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Review

The role of prostaglandin E_2 in human vascular inflammation

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ABSTRACT

Prostaglandins (PG) are the product of a cascade of enzymes such as cyclooxygenases and PG synthases. Among PG, PGE_2 is produced by 3 isoforms of PGE synthase (PGES) and through activation of its cognate receptors (EP1–4), this PG is involved in the pathophysiology of vascular diseases. Some anti-inflammatory drugs (e.g. glucocorticoids, nonsteroidal anti-inflammatory drugs) interfere with its metabolism or effects. Vascular cells can initiate many of the responses associated with inflammation. In human vascular tissue, PGE_2 is involved in many physiological processes, such as increasing vascular permeability, cell proliferation, cell migration and control of vascular smooth muscle tone. PGE_2 has been shown to contribute to the pathogenesis of atherosclerosis, abdominal aortic aneurysm but also in physiologic/adaptive processes such as angiogenesis. Understanding the roles of PGE_2 and its cognate receptors in vascular diseases could help to identify diagnostic and prognostic biomarkers. In addition, from these recent studies new promising therapeutic approaches like mPGES-1 inhibition and/or EP4-antagonism should be investigated.

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1. Introduction

Inflammation in vascular diseases involves circulating/infiltrating inflammatory/immune cells (neutrophils, lymphocytes, monocytes, macrophages) and constitutive cells of vascular tissue (smooth muscle, endothelial cells and fibroblast). This cellular interaction produces inflammatory mediators such as cytokines e.g., interleukins (IL, IL-1β, IL-6) and Tumor Necrosis Factor (TNF)-α, well known to activate prostaglandin (PG) E_2 production [1]. Furthermore, a recent publication [2] has shown that inflammasome activation results in a high production of PGE_2. This release causes fluid escape from plasma to intestine and peritoneal cavity resulting in the death of mice in less than 30 min. PGE_2 is a key mediator of the inflammatory process in the cardiovascular system. All clinical manifestations of inflammation: rubor (redness), tumor (swelling), dolor (pain) and fever are related to its cellular effects. Redness and edema result from increased blood flow into the inflamed tissue through PGE_2 -mediated vasodilation and increased microvascular permeability. Finally, PGE_2 is also involved in many vascular diseases (e.g., atherosclerosis, aneurysm) and angiogenesis. In contrast with other reviews about PGs and inflammation [3–5], this review will focus on the involvement of PGES and PGE_2 mainly in human vascular diseases.

2. Enzymes responsible for PGE_2 synthesis

Arachidonic acid is released from membrane phospholipids by phospholipase (PL) A_2 activity [6] and can be obtained directly from diet or synthesized from linoleic acid [7]. There are fifteen isoforms of PLA_2 involved in the hydrolysis of membrane phospholipids resulting in the release of free fatty acid. Cytosolic $cPLA_{2\alpha}$ (Group IVA) is now generally considered to be a central enzyme with a greater selectivity in the production of arachidonic acid, mediating generation of eicosanoids including prostanoids [6]. However, the other PLA_2 isoforms are also involved in arachidonic acid production [8]. Some of them are of particular interest in inflammatory processes and in cardiovascular biology because they could be useful biomarkers of inflammation. For instance, group IIA PLA_2 is a secreted enzyme that has been identified as an acute phase protein with a role in the inflammatory response [9].

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Table 1
Characteristics of the enzymes responsible for PGE_2 synthesis.

Gene	Chromosome	Exons	Regulators of gene expression	Knockout model	Protein (kDa)	References
COX-1	9q32–q33.3	11	AP-1, c-Jun, c-Fos, Sp1, NFκB (1 and 2)	Reduces atherosclerosis, increases cardiac ischemia	72	[16,141]
COX-2	1q25.2–25.3	10	PPARγ1 and 2, c-Jun, c-Fos, p53, NFκB	Delays breast cancer, increases cardiac ischemia	72	[16,141,142]
mPGES-1	9q34.4	3	NFκB, PPARγ, STAT1 (α and β) and 3, NF-1, p300, RelA, Erg-2	Reduces atherosclerosis, attenuates development of chronic renal failure, increases anemia	16	[20,143–145]
mPGES-2	9q33–q34	10	PPARγ1 and 2, STAT3, HNF-1A, c-Myc, Pax-2, SRF, ERK*	ND	33	[16,25,146,147]
cPGES	12q13.13	8	LUN-1, RFX-1, c-jun, c-Fos, E2F-1, E2F, ERK*	ND	21–26	[16,25,147,148]
15PGDH	4q34–q35	7	NFκB, PPARγ1 and 2, MEF-2A, GR-α and β	ND	29	[149]

