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Authors

Grkovich, Andrej

Dennis, Edward A

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Phosphatidic Acid Phosphohydrolase in the Regulation of Inflammatory Signaling

Andrej Grkovich and **Edward A. Dennis**
Department of Chemistry and Biochemistry and Department of Pharmacology School of Medicine, University of California at San Diego, La Jolla, California, 92093-0601

Introduction

Bacterial infections are often initiated by the introduction of a pathogenic bacterium into an open wound. To abrogate the infection, the immune system responds by deploying a variety of immune cell types which perform distinctive functions to eradicate the infection and restore homeostasis in the host tissues. One immune cell type, the tissue macrophage, performs a variety of functions including removal of unwanted particulates, the release of signaling molecules and antigen presentation. Inflammatory signaling in macrophages can be initiated through the binding of the bacterial endotoxin lipopolysaccharide (LPS) to the Toll-like receptor (TLR)-4 and results in Group IVA cytosolic phospholipase A_2 (GIVA PLA_2) activation and cyclooxygenase (COX)-2 expression, which are two hallmarks of inflammatory activation (Scheme 1) (Akundi et al., 2005;Dieter et al., 2002;Jiang et al., 2003). The GIVA PLA_2 is responsible for the agonist induced release of arachidonic acid (AA) from the *sn*-2 position of membrane phospholipids (Six et al., 2000; Schaloske et al., 2006; Dieter et al., 2002;Jiang et al., 2003). Experimental data suggests that GIVA PLA_2 expression is not upregulated by LPS treatment of the macrophages; however, AA release is significantly increased, suggesting that cellular GIVA PLA_2 activity is augmented (Buczynski et al., 2007;Balsinde et al., 2000). TLR-4 activated macrophages markedly upregulate COX-2 expression following exposure to LPS. Once expressed, COX-2 converts the available AA into PGH_2, which is then subsequently metabolized into inflammatory eicosanoids by terminal prostaglandin synthases (Lee et al, 2003;Sales, et al., 2003). Understanding the regulatory mechanism upstream of GIVA PLA_2 activation and COX-2 expression has been a central focus of inflammatory research for the past few decades. The goal of this review is to increase our understanding of this topic.

Diacylglycerol formation and PAP-1

During the past twenty years, investigators have discovered that diacylglycerol (DAG) participates in inflammatory signal transduction as an important second messenger. The signaling properties of DAG are derived from its ability to interact with C1 domain containing proteins, subsequently inducing the DAG-interacting protein to translocate to lipid membrane surfaces. Perhaps the most important DAG-binding protein in inflammation is protein kinase C (PKC), which is believed to play a central role on the nuclear membrane leading to the phosphorylation of the GIVA PLA_2 directly or indirectly (Exton et al., 1994; Li et al., 2007; Luo et al., 2006; Exton et al.,1990; Testerink et al., 2005; Newton et al., 2003; Brose et al., 2002; Cocco et al., 2004). In addition to its function as a signaling metabolite, DAG also lies at a central point in lipid metabolism, as it can be incorporated into a diverse assortment of membrane phospholipids as well as triacylglycerols (TAG) (Testerink et al., 2005; Brose et al., 2002; Carman et al., 2004).

DAG levels are tightly regulated and extremely low levels are present in macrophages at basal conditions. Therefore, cellular DAG levels must be actively augmented to elicit an effective signaling response. Cellular DAG levels are increased through at least three different biosynthetic processes (Carman et al., 2004). In the first mechanism, DAG is formed through two successive rounds of fatty acid acylation of glycerol-phosphate, followed by the loss of the phosphate. In a second mechanism, DAG is formed via phospholipid hydrolysis mediated by phospholipase C (PLC), resulting in the formation of DAG while also releasing the water-soluble head-group. In a third mechanism, DAG is formed from hydrolysis of membrane bound phosphatidic acid by phosphatidic acid phosphohydrolase (PAP) enzymes (also known as the phosphatidate phosphatase).

