mainly involved in suppressing cancer [17]. Many tumor cells can secrete PGE_2 to establish a TME not only favoring tumor growth but also suppressing anti-cancer immunity [212]. NSAIDs have been reported to prevent cancer and stop tumor growth by inhibiting PG synthesis through COX-2 hindrance [213–215]. Epidemiologic studies suggest that long-term use of NSAIDs has chemopreventive properties against colorectal cancer (CRC) [216]. In animal tumor models, NSAIDs or COX-2 inhibitors have been demonstrated to inhibit tumor growth by suppressing PGE_2 signaling [217]. A recent study revealed that the accumulation of immunosuppressive neutrophils in the lung impairs the antitumor efficacy of adoptively transferred T cells, leading to therapeutic failure. Inhibition of PGE_2 signaling, which effectively prevented the induction of immunosuppressive neutrophils, significantly enhanced the effectiveness of adoptive T cell therapy in the treatment of lung metastases of breast cancer in murine models [218]. PGE_2 and COX-2 levels in cancer patients are significantly elevated when macrophages infiltrate the tumor [219]. PGE_2 excretion from cancer cells is critical for macrophage infiltration of M2-type polarization by macrophages [220]. PGE_2-treated xenograft tumors also showed increased M2 type macrophage infiltration [221]. Moreover, PGE_2 has been shown to upregulate COX-2 through a COX-2-PGE_2-COX-2 positive feedback circuit, further eroding the immunosuppressive and immune-tolerating effects of PGE_2 [222]. The PGD_2 signaling pathway is purported to function as an oncogenic suppressor. A genetic deficit in the DP receptor has been shown to augment angiogenesis and neoplastic proliferation within a murine tumor xenograft model [223].

PGs play a crucial role in cancer progression, displaying complexity in their dual function of promoting and inhibiting tumor growth, as well as regulating inflammatory and immune processes. These findings underscore the potential therapeutic significance of targeting PG pathways in cancer treatment strategies, particularly in addressing the dual role of PG-induced immunosuppression and pro-inflammatory responses.

11. Prostaglandins and solid organ transplantation

In solid organ transplantation, the induction of tolerance can diminish the risk of acute and chronic graft rejection and thereby improve the survival of the allograft. The discovery of naturally occurring tolerance-inducing molecules offers a unique opportunity to design new therapeutic strategies to improve allograft survival [224].

PGE_2 is an important immunomodulator with immunosuppressive function [225]. PGE_2 exerts significant immunosuppressive effects through various mechanisms. These include directly inhibiting the proliferation and activation of NK cells and effector T cells, impairing antigen presentation by dendritic cells, and promoting the infiltration of MDSCs and Tregs [53]. Tregs, engineered to express chimeric antigen receptors (CAR), show promise in inducing transplant tolerance by targeting a broad range of antigens without Human Leukocyte Antigen (HLA) restriction. These CAR Tregs accumulate at the transplant site, maintaining their suppressive function more effectively than natural Tregs [226]. Further exploration of the role of PGs in immunoregulation and their mechanisms may facilitate the development of new therapeutic strategies to enhance post-transplant management and long-term health of patients.

12. Conclusion

In this review, we explore the pivotal role of prostaglandins in immune regulation, with a particular emphasis on their critical function in immune suppression. Prostaglandins interact with specific receptors to initiate complex signaling pathways that intricately modulate immune cell functions. This modulation involves the downregulation of inflammatory mediators, reduced migration, and infiltration of immune cells, effectively attenuating excessive immune responses and inflammation. These mechanisms are essential for preventing autoimmune diseases, maintaining immune tolerance following organ transplantation, and managing allergic disorders. Despite the therapeutic potential of prostaglandins and their analogues in treating immune-mediated conditions, their clinical application is currently hampered by several challenges and limitations. Future research should aim for a more comprehensive understanding of prostaglandin mechanisms in immune regulation and seek ways to address these challenges through improved drug design and therapeutic strategies.

In conclusion, the role of prostaglandins in immune suppression not only deepens our understanding of immune regulatory mechanisms but also establishes a robust foundation for the development of novel therapeutic approaches. Advancing our knowledge of prostaglandin functions and mechanisms in the immune system is crucial for creating more effective and targeted treatments, utilizing this key biological regulatory pathway to address a broad spectrum of immune-related disorders.

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CRediT authorship contribution statement

Minjie Luo: Writing – original draft, Formal analysis, Data curation. **Nina He:** Formal analysis, Data curation. **Qing Xu:** Formal analysis, Data curation. **Zhongchi Wen:** Formal analysis, Data curation. **Ziqin Wang:** Data curation. **Jie Zhao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Ying Liu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Data availability

The data that has been used is publicly available.

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Appendix A. Supplementary data

