Jpn Circ J 1998; **62:** 328–335

Roles of Plasma Platelet-Activating Factor Acetylhydrolase in Allergic, Inflammatory, and Atherosclerotic Diseases

Yoshiji Yamada, MD; Mitsuhiro Yokota, MD*

Platelet-activating factor (PAF) mediates a variety of physiologic and pathologic events by activating platelets, neutrophils, monocytes, macrophages, and smooth muscle cells. A strongly oxidizing environment induces fragmentation of the polyunsaturated fatty acids of membrane phospholipids, and the resulting oxidized phospholipids are structurally similar to PAF and mimic its biologic actions. The effects of PAF and oxidized phospholipids are abolished by hydrolysis of the *sn*-2 residue, a reaction catalyzed by PAF acetylhydrolase. Plasma and intracellular forms of PAF acetylhydrolase have been purified and characterized. The plasma form binds with high affinity to lipoproteins in plasma. Furthermore, changes in the activity of this enzyme are associated with various human diseases and animal models of human pathology, suggesting that it may play important roles in their pathogenesis. Studies that have defined the properties of this enzyme and its roles in physiologic and pathologic processes are reviewed. Such studies have provided insight into the functions of PAF and oxidized phospholipids as well as into the etiology of allergic, inflammatory, and atherosclerotic diseases. (*Jpn Circ J* 1998; **62:** 328–335)

Key Words: Platelet-activating factor acetylhydrolase; Oxidized phospholipids; Allergy; Inflammation; Atherosclerosis

Platelet-activating factor (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, PAF) is a phospholipid autacoid that exerts diverse biological actions[1–6] PAF acts by binding to a specific receptor, which has recently been characterized in detail as a result of the cloning of its cDNA and its expression in heterologous cells[7–15] The synthesis of PAF can occur through either of 2 described synthetic pathways[16,17] and is tightly regulated[18–22] PAF is degraded by PAF acetylhydrolase, which catalyzes the hydrolysis of the esterified acetate at the *sn*-2 position[23–31] In this paper, we will review the biochemical properties of human PAF acetylhydrolase, which has a major role in limiting the actions of PAF and structurally related oxidized phospholipids. In addition, we will examine the evidence that implicates this enzyme in the pathophysiology of allergic, inflammatory, and atherosclerotic diseases.

PAF

PAF activates platelets, neutrophils, monocytes, macrophages, and vascular smooth muscle cells at concentrations as low as 10^{-12} to 10^{-9} mol/L[1–6] Honda et al[7] and other investigators[8–10] isolated cDNAs encoding the PAF receptor from various tissues and species. The receptor is a member of the family of G protein-coupled receptors[7–10,12,14] and has been linked to inositol phospholipid turnover, changes in intracellular calcium, activation of protein kinase C and tyrosine kinases, and synthesis of eicosanoids[12] The human PAF receptor is encoded by a single gene that is located on chromosome 1[11] Two distinct promoters regulate the synthesis of 2 different forms of receptor mRNA in different tissues and cells[13,15]

PAF is implicated as a pathologic mediator in bronchial asthma and other allergic responses, vascular damage including ischemia-reperfusion injury, various forms of shock (especially endotoxin shock), acute respiratory distress syndrome, and inflammatory bowel disease[1,4,6,32] Intravenous infusions of PAF in animals markedly increase the vascular permeability and the adhesion of leukocytes to the endothelium, and reduce the cardiac output, which results in hypotension and shock[4,6,32,33] Selective administration in vivo or to isolated tissues can result in contraction of uterine muscle, bronchoconstriction, and gastrointestinal ulcers[4,6] PAF may also facilitate hemostasis and contributes to events associated with reproduction[6,32] Evidence supporting a role for PAF in pathologic processes includes the observation that several PAF receptor antagonists attenuate specific disorders in which PAF is suspected to act as a mediator[4,6,34] Thus, one mechanism for PAF-induced pathology would be the inappropriate activation of PAF synthesis in PAF-producing cells. Conversely, given that PAF is rapidly degraded by the action of PAF acetylhydrolase, reduced activity of this enzyme might also allow the accumulation of PAF and thereby provoke a pathologic response.

PAF produced by monocytes and polymorphonuclear leukocytes is secreted[35–37] However, PAF synthesized by vascular endothelial cells activated by various physiologic agonists, including thrombin, bradykinin, histamine,

(Received August 11, 1997; revised manuscript received November 26, 1997; accepted November 28, 1997)

Department of Geriatric Research, National Institute for Longevity Sciences, Obu, Aichi, Japan
**Department of Clinical Laboratory Medicine, Nagoya University School of Medicine, Nagoya, Japan*
Mailing address: Yoshiji Yamada, MD, Department of Geriatric Research, National Institute for Longevity Sciences, 36-3 Gengo, Morioka, Obu, Aichi 474, Japan

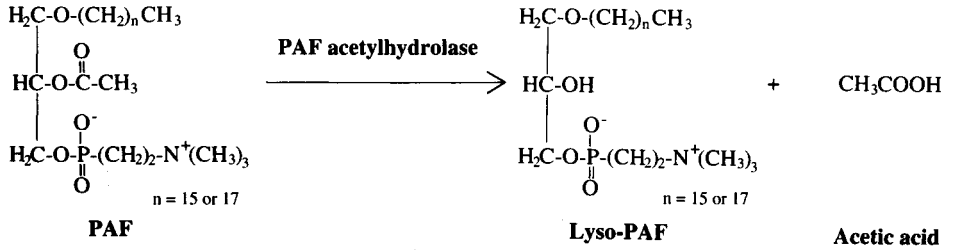

Fig 1 Degradation of PAF. PAF is degraded to lyso-PAF and acetic acid by hydrolysis of the acetyl residue at the *sn*-2 position in a reaction catalyzed by PAF acetylhydrolase.

