

Editorial

Cyclic Phosphatidic Acid: An Endogenous Antagonist of PPAR γ

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Lysophospholipids (LPLs) have long been recognized as membrane phospholipid metabolites. LPLs are small bioactive lipid molecules that are characterized by a single carbon chain and a polar head group. LPLs have been implicated in a number of pathological states and human diseases. LPLs include lysophosphatidic acid (LPA), alkyl-glycerol phosphate (AGP), sphingosine-1-phosphate, and cyclic phosphatidic acid (cPA). In recent years, cPA has been reported to be a target for many diseases, including obesity [1], atherosclerosis [2], cancer [3], and pain [4]. cPA is an analog of LPA that has a 5-atom ring linking the phosphate to 2 of the glycerol carbon atoms. cPA is found in diverse organisms, from slime molds to humans [5]. The concentration of cPA in human serum is estimated to be around 100 nM. cPA, along with PPAR γ agonists, prevents neointima formation, adipocytic differentiation, lipid accumulation, and upregulation of PPAR γ -target gene transcription in mouse macrophages [2]. These findings support our hypothesis that cPA is an endogenous antagonist of PPAR γ . These data suggest that cPA offers new therapeutic opportunities to improve the quality of patient care. Here, we discuss the current knowledge on the pathophysiological actions of cPA and attempt to link them with particular targets.

Enzymatic formation of cPA

Murakami-Murofushi et al. [6] reported that cPA is detected in mammalian biological fluids, including human serum. Many of the activities of cPA have been attributed to albumin-associated lipid factors. The first report of the generation of cPA by autotaxin (ATX) under non-physiological conditions appeared in 2006 [7,8]. ATX, also known as phosphodiesterase 2, is a secreted enzyme important for generating the lipid signaling molecule LPA [9]. ATX has lysophospholipase D activity and converts lysophosphatidylcholine (LPC) into LPA. The enzymatic formation and function of cPA are poorly characterized. In addition, the identity of the enzyme that contributes to the formation of cPA in biological fluids remains unknown. In our recent work, we identified phospholipase D2 (PLD2) as an enzyme that can generate cPA [2]. PLD, which hydrolyzes

phosphatidylcholine (PC) to generate choline and bioactive lipid, has been implicated in signal transduction, membrane trafficking, and cytoskeletal reorganization [10]. There are two PLD isoenzymes, PLD1 and PLD2, which are expressed in a variety of tissues and cells [11]. We labeled cultured cells with [³²P]-orthophosphate for 30 min and compared that to [³²P]-labeled cPA from vehicle control cells using two-dimensional thin layer chromatography. Furthermore, we used CHO cells stably expressing PLD1 or PLD2 or catalytically inactive forms of PLD1 and PLD2 to delineate the roles of the PLDs in cPA formation. PLD2-expressing cell lines had an elevated basal level of cPA and higher PMA-stimulated cPA production relative to control wild-type (WT) cells [2]. This finding provides evidence for the role of PLD2 activation in stimulus-coupled cPA production. In recent years, the physiological and pathophysiological functions of peroxisome proliferator-activated receptor γ (PPAR γ) ligands have been explored. In our recent work, we identified cPA as an endogenous PPAR γ antagonist generated by PLD2 [2].

Role of cPA in lipid signaling-related diseases

Recent reports have been shown that LPA plays an important role in the vascular system [12]. LPA is produced in serum after the activation of biochemical pathways linked to platelet activation. The PPAR γ agonists alkyl-LPA [13] and rosiglitazone (ROSI) induce neointima when applied topically within the carotid artery [14]. Neointimal lesions are characterized by the accumulation of cells within the arterial wall and are a prelude to atherosclerotic disease [14]. In recent reports, the knockdown of 1-acyl-*sn*-glycerol-3-phosphate acyltransferase β (AGPAT2) resulted in increased levels of cPA [15]. AGPAT2 is located the endoplasmic reticulum membrane and converts LPA to phosphatidic acid (PA). Mutations in this gene have been associated with congenital generalized lipodystrophy (CGL) [16]. Lipodystrophies, including CGL, are heterogeneous acquired or inherited disorders characterized by the selective loss of adipose tissue and development of severe insulin resistance. AGPAT2 is a member of a family of proteins with acyltransferase activity, and mediates the acylation of LPA into PA [17]. Subauste et al.

recently reported that overexpression of AGPAT2 decreases cPA levels [18]. Furthermore, the knockdown of AGPAT2 results in increases in the level of the saturated form of cPA 18:0 and cPA16:0 [15]. They also assessed the effect of AGPAT2 on PPAR γ transactivation and found that AGPAT2 increases PPAR γ -dependent luciferase activation. These data suggest that AGPAT2 modulates PPAR γ activity and glycerolipid levels. However, the physiological context of these mechanisms in PPAR γ signaling is still unclear. Further clarification of the PPAR γ -cPA axis will allow the synthesis of novel drugs that modulate PPAR γ function. In conclusion, we hope that we have provided interesting insights into these recent advances in elucidating the roles of the PPAR γ -cPA axis in various cardiovascular diseases. We expect that the reviews presented in this issue, which focus on the interplay between PPAR γ and the cardiovascular system, will be highly useful for those interested in phospholipid biology, nuclear receptor function, and their intersection with cardiovascular pathologies.

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