COX=cyclooxygenase; m/cPGES=microsomal or cytosolic prostaglandin E synthase, respectively and PGDH=hydroxyprostaglandin dehydrogenase. Protein (kDa) indicates the molecular weights estimated by Western blot analysis. ND=non determined. For all enzymes some of the regulators have been found on http://www.genecards.org

* indicates a regulator for rat gene expression.

Two other PLA_2 groups, $cPLA_{2\alpha}$ and the calcium-independent $iPLA_{2\beta}$ (Group VIA) are involved in leukocytes chemotaxis, a necessary process for monocytes and neutrophils migration from blood into tissues during inflammatory processes [10]. Finally, Group VII lipoprotein-associated PLA_2 (Lp-PLA_2) is a secreted enzyme produced in atherosclerotic plaques by inflammatory cells. The plasma concentration of this enzyme has been described recently as a new and promising biomarker for cardiovascular disease and in particular during atherosclerosis [11–13].

Following arachidonic acid release, a metabolic cascade is initiated by the cyclooxygenases (COX) (Table 1). The two COX isoforms (COX-1; COX-2), abundantly described in mammalian tissues [14], metabolize arachidonic acid into PGH_2. Results in humans are compatible with COX-1-derived products driving the initial phase of an acute inflammation, with COX-2 upregulation starting at later (hours) time points [15]. PGH_2 is the substrate for specific isomerases that synthesize prostanoids: PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$, and TXA_2. COX-1 couples functionally preferentially with thromboxane synthase, PGF synthase, and the cytosolic (c) PGE synthase isozymes. COX-2 couples preferentially with prostaglandin I synthase (PGIS) and the microsomal (m) PGES isozymes, both of which are often co-induced along with COX-2 by cytokines [16]. Within a given tissue or cell population, the profile of prostanoid production depends on the differential expression of PG synthases (Table 1).

In the vascular tissue, COX-1 is expressed constitutively while COX-2 expression is induced specifically in the endothelium and vascular smooth muscle cells (SMC) under increased sheer stress or inflammatory conditions [17–19], both of them are the limiting factors for PGE_2 synthesis. The association of COX-2 and COX-1 activities will produce a greater quantity of PGH_2, than COX-1 activity alone. Induction of COX-2 following stimulation with IL-1β, TNFα or lipopolysaccharide (LPS) involves the nuclear translocation of the transcription factor NF-κB. PGH_2 is metabolized by three PGE synthase isoforms (mPGES-1, mPGES-2 and cPGES) to produce PGE_2. These enzymes have received much attention; cPGES and mPGES-2 are constitutive enzymes while mPGES-1 is inducible. mPGES-1 belongs to the MAPEG family (membrane associated proteins involved in eicosanoid and glutathione metabolism) and is induced in inflammatory conditions by many mediators that include IL-1β and TNF-α [20] that activate several transcriptional factors [21] (Table 1).

2.1. Constitutive PGES

mPGES-2 and cPGES are expressed in most cell types. Localized in the cytosol, cPGES may allow coupling with proximal COX-1 in the endoplasmic reticulum rather than distal COX-2 in the perinuclear envelope [3]. On the other hand, mPGES-2 is produced as a Golgi membrane-associated protein. Paradoxically, after proteolytic cleavage of the N-terminal hydrophobic domain, it results in the formation of the mature protein whose cytosolic localization allows coupling with both COX-1 and COX-2 [3]. Despite the presence of these two constitutive PGES, the level of PGE_2 remains low in the absence of a pro-inflammatory condition. For example, in 2007, Gutiérrez-Venegas [22] showed a basal level of PGE_2 in human cultured gingival fibroblasts of less than 1 ng/ml. In this study, PGE_2 level was increased 10 fold following stimulation by LPS. This increased production can be explained by the induction of mPGES-1 and COX-2 expressions after LPS stimulation [23].

