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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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- 8-HETE, (CID:5283154)
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- 15-HETE, (CID:5280724)
- 9-HODE, (CID:5282945)
- 13-HODE, (CID:6443013)
- LT4, (CID:5280493)
- L6D2, (CID:5280136)
- 9-oxoODE, (CID:9839084)
- 13-oxoODE, (CID:6446027)
- PGD2, (CID:448457)
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- PGF2α, (CID:5280363)
- PGJ2, (CID:5282411)
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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 the arachidonic acid cascade, play a crucial role in the initiation and resolution of inflammation by shifting from pro-inflammatory prostaglandin (PG)E2 to anti-inflammatory PGD2 and PGJ2. 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 gamma (PPARγ) modulation (key enzymes involved in PGE2 and PGD2/PGJ2 metabolism), 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, dihydroxyeicosatetraenoic acid; 15d-PGJ2, 15-deoxy-Δ12-14-prostaglandin J2; 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; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; TXA2, thromboxane A2

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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 PGH2 which undergoes further conversion to PGE2 by three different PGE2 synthase isoforms [8]. Both cytosolic PGE2 synthase (cPGES) and microsomal PGE2 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 PGE2 production without altering the levels of other PGs. The upregulation of this enzyme and subsequent increase in PGE2 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, PGE2 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-

\[ \Delta^{12,14}- \text{prostaglandin J}_2 \text{ (15d-PGJ}_2) \] [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 PGA2 and 15d-PGJ2 [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 (IkBα 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 PGE2 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 speculate that mPGES-1 deletion not only decreases pro-inflammatory PGE2 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 PGs iso-enzymes, (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].

Our aim is to give a general, but updated, picture of the manifold enzymes, (which led to preferential functional coupling activity) is essential for the conversion of white-to-brown adipocytes [26,33,34] but, again, without any type of concomitant analysis in terms of PGJ2 and/or PGD2 production and transcriptional activity.

We aimed at providing a general, but updated, picture of the manifold enzymes, (which led to preferential functional coupling activity) is essential for the conversion of white-to-brown adipocytes [26,33,34] but, again, without any type of concomitant analysis in terms of PGJ2 and/or PGD2 production and transcriptional activity.

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