Minireview

# Biological effects of group IIA secreted phosholipase $A_2$

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**Abstract Group IIA secreted phospholipase $A_2$ (sPLA$_2$-IIA) is the most abundant element in human tissues of a large family of low molecular weight phospholipases $A_2$, which shows properties different from those displayed by the cytosolic phospholipase $A_2$ involved in the release of arachidonic acid. sPLA$_2$-IIA behaves as a ligand for a group of receptors inside the C-type multilectin mannose receptor family and also interacts with heparan sulfate proteoglycans such as glypican, the dermatan/chondroitin sulfate-rich decorin, and the chondroitin sulfate-rich versican, thus being able to internalize to specific compartments within the cell and producing biological responses. This review provides a short summary of the biological actions of sPLA$_2$-IIA on intracellular signaling pathways.**



*Key words:* Astrocyte; Atherosclerosis; Inflammation; Lipid mediator; Leukocyte; Protein kinase

## 1. Secreted phospholipases $A_2$ and cytosolic phospholipase $A_2$

Phospholipases $A_2$ ($PLA_2$) are a large family of related enzymes that have been classified into groups I–XII according to several criteria which include catalysis of the hydrolysis of the *sn*-2 ester bond of glycerophospholipids, complete protein sequence, existence of homologous enzymes, and finding of active splice variants [1–4]. Group I, II, V, and X $PLA_2$ are closely related enzymes, which can be collectively termed secreted phospholipases (sPL), are characterized by a low molecular mass of 13–18 kDa, several disulfide bonds, a requirement for millimolar amounts of $Ca^{2+}$ for catalytic activity, and a low selectivity for phospholipids with different polar heads and fatty acids. They share a common mechanism for cleaving the *sn*-2 ester bond of phospholipids, involving a catalytic histidine, but show a different pattern of expression among the different tissues. Thus, group IIE $PLA_2$ has been detected in human brain, lung and placenta [5]. Group V $sPLA_2$ is expressed in human heart and, less abundantly, in lung [6], and group X $sPLA_2$ is expressed in spleen, thymus and blood leukocytes [7].

Group IIA $PLA_2$ (also known as inflammatory $PLA_2$, sPLA$_2$-IIA) has been considered the main human element of the large family of $sPLA_2$ for several reasons: (i) its early characterization as a secreted enzyme from synovial fluid [8,9]; (ii) its broad expression pattern in human tissues as compared to other elements of group II enzymes [5]; (iii) the induction of its synthesis by endotoxin and cytokines via paracrine and/or autocrine processes during inflammatory processes of clinical relevance, which have allowed the characterization of this enzyme as a newly recognized acute phase protein [10]; (iv) its potent bactericidal effects, which support a role for this enzyme in the innate immunity against *Staphylococcus aureus* infection [11]. In this connection, studies intended to address the physiological relevance of sPLA$_2$-IIA in vivo have shown that its concentration in plasma may reach $\sim$1 μg/ml after injection of bacteria in experimental animals [12], thus agreeing with the range of concentrations which display antibacterial effects in vitro [13,14].

At present, there are several fields where the functional relevance of sPLA$_2$-IIA is a subject of active research, namely, pathophysiological events in the neural system, and inflammatory conditions such as arteriosclerosis, septic shock and rheumatoid arthritis. A relevant issue regarding its pathophysiological potential has been provided by the evidence that many of its biological actions depend on interactions with receptors similar to those involved in the toxic effects of $PLA_2$ found in venoms [15], and the ensuing effects on signal transduction pathways. This has prompted the appraisal of the pathways through which sPLA$_2$-IIA might exert its physiological functions and distinct mechanisms have been proposed to explain the signaling properties of sPLA$_2$-IIA: (i) generation as a result of its catalytic activity of both unesterified fatty acid and lysophospholipid [16]; (ii) perturbation of the cell membrane by its interfacial interaction with substrate phospholipids [17]; (iii) interaction with membrane receptors analogous to those binding other $sPLA_2$ [18]; (iv) binding to acceptor proteoglycans such as the heparan sulfate-rich glypican [19], the dermatan/chondroitin sulfate-rich decorin [20], and the chondroitin sulfate-rich versican [21]. This is of interest, since the aforementioned mechanisms of action can be cell-specific, thus leading to diverse biological effects on different tissues. For instance, interaction with the M-type receptor has been proposed as the main mechanism of action explaining the effects of sPLA$_2$-IIA in mast cells and macrophages [22–24], but unlike mouse sPLA$_2$-IIA, human sPLA$_2$-IIA has not been found to bind to the M-type receptor [25], thus making it