2.2. Inducible PGES

Constitutive expression of mPGES-1 has been reported [24,25] but mPGES-1 is mainly the result of induction by cytokines and growth factors [3]. The expression of enzymes responsible for PGE_2 synthesis is regulated by several receptors and transcription factors (Table 1). A major question, as far as pharmacological targets are concerned is the respective roles of COX versus mPGES-1 as the main source of PGE_2.

Payner and collaborators [24] demonstrated in a cultured human astroglioma cell line that COX-2 protein expression, in the absence of mPGES-1 protein, resulted in barely detectable PGE_2 production even in presence of cPGES. In contrast, in this study, low level COX-2 protein expression with abundant mPGES-1 protein expression resulted in 5–6 fold increase in PGE_2 production. A similar increase (3–4 fold) in PGE_2 synthesis has been measured in human smooth muscle cells under inflammatory stimulation and COX-2 induction [25]. This increase was due exclusively to mPGES-1 activity (among the 3 PGES), coupled equally to COX-1 and COX-2 activities. Taken together, these results are consistent with a major role of mPGES-1 in PGE_2 production provided that the substrate (PGH_2) is supplied by a COX activity.

Therefore, functional coupling of mPGES-1 and COX-2 results in highly increased PGE_2 production during inflammation as compared to non inflammatory conditions [25–27]. For example, the *ex-vivo* production of PGE_2 in internal mammary artery was considerably increased (13 fold) under inflammatory conditions after 24 h exposure to IL-1β and LPS [19]. The same increase of inducible PGES expression and PGE_2 concentration has been observed in inflammatory diseases such as rheumatoid arthritis [28] and cancer [29].

2.3. Enzymatic and non enzymatic synthesis of PGE_2

PGE_2 is rapidly synthesized by mPGES-1 (Vmax: 170 μmol min^{-1} mg^{-1} of tissue [30]), expressed by resident and circulating cells [31,32]. mPGES-1 activity is dependent on a cofactor (glutathione, GSH) allowing the formation of the mPGES-1-GSH-PGH_2 trimer. PGE_2 can also be synthesized by a non enzymatic mechanism [33]. Arachidonic

acid can be metabolized spontaneously (under oxidative condition) into PG-like molecules by the mechanism of lipid peroxidation to produce isoprostanes (such as 8-iso-PGE_2) [34]. Non enzymatically-derived PG can also activate the prostanoids receptors (mostly the TP) [35,36] and could increase the effects of PG. For this reason the investigation of the PGE_2 metabolic pathway must include analyses of PGES expression and also measurement of PGE_2 concentration (the sum of enzymatic and non enzymatic production).

2.4. Degradation of PGE_2

Despite an important production, in vivo studies have shown that PGE_2 has a short half-life (30 s) [37,38] and is rapidly degraded by the lung. However, in vitro studies have shown that PGE_2 has a longer half-life (more than 10 min) depending of the medium [37,38].

The kinetics of the catabolism of PGE_2 once synthesized is still sparsely known [39]; 15PGDH (hydroxy prostaglandin dehydrogenase) is the enzyme responsible for its degradation into PGA_2, a non active form of PG [40]. This rapid degradation maintains the stable level of PGE_2. Given this model, the limiting factors in PGE_2 biology seems to be related to production (both enzymatic and non enzymatic) and degradation. This short half-life of PGE_2 also confers this molecule an autocrine/paracrine role.

2.5. Respective roles of constitutive versus inducible PGES

In a mouse model of 2 h brain ischemia followed by 24 h reperfusion, mPGES-1 was over expressed [41]. Deletion of mPGES-1 in knock-out (KO) mice was not compensated by the other PGES isoforms and the concentration of brain PGE_2 remained low in the mPGES-1 KO mice submitted to ischemia/reperfusion. mPGES-1 was probably involved in brain edema because it was induced in endothelial cells (as well as microglia and neurons) and in situ injection of PGE_2 in mPGES-1 KO mice was able to reproduce edema observed in control mice. In contrast, PGE_2 synthesis was not different among tissues derived from cPGES or mPGES-2 KO mice versus their respective controls [42–44]. Finally, a low PGE_2 synthesis was measured in human embryonic kidney (HEK293) cells transfected with cPGES or mPGES-2 as compared with mPGES-1 [45,46]. Taken together, these observations clearly demonstrate a major role of mPGES-1-derived PGE_2 and suggest that mPGES1 can be a pharmacological target against inflammatory disease.

