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Review

Extracellular phospholipases in atherosclerosis

Sonia-Athina Karabina, Sarah Gora, Rajai Atout, Ewa Ninio*

INSERM UMRS 937, Université Pierre et Marie Curie UPMC-Paris 6, Faculté de Médecine Pierre et Marie Curie, 91 Boulevard de l'Hôpital, Paris 75634 Cedex 13, France

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ABSTRACT

Phospholipases A2 (PLA2) are a family of enzymes that catalyze the hydrolysis of the sn-2 ester bond of glycerophospholipids liberating lysophospholipids and free fatty acids; important second messengers involved in atherogenesis. Plasma PAF-acetylhydrolase (PAF-AH) or Lp-PLA2 is a Ca^{2+}-independent PLA2 which is produced by monocyte-derived macrophages and by activated platelets, and circulates in plasma associated with lipoproteins. PAF-AH catalyzes the removal of the acetyl/short acyl group at the sn-2 position of PAF and oxidized phospholipids produced during inflammation and oxidative stress. In humans, PAF-AH is mainly associated with small dense LDL and to a lesser extent with HDL and with lipoprotein(a). PAF-AH is N-glycosylated prior to secretion which diminishes its association with HDL raising the question of its distribution between the proatherogenic LDL vs the antiatherogenic HDL. Hypercholesterolemic patients have higher plasma PAF-AH activity which is reduced upon hypolipidemic therapy. PAF-AH specific inhibitor darapladib stabilizes human and swine plaques, therefore challenging the antiatherogenic potential of PAF-AH shown in small animal models.

Among secreted PLA2s (sPLA2), the group X sPLA2 (PLA2GX), due to its very high activity towards phosphatidylcholine the main phospholipid of LDL, became an attractive target in atherosclerosis. We showed that PLA2GX is present in human atherosclerotic lesions and that the PLA2GX-phospholipolysed LDL triggers human macrophage-foam cell formation. In contrast to other sPLA2s, including group IB, IIA and V, PLA2GX can efficiently hydrolyze PAF present in lipoproteins or vesicles indicating that PLA2GX may be a novel player in PAF regulation upon inflammatory processes.

By a genetic approach we uncovered a relatively rare polymorphism (Arg38Cys) which produces a catalytically inactive PLA2GX; although no association was observed with cardiovascular risk factors in the AtheroGene study, this result should be replicated in cohorts of other inflammatory diseases. We anticipate that mores studies will be necessary to sort out the exact role of extracellular PLA2 family members in atherosclerosis initiation and progression.

1. The phospholipase A2 family of enzymes

Phospholipids, essential components of lipoproteins and cell membranes, are composed of fatty acids bound to a glycerol backbone containing a polar head group and are substrates for phospholipases A2 (PLA2). The family of PLA2s is subdivided into 5 main categories; low molecular-weight, disulfide-rich Ca^{2+}-dependent, secreted PLA2 (sPLA2) with a histidine/aspartic acid dyad in the catalytic site; high-molecular-weight, cytosolic PLA2 (cPLA2) with a serine/aspartic acid dyad in the catalytic site, Ca^{2+}-independent PLA2 (iPLA2) enzymes, PAF-acetylhydrolases and lysosomal PLA2s which all contain serine/histidine/aspartic acid triad in the catalytic site [1]. The hydrolytic action of PLA2s on phospholipids generates fatty acids and lysophospholipids both of which are important lipid mediators and second messengers with a wide range of physiological and pathological effects, thus PLA2s are an important link between lipids and inflammation, both involved in atherosclerosis. In this review we will focus mainly on extracellular PLA2s, since their circulating levels were shown as independent predictors of death and new or recurrent myocardial infarction in patients with acute coronary syndrome [2] and a number of studies showed that plasma PAF-acetylhydrolase (PAF-AH) belonging to the PLA2 group VIIA (*gene*: *PLA2G7*), also known as the lipoprotein-associated PLA2 (Lp-PLA2) is an independent cardiovascular risk factor (reviewed in [3,4]). Alterations in PAF-AH activity levels have also been reported in several diseases such as systemic lupus erythematosus [5], allergy [6] and asthma [7]; however it is unclear, as yet, whether this enzyme protects or exacerbate the disease associated symptoms.

As PLA2s participate in various diseases, including atherosclerosis, where inflammation and lipid metabolism are key players, an understanding of their respective contributions and their

* Corresponding author. Tel./fax: +33 1 40 77 97 68.
E-mail address: ewa.ninio@upmc.fr (E. Ninio).

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mechanisms of action is of prime importance for a potential therapeutic approach. In this review we will give a brief overview on the recent advances in this fast moving field and we will essentially focus on PAF-AH and on one member of the sPLA2 family of enzymes, namely the group X sPLA2 (PLA2GX).

2. PAF-AH in atherosclerosis

Atherosclerosis is characterized by lipid accumulation and foam cell formation due to the uptake of modified forms of low density lipoprotein (LDL) in the vessel wall. Oxidation of LDL is one of the key events in atherosclerosis which is closely associated with inflammation and formation of oxidized phospholipids (reviewed in [8]). The latter have been detected in human atherosclerotic plaques and are substrates for PAF-AH [9], which was initially characterized as the enzyme that inactivates the potent phospholipid mediator, Platelet-Activating Factor (PAF), by hydrolyzing its sn-2 acetyl group. PAF-AH is associated with plasma lipoproteins; 70–80% of the total activity in human plasma is associated with LDL and the remaining binds mainly to HDL [10,11]. Unlike other classical phospholipases, PAF-AH is specific for short acyl groups esterified at the sn-2 position of the phospholipid substrate and additionally to PAF; it can also hydrolyze oxidized phospholipids produced during LDL oxidation, involving peroxidation of phosphatidylcholine [12] (Fig. 1).