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References

[1] U.S. von Euler, On the specific vaso-dilating and plain muscle stimulating substances from accessory genital glands in man and certain animals (prostaglandin and vesiglandin), J. Physiol. 88 (2) (1936) 213–234, https://doi.org/10.1113/jphysiol.1936.sp003433.
[2] M.J. Seo, D.K. Oh, Prostaglandin synthases: molecular characterization and involvement in prostaglandin biosynthesis, Prog. Lipid Res. 66 (2017) 50–68, https://doi.org/10.1016/j.plipres.2017.04.003.
[3] D. Jin, T.P. Zhong, Prostaglandin signaling in ciliogenesis and development, J. Cell. Physiol. 237 (6) (2022) 2632–2643, https://doi.org/10.1002/jcp.30659.
[4] S. Park, S. Kang, Association between polygenetic risk scores of low immunity and interactions between these scores and moderate fat intake in a large cohort, Nutrients 13 (8) (2021), https://doi.org/10.3390/nu13082849.
[5] M. Grafals, J.M. Thurman, The role of complement in organ transplantation, Front. Immunol. 10 (2019) 2380, https://doi.org/10.3389/fimmu.2019.02380.
[6] H. Hu, S.C. Sun, Ubiquitin signaling in immune responses, Cell Res. 26 (4) (2016) 457–483, https://doi.org/10.1038/cr.2016.40.
[7] V. Longo, N. Aloi, E. Lo Presti, et al., Impact of the flame retardant 2,2′4,4′-tetrabromodiphenyl ether (PBDE-47) in THP-1 macrophage-like cell function via small extracellular vesicles, Front. Immunol. 13 (2022) 1069207, https://doi.org/10.3389/fimmu.2022.1069207.
[8] X. Pan, C. Li, J. Feng, The role of LncRNAs in tumor immunotherapy, Cancer Cell Int. 23 (1) (2023) 30, https://doi.org/10.1186/s12935-023-02872-3.
[9] Y. Su, X. Huang, T. Raskovalova, et al., Cooperation of adenosine and prostaglandin E2 (PGE2) in amplification of cAMP-PKA signaling and immunosuppression, Cancer Immunol. Immunother. 57 (11) (2008) 1611–1623, https://doi.org/10.1007/s00262-008-0494-5.
[10] A.R. Brogliato, C.A. Antunes, R.S. Carvalho, et al., Ketoprofen impairs immunosuppression induced by severe sepsis and reveals an important role for prostaglandin E2, Shock 38 (6) (2012) 620–629, https://doi.org/10.1097/SHK.0b013e318272ff8a.
[11] N.S. Al-Waili, A potential concept in the management of tumors with modulation of prostaglandin, nitric oxide and antioxidants, ScientificWorldJournal 7 (2007) 466–478, https://doi.org/10.1100/tsw.2007.89.
[12] A.J. O'Brien, J.N. Fullerton, K.A. Massey, et al., Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2, Nat. Med. 20 (5) (2014) 518–523, https://doi.org/10.1038/nm.3516.
[13] V. Pascual, R. Dieli-Crimi, N. Lopez-Palacios, et al., Inflammatory bowel disease and celiac disease: overlaps and differences, World J. Gastroenterol. 20 (17) (2014) 4846–4856, https://doi.org/10.3748/wjg.v20.i17.4846.
[14] N. Gholijani, M. Gharagozloo, F. Kalantar, et al., Modulation of cytokine production and transcription factors activities in human Jurkat T cells by thymol and Carvacrol, Adv. Pharm. Bull. 5 (Suppl. 1) (2015) 653–660, https://doi.org/10.15171/apb.2015.089.
[15] N.S. Al-Waili, K.Y. Saloom, T. Al-Waili, et al., Modulation of prostaglandin activity, part 1: prostaglandin inhibition in the management of nonrheumatologic diseases: immunologic and hematologic aspects, Adv. Ther. 24 (1) (2007) 189–222, https://doi.org/10.1007/BF02850008.
[16] H. Harizi, The immunobiology of prostanoid receptor signaling in connecting innate and adaptive immunity, Biomed. Res. Int. 2013 (2013) 683405, https://doi.org/10.1155/2013/683405.
[17] Q. Wang, R.J. Morris, A.M. Bode, et al., Prostaglandin pathways: opportunities for cancer prevention and therapy, Cancer Res. 82 (6) (2022) 949–965, https://doi.org/10.1158/0008-5472.Can-21-2297.
[18] B. Cen, J.D. Lang, Y. Du, et al., Prostaglandin E(2) induces miR675-5p to promote colorectal tumor metastasis via modulation of p53 expression, Gastroenterology 158 (4) (2020) 971–984.e910, https://doi.org/10.1053/j.gastro.2019.11.013.
[19] C. Yao, S. Narumiya, Prostaglandin-cytokine crosstalk in chronic inflammation, Br. J. Pharmacol. 176 (3) (2019) 337–354, https://doi.org/10.1111/bph.14530.
[20] B. Shkodra-Pula, C. Kretzer, P.M. Jordan, et al., Encapsulation of the dual FLAP/mPEGS-1 inhibitor BRP-187 into acetalated dextran and PLGA nanoparticles improves its cellular bioactivity, J. Nanobiotechnol. 18 (1) (2020) 73, https://doi.org/10.1186/s12951-020-00620-7.
[21] X. Norel, Y. Sugimoto, G. Ozen, et al., International Union of Basic and Clinical Pharmacology. CIX. Differences and similarities between human and rodent prostaglandin E(2) receptors (EP1-4) and prostacyclin receptor (IP): specific roles in pathophysiologic conditions, Pharmacol. Rev. 72 (4) (2020) 910–968, https://doi.org/10.1124/pr.120.019331.
[22] T. Aoki, S. Narumiya, Prostaglandins and chronic inflammation, Trends Pharmacol. Sci. 33 (6) (2012) 304–311, https://doi.org/10.1016/j.tips.2012.02.004.
[23] C. Wu, Y. Xu, Q. He, et al., Ligand-induced activation and G protein coupling of prostaglandin F2α receptor, Nat. Commun. 14 (1) (2023), https://doi.org/10.1038/s41467-023-38411-x.
[24] G. Yang, L. Chen, An update of microsomal prostaglandin E Synthase-1 and PGE2 receptors in cardiovascular health and diseases, Oxidative Med. Cell. Longev. 2016 (2016) 5249086, https://doi.org/10.1155/2016/5249086.
[25] V.L. Schuster, Prostaglandin transport, Prostaglandins Other Lipid Mediat. 68-69 (2002) 633–647, https://doi.org/10.1016/s0090-6980(02)00061-8.
[26] S.K. Banu, J.A. Arosh, P. Chapdelaine, M.A. Fortier, Molecular cloning and spatio-temporal expression of the prostaglandin transporter: a basis for the action of prostaglandins in the bovine reproductive system, Proc. Natl. Acad. Sci. USA 100 (200) (2003) 11747–11752, https://doi.org/10.1073/pnas.1833330100.
[27] H.N. Jabbour, K.J. Sales, Prostaglandin receptor signalling and function in human endometrial pathology, Trends Endocrinol. Metab. 15 (8) (2004) 398–404, https://doi.org/10.1016/j.tem.2004.08.006.
[28] K. Li, J. Zhao, M. Wang, et al., The roles of various prostaglandins in fibrosis: a review, Biomolecules 11 (6) (2021), https://doi.org/10.3390/biom11060789.
[29] H.H. Tai, Prostaglandin catabolic enzymes as tumor suppressors, Cancer Metastasis Rev. 30 (3–4) (2011) 409–417, https://doi.org/10.1007/s10555-011-9314-z.
[30] H.H. Tai, C.M. Ensor, M. Tong, et al., Prostaglandin catabolizing enzymes, Prostaglandins Other Lipid Mediat. 68-69 (2002) 483–493, https://doi.org/10.1016/s0090-6980(02)00050-3.
[31] K. Iwasa, S. Yamamoto, K. Yamashina, et al., A peripheral lipid sensor GPR120 remotely contributes to suppression of PGD(2)-microglia-provoked neuroinflammation and neurodegeneration in the mouse hippocampus, J. Neuroinflammation 18 (1) (2021) 304, https://doi.org/10.1186/s12974-021-02361-2.
[32] F. Durchschein, A. Eherer, M. Grill, et al., Involvement of EP2 and EP4 receptors in eosinophilic esophagitis: a pilot study, Dig. Dis. Sci. 64 (10) (2019) 2806–2814, https://doi.org/10.1007/s10620-019-05623-5.
[33] B. Radnai, E.M. Sturm, A. Stancic, et al., Eosinophils contribute to intestinal inflammation via chemoattractant receptor-homologous molecule expressed on Th2 cells, CRTH2 experimental Crohn's disease, J. Crohns Colitis 10 (9) (2016) 1087–1095, https://doi.org/10.1093/ecco-jcc/jjw061.
[34] Y. Jin, Q. Liu, P. Chen, et al., A novel prostaglandin E receptor 4 (EP4) small molecule antagonist induces articular cartilage regeneration, Cell Discov. 8 (1) (2022) 24, https://doi.org/10.1038/s41421-022-00382-6.
[35] D.F. Woodward, R.L. Jones, S. Narumiya, International Union of Basic and Clinical Pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress, Pharmacol. Rev. 63 (3) (2011) 471–538, https://doi.org/10.1124/pr.110.003517.
[36] E. Goupil, D. Fillion, S. Clement, et al., Angiotensin II type I and prostaglandin F2alpha receptors cooperatively modulate signaling in vascular smooth muscle cells, J. Biol. Chem. 290 (5) (2015) 3137–3148, https://doi.org/10.1074/jbc.M114.631119.
[37] O.P. Smith, H.N. Jabbour, H.O. Critchley, Cyclooxygenase enzyme expression and E series prostaglandin receptor signalling are enhanced in heavy menstruation, Hum. Reprod. 22 (5) (2007) 1450–1456, https://doi.org/10.1093/humrep/del503.
[38] S. Caggia, S. Tapadar, B. Wu, et al., Small molecule inhibitors targeting Galpha(i) 2 protein attenuate migration of cancer cells, Cancers (Basel) 12 (6) (2020), https://doi.org/10.3390/cancers12061631.
[39] Q. Yang, M. Shi, Y. Shen, et al., COX-1–derived thromboxane A2 plays an essential role in early B-cell development via regulation of JAK/STAT5 signaling in mouse, Blood 124 (10) (2014) 1610–1621, https://doi.org/10.1182/blood-2014-03-559658.
[40] A. Jara-Gutierrez, V. Baladron, The role of prostaglandins in different types of cancer, Cells 10 (6) (2021), https://doi.org/10.3390/cells10061487.
[41] S.H. Kang, S.J. Hong, Y.K. Lee, et al., Oral vaccine delivery for intestinal immunity-biological basis, barriers, delivery system, and M cell targeting, Polymers (Basel) 10 (9) (2018), https://doi.org/10.3390/polym10090948.