3. PGE_2 receptor subtypes

PGE_2 contributes to the regulation of vascular smooth muscle tone by activating its receptors. Vasoconstriction induced by PGE_2 after activation of the EP1 and EP3 receptors, is mediated through intracellular Ca^{2+} pathway activation or cAMP decreases, respectively [47–49]. In contrast, PGE_2 stimulation of EP2 and EP4 receptors increases cAMP content and provokes vasodilation [48,50,51] (Table 2). In human vessels, most studies have demonstrated that EP3 and EP4 receptor subtypes are responsible for vascular tone control (Fig. 1) [51]. PGE_2 has other roles in physiological processes. For example, by activating the cAMP pathway and regulating the Wnt pathway by phosphorylating GSK-3 beta, PGE_2 regulates cell proliferation in human mesenchymal stem cells [52]. Another study using human umbilical vein endothelial cells has demonstrated that a selective COX-2 inhibitor (NS-398) suppresses cell migration, a process that is attenuated by adding PGE_2 [53]. On the other hand, PGE_2 has also an important pathophysiological role in inflammation in general and vascular inflammation in particular through EP2 or EP4 receptor activation present on almost all human blood cells (platelet and white blood cells; Fig. 1) [51].

4. PGE_2 as a mediator of inflammation

Inflammation is the orchestrated response of the organism to “danger” signals [54]. From a biological engineering point of view, the inflammatory response has several challenges: (i) recognize the “danger” signal; (ii) rapidly amplify the response; (iii) adapt the type and amplitude response to the type of “danger” signal; (iv) initiate reparatory mechanisms (healing); persistence of the “danger” or the impossibility to heal the process results in chronic inflammation; and (v) preserve memory of the “danger” and the response. Cellular mediators, such as cytokines and PGE_2, are produced by both immune/inflammatory and constitutive cells [51,55,56]. Vascular cells, such as fibroblasts, endothelial and SMCs, are also involved in the basal synthesis of PGE_2 [50,57,58] (Fig. 1) by the constitutive PGES isoforms cPGES and mPGES-2. During the inflammatory response, the inflammatory mediators activate the transcription of target genes such as COX-2 and mPGES-1 [59,60] and regulate PGE_2 synthesis by activating the NF-κB pathway. However, it has been also suggested that PGE_2 could be involved in the resolution of inflammation [61,62]. As an example of this effect, it has been shown in human rheumatoid arthritis cells, after stimulation by pro-inflammatory cytokines, PGE_2 synthesis is increased through activation of the NF-κB pathway. As a negative feedback, PGE_2, after stimulating its cognate receptors (mostly EP4), can inhibit the formation of NF-κB (p50 and p65) by preventing p65 translocation [63–65].

In vascular tissue as in a non vascular tissue, PGE_2 is synthesized through similar mechanisms to those of non vascular cells. Smooth muscle cells and macrophages express the pro-inflammatory cytokines and up-regulates PGE_2 synthesis [66]. In the same way, nitric oxide (NO) can amplify the inflammatory reaction and by a cGMP-dependent mechanism could interact with COX and increase PGE_2 production [67]. In cultured human amnion-like WISH cells, PGE_2 synthesis was increased in a concentration-dependent manner by sodium nitroprusside, a NO donor. However, PGE_2 could regulate this state by a paracrine action, by decreasing the effects of NO, but this reaction is still controversial [67].

The role of PGE_2 during the inflammatory reaction has been shown by Portanova and colleagues in a mouse model [68]. They showed that specific neutralisation of PGE_2 using antibodies yielded a similar inhibition of inflammation and IL-6 production as that induced by indomethacin. Taken together, these results

Table 2
Characteristics for the human EP receptor subtypes.