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*Abbreviations:* sPLA$_2$-IIA, group IIA secreted phospholipase $A_2$; cPLA$_2$, cytosolic phospholipase $A_2$; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MAP kinase, mitogen-activated protein kinase; MEK, MAP kinase kinase of the MAP/ERK group

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likely that not all of the physiological receptors for $sPLA_2$ have been characterized as yet. On the other hand, interaction of $sPLA_2$-IIA with decorin has been considered of relevance to explain the effect of $sPLA_2$-IIA on atherogenesis, since this would allow the modification of lipoproteins and the release of lipid mediators at places of lipoprotein retention in the arterial wall [20].

In contrast to $sPLA_2$, the cytosolic $PLA_2$ ($cPLA_2$) is an enzyme that hydrolyzes selectively arachidonic acid esterified at the *sn*-2 position of phospholipids, has a molecular mass of 85 kDa and is regulated by a biochemical mechanism that involves both docking to the cell membrane for access to phospholipid substrate and phosphorylation-dependent activation by mitogen-activated protein (MAP) kinases [26,27]. The $Ca^{2+}$-dependent binding of $cPLA_2$ to the membrane is due to a C2 domain located at the N-terminus of the enzyme, and this has been confirmed by mutation of the $Ca^{2+}$-binding residues D43 and D93 of the C2 domain [28].

In this review, we focus on the biological effects elicited by $sPLA_2$-IIA on 1321N1 astrocytoma cells and THP-1 monocytes, taking advantage of the extensive work carried out in these lines, and of the different physiological roles displayed by these cell types. This allows us to summarize both the connection of $sPLA_2$-IIA with different signaling systems and its potential pathogenetic role in some clinical conditions.

## 2. $sPLA_2$-IIA elicits a mitogenic response and activates arachidonic acid metabolism in astrocytoma cells

An important connection between $sPLA_2$ and signal transduction pathways emerged from the discovery that some mammalian isoforms, including $sPLA_2$-IIA, bind with high affinity to receptors first associated with the toxic effect of venom-secreted $PLA_2$ [15], thus leading to mitotic proliferation, and disclosing a novel biological effect of these enzymes independent of their catalytic activity. The initial identification of $sPLA_2$-binding proteins was carried out using a neurotoxic $PLA_2$ extracted from the venom of the snake *Oxyuranus scutellatus scutellatus*. Since the $sPLA_2$-binding protein is most abundant in brain, this first type of binding site was called the N-type (neuronal-type) receptor [18]. A second type of receptor for $sPLA_2$-IIA was initially found in skeletal muscle, and was termed the M-type (muscle-type) receptor [29]. Interestingly, the M-type receptor has been intensively studied and characterized as a member of a family of transmembrane proteins with a structural organization similar to that of the macrophage mannose receptor [29], thus making these receptors to constitute a new group within the C-type multilectin mannose receptor family [30]. Since a common property of this protein family is endocytosis, it has been proposed that the physiological role for the M-type $sPLA_2$ receptor is to internalize and deliver $sPLA_2$-IIA to specific compartments within the cell where the enzyme might exert its activity.