There are two distinctive classes of PAP enzymes, which are referred to as PAP-1 and PAP-2. These two classes can be distinguished by a number of different characteristics, including Mg^{+2} dependence, substrate preference, the nature of the enzyme-membrane interactions and chemical inhibitory effects (Nanjundan et al., 2003; Carman et al., 2006b; Balsinde et al., 1996). PAP-2, also known as lipid phosphate phosphohydrolase (LPP), is a plasma transmembrane protein with a broad lipid substrate specificity that does not require additional divalent cation cofactors (Nanjundan et al., 2003; Brindley et al., 2004). PAP-1, also known as lipin 1, is a cytosolic, membrane-associated protein with a substrate preference for PA and requirement for Mg^{+2} (Nanjundan et al., 2003; Carman et al., 2006).

Research into the cellular function of PAP-1 has lagged considerably behind that of PAP-2 due to only the recent cloning and characterization of the enzyme. However, George Carman's laboratory purified PAP-1 from *S. cerevisiae*, identifying it as Smp2p which is the yeast ortholog of the human lipin 1, an enzyme associated with adipose tissue development and fat metabolism (Carman et al., 2006; Han et al., 2006; Carman et al., 1997; Reue et al., 2008). Carman's group has also shown that DAG derived via PAP-1 is ultimately utilized in the synthesis of phosphatidylethanolamine and phosphatidylcholine as well as contributing to cellular levels of TAG (Carman et al., 1997; Brindley et al., 1984; Carman et al., 1999; Sorger et al., 2003). The lipin family of proteins currently consists of three distinctive members, and each has been shown to possess PAP activity (Donkor et al., 2007). PAP-1 is likely to function on the nuclear membrane surface as all three lipin proteins are known to contain nuclear localization signals and Smp2 has been shown to regulate nuclear membrane growth (Carman et al., 2006; Reue et al., 2008). Additionally, lipin 1 has been shown to be a selective physiological amplifier of the PGC-1α/PPAR α -mediated control of hepatic lipid metabolism which suggests a role in transcription (Finck et al., 2006). For further detailed information on the roles of lipin in adipose tissue development and PAP in lipid metabolism, the reader is encouraged to consult the recent review articles written by Karen Reue and George Carman, respectively (Carman et al., 2006; Reue et al., 2008). The focus of the current review is to summarize experimental data pertaining to the regulatory nature of PAP-1 in inflammatory signaling, particularly with regard to GIVA PLA_2 activation and COX-2 expression in the TLR-4 signaling pathway.

Diacylglycerol signaling and PAP-1 activation in the TLR-4 pathway

The formation of cellular diacylglycerol has been extensively studied in numerous cell types through the use of various inflammatory stimulants. In inflammatory macrophage models, DAG levels spike to maximal levels before dissipating to basal levels. In one particular study, RAW 264.7 macrophages stimulated with LPS displayed increased DAG levels at 2-3 minutes following stimulation. Within minutes of the sudden increase, DAG levels returned to background values and did not increase above the background for the duration of the time course (Zhang et al., 2001). Also, it is worth noting that the cellular DAG formation was sensitive to treatment of the cells with *n*-butanol, propranolol and D609, suggesting that the

PAP-1 and PLC-mediated DAG mechanisms are functional in this model. A similar finding was later described in U937 macrophages, in which DAG formation was markedly increased 2 minutes after stimulation (Grkovich et al., 2006). The DAG formation in this study was also sensitive to PAP-1 inhibition. In a third study, Chinese hamster ovary cells (CHO) that were engineered to overexpress CD14 displayed increased DAG levels when stimulated with LPS. However, it should be mentioned that the increased DAG levels in the activated CHO cells were sensitive to D609, which suggests that PLC is the source of DAG in this experiment (Maestre et al., 2003). In yet another macrophage study, U937 macrophages were activated with the MAPK activator docetaxel, resulting in distinctive increases in membrane PA levels at 1 and 10 minutes after stimulation, in addition to a propranolol-sensitive DAG spike at 2 minutes (Yamamoto et al., 1997). These experiments clearly articulate that inflammatory stimuli in macrophages elicit a brief, but potent burst of DAG immediately following administration of the stimulus. Further research is needed to clarify the contributions of the PLD/PAP-1 and PLC enzymes to cellular DAG levels. The current data suggests that a variety of variables including cell type, stimulus and signaling pathways may dictate which enzymes are responsible for the generation of the DAG.