Gene	Chromosome	Exons	Regulators of gene expression	kDa	Post transcriptionnal modification	Seconds messagers	References
EP1	19p13.1	3	Erg-1, 2 and 3, PPARγ1 and 2	42–64	Phosphorylation	Ca^{2+}↑	[150,151]
EP2	14q22.1	8	MEF-2A, Oct-B1, 2 and 3	53–68	Phosphorylation	cAMP↑	[150,152]
EP3	1p31.2	10	PPARγ1 and 2, TFIID, E2F-1, E2F, GR-α	52–72	Phosphorylation	cAMP↓	[150,153]
EP4	5p13.1	10	PPARγ1 and 2, CREB, GATA-2 p300, p53, SRF	52–75	Phosphorylation	cAMP↑ (PI3K↑)	[150,154,155]

Protein (kDa) indicates the molecular weights estimated by Western blot analysis. For all enzymes some of the regulators have been found on *http://www.genecards.org*

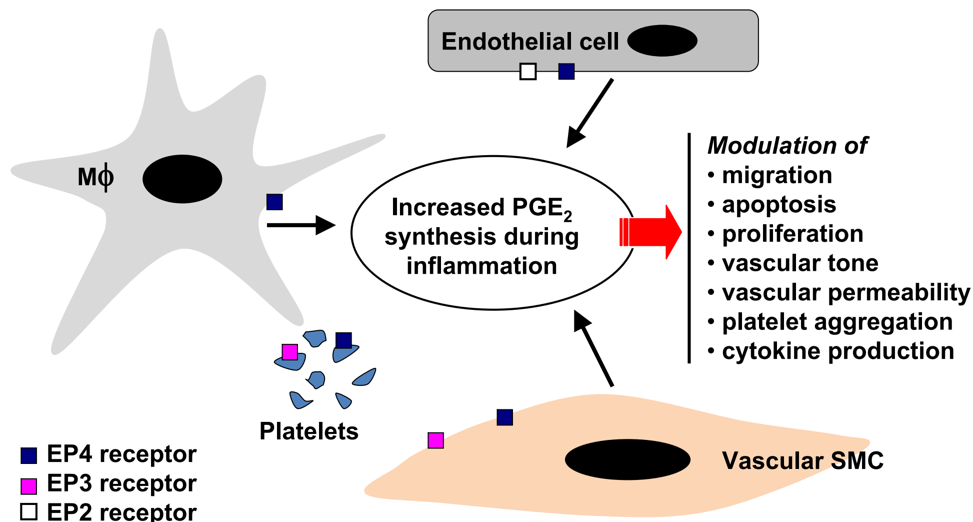

Fig. 1. Prostaglandin E_2 synthesis and EP-receptors activated during human vascular wall inflammation MΦ: macrophage; SMC: smooth muscle cell.

provide argument in a favor of a pro-inflammatory role of PGE_2 and it could be a target in anti-inflammatory therapy. In addition, PGE_2 could to a lesser extent mediate feedback effect to attenuate the inflammatory reaction.

5. Prostanoids in vascular pathologies

5.1. Atherosclerosis and cyclooxygenase pathway

Atherosclerosis is a systemic disease where lipid build-up causes stiffening and narrowing of arteries. The acute clinical manifestations (e.g., acute coronary syndromes, ischemic stroke) are due to plaque rupture resulting in luminal thrombosis. Inflammation occurs within the plaque but circulating monocytes and neutrophils are thought to contribute to inflammation and thrombosis by providing tissue factor and a pro-oxydant environment [69,70]. Several inflammatory markers including C-reactive protein (CRP), IL-6, PGE_2, vascular cell adhesion molecule (VCAM)-1, myeloperoxidase, secretory PLA_2 and COX-2, have been shown to be elevated in patients with acute coronary syndromes and to be associated with adverse clinical outcomes (myocardial infarction or death) at follow-up [71–73]. The exact mechanisms through which these markers are involved into the interaction between vulnerable plaques and blood [69,74] to finally result in luminal thrombosis are not known.