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[42] Y. Xiao, Y. Zhang, H. Yin, et al., Editorial: Frontiers on innate immunity and intercellular communication, Front. Immunol. 13 (2022) 1102776, https://doi.org/10.3389/fimmu.2022.1102776.
[43] Y. Wang, Z. Liang, F. Shen, et al., Exploring the immunomodulatory effects and mechanisms of Xinjiang fermented camel milk-derived bioactive peptides based on network pharmacology and molecular docking, Front. Pharmacol. 13 (2022) 1038812, https://doi.org/10.3389/fphar.2022.1038812.
[44] S. Sattler, The role of the immune system beyond the fight against infection, Adv. Exp. Med. Biol. 1003 (2017) 3–14, https://doi.org/10.1007/978-3-319-57613-8_1.
[45] X. Jiang, J. Wang, X. Deng, et al., The role of microenvironment in tumor angiogenesis, J. Exp. Clin. Cancer Res. 39 (1) (2020) 204, https://doi.org/10.1186/s13046-020-01709-5.
[46] D. Wang, R.N. DuBois, Immunosuppression associated with chronic inflammation in the tumor microenvironment, Carcinogenesis 36 (10) (2015) 1085–1093, https://doi.org/10.1093/carcin/bgv123.
[47] D.S. Chen, I. Mellman, Elements of cancer immunity and the cancer-immune set point, Nature 541 (7637) (2017) 321–330, https://doi.org/10.1038/nature21349.
[48] D. Wang, R.N. DuBois, Role of prostanoids in gastrointestinal cancer, J. Clin. Invest. 128 (7) (2018) 2732–2742, https://doi.org/10.1172/JCI97953.
[49] D. Wang, R.N. Dubois, Eicosanoids and cancer, Nat. Rev. Cancer 10 (3) (2010) 181–193, https://doi.org/10.1038/nrc2809.
[50] I. Silvestri, S. Cattarino, A.M. Agliano, et al., Beyond the immune suppression: the immunotherapy in prostate cancer, Biomed. Res. Int. 2015 (2015) 794968, https://doi.org/10.1155/2015/794968.
[51] T. Hirata, S. Narumiya, Prostanoids as regulators of innate and adaptive immunity, Adv. Immunol. 116 (2012) 143–174, https://doi.org/10.1016/B978-0-12-394300-2.00005-3.
[52] M. Agard, S. Asakrah, L.A. Morici, PGE(2) suppression of innate immunity during mucosal bacterial infection, Front. Cell. Infect. Microbiol. 3 (2013) 45, https://doi.org/10.3389/fcimb.2013.00045.
[53] D. Wang, C.S. Cabalag, N.J. Clemons, et al., Cyclooxygenases and prostaglandins in tumor immunology and microenvironment of gastrointestinal cancer, Gastroenterology 161 (6) (2021) 1813–1829, https://doi.org/10.1053/j.gastro.2021.09.059.
[54] R. Mizuno, K. Kawada, Y. Sakai, Prostaglandin E2/EP signaling in the tumor microenvironment of colorectal cancer, Int. J. Mol. Sci. 20 (24) (2019), https://doi.org/10.3390/ijms20246254.
[55] H. Cheng, H. Huang, Z. Guo, et al., Role of prostaglandin E2 in tissue repair and regeneration, Theranostics 11 (18) (2021) 8836–8854, https://doi.org/10.7150/thno.63396.
[56] K. Gudis, A. Tatsuguchi, K. Wada, et al., Microsomal prostaglandin E synthase (mPGES)-1, mPGES-2 and cytosolic PGES expression in human gastritis and gastric ulcer tissue, Lab. Investig. 85 (2) (2005) 225–236, https://doi.org/10.1038/labinvest.3700200.
[57] N. Ghosh, R. Chaki, V. Mandal, et al., COX-2 as a target for cancer chemotherapy, Pharmacol. Rep. 62 (2) (2010) 233–244, https://doi.org/10.1016/s1734-1140(10)70262-0.
[58] R. Duffin, R.A. O'Connor, S. Crittenden, et al., Prostaglandin E(2) constrains systemic inflammation through an innate lymphoid cell-IL-22 axis, Science 351 (6279) (2016) 1333–1338, https://doi.org/10.1126/science.aad9903.
[59] F. Santilli, A. Boccatonda, G. Davi, et al., The Coxib case: are EP receptors really guilty? Atherosclerosis 249 (2016) 164–173, https://doi.org/10.1016/j.atherosclerosis.2016.04.004.
[60] T. Okuyama, S. Ishihara, H. Sato, et al., Activation of prostaglandin E2-receptor EP2 and EP4 pathways induces growth inhibition in human gastric carcinoma cell lines, J. Lab. Clin. Med. 140 (2) (2002) 92–102, https://doi.org/10.1067/mlc.2002.125784.
[61] V. Sreeramkumar, M. Fresno, N. Cuesta, Prostaglandin E2 and T cells: friends or foes? Immunol. Cell Biol. 90 (6) (2012) 579–586, https://doi.org/10.1038/icb.2011.75.
[62] M.A. Caligiuri, Human natural killer cells, Blood 112 (3) (2008) 461–469, https://doi.org/10.1182/blood-2007-09-077438.
[63] C.J. Nicolai, N. Wolf, I.C. Chang, et al., NK cells mediate clearance of CD8$^+$ T cell–resistant tumors in response to STING agonists, Sci. Immunol. 5 (45) (2020), https://doi.org/10.1126/sciimmunol.aaz2738.
[64] N.H. Knudsen, R.T. Manguso, Tumor-derived PGE2 gives NK cells a headache, Immunity 53 (6) (2020) 1131–1132, https://doi.org/10.1016/j.immuni.2020.11.018.
[65] C.H. Van Elssen, J. Vanderlocht, T. Oth, et al., Inflammation-restraining effects of prostaglandin E2 on natural killer-dendritic cell (NK-DC) interaction are imprinted during DC maturation, Blood 118 (9) (2011) 2473–2482, https://doi.org/10.1182/blood-2010-09-307835.
[66] H. Harizi, Reciprocal crosstalk between dendritic cells and natural killer cells under the effects of PGE2 in immunity and immunopathology, Cell. Mol. Immunol. 10 (3) (2013) 213–221, https://doi.org/10.1038/cmi.2013.1.
[67] M.O. Raihan, B.M. Espelien, B.A. McGregor, et al., Modulation of inflammatory signaling molecules in Bordetella pertussis antigen-challenged human monocytes in presence of adrenergic agonists, Vaccines (Basel) 10 (2) (2022), https://doi.org/10.3390/vaccines10020321.
[68] V.L. Wehbi, K. Tasken, Molecular mechanisms for cAMP-mediated Immunoregulation in T cells - role of anchored protein kinase a signaling units, Front. Immunol. 7 (2016) 222, https://doi.org/10.3389/fimmu.2016.00222.
[69] R. Minakuchi, M.C. Wacholtz, L.S. Davis, et al., Delineation of the mechanism of inhibition of human T cell activation by PGE2, J. Immunol. 8 (1990) 2616–2625.
[70] A. Shimabukuro-Vornhagen, T.M. Liebig, T. Koslowsky, et al., The ratio between dendritic cells and T cells determines whether prostaglandin E2 has a stimulatory or inhibitory effect, Cell. Immunol. 281 (1) (2013) 62–67, https://doi.org/10.1016/j.cellimm.2013.01.001.
[71] J.M. Chemnitz, J. Driesen, S. Classen, et al., Prostaglandin E2 impairs CD4+ T cell activation by inhibition of lck: implications in Hodgkin's lymphoma, Cancer Res. 66 (2) (2006) 1114–1122, https://doi.org/10.1158/0008-5472.CAN-05-3252.
[72] M. Ahmadi, D.C. Emery, D.J. Morgan, Prevention of both direct and cross-priming of antitumor CD8+ T-cell responses following overproduction of prostaglandin E2 by tumor cells in vivo, Cancer Res. 68 (18) (2008) 7520–7529, https://doi.org/10.1158/0008-5472.CAN-08-1060.
[73] D. Thumkeo, S. Punyawatthananukool, S. Prasongtanakij, et al., PGE(2)-EP2/EP4 signaling elicits immunosuppression by driving the mregDC-Treg axis in inflammatory tumor microenvironment, Cell Rep. 39 (10) (2022) 110914, https://doi.org/10.1016/j.celrep.2022.110914.
[74] T. Wang, B. Jing, D. Xu, et al., PTGES/PGE(2) signaling links immunosuppression and lung metastasis in Gprc5a-knockout mouse model, Oncogene 39 (15) (2020) 3179–3194, https://doi.org/10.1038/s41388-020-1207-6.
[75] S.G. Harris, J. Padilla, L. Koumas, et al., Prostaglandins as modulators of immunity, Trends Immunol. 23 (3) (2002) 144–150, https://doi.org/10.1016/s1471-4906(01)02154-8.
[76] J.B. Burkett, A.C. Doran, M. Gannon, Harnessing prostaglandin E(2) signaling to ameliorate autoimmunity, Trends Immunol. 44 (3) (2023) 162–171, https://doi.org/10.1016/j.it.2023.01.004.
[77] B. Cheng, H.C. Chen, I.W. Chou, et al., Harnessing the early post-injury inflammatory responses for cardiac regeneration, J. Biomed. Sci. 24 (1) (2017) 7, https://doi.org/10.1186/s12929-017-0315-2.
[78] J. Shen, T. Yang, Y. Xu, et al., delta-tocotrienol isolated from rice bran, exerts an anti-inflammatory effect via MAPKs and PPARs signaling pathways in lipopolysaccharide-stimulated macrophages, Int. J. Mol. Sci. 19 (10) (2018), https://doi.org/10.3390/ijms19103022.
[79] A. Benedetti, C. Turco, G. Fontemaggi, et al., Non-coding RNAs in the crosstalk between breast cancer cells and tumor-associated macrophages, Noncoding RNA 8 (1) (2022), https://doi.org/10.3390/ncrna8010016.
[80] B. Shang, H. Cui, R. Xie, et al., Neutrophil extracellular traps primed intercellular communication in cancer progression as a promising therapeutic target, Biomark. Res. 11 (1) (2023) 24, https://doi.org/10.1186/s40364-023-00463-y.
[81] J. Saha, D. Sarkar, A. Pramanik, et al., PGE2-HIF1alpha reciprocal induction regulates migration, phenotypic alteration and immunosuppressive capacity of macrophages in tumor microenvironment, Life Sci. 253 (2020) 117731, https://doi.org/10.1016/j.lfs.2020.117731.
[82] F.M. Davis, L.C. Tsoi, R. Wasikowski, et al., Epigenetic regulation of the PGE2 pathway modulates macrophage phenotype in normal and pathologic wound repair, JCI Insight 5 (17) (2020), https://doi.org/10.1172/jci.insight.138443.
[83] B. Luan, Y.S. Yoon, J. Le Lay, et al., CREB pathway links PGE2 signaling with macrophage polarization, Proc. Natl. Acad. Sci. USA 112 (51) (2015) 15642–15647, https://doi.org/10.1073/pnas.1519644112.
[84] S. Shinomiya, H. Naraba, A. Ueno, et al., Regulation of TNFalpha and interleukin-10 production by prostaglandins I(2) and E(2): studies with prostaglandin receptor-deficient mice and prostaglandin E-receptor subtype-selective synthetic agonists, Biochem. Pharmacol. 61 (9) (2001) 1153–1160, https://doi.org/10.1016/s0006-2952(01)00586-x.
[85] K. Takayama, G. Garcia-Cardena, G.K. Sukhova, et al., Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor, J. Biol. Chem. 277 (46) (2002) 44147–44154, https://doi.org/10.1074/jbc.M204810200.
[86] H. Oshima, K. Hioki, B.K. Popivanova, et al., Prostaglandin E(2) signaling and bacterial infection recruit tumor-promoting macrophages to mouse gastric tumors, Gastroenterology 140 (2) (2011) 596–607, https://doi.org/10.1053/j.gastro.2010.11.007.
[87] E. Eruslanov, S. Kaliberov, I. Daurkin, et al., Altered expression of 15-hydroxy-prostaglandin dehydrogenase in tumor-infiltrated CD11b myeloid cells: a mechanism for immune evasion in cancer, J. Immunol. 182 (12) (2009) 7548–7557, https://doi.org/10.4049/jimmunol.0802358.
[88] K.F. MacKenzie, K. Clark, S. Naqvi, et al., PGE(2) induces macrophage IL-10 production and a regulatory-like phenotype via a protein kinase A-SIK-CRTC3 pathway, J. Immunol. 190 (2) (2013) 565–577, https://doi.org/10.4049/jimmunol.1202462.
[89] M. Yasui-Kato, S. Patlada, M. Yokode, et al., EP4 signalling is essential for controlling islet inflammation by causing a shift in macrophage polarization in obesity/type 2 diabetes, Diab. Vasc. Dis. Res. 17 (4) (2020) 1479164120945675, https://doi.org/10.1177/1479164120945675.
[90] A. Sauter, D.H. Yi, Y. Li, et al., The culture dish surface influences the phenotype and cytokine production of human monocyte-derived dendritic cells, Front. Immunol. 10 (2019) 2352, https://doi.org/10.3389/fimmu.2019.02352.
[91] H. Harizi, M. Juzan, C. Grosset, et al., Dendritic cells issued in vitro from bone marrow produce PGE(2) that contributes to the immunomodulation induced by antigen-presenting cells, Cell. Immunol. 209 (1) (2001) 19–28, https://doi.org/10.1006/cimm.2001.1785.
[92] H. Harizi, N. Gualde, Dendritic cells produce eicosanoids, which modulate generation and functions of antigen-presenting cells, Prostaglandins Leukot. Essent. Fat. Acids 66 (5–6) (2002) 459–466, https://doi.org/10.1054/plef.2002.0383.
[93] N. Obermajer, R. Muthuswamy, J. Lesnock, et al., Positive feedback between PGE2 and COX2 redirects the differentiation of human dendritic cells toward