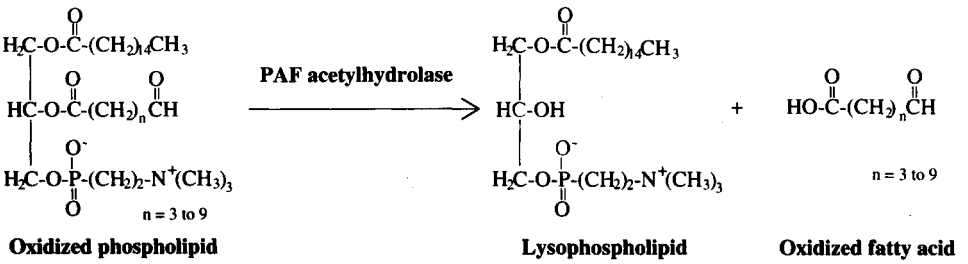

Fig 2 Degradation of oxidized phospholipids. Phospholipids with oxidatively fragmented fatty acids at the *sn*-2 position are hydrolyzed to lysophospholipids and oxidized fatty acids by PAF acetylhydrolase.

hydrogen peroxide, and leukotrienes C_4 and D_4, is expressed on the cell surface and is not released[38–45] Instead, it serves as a component of the signal that triggers the binding of neutrophils to endothelial cells[41,42,44,45] which probably serves a homeostatic function because leukocyte adhesion to the endothelium is the first step in the physiologic inflammatory response[4] However, inappropriate or excessive expression of the adhesion signal and the subsequent attraction and activation of large numbers of leukocytes might result in further vascular damage caused by the secretion of proteases and oxygen radicals by these cells[4]

Oxidized Phospholipids

Oxidized phospholipids are thought to play a key role in the mechanism of vascular inflammation and atherosclerosis[46] A strongly oxidizing environment induces fragmentation of the polyunsaturated fatty acids of membrane phospholipids[46,47] and such oxidized phospholipids have been associated with pathologic conditions including postischemic reperfusion, acute respiratory distress syndrome, and chronic inflammation[4,6] The oxidized phospholipids are structurally similar to PAF and mimic its biological actions by activating cells through the PAF receptor[48,49] These compounds are also produced during oxidative modification of low-density lipoprotein (LDL), which is a crucial step in atherosclerosis[50–56] Because oxidized phospholipids are produced by a free radical reaction, rather than by regulated enzymatic synthesis, they can potentially be generated in much larger amounts than PAF and at inappropriate times and places. The biological actions of oxidized phospholipids are abolished by hydrolysis of the *sn*-2 residue, a reaction catalyzed by PAF acetylhydrolase[57–60]

Biological Characteristics of PAF Acetylhydrolase

PAF acetylhydrolase (1-alkyl-2-acetylglycerophosphocholine esterase, 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine acetohydrolase, EC 3.1.1.47) is a member of the phospholipase A_2 family of enzymes with specificity for short acyl chains. PAF acetylhydrolase catalyzes the conversion of PAF to lyso-PAF by hydrolyzing esterified acetate at the *sn*-2 position[23–31] (Fig 1). As mentioned above, PAF acetylhydrolase also hydrolyzes phospholipids containing oxidatively fragmented residues at the *sn*-2 position[57–60] (Fig 2). Two forms of PAF acetylhydrolase have been identified: a secreted form present in plasma[24,25,27–29] and an intracellular form present in various blood cells and tissues[26,61–63] The activity of PAF acetylhydrolase is specific for short acyl groups ($C_{n<6}$) at the *sn*-2 position of the substrate phospholipid and does not require calcium[25,28,62,63] This highly restricted substrate specificity is essential to prevent the continuous hydrolysis of the phospholipids of lipoproteins and cell membranes[30] The plasma enzyme is resistant to proteolysis, and is unaffected either by reagents that target sulfhydryl or histidyl residues or by sodium fluoride[28,62,64] In contrast, the intracellular enzyme from human erythrocytes is inhibited by histidine and cysteine modification, and is sensitive to proteolysis and sodium fluoride[62,63,65] The activities of both types of the enzyme are markedly inhibited by the serine esterase inhibitor diisopropylfluorophosphate[28,64,65]

Plasma PAF acetylhydrolase interacts with high affinity with lipoproteins in blood: two-thirds of total enzyme activity is associated with LDL and the remaining one-third with high-density lipoprotein (HDL)[29] Furthermore, the activity shuttles between lipoproteins in a pH-dependent manner: at pH 6, the activity transfers to HDL, and at pH 8.5 it moves to LDL[29] Recently, plasma PAF acetylhydrolase has been shown to associate preferentially with small, dense LDL particles (LDL5) and with very high-density lipoprotein-1[66] In addition, the plasma enzyme is also associated with lipoprotein(a), with a 7-fold higher activity based on equal particle concentrations than LDL isolated from the same individuals[67] Although the physiologic role of the association of the

plasma enzyme with lipoproteins is not clear, the plasma enzyme is thought to protect LDL from oxidative modification and therefore to exert an antiatherosclerotic action[60,68] However, the activity of plasma PAF acetylhydrolase associated with LDL is progressively lost during oxidative modification of LDL[69] Furthermore, oxygen radicals rapidly and irreversibly inactivate PAF acetylhydrolase, a potential mechanism by which oxygen radicals may potentiate and prolong the proinflammatory effects of PAF and oxidized phospholipids[70]

Cultured human macrophages[71,72] human HL-60 promyelocytic leukemia cells[73,74] and human hepatoma Hep G2 cells[75,76] synthesize and secrete the plasma form of PAF acetylhydrolase. Thus, the in vivo sources of plasma PAF acetylhydrolase are thought to include macrophages and liver cells. Macrophages may contribute to the local regulation of PAF concentration because the precursor monocytes do not produce PAF acetylhydrolase;[71,72,77] the release of the plasma enzyme also increases during differentiation of HL-60 cells into cells with monocyte-macrophage characteristics[73,74] Secretion of the enzyme appears to occur independently of the secretion of lipoprotein particles, and the acetylhydrolase then associates either with nascent lipoproteins secreted by the cells in the absence of serum or with mature lipoproteins if serum is included in the culture medium[30] Injection of *Xenopus laevis* oocytes with polyadenylated RNA purified from human macrophages or Hep G2 cells resulted in the release of a PAF-degrading activity identical to human plasma PAF acetylhydrolase into the culture medium[78] Hep G2 cells, but not macrophages, produce apolipoprotein B100, a major constituent of LDL. These data indicate that, although plasma PAF acetylhydrolase binds tightly to lipoproteins in blood, this enzyme is not a component of lipoproteins themselves and that plasma PAF acetylhydrolase and lipoproteins are encoded by distinct genes[78] The plasma PAF acetylhydrolase activity in individuals with Tangier disease, a deficiency of HDL, is higher than that in normal subjects[79] In contrast, the plasma PAF acetylhydrolase activity in individuals with abetalipoproteinemia is similar to or slightly lower than that in normal subjects[78,80] These clinical observations indicate that the lipoprotein environment of plasma PAF acetylhydrolase influences its catalytic behavior[80]