Several studies have investigated the presence of prostanoids metabolic enzymes in atherosclerosis. They found that COX-1 is expressed in normal arteries and in atherosclerotic lesions, while COX-2 is observed only in atherosclerotic plaques [18,75]. In these lesions COX-2 is mainly expressed in macrophages located in the plaque shoulder. This enzyme is involved in atherosclerosis by several mechanisms such as activation of chemotaxis, production of inflammatory cytokines, modification of vascular permeability and stimulation of SMC migration [76]. Furthermore, studies have shown that in atherosclerotic plaques, mPGES-1 is co-regulated with COX-2 [77]. These upregulations could be prevented by glucocorticoids [78]. In 2008, Cipollone and collaborators have shown a significant increased expression of COX-2, mPGES-1, MMP-2 and MMP-9 in coronary plaques from patients with a recent stroke in comparison with asymptomatic patients [79]. Studies in mice showed increased COX-2 expression in atherosclerosis and demonstrated that celecoxib, a selective COX-2 inhibitor, can prevent the evolution of the atheroma lesions [72]. Nevertheless, inhibition of COX-2 activity in patients with atherosclerosis could also be detrimental in respect to plaque stability and therefore be associated with increased cardiovascular events and mortality [80,81]. This controversy could be explained by the fact that COX-2 inhibitors also inhibit the antithrombotic effects of PGI_2 and thus increase the risk of cardiovascular complications.

In human vascular SMCs, protease-activated receptors (PARs) mediate thrombin-induced proliferation, migration and matrix biosynthesis as well as generation of inflammatory and growth-promoting mediators. Thrombin-responsive PARs are transcriptionally down-regulated in human vascular SMC by PGI_2/PGE_2. The increased production of PGI_2/PGE_2 following COX-2 induction in atherosclerotic plaque could thus contribute to plaque stability [82]. Inhibition of COX-2 by coxibs could, by decreasing the production of PGI_2/PGE_2, result in plaque instability by increasing the expression/activity of PARs. Another study on macrophages and SMC obtained from atheroma plaques, demonstrates the regulatory role of PGE_2 in vascular inflammation. In co-cultures of these cells, it has been shown that PGE_2 produced by SMC could activate EP4 receptors expressed on macrophages and inhibit the inflammatory process [83].

In addition to an up-regulation of prostanoid activity, increased expression of CRP is observed in atherosclerotic plaques. A complex cross talk between CRP and PGs in the atheroma plaque has been reported. Grad and collaborators [84] have shown in human endothelium that aspirin can decrease the atherothrombotic effects of CRP. On the other hand, human monocytes exposed to CRP produce active liver X receptor (LXR) [85]. The activation of LXR has anti-atherogenic effects by deactivating the inflammatory cascade [86–89], for example mPGES-1 is inhibited in human tissue in the presence of a selective LXR agonist (GW3965) [90]. This opens the possibility of an LXR-mediated decrease of PGE_2 production in atheroma plaques upon exposure to CRP. A similar inhibition of PGE_2 synthesis could be attributed to the activation of another nuclear receptor, peroxisome proliferator-activated receptor (PPAR)-γ [91–93]. However, a greater expression of mPGES-1 [94] and PPAR-γ [95] have been described in human atherosclerotic plaque. This discrepancy between the in vitro models and the clinical studies remains unclear.

In addition, to intraplaque events, PGE_2 could modulate platelet adhesion to ruptured plaques. The presence of several PGE_2 receptor subtypes on human platelets and their involvement during human platelet aggregation (EP3 activation, EP4 inhibition)

has been recently demonstrated [96–98]. Consequently, some studies have shown that EP3 antagonists could be used as treatment for atherothrombosis [99,100]. However, this application is still controversial since Schober and colleagues have shown that PGE_2 (via EP3 and EP4 receptors), in a model of human atherosclerotic lesions, does not modulate atherothrombosis [73].