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stable myeloid-derived suppressor cells, Blood 118 (20) (2011) 5498–5505, https://doi.org/10.1182/blood-2011-07-365825.
[94] S.F. van Helden, M.M. Oud, B. Joosten, et al., PGE2-mediated podosome loss in dendritic cells is dependent on actomyosin contraction downstream of the RhoA-rho-kinase axis, J. Cell Sci. 121 (Pt 7) (2008) 1096–1106, https://doi.org/10.1242/jcs.020289.
[95] J.H. Yen, T. Khayrullina, D. Ganea, PGE2-induced metalloproteinase-9 is essential for dendritic cell migration, Blood 111 (1) (2008) 260–270, https://doi.org/10.1182/blood-2007-05-090613.
[96] H. Harizi, N. Gualde, Pivotal role of PGE2 and IL-10 in the cross-regulation of dendritic cell-derived inflammatory mediators, Cell. Mol. Immunol. 3 (4) (2006) 271–277.
[97] M.S. von Bergwelt-Baildon, A. Popov, T. Saric, et al., CD25 and indoleamine 2,3-dioxygenase are up-regulated by prostaglandin E2 and expressed by tumor-associated dendritic cells in vivo: additional mechanisms of T-cell inhibition, Blood 108 (1) (2006) 228–237, https://doi.org/10.1182/blood-2005-08-3507.
[98] Hedi Harizi, Monique Juzan, Vincent Pitard, et al., Cyclooxygenase-2-issued prostaglandin e(2) enhances the production of endogenous IL-10, which down-regulates dendritic cell functions, J. Immunol. 168 (5) (2002) 2255–2263, https://doi.org/10.4049/jimmunol.168.5.2255.
[99] D.S. Whittaker, K.S. Bahjat, L.L. Moldawer, et al., Autoregulation of human monocyte-derived dendritic cell maturation and IL-12 production by cyclooxygenase-2-mediated prostanoid production, J. Immunol. 165 (8) (2000) 4298–4304, https://doi.org/10.4049/jimmunol.165.8.4298.
[100] T. Condamine, D.I. Gabrilovich, Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function, Trends Immunol. 32 (1) (2011) 19–25, https://doi.org/10.1016/j.it.2010.10.002.
[101] P. Sinha, V.K. Clements, A.M. Fulton, et al., Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells, Cancer Res. 67 (9) (2007) 4507–4513, https://doi.org/10.1158/0008-5472.CAN-06-4174.
[102] Y. Yang, M. Zhang, Y. Zhang, et al., 5-fluorouracil suppresses colon tumor through activating the p53-Fas pathway to sensitize myeloid-derived suppressor cells to FasL(+) cytotoxic T lymphocyte cytotoxicity, Cancers (Basel) 15 (5) (2023), https://doi.org/10.3390/cancers15051563.
[103] M. Fujita, G. Kohanbash, W. Fellows-Mayle, et al., COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells, Cancer Res. 71 (7) (2011) 2664–2674, https://doi.org/10.1158/0008-5472.CAN-10-3055.
[104] C. Porta, F.M. Consonni, S. Morlacchi, et al., Tumor-derived prostaglandin E2 promotes p50 NF-kappaB-dependent differentiation of Monocytic MDSCs, Cancer Res. 80 (13) (2020) 2874–2888, https://doi.org/10.1158/0008-5472.CAN-19-2843.
[105] G. Yan, H. Zhao, Q. Zhang, et al., A RIPK3-PGE(2) circuit mediates myeloid-derived suppressor cell-potentiated colorectal carcinogenesis, Cancer Res. 78 (19) (2018) 5586–5599, https://doi.org/10.1158/0008-5472.CAN-17-3962.
[106] J. Chen, S. Cai, R. Li, et al., Blockade of Cycloxygenase-2 ameliorates sepsis induced immune-suppression by regulating myeloid-derived suppressor cells, Int. Immunopharmacol. 104 (2022) 108506, https://doi.org/10.1016/j.intimp.2021.108506.
[107] D. Wang, R.N. DuBois, An inflammatory mediator, prostaglandin E2, in colorectal cancer, Cancer J. 19 (6) (2013) 502–510, https://doi.org/10.1097/PPO.0000000000000003.
[108] T. Shimozato, P.W. Kincade, Prostaglandin E(2) and stem cell factor can deliver opposing signals to B lymphocyte precursors, Cell. Immunol. 198 (1) (1999), https://doi.org/10.1006/cimm.1999.1575.
[109] M. Prijatelj, T. Celhar, I. Mlinaric-Rascan, Prostaglandin EP4 receptor enhances BCR-induced apoptosis of immature B cells, Prostaglandins Other Lipid Mediat. 95 (1–4) (2011) 19–26, https://doi.org/10.1016/j.prostaglandins.2011.04.001.
[110] R.L. Roper, R.P. Phipps, Prostaglandin E2 and cAMP inhibit B lymphocyte activation and simultaneously promote IgE and IgG1 synthesis, J. Immunol. 149 (9) (1992) 2984–2991.
[111] J. Murn, O. Alibert, N. Wu, et al., Prostaglandin E2 regulates B cell proliferation through a candidate tumor suppressor, Ptger4, J. Exp. Med. 205 (13) (2008) 3091–3103, https://doi.org/10.1084/jem.20081163.
[112] Z. Han, Y. Jing, S. Zhang, Y. Liu, Y. Shi, L. Wei, The role of immunosuppression of mesenchymal stem cells in tissue repair and tumor growth, Cell Biosci. 2 (1) (2012) 8, https://doi.org/10.1186/2045-3701-2-8.
[113] S.L. Dorris, R.S. Peebles, PGI2as a regulator of inflammatory diseases, Mediat. Inflamm. 2012 (2012) 1–9, https://doi.org/10.1155/2012/926968.
[114] F.J. Kellie, Prostaglandin a for treating pre-eclampsia, Cochrane Database Syst. Rev. (2017), https://doi.org/10.1002/14651858.CD009657.pub2.
[115] W. Zhou, T.S. Blackwell, K. Goleniewska, et al., Prostaglandin I2 analogs inhibit Th1 and Th2 effector cytokine production by CD4 T cells, J. Leukoc. Biol. 81 (3) (2007) 809–817, https://doi.org/10.1189/jlb.0606375.
[116] M.G. Boswell, W. Zhou, D.C. Newcomb, et al., PGI2 as a regulator of CD4+ subset differentiation and function, Prostaglandins Other Lipid Mediat. 96 (1–4) (2011) 21–26, https://doi.org/10.1016/j.prostaglandins.2011.08.003.
[117] A.E. Norlander, M.H. Bloodworth, S. Toki, et al., Prostaglandin I2 signaling licenses Treg suppressive function and prevents pathogenic reprogramming, J. Clin. Invest. 131 (7) (2021), https://doi.org/10.1172/jci140690.
[118] W. Zhou, S. Toki, J. Zhang, et al., Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses, Am. J. Respir. Crit. Care Med. 193 (1) (2016) 31–42, https://doi.org/10.1164/rccm.201410-1793OC.
[119] W. Zhou, J. Zhang, K. Goleniewska, et al., Prostaglandin I2 suppresses proinflammatory chemokine expression, CD4 T cell activation, and STAT6-independent allergic lung inflammation, J. Immunol. 197 (5) (2016) 1577–1586, https://doi.org/10.4049/jimmunol.1501063.