Tjoelker et al[81] isolated a cDNA encoding plasma PAF acetylhydrolase from human macrophages. The predicted 441-amino acid protein is cleaved between Lys-41 and Ile-42 to generate a mature enzyme with a calculated molecular mass of 45,388 Da. The catalytic site contains the Gly-X-Ser-X-Gly consensus sequence characteristic of lipases and esterases[81] The recombinant protein markedly inhibited activation of leukocytes induced by PAF in vitro. It also reduced PAF-induced paw edema and pleural effusion in rats[81] With the use of site-directed mutagenesis, Tjoelker et al[82] also showed that Ser-273 of the Gly-X-Ser-X-Gly motif, Asp-296, and His-351 are essential for catalytic activity. The linear orientation and spacing of these catalytic residues are consistent with the α/β hydrolase conformation of other lipases and esterases[82]

PAF acetylhydrolase activity in plasma increases gradually with age[83] It is lower in premenopausal women than in men; however, the difference between men and women is less marked in individuals over 50 years of age[83] In women, PAF acetylhydrolase activity in plasma is negatively correlated with plasma estrogen concentration[84] Administration of estrogen to rats reduces the plasma PAF acetylhydrolase activity, probably because estrogen inhibits secretion of the enzyme by hepatocytes[27,75,84,85] Together, these observations suggest that estrogen reduces the activity of PAF acetylhydrolase in plasma, and that the smaller difference in enzyme activity between older men and women is attributable to loss of the suppressive effect of estrogen in women[30] Administration of glucocorticoids increases the activity of plasma PAF acetylhydrolase in rats and reverses the suppressive action of estrogen[84] suggesting that the anti-inflammatory action of glucocorticoids is mediated in part by an increase in this enzyme activity that catalyzes the removal of PAF and oxidized phospholipids[30,84] The activity of PAF acetylhydrolase in the plasma of pregnant rabbits gradually decreases during the later stages of gestation, falls rapidly at delivery, and then recovers rapidly to basal values[86] These changes are thought to allow PAF to enhance the contraction of the uterus at the initiation of labor[86]

Deficiency of Plasma PAF Acetylhydrolase Activity

The activity of plasma PAF acetylhydrolase differs among individuals and among races. In the United States, individuals with a deficiency of plasma PAF acetylhydrolase have not been detected[30] In contrast, Miwa et al[87] reported that about 4% of Japanese children and adults lack PAF acetylhydrolase activity in plasma. These investigators studied 5 families, and concluded that the enzyme deficiency was inherited in an autosomal recessive manner. They also observed that the frequency of plasma PAF acetylhydrolase deficiency in children with severe bronchial asthma was 12%, 3 times that in all children with bronchial asthma or healthy children (3.8%). This association of plasma PAF acetylhydrolase deficiency with severe asthma in children suggests that the enzyme may play a role in limiting inflammatory and allergic responses[30] However, some individuals with a deficiency or a low activity of plasma PAF acetylhydrolase have been identified who do not show a defined phenotype[30] These observations suggest that exposure of individuals with plasma PAF acetylhydrolase deficiency to severe allergic or inflammatory stimulation is associated with an increased risk of severe pathologic consequences.

Stafforini et al[88] determined the structure of the human plasma PAF acetylhydrolase gene, and showed that it is located at chromosomal region 6p12-21.1, comprises 12 exons, and spans at least 45 kb of DNA. These researchers also detected a single point mutation (a G→T transversion) at nucleotide position 994 in exon 9, which encodes the catalytic domain, in 14 Japanese families with a deficiency of plasma PAF acetylhydrolase activity. This change in nucleotide results in a Val→Phe substitution at amino acid residue 279 of the mature protein and is responsible for the loss of catalytic activity[88] We detected another missense mutation, an A→G transition at nucleotide position 1001 in exon 9, resulting in a Gln→Arg substitution at amino acid residue 281. This amino acid change also leads to a loss of catalytic activity of plasma PAF acetylhydrolase[89]

Roles of Plasma PAF Acetylhydrolase in Allergic and Inflammatory Diseases

PAF acetylhydrolase activity in plasma changes in various allergic and inflammatory diseases, suggesting that this enzyme is important in these disorders. Plasma PAF acetylhydrolase activity is reduced in individuals with active systemic lupus erythematosus;[90] necrotizing enterocolitis;[91] sepsis or septic shock;[92] or severe bronchial asthma.[87] A consequent increase in the plasma concentration of PAF or oxidized phospholipids may thus contribute to the pathologic process in these disorders. In contrast, plasma PAF acetylhydrolase activity is increased in individuals with diabetes mellitus;[93] essential hypertension;[94] or rheumatoid or other forms of arthritis.[95] PAF acetylhydrolase activity is also high in the plasma of individuals with chronic cholestasis caused by liver diseases such as sclerosing cholangitis, advanced primary biliary cirrhosis, or cholangiocarcinoma; the activity normalizes after successful liver transplantation.[96] The mechanism by which the enzyme activity increases in these disorders is not clear, but it may represent a protective response to stress caused by PAF, oxidized phospholipids, or both generated during the pathologic process.[30] In addition, PAF acetylhydrolase activity may be affected by multiple factors that mediate allergic and inflammatory responses. These responses may be complex and may fluctuate during different stages of disease.[30] Satoh et al[75] suggest that PAF itself, generated during pathologic inflammation, stimulates the synthesis and secretion of the plasma form of PAF acetylhydrolase in the liver. Treatment of rats with dexamethasone, a potent anti-inflammatory steroid hormone, increases the plasma activity of the enzyme.[84,97] These clinical and experimental observations suggest that PAF (and oxidized phospholipids) plays an important role in the pathology of allergy and inflammation and that PAF acetylhydrolase may serve as a defense mechanism in such disorders.[98]

Roles of Plasma PAF Acetylhydrolase in Atherosclerosis

PAF is synthesized locally at the site of endothelial injury during thrombosis and that accumulates in the atherosclerotic plaques of some individuals with advanced coronary artery disease, suggesting that PAF actively participates in the pathophysiology of thrombosis and atherosclerosis.[99] The activity of PAF acetylhydrolase in plasma has been shown to be increased in individuals with atherosclerotic diseases such as myocardial infarction;[100] peripheral vascular disease;[101] and ischemic stroke.[102,103] In contrast, other studies have shown that PAF acetylhydrolase activity in plasma is decreased in individuals with severe coronary artery disease[104] or acute myocardial infarction.[105] We demonstrated that the plasma enzyme activity in men with myocardial infarction was significantly lower than that in control subjects.[106] The reason for this discrepancy between our and the previous studies[100–103] is not clear. It is possible that the increase in plasma enzyme activity in patients in the previous studies[100–103] is an effect rather than the cause of the atherosclerotic process.[30,106]

