

## Review Article

# Lipoprotein associated phospholipase A<sub>2</sub> enzyme; possible new roles and inhibition for therapeutic intervention

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### ABSTRACT

Lipoprotein-Associated Phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) is a 45-kDa protein of 441 amino acids encoded by the pla2g7 gene in the humans. In the blood it is associated mainly with Low Density Lipoprotein (LDL) and less than 20% is associated with High Density Lipoprotein (HDL). This enzyme is characterized by its ability to specifically hydrolyze PAF as well as glycerophospholipids containing short, truncated, and/or oxidized fatty acyl groups at the *sn*-2 position of the glycerol backbone. Genetic studies conducted in humans harboring an inactivating mutation at this locus suggest that loss of Lp-PLA<sub>2</sub> function is a risk factor for inflammatory and vascular conditions. Consistently, overexpression of Lp-PLA<sub>2</sub> has anti-inflammatory or pro-inflammatory actions and anti-atherogenic properties in animal models. This article discusses two simple techniques to estimate Lp-PLA<sub>2</sub> activity. New therapeutic agents inhibiting the activity of Lp-PLA<sub>2</sub> are being investigated for curative purpose.

**Keywords:** PLA<sub>2</sub>, Phospholipid, Inflammation, Thyroxine, Grave's disease, PAF

### INTRODUCTION

Lp-PLA<sub>2</sub> is a unique member of the PLA<sub>2</sub> super-family that contains about fifteen separate, identifiable groups and numerous subgroups. These enzymes are characterized by their ability to hydrolyze the *sn*-2 ester bond of phospholipid substrates and are assigned to groups based on sequence, molecular weight, disulfide bonding patterns, the requirement for Ca<sup>2+</sup>, and other features. This enzyme is produced by myeloid derived cells and it functions to hydrolyze oxidized/polar phospholipids. This enzyme was discovered based on its ability to catalyze hydrolysis of the acetyl group at the *sn*-2 position of PAF to generate lyso-PAF and acetate.<sup>1,2</sup> To illustrate the ability of Lp-PLA<sub>2</sub> to inactivate PAF, which has been implicated in a variety of inflammatory diseases,<sup>3</sup> the enzyme was referred to as the secreted/plasma form of PAF acetylhydrolase or PAF-AH. Lp-PLA<sub>2</sub> is primarily produced by macrophages<sup>4</sup> and

circulates in plasma in active form as a complex with LDL and HDL. A small fraction of the enzyme is carried in Lp(a) in subjects that express this particle.<sup>5</sup> Multiple inflammatory cells involved in atherogenesis secrete Lp-PLA<sub>2</sub>, including monocytes, macrophages, neutrophils, activated bone marrow-derived mast cells, and activated platelets. Monocyte/macrophages are key players in both initiation and progression of atherosclerosis, and they have been proposed as new potential therapeutic targets for the prevention and treatment of this disease.<sup>6,7</sup> Lp-PLA<sub>2</sub> is a calcium-independent serine lipase that is associated with Low Density Lipoprotein (LDL) in human plasma and serum<sup>1</sup> and is distinct from other phospholipases such as cPLA<sub>2</sub> and sPLA<sub>2</sub>.<sup>8</sup> Lp-PLA<sub>2</sub> is produced by macrophages and is expressed in greater concentrations in atherosclerotic lesions.<sup>9</sup> Several lines of evidence suggest that oxidation of LDL plays a critical step in the development and progression of atherosclerosis.<sup>10</sup> Lp-PLA<sub>2</sub> participates in the oxidative

modification of LDL by hydrolyzing oxidized phosphatidylcholine, generating lysophosphatidylcholine and oxidized free fatty acids, both of which are potent pro-inflammatory products that contribute to the formation of atherosclerotic plaques. On the other hand, hypothyroidism has been shown to be associated with hypertriglyceridemia as well as hypercholesterolemia.<sup>11</sup> Thyroid hormone and thyromimetics are known to exert several actions that lead to lowered serum cholesterol levels, and an improved lipid profile, which is associated with a decreased risk of atherosclerosis. Whether thyroid hormones significantly affect Lp-PLA<sub>2</sub> activity needs to be investigated comprehensively.<sup>12</sup> This article also discusses two simple techniques to estimate Lp-PLA<sub>2</sub> enzyme activity.