[120] A.E. Norlander, M.H. Bloodworth, S. Toki, et al., Prostaglandin I2 signaling licenses Treg suppressive function and prevents pathogenic reprogramming, J. Clin. Invest. 131 (7) (2021), https://doi.org/10.1172/JCI140690.
[121] W. Zhou, K. Goleniewska, J. Zhang, et al., Cyclooxygenase inhibition abrogates aeroallergen-induced immune tolerance by suppressing prostaglandin I2 receptor signaling, J. Allergy Clin. Immunol. 134 (3) (2014) 698–705, https://doi.org/10.1016/j.jaci.2014.06.004.
[122] S. Toki, W. Zhou, K. Goleniewska, et al., Endogenous PGI2 signaling through IP inhibits neutrophilic lung inflammation in LPS-induced acute lung injury mice model, Prostaglandins Other Lipid Mediat. 136 (2018) 33–43, https://doi.org/10.1016/j.prostaglandins.2018.04.001.
[123] B. Raychaudhuri, A. Malur, T.L. Bonfield, et al., The prostacyclin analogue treprostinil blocks NFkappaB nuclear translocation in human alveolar macrophages, J. Biol. Chem. 277 (36) (2002) 33344–33348, https://doi.org/10.1074/jbc.M203567200.
[124] Weisong Zhou, Koichi Hashimoto, Kasia Goleniewska, et al., Prostaglandin I2 analogs inhibit proinflammatory cytokine production and T cell stimulatory function of dendritic cells, J. Immunol. 178 (2) (2007) 702–710, https://doi.org/10.4049/jimmunol.178.2.702.
[125] L. Wu, Q. Lin, Z. Ma, et al., Mesenchymal PGD(2) activates an ILC2-Treg axis to promote proliferation of normal and malignant HSPCs, Leukemia 34 (11) (2020) 3028–3041, https://doi.org/10.1038/s41375-020-0843-8.
[126] T. Nakamura, Y. Fujiwara, R. Yamada, et al., Mast cell-derived prostaglandin D(2) attenuates anaphylactic reactions in mice, J. Allergy Clin. Immunol. 140 (2) (2017) 630–632.e639, https://doi.org/10.1016/j.jaci.2017.02.030.
[127] K. Kobayashi, Y. Tsubosaka, M. Hori, et al., Prostaglandin D2-DP signaling promotes endothelial barrier function via the cAMP/PKA/Tiam1/Rac1 pathway, Arterioscler. Thromb. Vasc. Biol. 33 (3) (2013) 565–571, https://doi.org/10.1161/ATVBAHA.112.300993.
[128] T. Matsuoka, S. Narumiya, Prostaglandin receptor signaling in disease, ScientificWorldJournal 7 (2007) 1329–1347, https://doi.org/10.1100/tsw.2007.182.
[129] M. Kupczyk, P. Kuna, Targeting the PGD(2)/CRTH2/DP1 signaling pathway in asthma and allergic disease: current status and future perspectives, Drugs 77 (12) (2017) 1281–1294, https://doi.org/10.1007/s40265-017-0777-2.
[130] A.S. Ahmad, H. Ottallah, C.B. Maciel, et al., Role of the L-PGDS-PGD2-DP1 receptor axis in sleep regulation and neurologic outcomes, Sleep 42 (6) (2019), https://doi.org/10.1093/sleep/zsz073.
[131] M. Rossitto, S. Ujjan, F. Poulat, et al., Multiple roles of the prostaglandin D2 signaling pathway in reproduction, Reproduction 149 (1) (2015) R49–R58, https://doi.org/10.1530/REP-14-0381.
[132] J. Li, D. Kong, Q. Wang, et al., Niacin ameliorates ulcerative colitis via prostaglandin D(2)-mediated D prostanoid receptor 1 activation, EMBO Mol. Med. 9 (5) (2017) 571–588, https://doi.org/10.15252/emmm.201606987.
[133] L. Cosmi, F. Annunziato, M.I.G. Galli, et al., CRTH2 is the most reliable marker for the detection of circulating human type 2 Th and type 2 T cytotoxic cells in health and disease, Eur. J. Immunol. 30 (10) (2000) 2972–2979, https://doi.org/10.1002/1521-4141(200010)30:10<2972::AID-IMMU2972>3.0.CO;2-#.
[134] T.C. Moon, E. Campos-Alberto, T. Yoshimura, et al., Expression of DP2 (CRTh2), a prostaglandin D(2) receptor, in human mast cells, PLoS ONE 9 (9) (2014) e108595, https://doi.org/10.1371/journal.pone.0108595.
[135] B. Zhang, Q. Bie, P. Wu, et al., PGD2/PTGDR2 signaling restricts the self-renewal and tumorigenesis of gastric cancer, Stem Cells 36 (7) (2018) 990–1003, https://doi.org/10.1002/stem.2821.
[136] E.D. Wojno, L.A. Monticelli, S.V. Tran, et al., The prostaglandin D(2) receptor CRTH2 regulates accumulation of group 2 innate lymphoid cells in the inflamed lung, Mucosal Immunol. 8 (6) (2015) 1313–1323, https://doi.org/10.1038/mi.2015.21.
[137] K. Jandl, A. Heinemann, The therapeutic potential of CRTH2/DP2 beyond allergy and asthma, Prostaglandins Other Lipid Mediat. 133 (2017) 42–48, https://doi.org/10.1016/j.prostaglandins.2017.08.006.
[138] E. Bellei, A. Vilella, E. Monari, et al., Serum protein changes in a rat model of chronic pain show a correlation between animal and humans, Sci. Rep. 7 (2017) 41723, https://doi.org/10.1038/srep41723.
[139] M. Herve, V. Angeli, E. Pinzar, et al., Pivotal roles of the parasite PGD2 synthase and of the host D prostanoid receptor 1 in schistosome immune evasion, Eur. J. Immunol. 33 (10) (2003) 2764–2772, https://doi.org/10.1002/eji.200324143.
[140] R. Vijay, A.R. Fehr, A.M. Janowski, et al., Virus-induced inflammasome activation is suppressed by prostaglandin D(2)/DP1 signaling, Proc. Natl. Acad. Sci. USA 114 (27) (2017) E5444–E5453, https://doi.org/10.1073/pnas.1704099114.
[141] A.K. Verma, J. Zheng, M. Mack, et al., Differential effects of prostaglandin D(2) signaling on macrophages and microglia in murine coronavirus encephalomyelitis, mBio 12 (5) (2021) e0196921, https://doi.org/10.1128/mBio.01969-21.
[142] C. Li, Z. Sun, F. Yuan, et al., Mechanism of indoleamine 2, 3-dioxygenase inhibiting cardiac allograft rejection in mice, J. Cell. Mol. Med. 24 (6) (2020) 3438–3448, https://doi.org/10.1111/jcmm.15024.
[143] N.K. Bassal, B.P. Hughes, M. Costabile, Prostaglandin D2 is a novel repressor of IFNgamma induced indoleamine-2,3-dioxygenase via the DP1 receptor and cAMP pathway, Prostaglandins Leukot. Essent. Fat. Acids 110 (2016) 48–54, https://doi.org/10.1016/j.plefa.2016.01.006.
[144] M.A. Syed, M. Joo, Z. Abbas, et al., Expression of TREM-1 is inhibited by PGD2 and PGJ2 in macrophages, Exp. Cell Res. 316 (19) (2010) 3140–3149, https://doi.org/10.1016/j.yexcr.2010.08.009.