The pathogenesis of atherosclerosis is complex, with many mediators, including growth factors and cytokines, playing a role.[107] One of the early key events in the development of atherosclerosis is thought to be the oxidative modification of LDL.[51,52,56] The modified LDL particles are thought to be produced from native particles by oxidation.[51–54] Although the molecular mechanism of LDL oxidation is not fully understood, the modification of apolipoprotein B100 is an important component.[51,52,54,55] Oxidized LDL injures the endothelium directly, and also induces the adherence and migration of monocytes.[51,52] Blood monocytes infiltrate the endothelium, differentiate into macrophages, and can then become loaded with additional oxidixed LDL that is taken up by scavenger receptors.[50] The uncontrolled uptake of oxidized LDL by macrophages leads to an increase in the number of foam cells and the subsequent formation of fatty streaks, which are characterized histologically by an accumulation of cells loaded with cholesterol esters.[50–52,107,108] PAF is produced by endothelial cells in response to oxidative stress or various physiologic agonists, including thrombin, bradykinin, and histamine, and can induce macrophages to produce superoxide anions.[4] The local synthesis of PAF in segments of the vascular wall undergoing atherosclerotic changes may increase the oxidative modification of LDL, resulting in an amplification of the pathogenic process.[6]

We have investigated whether the G→T missense mutation at nucleotide 994 in exon 9 of the plasma PAF acetylhydrolase gene is an independent risk factor for coronary artery disease in the Japanese population.[106] The genotype of plasma PAF acetylhydrolase (*MM*, normal; *Mm*, heterozygote; and *mm*, mutant homozygote) was determined with an allele-specific polymerase chain reaction assay in a total of 1056 unrelated Japanese subjects (454 individuals with myocardial infarction and 602 control subjects). The plasma activity in individuals with the *MM* genotype significantly exceeded that in those with the *Mm* genotype; no activity was detected in *mm* homozygotes. The frequency of the *m* allele was significantly higher in subjects with myocardial infarction than in controls for men but not for women. In a low-risk group defined as individuals with a body mass index of less than 27 kg/m^2 and no history of hypertension, diabetes mellitus, or hypercholesterolemia, an increased association of the *m* allele with myocardial infarction in men was apparent. Our observations thus indicate that the G-994→T missense mutation, which results in a loss of catalytic activity, is an independent risk factor for coronary artery disease in Japanese men, and that the determination of plasma PAF acetylhydrolase genotype or enzyme activity may contribute to the prevention and management of coronary artery disease, especially for men who lack the conventional risk factors.[106]

Tew et al[109] proposed that PAF acetylhydrolase exerts 2 opposing effects in vivo. On the one hand, it degrades PAF and therefore would be expected to play an anti-inflammatory role; on the other hand, given that it is responsible for the lysophosphatidylcholine content and the monocyte chemoattractant properties of oxidized LDL, its ability to hydrolyze oxidized phospholipids in LDL may confer a proinflammatory role. Among the changes that occur during LDL modification, oxidized phosphatidylcholine molecules are generated and are then hydrolyzed to lysophosphatidylcholine and oxidized fatty acids.[53,57] The latter derivatize apolipoprotein B100, thereby resulting in an altered receptor recognition of the particle.[54,55] Stafforini et al[60] postulated that intact

oxidized phospholipids may remain associated with LDL and react with amino acids in apolipoprotein B100, as they are more hydrophobic than their fatty acid products, which are water soluble and would be readily bound by other serum components such as albumin. Thus, the hydrolysis of oxidized phospholipids might actually be beneficial. These researchers showed that the hydrolysis of oxidized phospholipids by PAF acetylhydrolase is not necessary for LDL modification and that the catalytic activity of the enzyme prevents the oxidation of LDL.[60] These observations suggest that PAF acetylhydrolase is not proinflammatory, but acts as an anti-inflammatory and antiatherosclerotic enzyme. Our observations[106] suggest that reduced plasma PAF acetylhydrolase activity is a risk factor for coronary artery disease; that is the enzyme exerts a protective effect against this condition, supporting the results of Stafforini et al.[60]

Intracellular PAF Acetylhydrolase

The roles of intracellular PAF acetylhydrolase are not clear. Stafforini et al[63] proposed that the enzyme in erythrocytes protects the cell membrane from oxidative damage by hydrolyzing oxidized phospholipids produced as a result of exposure of the membrane to oxygen free radicals.[63] The high concentrations of oxygen and iron in erythrocytes render them especially susceptible to oxidative damage.[63] The PAF acetylhydrolase in erythrocytes might also contribute to the hydrolysis of PAF if the cells are lysed at a site of inflammation.[63]

In bovine brain, kidney, and liver, isoforms Ib and II were detected as cytosolic proteins.[110,111] The isoform Ib is a heterotrimeric enzyme composed of 45-(α), 30-(β), and 29-(γ) kDa subunits.[110] Cloning of a cDNA encoding α-subunit of bovine brain PAF acetylhydrolase[112] revealed that it shares 99% sequence homology with the human *LIS1* gene, mutation in which is responsible for Miller-Dieker lissencephaly, an abnormality of development and differentiation of the human brain.[113] This observation suggests that PAF and PAF acetylhydrolase are important in the development and differentiation of the brain cortex.[112] Complementary DNAs encoding 2 catalytic subunits (β- and γ-subunits) of bovine brain PAF acetylhydrolase have also been cloned and characterized.[114–116] The γ-subunit is predicted to comprise 232 amino acids, and the sequence of about 30 amino acids located 6 residues downstream from the active serine is similar to that of the first transmembrane region of the PAF receptor.[114] Although the ligand-binding domain of the PAF receptor has not been determined, this similarity suggests that both sequences contribute to the recognition of PAF.[114] The β-subunit is predicted to comprise 229 amino acids, which is homologous (63.2% identity) to that of the γ-subunit, especially (86% identity) in the catalytic and PAF receptor homologous domains.[116] Recently, the crystal structure of the α_1-subunit of bovine brain PAF acetylhydrolase, previously described as γ-subunit[114,115] was determined.[117] The tertiary fold of this protein closely resembles that of Ras and other GTPases, and the active site comprises a triad of Ser-47, His-195, and Asp-192, which differs from a catalytic triad of the plasma PAF acetylhydrolase.[82]