## TECHNIQUES FOR ESTIMATING Lp-PLA<sub>2</sub>

### a) Scintillography based technique

The method is based on an earlier technique shown by KoK-Hay et al.<sup>13</sup> Plasma aliquots prepared from blood samples are collected at baseline and stored at -80°C, and Lp-PLA<sub>2</sub> activity is measured with a high-throughput radiometric activity assay. Briefly, plasma samples are divided into aliquots, placed in 96-well microtiter plates, and mixed with a substrate solution consisting of 0.4 μmol/L [<sup>3</sup>H]-PAF (specific activity, 21.5 Ci/mmol, Perkin Elmer life sciences) and 99.6 μmol/L C16-PAF (Avanti Polar lipids Inc) in assay buffer (100 mmol/L HEPES, 150 mmol/L NaCl, 5 mmol/L EDTA, pH 7.4). The reactions are allowed to proceed at room temperature for 5 minutes before sequestering of the phospholipid substrates by an ice-cold fatty acid-free BSA solution at a final concentration of 16.1 mg/mL. The BSA-lipid complexes are then precipitated with ice-cold trichloroacetic acid at a final concentration of 7.8% and pelleted by centrifugation at about 6000 g for 15 minutes at 4°C. Aliquots of the supernatant containing the reaction products are transferred to another microplate (Perkin Elmer), and radioactivity is counted in a Topcount liquid scintillation counter (Perkin Elmer life sciences) on addition of Microscint-20 scintillation cocktail (Perkin Elmer life sciences). Lp-PLA<sub>2</sub> activity is expressed as nanomoles of PAF hydrolyzed per minute per 1 mL plasma samples.

### b) Spectrophotometric based technique

The spectrophotometric estimation of PAF-AH hydrolysis of PAF analogues with 4-nitrophenyl is observed spectrophotometrically at 405 nm by monitoring the absorption change due to the liberation of 4-nitrophenol from the substrate upon phospholipid hydrolysis.<sup>14</sup> A standard spectrophotometer (T60 LAB India UV-VIS spectrophotometer, UK) can be used for this purpose. A 3-μl volume of sample and 240 μl of reagent A (200 mmol/l NaCl, 15 mmol/l EDTA, 9.6 mmol/l sodium 1-nonanesulfonate, 7 mmol/l CHAPS, and 100 mmol/l HEPES, pH 7.6) are mixed, and

preincubated at 37°C for 5 min. The reaction is then started by adding 80 μl of reagent B (18 mmol/l citric acid monohydrate, 8.64 mmol/l sodium 1-nonanesulfonate, 10% ethanol, and 3.2 mmol/l 1-myristoyl-2-(4-nitrophenylsuccinyl) phosphatidylcholine, pH 4.5). The absorption is measured at 2 and 5 minute time intervals after the addition of the substrate solution (Reagent B).

The activities are calculated using the difference ( $\Delta A$ ) between the absorbances of the above measuring points and the extinction coefficient ( $\epsilon=12.3 \times 10^3$  l/mol/cm at pH 7.6) of 4-nitrophenol.

## REGULATION OF Lp-PLA<sub>2</sub> EXPRESSION

It has previously been demonstrated that maturation of monocytes into macrophages is accompanied by dramatic increases in Lp-PLA<sub>2</sub> mRNA and protein these observations were recently confirmed. Treatment of macrophages with acetylated LDL generates foam cells *in vitro* and further increases Lp-PLA<sub>2</sub> expression, which is consistent with observations in human atherosclerotic plaques.<sup>15,16</sup>