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[145] T.J. Hall, J. Brostoff, Inhibition of human natural killer cell activity by prostaglandin D2, Immunol. Lett. 7 (3) (1983) 141–144, https://doi.org/10.1016/0165-2478(83)90061-5.
[146] Y. Chen, B. Perussia, K.S. Campbell, Prostaglandin D2 suppresses human NK cell function via signaling through D prostanoid receptor, J. Immunol. 179 (5) (2007) 2766–2773, https://doi.org/10.4049/jimmunol.179.5.2766.
[147] J.C. Tseng, J.X. Yang, C.Y. Lee, et al., Induction of immune responses and phosphatidylserine exposure by TLR9 activation results in a cooperative antitumor effect with a phosphatidylserine-targeting prodrug, Int. J. Biol. Sci. 19 (9) (2023) 2648–2662, https://doi.org/10.7150/ijbs.81683.
[148] D. Torres, J. Fontaine, T. Mallevaey, T. Matsuoka, T. Maruyama, S. Narumiya, M. Capron, P. Gosset, C. Faveeuw, F. Trottein, Prostaglandin D2 inhibits the production of IFN-gamma by invariant NK T cells: consequences in the control of B16 melanoma, J. Immunol. 180 (2) (2008) 783–792, https://doi.org/10.4049/jimmunol.180.2.783.
[149] P. Gosset, M. Pichavant, C. Faveeuw, et al., Prostaglandin D2 affects the differentiation and functions of human dendritic cells: impact on the T cell response, Eur. J. Immunol. 35 (5) (2005) 1491–1500, https://doi.org/10.1002/eji.200425319.
[150] G. Theiner, A. Gessner, M.B. Lutz, The mast cell mediator PGD2 suppresses IL-12 release by dendritic cells leading to Th2 polarized immune responses in vivo, Immunobiology 211 (6–8) (2006) 463–472, https://doi.org/10.1016/j.imbio.2006.05.020.
[151] J. Zhao, J. Zhao, K. Legge, et al., Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice, J. Clin. Invest. 121 (12) (2011) 4921–4930, https://doi.org/10.1172/JCI59777.
[152] S. Trabanelli, M.F. Chevalier, A. Martinez-Usatorre, et al., Tumour-derived PGD2 and NKp30-B7H6 engagement drives an immunosuppressive ILC2-MDSC axis, Nat. Commun. 8 (1) (2017) 593, https://doi.org/10.1038/s41467-017-00678-2.
[153] M. Hamberg, J. Svensson, B. Samuelsson, Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides, Proc. Natl. Acad. Sci. USA 72 (8) (1975) 2994–2998, https://doi.org/10.1073/pnas.72.8.2994.
[154] E.M. Smyth, Thromboxane and the thromboxane receptor in cardiovascular disease, Clin. Lipidol. 5 (2) (2010) 209–219, https://doi.org/10.2217/clp.10.11.
[155] P. Needleman, M. Minkes, A. Raz, Thromboxanes: selective biosynthesis and distinct biological properties, Science 193 (4248) (1976) 163–165, https://doi.org/10.1126/science.945611.
[156] P. Needleman, S. Moncada, S. Bunting, et al., Identification of an enzyme in platelet microsomes which generates thromboxane A2 from prostaglandin endoperoxides, Nature 261 (5561) (1976) 558–560, https://doi.org/10.1038/261558a0.
[157] T.H. Chueh, Y.H. Cheng, K.H. Chen, et al., Thromboxane A2 synthase and thromboxane receptor deletion reduces Ischaemia/reperfusion-evoked inflammation, apoptosis, Autophagy Pyroptos. Thromb Haemost. 120 (2) (2020) 329–343, https://doi.org/10.1055/s-0039-3400304.
[158] C.W. Yang, E.R. Unanue, Neutrophils control the magnitude and spread of the immune response in a thromboxane A2-mediated process, J. Exp. Med. 210 (2) (2013) 375–387, https://doi.org/10.1084/jem.20122183.
[159] F. Moalli, J. Cupovic, F. Thelen, et al., Thromboxane A2 acts as tonic immunoregulator by preferential disruption of low-avidity CD4+ T cell–dendritic cell interactions, J. Exp. Med. 211 (13) (2014) 2507–2517, https://doi.org/10.1084/jem.20140137.
[160] K. Kabashima, T. Murata, H. Tanaka, et al., Thromboxane A2 modulates interaction of dendritic cells and T cells and regulates acquired immunity, Nat. Immunol. 4 (7) (2003) 694–701, https://doi.org/10.1038/ni943.
[161] G. Remuzzi, M. Noris, A. Benigni, et al., Thromboxane A2 receptor blocking abrogates donor-specific unresponsiveness to renal allografts induced by thymic recognition of major histocompatibility allopeptide, J. Exp. Med. 180 (5) (1994) 1967–1972, https://doi.org/10.1084/jem.180.5.1967.
[162] Q. Yang, M. Shi, Y. Shen, et al., COX-1-derived thromboxane A2 plays an essential role in early B-cell development via regulation of JAK/STAT5 signaling in mouse, Blood 124 (10) (2014) 1610–1621, https://doi.org/10.1182/blood-2014-03-559658.
[163] L. Riaposova, S.H. Kim, A.C. Hanyaloglu, et al., Prostaglandin F2alpha requires activation of calcium-dependent signalling to trigger inflammation in human myometrium, Front. Endocrinol. 14 (2023) 1150125, https://doi.org/10.3389/fendo.2023.1150125.
[164] S. Basu, Novel cyclooxygenase-catalyzed bioactive prostaglandin F2alpha from physiology to new principles in inflammation, Med. Res. Rev. 27 (4) (2007) 435–468, https://doi.org/10.1002/med.20098.
[165] J. Helmersson-Karlqvist, J. Arnlov, A. Larsson, et al., Prostaglandin F2alpha formation is associated with mortality in a Swedish community-based cohort of older males, Eur. Heart J. 36 (4) (2015) 238–243, https://doi.org/10.1093/eurheartj/eht212.
[166] A.C.A. Santos, T. Sartori, P. Borelli, et al., Prostaglandin F2alpha in vitro can affect basic inflammatory parameters of mesenchymal stem cells and slight modulating some of their immunomodulatory properties, Prostaglandins Leukot. Essent. Fat. Acids 163 (2020) 102210, https://doi.org/10.1016/j.plefa.2020.102210.
[167] A.E. Wallace, K.J. Sales, R.D. Catalano, et al., Prostaglandin F2alpha-F-prostanoid receptor signaling promotes neutrophil chemotaxis via chemokine (C-X-C motif) ligand 1 in endometrial adenocarcinoma, Cancer Res. 69 (14) (2009) 5726–5733, https://doi.org/10.1158/0008-5472.CAN-09-0390.
[168] T. Maehara, K. Fujimori, Inhibition of prostaglandin F2α receptors exaggerates HCl-induced lung inflammation in mice, Int. J. Mol. Sci. 22 (23) (2021), https://doi.org/10.3390/ijms222312843.