The reports showing the existence of binding structures for $sPLA_2$-IIA in cell membranes have been complemented by the description of the activation by $sPLA_2$-IIA of intracellular signaling pathways in different cell types, thus mimicking the transducing mechanism conveyed by conventional stimuli acting on membrane receptors which activate intracellular phospholipases and release arachidonic acid. Since the release of arachidonic acid from membrane phospholipids is a finely regulated process, which involves the activation of $cPLA_2$, these findings have been considered evidence of an effect of $sPLA_2$-IIA on $cPLA_2$ via a signaling cascade that mimics the transducing mechanism conveyed by physiological activators of $cPLA_2$. Preliminary studies addressing these issues have been conducted in both platelets and rat mesangial cells. The studies in human platelets showed that $sPLA_2$-IIA elicits optical aggregation, generation of thromboxane $A_2$, influx of calcium ions, and time-dependent tyrosine phosphorylation of several platelet proteins. These responses were abrogated by pretreatment with both heparitinase and phosphatidylinositol-specific phospholipase C, thus suggesting that a glysophosphatidylinositol-anchored platelet-membrane heparan sulfate proteoglycan is the binding site for $sPLA_2$-IIA in human platelets, and also that the engagement of this structure leads to the release of the arachidonic acid needed for thromboxane $A_2$ production [31]. As regards mesangial cells, early studies showing cross-talk between $sPLA_2$-IIA and $cPLA_2$ [32] have been recently enlarged by the description of a synergistic effect of peroxisome proliferator-activated receptor and tumor necrosis factor-α (TNF-α) on $sPLA_2$-IIA expression [33], and by the finding that interleukin-1β enhances the expression of both $sPLA_2$-IIA and group V $sPLA_2$ in rat mesangial cells [34], thus pointing to the positive modulation of $sPLA_2$-IIA expression as a relevant factor for kidney pathology.

The biological effects of $sPLA_2$-IIA have also been addressed in the astrocytoma cell line 1321N1, since this cell line has a wide variety of surface receptors and responds to many stimuli to which neurons are also responsive, thus making it an adequate model for the study of signal transduction pathways in the nervous system [35]. In this cell line, $sPLA_2$-IIA produces mobilization of $Ca^{2+}$ from intracellular stores by a mechanism involving the formation of inositol 1,4,5-trisphosphate from phosphatidylinositol bisphosphate by a phospholipase Cγ, which requires tyrosine phosphorylation reactions and targeting to the membrane, thus involving a phospholipase C subtype different from the β isoform that is recruited by agonists acting through G protein-coupled receptors [36]. This was accompanied by the decrease in electrophoretic mobility (band-shift) that is characteristic of the phosphorylation of $cPLA_2$, and arachidonic acid release. Activation of all of the modules of the MAP kinase family involving p42-MAP/extracellular signal-regulated kinase (ERK) kinase, c-Jun N-terminal kinase (JNK), and p38-MAP kinase was also observed, as well as cell proliferation, as judged from

Table 1
Effect of $sPLA_2$-IIA on astrocytoma cells and comparison with the actions of stimuli acting on other types of receptors

| | $PLA_2$-IIA [37] | Thrombin [53] | Muscarinic $M_3$ [54,56] | TNF-R [55] |
|---|---|---|---|---|
| Activation of the Rel/NF-κB system | − | + | − | + |
| Mobilization of $Ca^{2+}$ | + | + | + | − |
| Activation of the ERK module of MAP kinase | + | + | + | − |
| Activation of the stress module of MAP kinase | + | + | − | + |
| Proliferation/apoptosis | Mitosis | Mitosis | Irrelevant | Apoptosis |