Hattori et al[118] isolated cDNAs that encode human and bovine intracellular PAF acetylhydrolase isoform II, each of which is predicted to contain 392 amino acids. The enzyme from both species contains the Gly-X-Ser-X-Gly motif that is characteristic of lipases and esterases, and the amino acid sequence shows 41% identity with that of plasma PAF acetylhydrolase. The substrate specificity of the isoform II is similar to that of the plasma enzyme.[111] The isoform II catalyzes the hydrolysis of phospholipids with acyl chains containing up to 5 methylene groups. This suggests that one function of isoform II may be to scavenge oxidatively fragmented phospholipids like the plasma enzyme.[111,119] On the other hand, the isoform Ib is entirely specific for PAF hydrolysis. It does not recognize oxidized phospholipids as substrates, indicating that its function is to regulate PAF levels exclusively.[111,119]

Conclusion

Substantial clinical and experimental evidence indicates that plasma PAF acetylhydrolase is important in the pathogenesis of allergic, inflammatory, and atherosclerotic diseases. However, information is lacking on changes in intracellular PAF acetylhydrolase activity associated with pathologic processes or specific diseases. We anticipate that further investigations into the roles of PAF acetylhydrolase in disease will lead to the development of new therapeutic agent.

References

1. Hanahan DJ: Platelet activating factor: a biologically active phosphoglyceride. *Annu Rev Biochem* 1986; **55:** 483–509
2. Prescott SM, Zimmerman GA, McIntyre TM: Platelet-activating factor. *J Biol Chem* 1990; **265:** 17381–17384
3. Snyder F: Platelet-activating factor and related acetylated lipids as potent biologically active cellular mediators. *Am J Physiol* 1990; **259:** C697–C708
4. Zimmerman GA, Prescott SM, McIntyre TM: Platelet-activating factor and cell-associated mediator of inflammation. *In:* Gallin JI, Goldstein IM, Snyderman R, editors. Inflammation: basic principles and clinical correlates, 2nd edn. New York: Raven Press, 1992: 149–176
5. Venable ME, Zimmerman GA, McIntyre TM, Prescott SM: Platelet-activating factor: a phospholipid autocoid with diverse actions. *J Lipid Res* 1993; **34:** 691–702
6. Imaizumi T, Stafforini DM, Yamada Y, McIntyre TM, Prescott SM, Zimmerman GA: Platelet-activating factor: a mediator for clinicians. *J Intern Med* 1995; **238:** 5–20
7. Honda Z, Nakamura M, Miki I, Minami M, Watanabe T, Seyama Y, et al: Cloning by functional expression of platelet-activating factor receptor from guinea-pig lung. *Nature* 1991; **349:** 342–346
8. Ye RD, Prossnitz ER, Zou A, Cochrane CG: Characterization of a human cDNA that encodes a functional receptor for platelet activating factor. *Biochem Biophys Res Commun* 1991; **180:** 105–111
9. Kunz D, Gerard NP, Gerard C: The human leukocyte platelet-activating factor receptor. *J Biol Chem* 1992; **267:** 9101–9106
10. Sugimoto T, Tsuchimori H, McGregor CGA, Mutoh H, Shimizu T, Kurachi Y: Molecular cloning and characterization of the platelet-activating factor receptor gene expressed in the human heart. *Biochem Biophys Res Commun* 1992; **189:** 617–624
11. Seyfried CE, Schweickart VL, Godiska R, Gray PW: The human platelet-activating factor receptor gene (PTAFR) contains no introns and maps to chromosome 1. *Genomics* 1992; **13:** 832–834
12. Shukla SD: Platelet-activating factor receptor and signal transduction mechanism. FASEB J *1992;* 6: **2296**–2301
13. Mutoh H, Bito H, Minami M, Nakamura M, Honda Z, Izumi T, et al: Two different promoters direct expression of two distinct forms of mRNAs of human platelet-activating factor receptor. *FEBS Lett* 1993; **322:** 129–134
14. Kravchenko VV, Pan Z, Han J, Herbert J-M, Ulevitch RJ, Ye RD: Platelet-activating factor induces NF-κB activation through a G protein-coupled pathway. *J Biol Chem* 1995; **270:** 14928–14934
15. Mutoh H, Fukuda T, Kitamaoto T, Masushige S, Sasaki H, Shimizu T, et al: Tissue-specific response of the human platelet-activating factor receptor gene to retinoic acid and thyroid hormone by