Perhaps the most pronounced difference between PAP-1 and PAP-2 is the nature of the association between the respective PAP enzyme and the lipid membrane. Unlike PAP-2, which is a transmembrane protein, the cytosolic PAP-1 must undergo translocation to lipid membrane surfaces where it interacts with its substrate PA (Jamdar et al., 1973; Johnston et al., 1967; Walton et al., 1984). Several published studies have demonstrated a functional change in PAP-1 in response to agonist induced translocation. U937 macrophages displayed reduced cytosolic PAP-1 activity within 2 minutes of LPS stimulation, suggesting that PAP-1 had undergone translocation from the cytosol. This result is also consistent with the temporal formation of the DAG spike at 2 minutes after LPS stimulation (Grkovich et al., 2006). In a separate study, PAP activity was discovered in A431 cells complexed with PKCε to the epidermal growth factor receptor (EGFr) (Jiang et al., 1996). Interestingly, the PAP activity was markedly reduced upon treatment of the EGFr complex with the EGF ligand, suggesting that it is released from the complex upon the binding of the agonist to the EGF receptor. In a third study conducted by Jesus Balsinde's laboratory, inhibition of PAP-1 in a number of macrophage cell lines resulted in the activation of a number of apoptotic hallmarks, suggesting that PAP-1 may play a role in the cellular life cycle and apoptosis (Fuentes et al., 2003). Collectively, these experiments suggest that PAP-1 may participate in a number of cellular processes.

PAP-1 in GIVA PLA_2 activation and COX-2 expression

A wealth of published data has demonstrated that PKC mediates cellular GIVA PLA_2 activation (Pettus et al., 2004). Furthermore, data suggest that PAP-1 participates in the cellular activation of GIVA PLA_2 via PKC. First, AA release from LPS treated RAW 264.7 macrophages has been shown to be sensitive to PAP-1 chemical inhibition, suggesting that PAP-1 participates in GIVA PLA_2 activation (Grkovich et al., 2008). Studies conducted on rat polymorphonuclear neutrophils (PMN) and mast cells demonstrate that agonist induced GIVA PLA_2 activation is sensitive to PLD inhibition, suggesting that PLD also is a participant in this mechanism (Fujita et al., 1996; Kitatani et al., 2000). In a similar experimental design, AA release from PMA differentiated U937 macrophages stimulated with fMLP was sensitive to ethanol inhibition, as was the formation of DAG. This study further described that undifferentiated U937 cells displayed greatly reduced DAG levels and were unable to elicit AA release in response to the fMLP agonist, suggesting an important correlation between the formation of PLD-derived DAG and activation of the GIVA PLA_2 (Burke et al., 1999). Collectively, these published reports suggest that PLD and PAP-1 participate together in the activation of the inflammatory GIVA PLA_2, at least in some cellular systems.

Biochemical and genetic approaches have demonstrated that LPS stimulation of TLR-4 results in the NF-κB-mediated upregulation of COX-2 (Liu et al., 1999; Kojima et al., 2000; Caivano et al., 2000; Pistritto et al., 1999; Lo et al., 1998). PKC is known to participate in NF-κB-mediated COX-2 expression in the TLR-4 pathway by phosphorylating I-κB as well as targeting MAPK (Lin et al., 1999; Wang et al., 1999; Giroux et al., 2000; Chiang et al., 2000; Peng et al., 2008). A number of published reports provide evidence that suggests that PAP-1 participates in the upregulation of COX-2 expression through PKC. In a study from our laboratory, amnionic WISH cells stimulated with phorbol ester (PMA) displayed reduced COX-2 expression when treated with PAP-1 chemical inhibitors or primary alcohols, suggesting that PLD and PAP-1 are necessary for COX-2 expression in this cellular system (Johnson et al., 1999). A later study utilized a TLR-4 activated U937 macrophage model rather than a PMA activated amnionic cell line. In the second study consistent with the previous, inhibition of either PAP-1 or PLD resulted in the blockage of the LPS-induced expression of COX-2 (Grkovich et al., 2006). A number of additional publications describe pretreatment of macrophages with primary alcohols resulting in marked inhibition of COX-2 expression, further bolstering the evidence for the possible participation of PLD and PAP-1 in the regulation of COX-2 expression (Lee et al., 2003; Kim et al., 2004). Pretreatment of cat esophageal circular muscle with the PAP-1 inhibitor BEL prior to interleukin-1 (IL-1) stimulation resulted in blocked PGE_2 release; however, BEL did not affect PGE_2 release through dopamine stimulation (Hellstrand et al., 2002). Taken collectively, these results suggest that PAP-1 participates in COX-2 expression via the interleukin receptor activated kinase (IRAK) signaling cascade and may indicate that PLD/PAP-1 derived DAG has evolved through specified signaling cascades.