[169] T. Maehara, F. Higashitarumi, R. Kondo, et al., Prostaglandin F(2alpha) receptor antagonist attenuates LPS-induced systemic inflammatory response in mice, FASEB J. 34 (11) (2020) 15197–15207, https://doi.org/10.1096/fj.202001481R.
[170] K.J. Witek, A.J. Ziecik, I. Malysz-Cymborska, et al., The presence of CC chemokines and their aberrant role in the porcine corpus luteum, Reprod. Domest. Anim. 55 (5) (2020) 632–646, https://doi.org/10.1111/rda.13663.
[171] G.Y. Park, J.W. Christman, Involvement of cyclooxygenase-2 and prostaglandins in the molecular pathogenesis of inflammatory lung diseases, Am. J. Phys. Lung Cell. Mol. Phys. 290 (5) (2006) L797–L805, https://doi.org/10.1152/ajplung.00513.2005.
[172] D. Calebiro, V.O. Nikolaev, M.C. Gagliani, et al., Persistent cAMP-signals triggered by internalized G-protein-coupled receptors, PLoS Biol. 7 (8) (2009) e1000172, https://doi.org/10.1371/journal.pbio.1000172.
[173] X. Liu, C.M. Davis, N.J. Alkayed, P450 eicosanoids and reactive oxygen species interplay in brain injury and neuroprotection, Antioxid. Redox Signal. 28 (10) (2018) 987–1007, https://doi.org/10.1089/ars.2017.7056.
[174] A. Drozd, M. Szczuko, A. Bohatyrewicz, et al., High levels of thromboxane (TX) are associated with the sex-dependent non-dipping phenomenon in ischemic stroke patients, J. Clin. Med. 11 (9) (2022), https://doi.org/10.3390/jcm11092652.
[175] K. Tsuchida, T. Ibuki, K. Matsumura, Bromoenol lactone, an inhibitor of calcium-independent phospholipase A2, suppresses carrageenan-induced prostaglandin production and hyperalgesia in rat hind paw, Mediat. Inflamm. 2015 (2015) 605727, https://doi.org/10.1155/2015/605727.
[176] G. Sui, G. Cheng, J. Yuan, et al., Interleukin (IL)-13, prostaglandin E2 (PGE2), and prostacyclin 2 (PGI2) activate hepatic stellate cells via protein kinase C (PKC) pathway in hepatic fibrosis, Med. Sci. Monit. 24 (2018) 2134–2141, https://doi.org/10.12659/msm.906442.
[177] D.D. Smith, X. Tan, V.V. Raveendran, et al., Mast cell deficiency attenuates progression of atherosclerosis and hepatic steatosis in apolipoprotein E-null mice, Am. J. Physiol. Heart Circ. Physiol. 302 (12) (2012) H2612–H2621, https://doi.org/10.1152/ajpheart.00879.2011.
[178] T. Kobayashi, Y. Tahara, M. Matsumoto, et al., Roles of thromboxane A2 and prostacyclin in the development of atherosclerosis in apoE-deficient mice, J. Clin. Invest. 114 (6) (2004) 784–794, https://doi.org/10.1172/jci200421446.
[179] P.A.T. Pereira, P.A. Assis, M.K.B. Prado, et al., Prostaglandins D(2) and E(2) have opposite effects on alveolar macrophages infected with Histoplasma capsulatum, J. Lipid Res. 59 (2) (2018) 195–206, https://doi.org/10.1194/jlr.M078162.
[180] H. Shojo, C.V. Borlongan, T. Mabuchi, Genetic and histological alterations reveal key role of prostaglandin synthase and cyclooxygenase 1 and 2 in traumatic brain injury-induced neuroinflammation in the cerebral cortex of rats exposed to moderate fluid percussion injury, Cell Transplant. 26 (7) (2017) 1301–1313, https://doi.org/10.1177/0963689717715169.
[181] C. Qiu, X. Zhao, L. She, et al., Baricitinib induces LDL-C and HDL-C increases in rheumatoid arthritis: a meta-analysis of randomized controlled trials, Lipids Health Dis. 18 (1) (2019) 54, https://doi.org/10.1186/s12944-019-0994-7.
[182] L.J. Crofford, R.L. Wilder, A.P. Ristimäki, et al., Cyclooxygenase-1 and -2 expression in rheumatoid synovial tissues. Effects of interleukin-1 beta, phorbol ester, and corticosteroids, J. Clin. Invest. 93 (3) (1994) 1095–1101, https://doi.org/10.1172/JCI117060.
[183] E. Ricciotti, G.A. FitzGerald, Prostaglandins and inflammation, Arterioscler. Thromb. Vasc. Biol. 31 (5) (2011) 986–1000, https://doi.org/10.1161/atvbaha.110.207449.
[184] J.M. McCoy, J.R. Wicks, L.P. Audoly, The role of prostaglandin E2 receptors in the pathogenesis of rheumatoid arthritis, J. Clin. Invest. 110 (5) (2002) 651–658, https://doi.org/10.1172/jci0215528.
[185] Q. Ding, W. Hu, R. Wang, et al., Signaling pathways in rheumatoid arthritis: implications for targeted therapy, Signal Transduct. Target. Ther. 8 (1) (2023) 68, https://doi.org/10.1038/s41392-023-01331-9.
[186] P.F. Gomez, M.H. Pillinger, M. Attur, et al., Resolution of inflammation: prostaglandin E2 dissociates nuclear trafficking of individual NF-kappaB subunits (p65, p50) in stimulated rheumatoid synovial fibroblasts, J. Immunol. 175 (10) (2005) 6924–6930, https://doi.org/10.4049/jimmunol.175.10.6924.
[187] A. Mirshafiey, F. Jadidi-Niaragh, Prostaglandins in pathogenesis and treatment of multiple sclerosis, Immunopharmacol. Immunotoxicol. 32 (4) (2010) 543–554, https://doi.org/10.3109/08923971003667627.
[188] T. Yagami, H. Koma, Y. Yamamoto, Pathophysiological roles of cyclooxygenases and prostaglandins in the central nervous system, Mol. Neurobiol. 53 (7) (2016) 4754–4771, https://doi.org/10.1007/s12035-015-9355-3.
[189] Z. Xiang, T. Lin, S.A. Reeves, 15d-PGJ2 induces apoptosis of mouse oligodendrocyte precursor cells, J. Neuroinflammation 4 (2007) 18, https://doi.org/10.1186/1742-2094-4-18.
[190] S. Palumbo, C.D. Toscano, L. Parente, et al., The cyclooxygenase-2 pathway via the PGE(2) EP2 receptor contributes to oligodendrocytes apoptosis in cuprizone-induced demyelination, J. Neurochem. 121 (3) (2012) 418–427, https://doi.org/10.1111/j.1471-4159.2011.07363.x.
[191] S. Gulla, D. Lomada, A. Lade, et al., Role of prostaglandins in multiple sclerosis, Curr. Pharm. Des. 26 (7) (2020) 730–742, https://doi.org/10.2174/1381612826666200107141328.
[192] M. Liu, L. Xiao, S. Liu, et al., Immunoregulation of myelin-specific CD4+ T cell response by neural stem/progenitor cells: role of prostaglandin E2, J. Neuroimmunol. 255 (1–2) (2013) 32–38, https://doi.org/10.1016/j.jneuroim.2012.10.013.