alternative promoter usage. *Proc Natl Acad Sci USA* 1996; **93:** 774–779
16. Alonso F, Gil MG, Sanchez-Crespo M, Mato JM: Activation of 1-alkyl-2-lyso-glycero-3-phosphocholine: acetyl-CoA transferase during phagocytosis in human polymorphonuclear leukocytes. *J Biol Chem* 1982; **257:** 3376–3378
17. Blank ML, Lee YJ, Cress EA, Snyder F: Stimulation of the de novo pathway for the biosynthesis of platelet-activating factor (PAF) via cytidylyltransferase activation in cells with minimal endogenous PAF production. *J Biol Chem* 1988; **263:** 5656–5661
18. McIntyre TM, Reinhold SL, Prescott SM, Zimmerman GA: Protein kinase C activity appears to be required for the synthesis of platelet-activating factor and leukotriene B_4 by human neutrophils. *J Biol Chem* 1987; **262:** 15370–15376
19. Whatley RE, Nelson P, Zimmerman GA, Stevens DL, Parker CJ, McIntyre TM, et al: The regulation of platelet-activating factor production in endothelial cells: the role of calcium and protein kinase C. *J Biol Chem* 1989; **264:** 6325–6333
20. Whatley RE, Fennell DF, Kurrus JA, Zimmerman GA McIntyre TM, Prescott SM: Synthesis of platelet-activating factor by endothelial cells: the role of G proteins. *J Biol Chem* 1990; **265:** 15550–15559
21. Elstad MR, McIntyre TM, Prescott SM, Zimmerman GA: Protein kinase C regulates the synthesis of platelet-activating factor by human monocytes. *Am J Respir Cell Mol Biol* 1991; **4:** 148–155
22. Holland MR, Venable ME, Whatley RE, Zimmerman GA, McIntyre TM, Prescott SM: Activation of the acetyl-coenzyme A: lysoplatelet-activating factor acetyltransferase regulates platelet-activating factor synthesis in human endothelial cells. *J Biol Chem* 1992; **267:** 22883–22890
23. Blank ML, Lee T-C, Fitzgerald V, Snyder F: A specific acetylhydrolase for 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine (a hypotensive and platelet-activating lipid). *J Biol Chem* 1981; **256:** 175–178
24. Blank ML, Hall MN, Cress EA, Snyder F: Inactivation of 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine by a plasma acetylhydrolase: higher activities in hypertensive rats. *Biochem Biophys Res Commun* 1983; **113:** 666–671
25. Wardlow ML, Cox CP, Meng KE, Greene DE, Farr RS: Substrate specificity and partial characterization of the PAF-acetylhydrolase in human serum that rapidly inactivates platelet-activating factor. *J Immunol* 1986; **136:** 3441–3446
26. Blank ML, Spector AA, Kaduce TL, Le T-C, Snyder F: Metabolism of platelet-activating factor (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) and 1-alkyl-2-acetyl-*sn*-glycerol by human endothelial cells. *Biochim Biophys Acta* 1986; **876:** 373–378
27. Prichard PH: The degradation of platelet-activating factor by high-density lipoprotein in rat plasma. *Biochem J* 1987; **246:** 791–794
28. Stafforini DM, Prescott SM, McIntyre TM: Human platelet-activating factor acetylhydrolase: purification and properties. *J Biol Chem* 1987; **262:** 4223–4230
29. Stafforini DM, McIntyre TM, Carter ME, Prescott SM: Human plasma platelet-activating factor acetylhydrolase: association with lipoprotein particles and role in the degradation of platelet-activating factor. *J Biol Chem* 1987; **262:** 4215–4222
30. Imaizumi T, Stafforini DM, Yamada Y, Zimmerman GA, McIntyre TM, Prescott SM: The fate of platelet-activating factor: PAF acetylhydrolase from plasma and tissues. *In:* Gross R, editor. Advances in lipobiology. Connecticut: JAI Press, 1996; **1:** 141–162
31. Stafforini DM, Prescott SM, Zimmerman GA, McIntyre TM: Mammalian platelet-activating factor acetylhydrolases. *Biochim Biophys Acta* 1996; **1301:** 161–173
32. Holland MR, McIntyre TM, Zimmerman GA, Prescott SM: Cardiovascular effects of platelet-activating factor. *Trends Cardiovasc Med* 1991; **1:** 117–121
33. Levi R, Burke JA, Guo Z-G, Hattori Y, Hoppens CM, McManus LM, et al: Acetyl glyceryl ether phosphorylcholine (AGEPC): a putative mediator of cardiac anaphylaxis in the guinea pig. *Circ Res* 1984; **54:** 117–124
34. Ioculano M, Squadrito F, Altavilla D, Canale P, Campo GM, Bussolino F, et al: Protective effects of L-659989, a platelet-activating factor receptor antagonist, in myocardial ischemia and reperfusion in rats. *J Cardiovasc Pharmacol* 1994; **23:** 7–12
35. Sisson JH, Prescott SM, McIntyre TM, Zimmerman GA: Production of platelet-activating factor by stimulated human polymorphonuclear leukocytes: correlation of synthesis with release, functional events, and leukotriene B4 metabolism. *J Immunol* 1987; **138:** 3918–3926
36. Elstad MR, Prescott SM, McIntyre TM, Zimmerman GA: Synthesis and release of platelet-activating factor by stimulated human mononuclear phagocytes. *J Immunol* 1988; **140:** 1618–1624
37. Miwa M, Sugatani J, Ikemura T, Okamoto Y, Ino M, Saito K, et al: Release of newly synthesized platelet-activating factor (PAF) from human polymorphonuclear leukocytes under in vitro conditions: contribution of PAF-releasing factor in serum. *J Immunol* 1992; **148:** 872–880
38. Prescott SM, Zimmerman GA, McIntyre TM: Human endothelial cells in culture produce platelet-activating factor (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) when stimulated with thrombin. *Proc Natl Acad Sci USA* 1984; **81:** 3534–3538
39. McIntyre TM, Zimmerman GA, Satoh K, Prescott SM: Cultured endothelial cells synthesize both platelet-activating factor and prostacyclin in response to histamine, bradykinin, and adenosine triphosphate. *J Clin Invest* 1985; **76:** 271–280
40. Zimmerman GA, McIntyre TM, Prescott SM: Production of platelet-activating factor by human vascular endothelial cells: evidence for a requirement for specific agonists and modulation by prostacyclin. *Circulation* 1985; **72:** 718–727
41. Zimmerman GA, McIntyre TM, Prescott SM: Thrombin stimulates the adherence of neutrophils to human endothelial cells in vitro. *J Clin Invest* 1985; **76:** 2235–2246
42. McIntyre TM, Zimmerman GA, Prescott SM: Leukotrienes C4 and D4 stimulate human endothelial cells to synthesize platelet-activating factor and bind neutrophils. *Proc Natl Acad Sci USA* 1986; **83:** 2204–2208
43. Whatley RE, Zimmerman GA, McIntyre TM, Prescott SM: Endothelium from diverse vascular sources synthesizes platelet-activating factor. *Arteriosclerosis* 1988; **8:** 321–331
44. Lewis MS, Whatley RE, Cain P, McIntyre TM, Prescott SM, Zimmerman GA: Hydrogen peroxide stimulates the synthesis of platelet-activating factor by endothelium and induces cell-dependent neutrophil adhesion. *J Clin Invest* 1988; **82:** 2045–2055
45. Zimmerman GA, McIntyre TM, Mehra M, Prescott SM: Endothelial cell-associated platelet-activating factor: a novel mechanism for signaling intercellular adhesion. *J Cell Biol* 1990; **110:** 529–540
46. Prescott SM, Patel KD, Smiley PL, Stafforini DM, Lorant DE, Zimmerman GA, et al: Potential roles for oxidized phospholipids in inflammation and atherogenesis. *In:* Weber PC, Leaf A, editors. Atherosclerosis review. New York: Raven Press, 1993; **25:** 59–68
47. Patel KD, Zimmerman GA, Prescott SM, McIntyre TM: Novel leukocyte agonists are released by endothelial cells exposed to peroxide. *J Biol Chem* 1992; **267:** 15168–15175
48. Smiley PL, Stremler KE, Prescott SM, Zimmerman GA, McIntyre TM: Oxidatively fragmented phosphatidylcholines activate human neutrophils through the receptor for platelet-activating factor. *J Biol Chem* 1991; **266:** 11104–11110
49. Heery JM, Kozak M, Stafforini DM, Jones DA, Zimmerman GA, McIntyre TM, et al: Oxidatively modified LDL contains phospholipids with platelet-activating factor-like activity and stimulates the growth of smooth muscle cells. *J Clin Invest* 1995; **96:** 2322–2330
50. Brown MS, Goldstein JL: Lipoprotein metabolism in the macrophage: implication for cholesterol deposition in atherosclerosis. *Annu Rev Biochem* 1983; **52:** 223–261
51. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL: Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989; **320:** 915–924
52. Witztum JL, Steinberg D: Role of oxidized low density lipoprotein in atherogenesis. *J Clin Invest* 1991; **88:** 1785–1792
53. Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D: Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. *Proc Natl Acad Sci USA* 1984; **81:** 3883–3887
54. Steinbrecher UP: Oxidation of low density lipoprotein results in derivatization of lysine residues of apolipoprotein B by lipid peroxide decomposition products. *J Biol Chem* 1987; **262:** 3603–3608
55. Steinbrecher UP, Lougheed M, Kwan W-C, Dirks M: Recognition of oxidized low density lipoprotein by the scavenger receptor of macrophages results from derivatization of apolipoprotein B by products of fatty acid peroxidation. *J Biol Chem* 1989; **264:** 15216–15223
56. Regnström J, Nilsson J, Tornvall P, C. Landou C, Hamsten A: Susceptibility to low-density lipoprotein oxidation and coronary atherosclerosis in man. *Lancet* 1992; **339:** 1183–1186
57. Steinbrecher UP, Prichard PH: Hydrolysis of phosphatidylcholine during LDL oxidation is mediated by platelet-activating factor acetylhydrolase. *J Lipid Res* 1989; **30:** 305–315
58. Stremler KE, Stafforini DM, Prescott SM, Zimmerman GA,