The current discussion has focused on the role of PAP-1 in the activation of GIVA PLA_2 and expression of COX-2. For the sake of completion, it is essential to consider alternate methods of cellular DAG formation in inflammatory signaling. Studies conducted using rat microglia, cardiomyocytes and canine smooth muscle cells have shown that PLC inhibition results in blocked LPS induced COX-2 expression, which suggests that PLC participates in COX-2 expression within these cellular models (Akundi et al., 2005; Luo et al., 2003; Shen et al., 2007). In another study conducted with LPS stimulated RAW 264.7 macrophages, COX-2 expression was sensitive to either inhibition of PLC or PLD, suggesting that both DAG evolving pathways may be active (Lee et al., 2003). Considering a similar result, MDCK cells stimulated with bradykinin demonstrated GIVA PLA_2 activation that was also sensitive to either PLC or PLD inhibition (Kennedy et al., 1996). In consideration of these publications, it is clear that DAG is an essential component of inflammatory signaling. However it appears that additional research is needed to identify the distinctive signaling functions of DAG derived from PLD/PAP-1 and PLC.

Summary

Since the cloning and characterization of PAP-1 by Carman's group, a preponderance of new information has emerged pertaining to the molecular function of the enzyme and its physiological function in lipid metabolism (Carman et al., 2006; Donkor et al., 2007). As a consequence of this development, PAP-1 and lipin research have informed us further regarding lipid metabolism and adipose tissue development (Carman et al., 2006; Reue et al., 2008). In recent years, the field of inflammatory lipid signaling has undergone a great expansion and has come to identify a wide variety of protein and metabolic inflammatory mediators, including PAP-1 as well as PLD, PKC, PLC and DAG. The focus of this review was to summarize experimental evidence supporting a role for PAP-1 in inflammatory signaling, which is summarized in Scheme 2 (Grkovich et al., 2008). Further clarification is needed to identify the precise signaling functions and downstream targets of DAG forming enzymes, such as PLD/PAP-1 and PLC, as evidence supports both as participants in inflammatory signaling in

different systems. Clarification of these regulatory questions should lead to a more complete understanding of inflammatory signaling while helping to identify future pharmacological targets.

Summary

LIST OF POSSIBLE MAJOR TOPICS

1. Inlfammatory signaling
2. Lipopolysaccharide
3. Phosphatidic acid phosphohydrolase 1
4. Lipin
5. Diacylglycerol
6. Group IVA Phospholipase A_2
7. Cyclooxygenase 2
8. Phospholipase C
9. Phospholipase D
10. Toll-like recptor 4
11. Lipid signaling
12. Phosphatidic acid
13. Triacylglycerol
14. Phospholipid
15. NF kappaB

