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The functional link between microsomal prostaglandin E synthase-1 (mPGES-1) and peroxisome proliferator-activated receptor γ (PPARγ) in the onset of inflammation

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Chemical compounds studied in this article:
Arachidonic acid (CID:444899)
5-HETE, (CID:5353349)
8-HETE, (CID:5283154)
12-HETE, (CID:5283154)
15-HETE, (CID:5280724)
9-HODE, (CID:5282945)
13-HODE, (CID:6443013)
LTB4, (CID:5280492)
LTC4, (CID:5280493)
LTE4, (CID:5280879)
9-oxoODE, (CID:9839084)
13-oxoODE, (CID:6446027)
PGD_2, (CID:448457)
PGE_2, (CID:5280360)
$PGF_{2\alpha}$, (CID:5280363)
PGI_2, (CID:5282411)
TXA_2, (CID:5280497)

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ABSTRACT

Many years have elapsed since the discovery of anti-inflammatories as effective therapeutics for the treatment of inflammatory-related diseases, but we are still uncovering their various mechanisms of action. Recent biochemical and pharmacological studies have shown that in different tissues and cell types lipid mediators from thearachidonic acid cascade, play a crucial role in the initiation and resolution of inflammation by shifting from pro-inflammatory prostaglandin (PG)E_2 to anti-inflammatory PGD_2 and PGJ_2. Considering that until now very little is known about the biological effects evoked by microsomal prostaglandin E synthase-1 (mPGES-1) and contextually by peroxisome proliferator-activated receptor γ (PPARγ) modulation (key enzymes involved in PGE_2 and PGD_2/PGJ_2metabolism), in this opinion paper we sought to define the coordinate functional regulation between these two enzymes at the "crossroads of phlogistic pathway" involved in the induction and resolution of inflammation.

1. Opinion paper

Inflammation is a complex biological self-defense reaction triggered by tissue injury or infection by pathogens [1]. This event is regulated by the time- and cell type-dependent production of range of mediators including cyto-chemokines and signaling molecules such as prostaglandins (PGs) [2]. From "a cellular point of view" neutrophils dominate the initial influx of leukocytes followed by monocytes and macrophages. The recruitment of inflammatory monocytes correlates with a transient increase of pro-inflammatory mediators including, cytokines, chemokines, PGs and leukotrienes (LTs) [3–5]. Indeed, inappropriate cellular survival function or their overactivation, in addition to lipid mediator overproduction, perpetuate inflammatory pathways and strengthens disease activity [6,7].

Abbreviations: COXs, cyclooxygenases; cPGES, cytosolic prostaglandin E synthase; DHET, dihydroxyeicosatrienoic acid; 15d-PGJ_2, 15-deoxy-Δ1214-prostaglandin J_2; EET, epoxyeicosatrienoic acids; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; IκBα, nuclear factor of kappa-light-polypeptide-gene-enhancer in B cells inhibitor alpha; LTs, leukotrienes; mPGES, microsomal prostaglandin E synthase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGs, prostaglandins; PPARγ, peroxisome proliferator-activated receptor gamma; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; TXA_2, thromboxane A_2