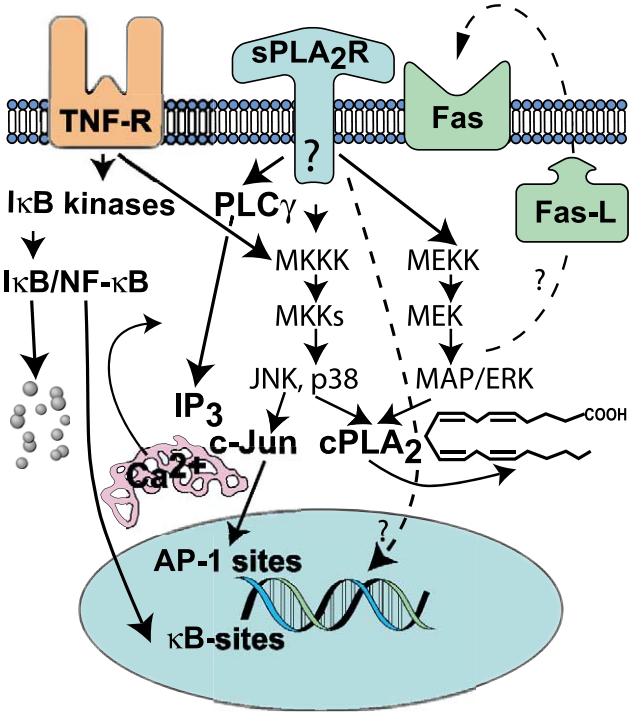


Fig. 1. Overview of signaling events coupled to the $sPLA_2$ receptor and connections with other receptors focusing on the results obtained in 1321N1 astrocytoma cells and THP-1 monocytic cells. Up-regulation of Fas ligand and synergism with TNF-α-mediated signaling have been shown in THP-1 monocytic cells expressing M-type $sPLA_2$ receptor, whereas activation of the MAP kinase cascade has also been reported in astrocytoma cells, mesangial cells and mast cells. Activation of phospholipase Cγ has been shown in astrocytoma cells. The question mark placed in the $sPLA_2$ receptor indicates that these effects have also been observed in cells lacking the M-type receptor, for instance 1321N1 cells (Fig. 2A), thus challenging the notion that this structure is an absolute requirement for these responses. AP-1, activation protein-1; $IP_3$, inositol trisphosphate; Fas-L, Fas ligand; IκB, inhibitor of NF-κB; MKK, MAP kinase kinase of the stress family of MAP kinase; MKKK, MAP kinase kinase kinase; p38, p38 isoform of MAP kinase; PLCγ, phospholipase Cγ; TNF-R, TNF receptor.

an increased incorporation of [$^3$H]thymidine into the trichloroacetic acid-precipitable fraction of 1321N1 cells incubated in the presence of $sPLA_2$-IIA (Table 1). Treatment with the MAP kinase kinase of the MAP/ERK group (MEK) inhibitor PD-98059 inhibited the activation of both $cPLA_2$ and p42-MAP kinase, thus suggesting the coupling of $cPLA_2$ to the ERK pathway in response to $sPLA_2$-IIA [37]. Fig. 1 summarizes the signaling pathways engaged by $sPLA_2$-IIA. These responses show some overlap with those elicited by agonists engaging G protein-coupled receptors as well as TNF-α receptors, but a number of differences can be delineated.

### 3. $sPLA_2$-IIA promotes pro-inflammatory effects and activates Fas ligand in monocytic cells

Recent studies have suggested a role for $sPLA_2$-IIA in the pathogenesis of atherosclerosis on the basis of a series of observations, which support a role for this enzyme both on plasma lipoproteins [38,39] and in the arterial wall [40–42]. In fact, circulating levels of $sPLA_2$-IIA have been shown to be sensitive predictors of coronary events in patients with coronary arterial disease [43], and high amounts of $sPLA_2$-IIA have been found in human atherosclerotic arterial walls and related to the development of atherosclerotic plaques [44]. As mentioned before, $sPLA_2$-IIA has been found to associate with decorin, a proteoglycan which forms part of the collagen network in human arteries and links native low density lipoprotein (LDL) to collagen [20]. Thus, $sPLA_2$-IIA may contribute to the pathogenesis of atherosclerosis by modifying lipoproteins and releasing lipid mediators at places of lipoprotein retention in the arterial wall, as well as by inducing mitotic proliferation of human vascular smooth muscle cells [45]. In addition, mildly oxidized LDL induces expression of $sPLA_2$-IIA in human macrophages [46], and induction of $sPLA_2$-IIA expression is a characteristic of the differentiation of human arterial smooth muscle cells on exposure to interferon-γ and other cytokines [47], thus pointing to the involvement of $sPLA_2$-IIA in the inflammatory reaction of atherosclerosis. Attempts to disclose the biological effects of $sPLA_2$-IIA in human macrophages have been carried out with $sPLA_2$-IIA at concentrations similar to those found in plasma [48]. Under these conditions, $sPLA_2$-IIA induced the production of the monocyte chemoattractant chemokine monocyte chemotactic protein-1 (MCP-1) and upregulated the surface display of Fas ligand (Fig. 2B,C) without affecting the distribution of cells in the different phases of the cell cycle, thus suggesting the upregulation of a juxtacrine mechanism of signaling involving Fas ligand expressed and/or released on monocytic cells and Fas expressed on other cells such as infiltrating leukocytes and endothelial cells. This finding might be of pathophysiological relevance in view of the increased expression of $sPLA_2$-IIA in clinical conditions such as atherosclerosis and rheumatoid arthritis [49], where the Fas-signal-