Understanding the biology of PGES, PGE_2 and EP receptors is a preliminary step before pharmacological and therapeutic manipulation of PGES and EP receptors in humans. It is noteworthy that in humans, the level of manipulation of PG pathways has revealed an impressive complexity. Although the beneficial effects of aspirin for secondary prevention of atherosclerosis have been documented for years, selective inhibition of COX-2 by coxibs in the treatment of rheumatoid arthritis has been associated with unexpected deleterious effects in several prospective randomised trials [80,81]. Experimental studies in mice [81,101,102] have demonstrated that the potentially deleterious effects of coxibs in humans could be explained by the fact that endothelial and vascular SMC COX-2 is responsible for most of the PGI_2 (and to a smaller extent of PGE_2) production and therefore inhibition of COX-2 function results in mice in a hypertensive and prothrombotic phenotype. The prothrombotic phenotype of endothelial/vascular SMC COX-2 deletion was mimicked by mice with a deletion of the PGI_2 receptor (IP). However, in most experimental models, COX-2 induction is associated with striking increases of PGI_2 and PGE_2 productions [17,19,25,33,103,104]. For this reason, deleterious cardiovascular effects of coxibs could be related to the inhibition of the antithrombotic effect of PGI_2 and PGE_2. In this context, several questions are relevant concerning PGES and EP receptors in human rheumatoid arthritis as novel therapeutic targets. Will inhibition of PGES divert the flow of arachidonic acid toward increased PGI_2 production through preserved COX-2 function? In this case, inhibition of PGE_2 synthesis could promote the beneficial effects of PGI_2. What could be the impact of global inhibition of EP receptors in endothelium, vascular SMC but also in platelets? More specifically, this question concerns the inhibition of the EP4 receptor subtype, which seems to be mostly implicated in pain and progress of rheumatoid arthritis [98,105]. In both cases, pharmacological inhibition of mPGES-1 or EP4 receptor, the vasodilatator and anti-aggregant effects [98] of PGE_2 mediated via EP4 receptors will be reduced in humans and that should be taken into consideration for clinical trials.

5.2. Role of PGE_2 in arterial aneurysms

Arterial aneurysms are characterized by abnormal dilatation of the artery leading to vascular wall remodeling, weakening and rupture. A large number of inflammatory mediators have been investigated for association with abdominal aortic aneurysm (AAA) such as inflammatory cytokines and PGE_2 [106–111]. The identification of biomarkers such as PGE_2 associated with the development of AAA may suggest possible targets for new treatments to reduce AAA progression.

The role of PGs in the pathophysiology of arterial aneurysms was initially studied by Juncos and collaborators 1977 [112]. Several studies demonstrated that patients, under chronic non-steroidal anti-inflammatory drugs (NSAIDs) therapy, present a lower median AAA growth rate in comparison to patients not taking NSAIDs [1,108]. Recently, a study has shown that aspirin, a non selective COX inhibitor, taken once daily to 3 times a week decreased the risk of intracranial artery aneurysm progression to rupture [113]. These authors suggest an inhibitory effect of aspirin on the macrophages-dependent inflammatory process implicated in aneurysm formation.

The pathological role of PGE_2 has been also demonstrated in AAA rupture. In fact, several studies have shown that PGE_2, TxA_2, MCP-1 and IL-6 secretions were significantly higher in human cultured explants of ruptured AAA in comparison with non-ruptured AAA [114,115]. COX inhibitors and in particular COX-2 inhibitors, significantly reduced the secretion of IL-1β, IL-6 and PGE_2 in cultured AAA explants although the MMP-9 release was unchanged on macrophage-like cells [108,116]. In addition, the deletion of mPGES-1, protected against AAA formation induced by angiotensin II in hyperlipidemic mice [117]. These observations could be related to a direct stimulatory effect of PGE_2 on DNA synthesis and proliferation of SMCs during aneurysm expansion [108].

The expression of PGE_2 receptors and their roles in arterial aneurysms were also examined. Human aortic biopsy specimens from AAA demonstrated the expression of EP2, EP3 and EP4 mRNA receptors subtypes [118]. In the previous study, the production of IL-6 in AAA explants was inhibited by indomethacin, a non selective COX inhibitor. This inhibition was also partially restored by exogenous PGE_2 through EP4 receptor activation [118].

In studies [108,116,118] on AAA, the EP4 receptor and COX-2 expression was mainly detected in macrophage-like cells that could be either macrophages and/or transformed SMC displaying a phagocyte phenotype [119].

Taken together, these results demonstrate the importance of PGE_2 as an inflammatory mediator and a putative biomarker in AAA expansion, leading to the potential use of COX inhibitors as drugs to prevent or attenuate the risk of AAA rupture. Nevertheless, given the fact that AAA is often associated with diffuse atheroma and the above-discussed effects of COX-2 inhibitors in humans with diffuse atheroma, their clinical use is probably limited in this indication. Therefore, development of clinically usable PGES inhibitors or EP4 antagonists could represent a therapeutic solution with the same limitations as for atherosclerosis or rheumatoid arthritis (see above). However, using a PGES inhibitor could imply a change in synthesis for other prostanoids due to increased PGH_2 availability for other PG synthases as observed in mPGES-1-KO mice model [117]. The consequences of such changes in PG metabolism are difficult to predict and a detailed analysis of the effect of individual PG in different vascular diseases is required.