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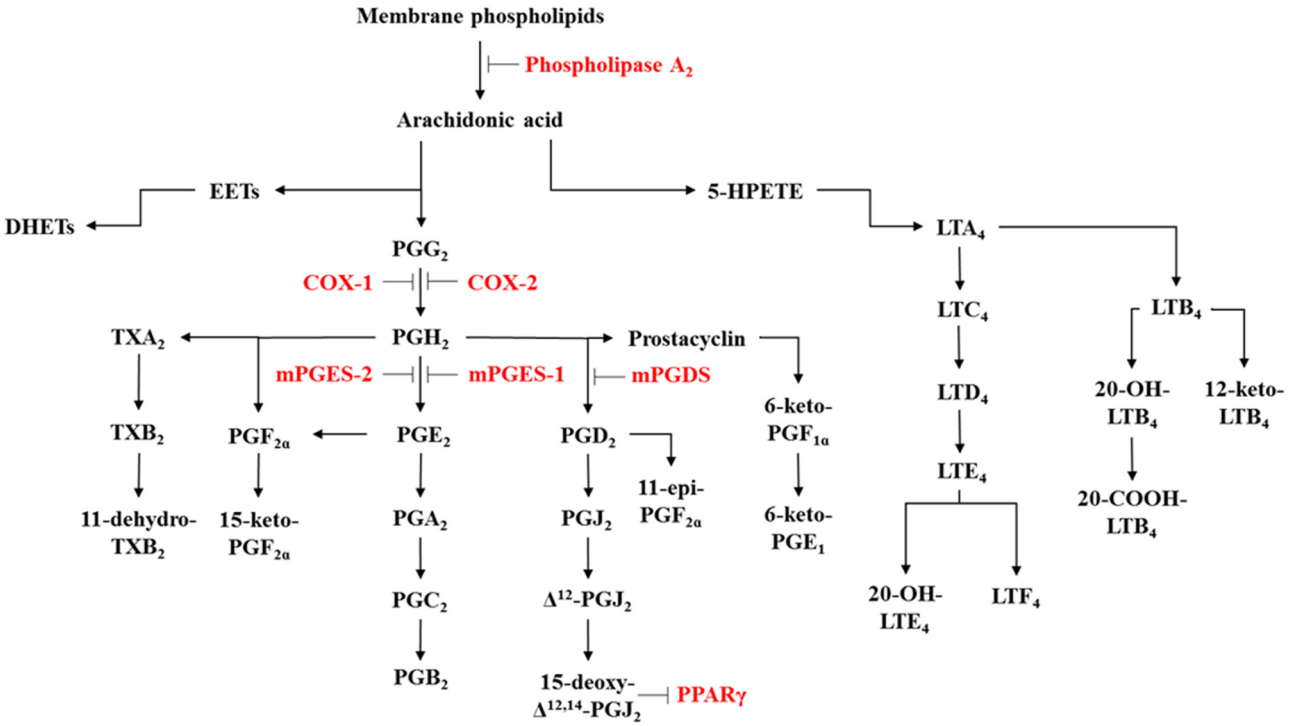

Fig. 1. Schematic diagram of the key enzymes and related lipid mediators of the arachidonic acid cascade. In red are reported the main enzymes involved in the production of pro- and anti-inflammatory, intermediate or final, mediators of the phlogistic response.

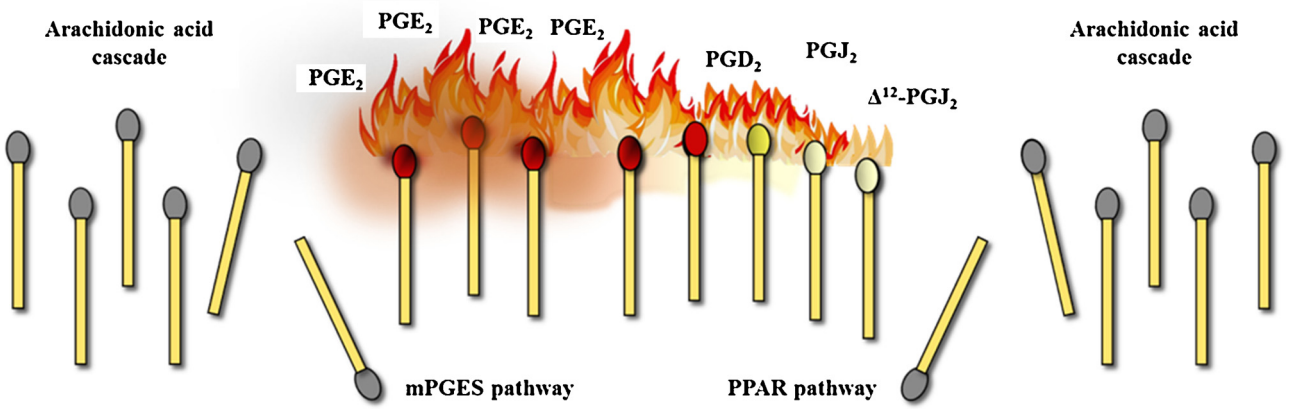

Fig. 2. Schematic representation of the link between the pro-inflammatory and anti-inflammatory systems in the arachidonic acid cascade. In healthy conditions state (top left and right), the pro- and anti-inflammatory pathways state (middle left and right), are linked with each other *in equilibrium*. However, after noxious stimuli of different nature, changes in this *equilibrium* prompt an endogenous response that helps the host deal with these challenges.