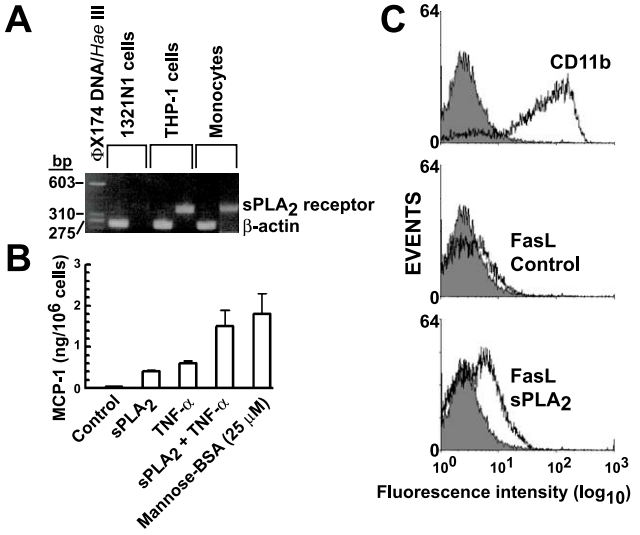


Fig. 2. Effect of $sPLA_2$-IIA in cells expressing the M-type receptor for $sPLA_2$-IIA. Total mRNA was taken from 1321N1 astrocytoma cells, THP-1 cells, and human monocytes and used for RT-PCR reactions using oligonucleotide primers designed from the human sequence of the $sPLA_2$ M-type receptor. The expression of β-actin was used as a control for the assay of a constitutively expressed gene. PCR products were identified by automatic sequencing of the DNA eluted from the agarose gel by excision of the band under UV light followed by purification (A). The production of MCP-1 by human monocytes incubated for 24 h in the presence of different additions is shown in B. The effect of $sPLA_2$-IIA on the surface display of Fas ligand was addressed by flow cytometry in human monocytes adhered to plastic dishes and identified by the surface expression of CD11b (C). Taken from [48], with permission.

Table 2
Effect of $sPLA_2$-IIA on different cell types

| Mast cells [22–24,57,58] | Synovial cells [59,60] | Macrophages [48,61] | Neurons [62–64] |
|---|---|---|---|
| Degranulation | Cytokine production | Cytokine production | Mobilization of $Ca^{2+}$ |
| NF-κB activation | NF-κB activation | NF-κB activation | Release of substance P |
| Arachidonic acid release | Cyclooxygenase-2 induction | β-Glucuronidase release | Arachidonic acid release |
| Activation of the MAP kinase cascade | | Induction of nitric oxide synthase | Potentiation of glutamate-induced cell death |
| Inhibition of apoptosis | | Upregulation of Fas ligand | Neuronal cell death |

ing pathway has been proposed to play a role in their pathogenesis [50–52]. Since apoptosis mediated by Fas ligand release from mononuclear phagocytes is a mechanism of resolution of inflammation under non-phlogistic conditions, it is possible to propose a programmed sequence of functions for $sPLA_2$-IIA on mononuclear phagocytes: (i) a set of pro-inflammatory changes including activation of the MAP kinase cascade, induction of cyclooxygenase-2, and mobilization of monocytes; (ii) a contribution to the safe clearance of infiltrating leukocytes through the triggering of the Fas/Fas ligand system. Taken together, these findings enlarge the scope of biological functions for $sPLA_2$-IIA (Table 2) and stress the variety of effects elicited on different cell types.

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