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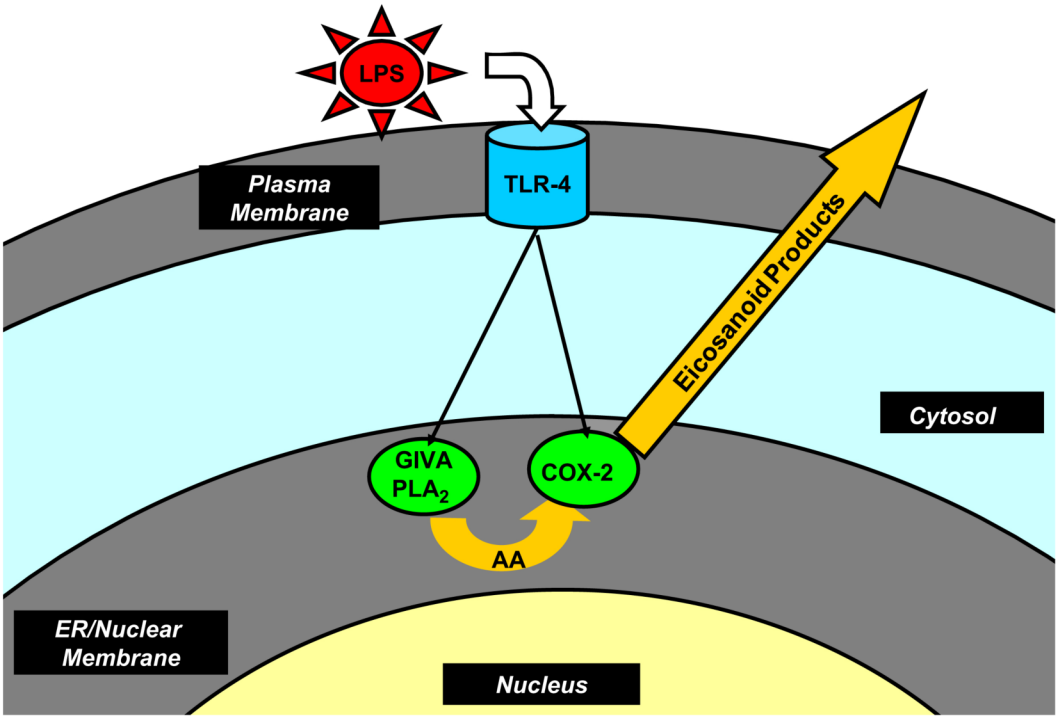
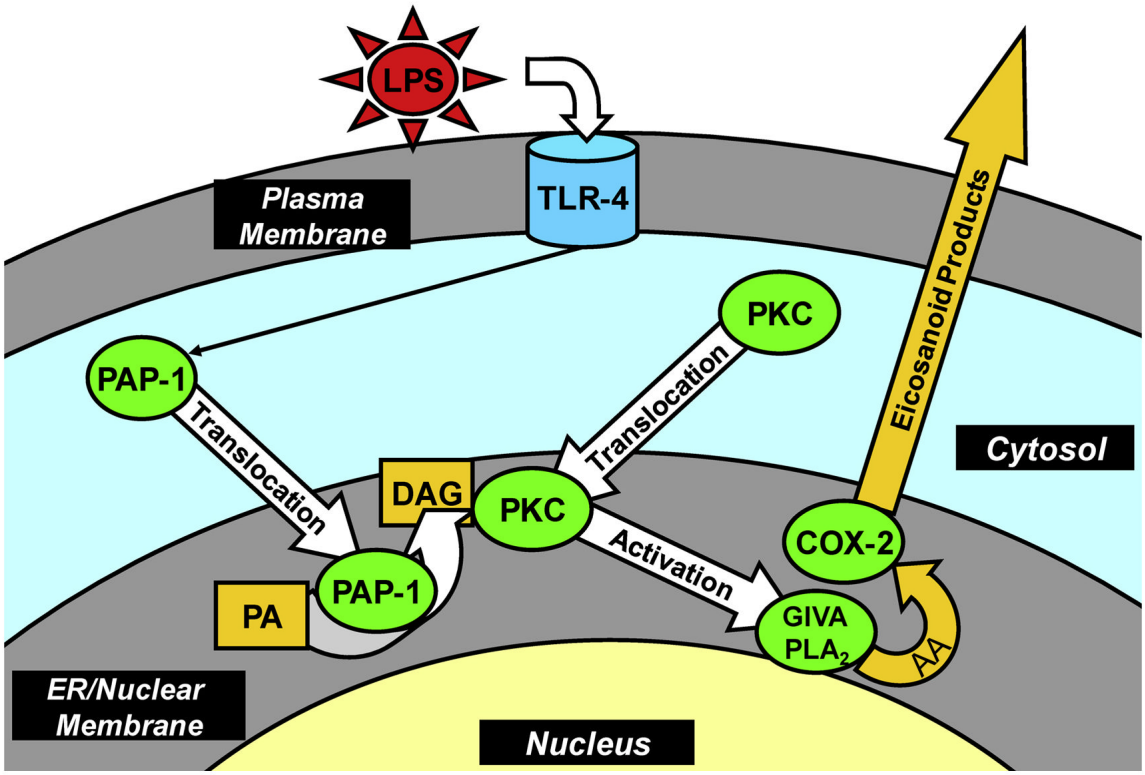


Scheme 1.
Inflammatory signaling through TLR-4 in macrophages.



Scheme 2.
Role of PAP-1 in TLR-4 activation of eicosanoid signaling in macrophages. Adapted from (Grkovich et al., 2008).