McIntyre TM: An oxidized derivative of phosphatidylcholine is a substrate for the platelet-activating factor acetylhydrolase from human plasma. *J Biol Chem* 1989; **264:** 5331–5334
59. Stremler KE, Stafforini DM, Prescott SM, McIntyre TM: Human platelet-activating factor acetylhydrolase: oxidatively fragmented phospholipids as substrates. *J Biol Chem* 1991; **266:** 11095–11103
60. Stafforini DM, Zimmerman GA, McIntyre TM, Prescott SM: The platelet-activating factor acetylhydrolase from human plasma prevents oxidative modification of low-density lipoprotein. *Trans Assoc Am Physicians* 1992; **105:** 44–63
61. Yanoshita R, Kudo I, Ikizawa K, Chang HW, Kobayashi S, Ohno M, et al: Hydrolysis of platelet activating factor and its methylated analogs by acetylhydrolases. *J Biochem* (Tokyo) 1988; **103:** 815–819
62. Stafforini DM, Prescott SM, Zimmerman GA, McIntyre TM: Platelet-activating factor acetylhydrolase activity in human tissues and blood cells. *Lipids* 1991; **26:** 979–985
63. Stafforini DM, Rollins EN, Prescott SM, McIntyre TM: The platelet-activating factor acetylhydrolase from human erythrocytes: purification and properties. *J Biol Chem* 1993; **268:** 3857–3865
64. Stafforini DM, McIntyre TM, Prescott SM: Platelet-activating factor acetylhydrolase from human plasma. *Methods Enzymol* 1990; **187:** 344–357
65. Stafforini DM, Prescott SM, McIntyre TM: Platelet-activating factor acetylhydrolase in human erythrocytes. *Methods Enzymol* 1991; **197:** 411–425
66. Tselepsis AD, Dentan C, Karabina S-A P, Chapman MJ, Ninio E: PAF-degrading acetylhydrolase is preferentially associated with dense LDL and VHDL-1 in human plasma: catalytic characteristics and relation to the monocyte-derived enzyme. *Arterioscler Thromb Vasc Biol* 1995; **15:** 1764–1773
67. Blencowe C, Hermetter A, Kostner GM, Deigner HP: Enhanced association of platelet-activating factor acetylhydrolase with lipoprotein (a) in comparison with low density lipoprotein. *J Biol Chem* 1995; **270:** 31151–31157
68. Watson AD, Navab M, Hama SY, Sevanian A, Prescott SM, Stafforini DM, et al: Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. *J Clin Invest* 1995; **95:** 774–782
69. Dentan C, Lesnik P, Chapman J, Ninio E: PAF-aceter-degrading acetylhydrolse in plasma LDL is inactivated by copper-and cell-mediated oxidation. *Arterioscler Thromb* 1994; **14:** 353–360
70. Ambrosio G, Oriente A, Napoli C, Palumbo G, Chiariello P, Marone G, et al: Oxygen radicals inhibit human plasma acetylhydrolase, the enzyme that catabolizes platelet-activating factor. *J Clin Invest* 1994; **93:** 2408–2416
71. Stafforini DM, Elstad MR, McIntyre TM, Zimmerman GA, Prescott SM: Human macrophages secrete platelet-activating factor acetylhydrolase. *J Biol Chem* 1990; **265:** 9682–9687
72. Narahara H, Johnston JM: Effects of endotoxins and cytokines on the secretion of platelet-activating factor-acetylhydrolase by human decidual macrophages. *Am J Obstetr Gynecol* 1993; **169:** 531–537
73. Narahara H, Frenkel RA, Johnston JM: Secretion of platelet-activating factor acetylhydrolase following phorbol ester-stimulated differentiation of HL-60 cells. *Arch Biochem Biophys* 1993; **301:** 275–281
74. Lee T-C, Fitzgerald V, Chatterjee R, Malone B, Snyder F: Differentiation induced increase of platelet-activating factor acetylhydrolase in HL-60 cells. *J Lipid Mediat Cell Signal* 1994; **9:** 267–283
75. Satoh K, Imaizumi T, Kawamura Y, Yoshida H, Hiramoto M, Takamatsu S, et al: Platelet-activating factor (PAF) stimulates the production of PAF acetylhydrolase by the human hepatoma cell line, Hep G2. *J Clin Invest* 1991; **87:** 476–481
76. Tarbet EB, Stafforini DM, Elstad MR, Zimmerman GA, McIntyre TM, Prescott SM: Liver cells secrete the plasma form of platelet-activating factor acetylhydrolase. *J Biol Chem* 1991; **266:** 16667–16673
77. Elstad MR, Stafforini DM, McIntyre TM, Prescott SM, Zimmerman GA: Platelet-activating factor acetylhydrolase increases during macrophage differentiation. *J Biol Chem* 1989; **264:** 8467–8470
78. Yamada Y, Stafforini DM, Imaizumi T, Zimmerman GA, McIntyre TM, Prescott SM: Characterization of the platelet-activating factor acetylhydrolase from human plasma by heterologous expression in *Xenopus laevis* oocytes. *Proc Natl Acad Sci USA* 1994; **91:** 10320–10324
79. Pritchard PH, Chonn A, Yeung CCH: The degradation of platelet-activating factor in the plasma of a patient with familial high density lipoprotein deficiency (Tangier disease). *Blood* 1985; **66:** 1476–1478