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[193] L. Steinman, S.S. Zamvil, How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis, Ann. Neurol. 60 (1) (2006) 12–21, https://doi.org/10.1002/ana.20913.
[194] J. Xu, S. Guo, Z. Jia, et al., Additive effect of prostaglandin E2 and adenosine in mouse experimental autoimmune encephalomyelitis, Prostaglandins Other Lipid Mediat. 100-101 (2013) 30–35, https://doi.org/10.1016/j.prostaglandins.2012.11.004.
[195] M. Karaky, G. Boucher, S. Mola, et al., Prostaglandins and calprotectin are genetically and functionally linked to the inflammatory bowel diseases, PLoS Genet. 18 (9) (2022) e1010189, https://doi.org/10.1371/journal.pgen.1010189.
[196] K. Kashiwagi, K. Jimbo, M. Suzuki, et al., Impact of anti-TNFalpha treatment on the humoral response to the BNT162b2 mRNA COVID-19 vaccine in pediatric inflammatory bowel disease patients, Vaccines (Basel) 10 (10) (2022), https://doi.org/10.3390/vaccines10101618.
[197] S. Sasaki, I. Hirata, K. Maemura, et al., Prostaglandin E2 inhibits lesion formation in dextran sodium sulphate-induced colitis in rats and reduces the levels of mucosal inflammatory cytokines, Scand. J. Immunol. 51 (1) (2000) 23–28, https://doi.org/10.1046/j.1365-3083.2000.00623.x.
[198] P. Lan, Y. Zhang, L.C. Smith, et al., Immunomodulatory effect of urine-derived stem cells on inflammatory bowel diseases via downregulating Th1/Th17 immune responses in a PGE2-dependent manner, J. Crohn's Colitis 14 (5) (2020) 654–668, https://doi.org/10.1093/ecco-jcc/jjz200.
[199] Y.S. Kim, H.J. Park, H. Kim, et al., Gastroprotective effects of Paeonia extract mixture HT074 against experimental gastric ulcers in rats, Evid. Based Complement. Alternat. Med. 2019 (2019) 3546258, https://doi.org/10.1155/2019/3546258.
[200] J.L. Wallace, Prostaglandin biology in inflammatory bowel disease, Gastroenterol. Clin. N. Am. 30 (4) (2001) 971–980, https://doi.org/10.1016/s0889-8553(05)70223-5.
[201] K. Kabashima, New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity, J. Dermatol. Sci. 70 (1) (2013) 3–11, https://doi.org/10.1016/j.jdermsci.2013.02.001.
[202] E.N. Charlesworth, A. Kagey-Sobotka, P.S. Norman, et al., Cutaneous late-phase response in food-allergic children and adolescents with atopic dermatitis, Clin. Exp. Allergy 23 (5) (1993) 391–397, https://doi.org/10.1111/j.1365-2222.1993.tb00344.x.
[203] D.A. Yanes, J.L. Mosser-Goldfarb, Emerging therapies for atopic dermatitis: the prostaglandin/leukotriene pathway, J. Am. Acad. Dermatol. 78 (3 Suppl 1) (2018) S71–S75, https://doi.org/10.1016/j.jaad.2017.12.021.
[204] C.T. Robb, H.J. McSorley, J. Lee, et al., Prostaglandin E(2) stimulates adaptive IL-22 production and promotes allergic contact dermatitis, J. Allergy Clin. Immunol. 141 (1) (2018) 152–162, https://doi.org/10.1016/j.jaci.2017.04.045.
[205] V. Angeli, D. Staumont, A.S. Charbonnier, et al., Activation of the D prostanoid receptor 1 regulates immune and skin allergic responses, J. Immunol. 172 (6) (2004) 3822–3829, https://doi.org/10.4049/jimmunol.172.6.3822.
[206] V. Angeli, C. Faveeuw, O. Roye, et al., Role of the parasite-derived prostaglandin D2 in the inhibition of epidermal Langerhans cell migration during schistosomiasis infection, J. Exp. Med. 193 (10) (2001), https://doi.org/10.1084/jem.1193.1010.1135.
[207] C. Binda, S. Genier, J. Degrandmaison, et al., L-type prostaglandin D synthase regulates the trafficking of the PGD(2) DP1 receptor by interacting with the GTPase Rab4, J. Biol. Chem. 294 (45) (2019) 16865–16883, https://doi.org/10.1074/jbc.RA119.008233.
[208] S.A. Boehme, K. Franz-Bacon, E.P. Chen, et al., A small molecule CRTH2 antagonist inhibits FITC-induced allergic cutaneous inflammation, Int. Immunol. 21 (1) (2009) 81–93, https://doi.org/10.1093/intimm/dxn127.
[209] Z. Zaslona, E. Flis, M.M. Wilk, et al., Caspase-11 promotes allergic airway inflammation, Nat. Commun. 11 (1) (2020) 1055, https://doi.org/10.1038/s41467-020-14945-2.
[210] R.S. Peebles Jr., Prostaglandins in asthma and allergic diseases, Pharmacol. Ther. 193 (2019) 1–19, https://doi.org/10.1016/j.pharmthera.2018.08.001.
[211] N.J. Monteleone, A.E. Moore, J.R. Iacona, et al., miR-21-mediated regulation of 15-hydroxyprostaglandin dehydrogenase in colon cancer, Sci. Rep. 9 (1) (2019) 5405, https://doi.org/10.1038/s41598-019-41862-2.
[212] S. Zelenay, A.G. van der Veen, J.P. Bottcher, et al., Cyclooxygenase-dependent tumor growth through evasion of immunity, Cell 162 (6) (2015) 1257–1270, https://doi.org/10.1016/j.cell.2015.08.015.
[213] F.R. Greten, S.I. Grivennikov, Inflammation and cancer: triggers, mechanisms, and consequences, Immunity 51 (1) (2019) 27–41, https://doi.org/10.1016/j.immuni.2019.06.025.
[214] S.M. Nachvak, D. Soleimani, M. Rahimi, et al., Ginger as an anticolorectal cancer spice: a systematic review of in vitro to clinical evidence, Food Sci. Nutr. 11 (2) (2023) 651–660, https://doi.org/10.1002/fsn3.3153.
[215] E. Gurpinar, W.E. Grizzle, G.A. Piazza, COX-independent mechanisms of cancer chemoprevention by anti-inflammatory drugs, Front. Oncol. 3 (2013) 181, https://doi.org/10.3389/fonc.2013.00181.
[216] C. Stolfi, V. De Simone, F. Pallone, et al., Mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine in the chemoprevention of colorectal cancer, Int. J. Mol. Sci. 14 (9) (2013) 17972–17985, https://doi.org/10.3390/ijms140917972.
[217] Y. Take, S. Koizumi, A. Nagahisa, Prostaglandin E receptor 4 antagonist in cancer immunotherapy: mechanisms of action, Front. Immunol. 11 (2020) 324, https://doi.org/10.3389/fimmu.2020.00324.
[218] Z. Gong, Q. Li, J. Shi, et al., Immunosuppressive reprogramming of neutrophils by lung mesenchymal cells promotes breast cancer metastasis, Sci. Immunol. 8 (80) (2023) eadd5204, https://doi.org/10.1126/sciimmunol.add5204.
[219] D. Che, S. Zhang, Z. Jing, et al., Macrophages induce EMT to promote invasion of lung cancer cells through the IL-6-mediated COX-2/PGE(2)/beta-catenin signalling pathway, Mol. Immunol. 90 (2017) 197–210, https://doi.org/10.1016/j.molimm.2017.06.018.
[220] D. Tong, Q. Liu, L.A. Wang, et al., The roles of the COX2/PGE2/EP axis in therapeutic resistance, Cancer Metastasis Rev. 37 (2–3) (2018) 355–368, https://doi.org/10.1007/s10555-018-9752-y.
[221] H. Furuya, P.M. Tamashiro, Y. Shimizu, et al., Sphingosine kinase 1 expression in peritoneal macrophages is required for colon carcinogenesis, Carcinogenesis 38 (12) (2017) 1218–1227, https://doi.org/10.1093/carcin/bgx104.
[222] J. Miao, X. Lu, Y. Hu, et al., Prostaglandin E2 and PD-1 mediated inhibition of antitumor CTL responses in the human tumor microenvironment, Oncotarget 8 (52) (2017) 89802–89810, https://doi.org/10.18632/oncotarget.21155.
[223] T. Murata, M.I. Lin, K. Aritake, et al., Role of prostaglandin D2 receptor DP as a suppressor of tumor hyperpermeability and angiogenesis in vivo, Proc. Natl. Acad. Sci. USA 105 (50) (2008) 20009–20014, https://doi.org/10.1073/pnas.0805171105.
[224] A. Ajith, V. Portik-Dobos, D.D. Horuzsko, et al., HLA-G and humanized mouse models as a novel therapeutic approach in transplantation, Hum. Immunol. 81 (4) (2020) 178–185, https://doi.org/10.1016/j.humimm.2020.02.006.
[225] D.M. Kofler, A. Marson, M. Dominguez-Villar, et al., Decreased RORC-dependent silencing of prostaglandin receptor EP2 induces autoimmune Th17 cells, J. Clin. Invest. 124 (6) (2014) 2513–2522, https://doi.org/10.1172/JCI72973.
[226] M. Kaljanac, H. Abken, Do Treg speed up with CARs? Chimeric antigen receptor Treg engineered to induce transplant tolerance, Transplantation 107 (1) (2023) 74–85, https://doi.org/10.1097/TP.0000000000004316.

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