From a "molecular point of view", cyclooxygenases (COXs) regulate the initial steps of the inflammatory cascade. These enzymes catalyze the conversion of arachidonic acid into intermediate PGH_2 which undergoes further conversion to PGE_2 by three different PGE_2 synthase isoforms [8]. Both cytosolic PGE_2 synthase (cPGES) and microsomal PGE_2 synthase-2 (mPGES-2) are constitutively expressed, whereas mPGES-1 is an inducible isoform linked with COX-2 enzymatic activity [9]. Inducible mPGES-1 plays a critical role in the final steps of PGE_2 production without altering the levels of other PGs. The upregulation of this enzyme and subsequent increase in PGE_2 production plays a significant role in the pathogenesis of several inflammatory conditions including, rheumatoid arthritis, gouty arthritis and atherosclerosis [10,11,12,13,14].

Conversely, PGE_2 release can also be modulated by alternative pathways, one such example is peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor stimulated by 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2) [15]. During an inflammatory response all PPAR isoforms (PPARα, PPARβ/δ, and PPARγ) can potentially be stimulated by fatty acids, including polyunsaturated (PUFA), and more potently by PGA_2 and 15d-PGJ_2 [16–18]. Upon PPARs activation, two major biological functions can follow: i) blocking of the activation of p65 nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB, a transcription factor involved in inflammatory processes) and overexpression of nuclear factor of kappa-light-polypeptide-gene-enhancer in B cells inhibitor alpha (IκBα a natural inhibitor of NF-κB); ii) increase in the production of active resolution mediators including antioxidant enzymes such as catalase, superoxide dismutase, and heme oxygenase-1 [19,20].

Several recent studies highlighted an indirect connection between PPARs and PGs in the control of phlogistic processes [15,21,22], neuropathic pain [23] and certain neurological disorders [24,25]. In particular, in mice genetically deficient for mPGES-1, it has been reported

that under basal conditions an elevation of PPARγ expression and transcriptional activity associated with reduced PGE_2 is observed [26]. Furthermore, a coordinate functional regulation between these two enzymes was essential for the conversion of white-to-brown adipocytes [27] and on the pathogenesis of fatty liver disease [28,29].

Collectively, these studies allow us to speculative suggest, that mPGES-1 deletion not only decreases pro-inflammatory PGE_2 but also upregulates anti-inflammatory PPARs. Thus, mPGES-1 and PPARs pathway may limit inflammation by multiple mechanisms [30].

Our opinion is that several biochemical and pharmacological studies report and describe only a partial link between these two enzymatic pathways. The molecular interaction between COXs and PGE_S isoenzymes, (which led to preferential functional coupling activity) is correlated with NF-κB activity [8,9] through a subtle balance of lipid mediators that, depending on the tissue and the type of pro-inflammatory insult, induce a balance between those we classically defined as pro- or anti-inflammatory mediators (Fig. 1) [10,12,31,32]. Consistently, the upregulation of mPGES-1 expression and the involvement of COX-2/mPGES-1/PGE_2 cascade in terms of PGs production has been extensively reported in pathological settings in which PGE_2 is implicated, such as fever, pain and inflammatory-based disease [33,34] but, again, without any type of concomitant analysis in terms of PGJ_2 and/or PGD_2 production and transcriptional activity.

Our aim is to give a general, but updated, picture of the manifold pathways that link beneficial and detrimental molecular mechanisms involved in the onset of inflammation (Fig. 2) and attempt to highlight the therapeutic potential of this burgeoning field of research in both the treatment of acute and chronic inflammatory-related disorders. Even if the fully molecular mechanisms that explain how these phenomena are achieved and regulated remain to be fully elucidated, it provides an excellent starting point for researchers to unravel and further strengthen our existing preliminary evidences for these novel molecular interactions.

Author contributions

FM, GMC and FR drafted and wrote the manuscript. AJI and NM edited and revised the manuscript. All Authors gave final approval to the publication.

Declaration of Competing Interest

This article has been conducted and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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