The properties of macrophages in atherosclerotic lesions can vary dramatically between two extremes: pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages; these cells can switch from one phenotype to the other depending on microenvironmental cues, such as differentiation factors produced in the lesion and T-cell-derived polarizing cytokines. It has been shown that IFN- $\gamma$ , which has been implicated as a promoter of foam cell formation and an inducer of M1 pro-inflammatory phenotypes, decreased expression of Lp-PLA<sub>2</sub> at the transcriptional level. In fact, M-CSF, which induces an M2-like, anti-inflammatory phenotype, increased monocyte Lp-PLA<sub>2</sub> expression to a much higher extent compared with the M1-inducer GM-CSF. De Keyzer and colleagues showed that a high-fat diet, which caused to increased levels of oxidized LDL, was accompanied by robust increases in Lp-PLA<sub>2</sub> activity.<sup>17</sup> When this response was modeled in a cellular system, the investigators found that oxidized LDL robustly increased expression of Lp-PLA<sub>2</sub> mRNA in THP1 cells and, to a lesser extent, human monocyte-derived macrophages. Both pharmacologic and genetic depletion of Lp-PLA<sub>2</sub> in minimally modified lipoproteins enhanced monocyte adhesion to aortic endothelial cells compared with minimally modified lipoproteins that expressed normal activity levels.<sup>14</sup> Similarly, exogenous Lp-PLA<sub>2</sub> reduced cellular uptake of oxidized LDL and Lp(a), and cholesterol accumulation by monocyte-derived macrophages, compared with parallel assays conducted with inactive enzyme. These results suggest that the enzymatic activity of Lp-PLA<sub>2</sub> limits monocyte recruitment and foam cell formation within atherosclerotic lesions.<sup>18</sup>

## **THYROID HORMONE DYSFUNCTION AND EFFECTS ON LIPOPROTEINS AND POSSIBLE INFLUENCE OF Lp-PLA<sub>2</sub>**

Thyroid hormones play an important role in lipid and lipoprotein metabolism. Hypothyroidism is usually accompanied by dyslipidaemia characterized by elevated Low Density Lipoprotein Cholesterol (LDL-C) and it enhances the susceptibility to oxidation of the increased LDL-C, which may contribute to the increased risk of atherosclerosis.<sup>19</sup>

Lipid abnormalities can also be seen in hyperthyroidism although it is not as frequent as seen in hypothyroidism. Increased oxidized LDL-C levels have been reported in patients with hyperthyroidism.<sup>20</sup>

In some studies, impaired glucose tolerance or insulin resistance which is known to be risk factor for the development of atherosclerosis has been documented in hyperthyroidism. Despite the increased activity of the HMG-CoA reductase, levels of TC, LDL-C, ApoB and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism. This is due to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. Moreover, no difference in LDL sub-fraction distribution has been observed between subclinical or overt hyperthyroid versus euthyroid subjects.<sup>21</sup>

Furthermore, hyperthyroidism results in enhanced LDL oxidability, which is related to FT<sub>4</sub> levels. Hyperthyroidism not only consists a significant cause of acquired hypobetalipoproteinemia, but it can also be the underlying cause of unexpected improvement of lipid profile in hyperlipidemic patients. In the latter case, therapy of thyrotoxicosis restores the lipid parameters to the previously elevated levels. In addition, thyroxine therapy increased HDL-associated Lp-PLA<sub>2</sub> activity in SH subjects.<sup>22</sup> Thus it can be suggested that in hyperthyroid conditions like the Grave's disease the Lp-PLA<sub>2</sub> activity may be increased and this needs to be thoroughly investigated by more comprehensive studies.<sup>23,24</sup>

## **ROLE OF Lp-PLA<sub>2</sub> IN INFLAMMATION**

Recent studies suggest that over expression of Lp-PLA<sub>2</sub> has anti-inflammatory activity and this depends of various factors and interaction with other molecules. This new evidence over rides other previous studies about its pro-inflammatory action. When Lp-PLA<sub>2</sub> hydrolyzes bioactive lipids, reducing their biological activity, the most generated metabolites are the lysophospholipids. These lipids are involved with atherosclerotic process and show a deleterious role of Lp-PLA<sub>2</sub>, contributing to the inflammatory response against oxidized lipoproteins.<sup>25</sup>

These compounds generated by phospholipases A<sub>2</sub> during cell activation, injury, or apoptosis, are known to affect

the function of neutrophils and of a diversity of cell types, and can be also produced by phospholipase A<sub>1</sub> and by the action of Lecithin-Cholesterol Acyltransferase (LCAT) or endothelial lipase. There are many lysophospholipids, but the main product of Lp-PLA<sub>2</sub> action is lysophosphatidylcholine; these metabolic processes occur in physiological conditions.<sup>26</sup>

