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Review

Proteomic studies on protein modification by cyclopentenone prostaglandins: Expanding our view on electrophile actions

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ABSTRACT

Cyclopentenone prostaglandins (cyPG) are lipid mediators that participate in the mechanisms regulating inflammation and tumorigenesis. cyPG are electrophilic compounds that act mainly through the covalent modification of cellular proteins. The stability of many cyPG-protein adducts makes them suitable for proteomic analysis. Indeed, methodological advances in recent years have allowed identifying many cyPG targets, including components of pro-inflammatory transcription factors, cytoskeletal proteins, signaling kinases and proteins involved in redox control. Insight into the diversity of cyPG targets is providing a better understanding of their mechanism of action, uncovering novel links between resolution of inflammation, proliferation and redox regulation. Moreover, identification of the target residues has unveiled the selectivity of protein modification by these electrophiles, providing valuable information for potential pharmacological applications. Among the challenges ahead, the detection of proteins modified by endogenous cyPG and the quantitative aspects of the modification require further efforts. Importantly, only a few years after the appearance of the first proteomic studies, research on cyPG targets is yielding new paradigms for redox and electrophilic signaling.

Contents

Abbreviations: cyPG, cyclopentenone prostaglandins; COX, cyclooxygenase; AA, arachidonic acid; HNE, 4-hydroxynonenal; PPAR, peroxisome proliferator activated receptor; HO-1, heme oxygenase-1; $hPGD_2s$, hematopoietic prostaglandin D_2 synthase; 15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2; 15d-PGJ_2-B, biotinylated 15d-PGJ_2; PGA_1-B, biotinylated PGA_1; Trx, thioredoxin; TrxR, thioredoxin reductase; GSH, glutathione; GST, glutathione S-transferase.

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1. Introduction

Cyclopentenone prostaglandins (cyPG) are endogenous electrophilic lipid mediators involved in the resolution of inflammation and the control of cell proliferation, among other functions. Due to their potent anti-inflammatory and anti-proliferative effects in some experimental systems, cyPG are being considered as potential therapeutic compounds. Generation of cyPG is usually low under basal conditions and increases in situations of acute or chronic inflammation, associated with COX-2 expression or with oxidative stress. Most studies point towards a protective role of cyPG in pathophysiology and consider their generation as part of the defense mechanisms favoring the resolution of inflammation: cyPG have been proposed to participate in the switch from inflammatory to pro-resolving mediators, to reduce the activity of pro-inflammatory transcription factors and to promote the expression of proteins involved in inflammatory resolution by acting on transcription factor regulators and/or by epigenetic mechanisms. Several reports, however, raise the possibility that cyPG may also be involved in certain pathogenic mechanisms, like neurodegeneration.

After several years of intense research it is clear that cyPG may interact with multiple cellular targets. Development of proteomic approaches has greatly contributed to our understanding of the interaction of these compounds with cellular components. Moreover, these studies are unveiling novel targets and mechanisms of action that can be common to other electrophilic mediators, natural electrophilic compounds and redox-mediated processes.

In this article we summarize the main characteristics of cyPG signaling and review the proteomic studies which have contributed to the identification of cyPG targets, thus expanding our view on electrophile actions.

1.1. *Generation, chemical features and metabolism of cyPG*

cyPG derive from membrane fatty acids, mostly arachidonic acid (Fig. 1). Arachidonic acid (AA) can give rise to various electrophilic lipids by enzymatic and non-enzymatic transformations. Along the cyclooxygenase (COX) pathway, AA released by phospholipases first suffers a two-step reaction involving cyclooxygenation and peroxidation catalyzed by COX enzymes. The PGH_2 product can then be transformed by various prostaglandin synthases, generating PGE_2 and PGD_2, among other prostanoids. From these, the cyPG are formed through a dehydration reaction within the cyclopentane ring. Thus, dehydration of PGE_2 and PGD_2 would yield the cyPG PGA_2 and PGJ_2, respectively [1–4]. In turn, PGJ_2 can be non-enzymatically dehydrated to yield the cyPG 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2)-PGJ_2 or it can be transformed to Δ^{12}-PGJ_2 in an albumin-dependent manner [4]. The cyPG PGA_1 is formed by non-enzymatic dehydration of PGE_1, which can arise from γ-linolenic acid by the action of COX as well [5].

A mechanism for cyPG generation independent from COX activity has been proposed to proceed through the isoprostane pathway. Isoprostanes are structural isomers of PG that arise by non-enzymatic peroxidation of AA in oxidative stress environments and potentially, in other inflammatory situations in vivo. Isoprostanes containing E- and D-type prostane rings can undergo epimerization, yielding PGE_2 and PGD_2 [6]. In addition, in a recent work, nonenzymatic free radical-catalyzed generation of 15d-PGJ_2-like compounds (deoxy-J_2 -isoprostanes) has been shown to occur in vivo [7].

A structural characteristic of cyPG is that they contain an electrophilic carbon in the cyclopentene ring, which allows these molecules to form Michael adducts with cellular nucleophiles such as glutathione (GSH) or nucleophilic residues in cellular proteins, like cysteine (Fig. 2) or histidine [8]. cyPG could also form Schiff bases with amino groups. Interestingly, several cyPG possess a second reactive electrophilic carbon located on one of the side chains (Fig. 1). This is the case of Δ^{12}-PGJ_2 and 15d-PGJ_2, among naturally occurring PG, and of some derivatives of PGA_1 obtained through chemical synthesis to achieve higher potency or stability [9]. The reactions of cyPG with thiols have been studied in detail for GSH and some cysteine derivatives [10,11]. In the case of GSH it has been observed that adduct formation is reversible, but that important differences in kinetics and reversibility exist among cyPG with different structure. A dienone cyPG reacted with