5.3. Role of PGE_2 in angiogenesis

One domain where angiogenesis has been extensively studied is cancer. Studies have demonstrated that inflammatory mediators (such as PGE_2, CRP, IL-6 and TNF-α) are increased in these pathologies [120–124]. Increased PGE_2 concentrations are associated with up-regulation of COX-2 and mPGES-1 expression suggesting an important role of these enzymes in cancer progression [125]. As an inflammatory mediator, PGE_2 is involved in tumor growth and the development of malignant tumors (such as colon, lung, breast and neck) [126]. Furthermore, 15PGDH responsible for PGE_2 degradation is lacking or is barely expressed in malignant tissue [127,128]. This deficiency could explain the high content in PGE_2 of malignant tissue. Depending on the receptor type activated (EP1–4) PGE_2 may activate different intracellular pathways such as the ERK pathway for cell proliferation, the MMP activation pathway for the cell migration and invasion or the Akt pathway for the cell survival [126,129,130]. A study has shown that angiogenesis in human colorectal cancer is promoted by CXCL1 (a pro-angiogenic chemokine) stimulated by PGE_2 [131]. In human prostate cancer angiogenesis is up-regulated via activation of endothelial growth factor receptor (EGFR) [132]. Furthermore, a study has demonstrated that PGE_2 and EGFR induced colorectal carcinoma cells their migration through a complex mechanism. PGE_2 via EP4 receptor activates EGF-like ligand and consequently EGFR [126,133]. Together, these studies suggest that PGE_2 could also promote indirectly the angiogenesis via EGFR.

In contrast, PGE_2 can modulate the expression of vascular endothelial growth factor (VEGF) and its inhibition was observed in a human colon cancer cell line (Caco-2) [134] while an up-regulation was shown in gastric cancer [135]. Recent studies have demonstrated that COX inhibitors could decrease angiogenesis in cancer [125,136].

Another hypothesis of PGE_2 implication in cancer is the regulation of immune cells activity [56]. Despite the fact that PGE_2 can promote the attraction of immune cells, it paradoxically inhibits certain aspects of their activation. For example, PGE_2 by suppressing cytosolic effector functions inhibits NK cells with suppression of IL-12 and IL-15 responsiveness [137,138]. In macrophages, via EP2 receptor activation PGE_2 inhibits macrophage phagocytosis function [139] and their pathogen-killing function by inactivating NADPH oxidase [140]. In this case, PGE_2 could enhance cancer progression by suppressing the immune response.

6. Conclusion

It is well documented that inflammation involves the production of numerous mediators such as cytokines that induce the expression of COX-2, the enzyme responsible for prostanoids production. Although, TxB_2 and PGI_2 remain the most frequently measured bioactive lipids in cardiovascular clinical studies, PGE_2 is increasingly attracting attention as a marker and potential therapeutic target in several vascular diseases. In this review we underline the fact that in several vascular pathologies are characterized by up-regulation of COX-2 and mPGES-1 expression, resulting in increased PGE_2 synthesis. Nevertheless, the detailed mechanisms explaining these observations require further investigations on the role of PGE_2 metabolism and receptors in the development of these pathologies. Given the limitations of COX-1 and COX-2 inhibition in patients with diffuse atheroma and other cardiovascular diseases, new pharmacological targets that include inhibition of PGE_2 synthesis or EP4 receptor antagonism could find therapeutic applications in atherosclerosis, arterial aneurysms or angiogenesis during cancer. Some limitations to these applications exist, inhibition of mPGES-1 as a therapeutic target may not necessarily be successful as other prostanoids may be over-synthesized and produce unexpected effects. Finally, the effects of the EP ligands on thrombosis should be also be considered since PGE_2 receptor subtypes (EP3, EP4) are involved in human platelet aggregation [51].

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