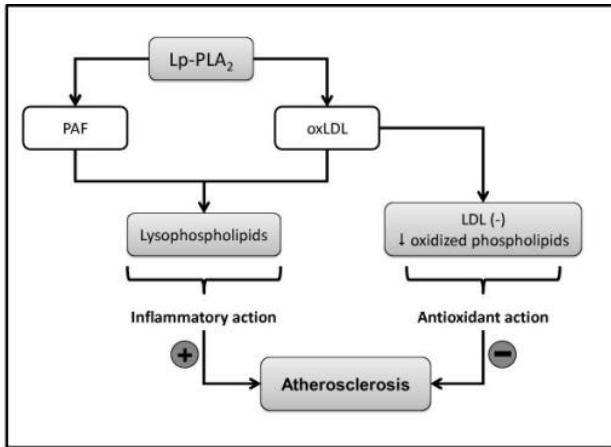
Furthermore, lysophospholipids from apoptotic cells contribute to attract monocytic cells and primary macrophages. In this context, Steinbrecher & Pritchard showed that oxLDL, on the presence of Phenyl Methane Sulphonyl Fluoride (PMSF), an inhibitor of Lp-PLA<sub>2</sub>, has lower values of lysophospholipids. In this fashion, Muller et al proposed that lysophosphatidylcholine was a biomarker of the intensity of the reactive oxygen species production at the inflammatory site.<sup>27</sup>

## **DRUG INDUCED MODIFICATION OF Lp-PLA<sub>2</sub> ACTIVITY**

Pharmacotherapy has been shown to modulate the activity of Lp-PLA<sub>2</sub> activity in humans. O'Donoghue et al.<sup>28</sup> found that an intensive statin therapy was responsible for 20% of reduction in LDL-Lp-PLA<sub>2</sub> in average. Likewise, Schaefer et al.<sup>29</sup> showed that simvastatin determined a reduction of the Lp-PLA<sub>2</sub> mass in 26%. In the same way, atorvastatin or fenofibrate therapies can increase the ratio of HDL-Lp-PLA<sub>2</sub> to plasma Lp-PLA<sub>2</sub> (or to LDL-Lp-PLA<sub>2</sub>).

Schaefer et al., while comparing the effect of atorvastatin with placebo in coronary heart disease patients observed a decrease in of Lp-PLA<sub>2</sub> under therapy. The use of darapladib (oral Lp-PLA<sub>2</sub> inhibitor) by coronary patients caused a reduction of 59% of the enzyme activity after 12 months of treatment; concomitantly, the placebo group presented a significant increase of necrotic core volume when compared to the therapy group. In another study, investigating patients under low-fat-diet and orlistat treatment, fenofibrate or both drugs during six months, it was observed a significant reduction of Lp-PLA<sub>2</sub> activity in all groups (14%, 22% and 35%, respectively) when compared to basal time.

Darapladib is a selective Lp-PLA<sub>2</sub> inhibitor under development by GlaxoSmithKline (GSK). The drug is targeted at Coronary Heart Disease (CHD) and is in Phase III development. Darapladib symbolises a new class of therapeutic agents that targets atherosclerosis, the leading cause of CHD. Darapladib is an anti-atherosclerosis agent that inhibits the lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) enzyme. Despite using a wide range of cholesterol-lowering drugs, many people continue to be at risk of developing CHD and suffer heart attacks and stroke. Darapladib works to inhibit the activity of the Lp-PLA<sub>2</sub> enzyme. It helps in preventing the expansion of the necrotic core of plaques, safeguarding them from rupture. This, in turn, helps lower the risk of CHD and other coronary diseases.<sup>30</sup>



**Figure 1: Lp-PLA<sub>2</sub> action on atherosclerosis**  
(Courtesy Isis T Silva et al. *Lipids in health and disease* 2011;10:170).

## CONCLUSIONS

The Lp-PLA<sub>2</sub> enzyme now is recognized as an important enzyme serving various pathophysiological conditions in the body. Lp-PLA<sub>2</sub>, in this sense, represents an important factor, reducing the oxLDL atherogenicity. Nowadays, however its association with cardiovascular events is the most outstanding characteristic observed. Therefore biochemical screening for thyroid dysfunction is critical in all dyslipidemic patients, as well in all patients with unexpected improvement or worsening of their lipid profile. Whether it may be contributing in the cardiovascular and metabolic events of the Grave's disease needs to be carefully examined. Lp-PLA<sub>2</sub> inhibition is also being exploited for therapeutic purposes.

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