As PAF-AH degrades PAF and oxidized phospholipids, but not constitutive phospholipids, it may play an important role in atherosclerosis and cardiovascular diseases (CVD). The antiatherogenic role of PAF-AH due to the inactivation of PAF and oxidized phospholipids has been supported by animal [13] and genetic studies; indeed a missense mutation (Val279Phe) which leads to a complete loss of PAF-AH activity and protein [14] suggests that PAF-AH deficiency is an independent risk factor for CVD [15] and stroke [16] in Japanese population. On the other hand during hydrolysis of oxidized phospholipids PAF-AH liberates large amounts of lysophosphatidylcholine which participate in several aspects of plaque formation, so this enzyme is also considered as proatherogenic (reviewed in [4]). Two points merit attention: first, in contrast to humans where the majority of PAF-AH is associated with LDL through binding to the carboxyl terminus of apoB-100 [17] in atherogenic mice which express little LDL, the enzyme associates almost exclusively with HDL particles [18] and is antiatherogenic [13]. Although pigs have a similar lipoprotein profile to that of humans, 90% of their PAF-AH is bound to HDL and only 5% to LDL. However upon cholesterol feeding PAF-AH raises several-fold and reaches then 17% in LDL. This diet induced increase in PAF-AH correlates with plasma lysophosphatidylcholine and oxidized LDL concentration as well as with accelerated atherosclerosis in those animals [19]. The pro- or antiatherogenic potential of PAF-AH may thus depend on its lipoprotein carrier in plasma, as also pointed out by Tellis et al. [20] and indeed there is evidence to suggest that the lipoprotein environment can alter the catalytic efficiency of this enzyme [21]. Second, the epidemiological data from a Caucasian population demonstrated that high PAF-AH levels may be a marker and/or a risk factor for CVD (reviewed in [22]). The genetic studies in the latter population showed that the minor 379Val allele of *PLA2G7* was associated with lower risk of cardiovascular events [23,24]; surprisingly the plasma activity of PAF-AH was higher in these individuals as compared to Ala379 carriers [24] raising the question how this polymorphism modifies the enzyme function towards a less atherogenic form.

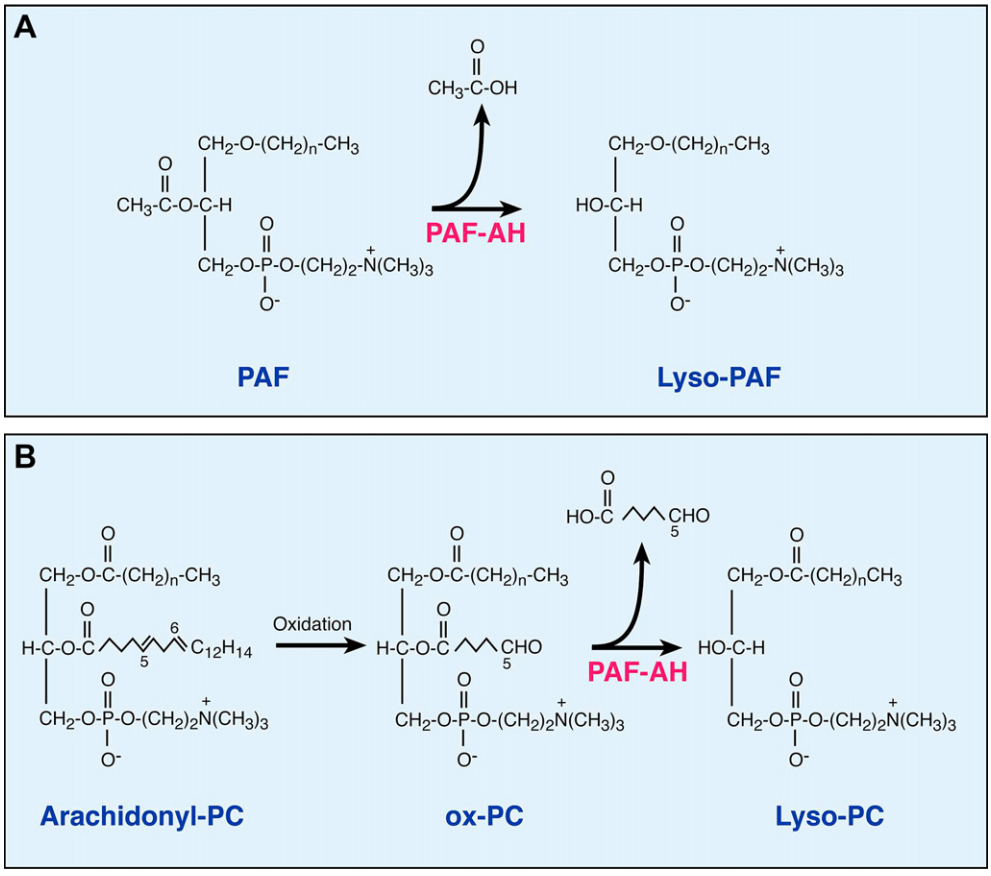

Fig. 1. Degradation of PAF to lyso-PAF (A) and oxidized phosphatidylcholine (ox-PC) to lysophosphatidylcholine (lyso-PC) (B) by PAF-AH (reproduced with permission from [3]).