80. Stafforini DM, Carter ME, Zimmerman GA, McIntyre TM, Prescott SM: Lipoproteins alter the catalytic behavior of the platelet-activating factor acetylhydrolase in human plasma. *Proc Natl Acad Sci USA* 1989; **86:** 2393–2397
81. Tjoelker LW, Wilder C, Eberhardt C, Stafforini DM, Dietsch G, Schimp B, et al: Anti-inflammatory properties of recombinant human plasma platelet-activating factor acetylhydrolase. *Nature* 1995; **374:** 549–553
82. Tjoelker LW, Eberhardt C, Unger J, Trong HL, Zimmerman GA, McIntyre TM, et al: Plasma platelet-activating factor acetylhydrolase is a secreted phospholipase A_2 with a catalytic triad. *J Biol Chem* 1995; **270:** 25481–25487
83. Satoh K, Imaizumi T, Yoshida H, Kawamura Y, Takamatsu S, Takamatsu M, et al: Platelet-activating factor acetylhydrolase in plasma lipoproteins of healthy men and women. *Clin Chim Acta* 1991; **202:** 95–104
84. Miyaura S, Maki N, Byrd W, Johnston JM: The hormonal regulation of platelet-activating factor acetylhydrolase activity in plasma. *Lipids* 1991; **26:** 1015–1020
85. Satoh K, Imaizumi T, Yoshida H, Takamatsu S: Effect of 17β-estradiol on secretion of platelet-activating factor acetylhydrolase by Hep G2 cells. *Metabolism* 1993; **42:** 672–677
86. Maki N, Hoffman DR, Johnston LM: Platelet-activating factor acetylhydrolase activity in maternal, fetal, and newborn rabbit plasma during pregnancy and lactation. *Proc Natl Acad Sci USA* 1988; **85:** 728–732
87. Miwa M, Miyake T, Yamanaka T, Sugatani J, Suzuki Y, Sakata S, et al: Characterization of serum platelet-activating factor (PAF) acetylhydrolase: correlation between deficiency of serum PAF acetylhydrolase and respiratory symptoms in asthmatic children. *J Clin Invest* 1988; **82:** 1983–1991
88. Stafforini DM, Satoh K, Atkinson DL, Tjoelker LW, Eberhardt C, Yoshida H, et al: Platelet-activating factor acetylhydrolase deficiency: a missense mutation near the active site of an anti-inflammatory phospholipase. *J Clin Invest* 1996; **97:** 2784–2791
89. Yamada Y, Yokota M: Loss of activity of plasma platelet-activating factor acetylhydrolase due to a novel Gln^{281}→Arg mutation. *Biochem Biophys Res Commun* 1997; **236:** 772–775
90. Tetta C, Bussolino F, Modena V, Montrucchio G, Segoloni G, Pescarmona G, et al: Release of platelet-activating factor in systemic lupus erythematosus. *Int Arch Allergy Appl Immunol* 1990; **91:** 244–256
91. Caplan MS, Sun X-M, Hsueh W, Hageman JR: Role of platelet activating factor and tumor necrosis factor-alpha in neonatal necrotizing enterocolitis. *J Pediatr* 1990; **116:** 960–964
92. Graham RM, Stephens CJ, Silvester W, Leong LLL, Sturm MJ, Taylor RR: Plasma degradation of platelet-activating factor in severely ill patients with clinical sepsis. *Crit Care Med* 1994; **22:** 204–212
93. Hoffman B, Ruhling K, Spangenberg P, Osterman G: Enhanced degradation of platelet-activating factor in serum from diabetic patients. *Haemostasis* 1989; **19:** 180–184
94. Sato K, Imaizumi T, Kawamura Y, Yoshida H, Takamatsu S, Takamatsu M: Increased activity of the platelet-activating factor acetylhydrolase in plasma low density lipoprotein from patients with essential hypertension. *Prostaglandins* 1989; **37:** 673–682
95. Dulioust A. Hilliquin P, Menkes C-J, Benveniste J, Arnoux B: Paf-acether acetylhydrolase activity is increased in patients with rheumatic diseases. *Scand J Rheumatol* 1992; **21:** 161–164
96. Meade CJ, Metcalfe S, Svvennsen R, Jamieson N, Watson C, Calne RY, et al: Serum PAF acetylhydrolase and chronic cholestasis. *Lancet* 1991; **338:** 1016–1017
97. Ihara Y, Frenkel RA, Johnston JM: Hormonal regulation of platelet-activating factor-acetylhydrolase activity in rat tissues. *Arch Biochem Biophys* 1993; **304:** 503–507
98. Bazan NG: A signal terminator. *Nature 1995;* 374: **501**–502
99. Mueller HW, Haught CA, McNatt JM, Cui K, Gaskell SJ, Johnston DA, et al: Measurement of platelet-activating factor in a canine model of coronary thrombosis and in endarterectomy samples from patients with advanced coronary artery disease. *Circ Res* 1995; **77:** 54–63
100. Osterman G, Lang A, Holtz H, Ruhling K, Winkler L, Till U: The degradation of platelet-activating factor in serum and its discriminative value in atherosclerotic patients. *Thromb Res* 1988; **52:** 529–540
101. Osterman G, Ruhling K, Zabel-Langhenning R, Winkler L, Schlag B, Till U: Plasma from atherosclerotic patients exerts an increased degradation of platelet-activating factor. *Thromb Res* 1987; **47:** 279–285
102. Satoh K, Imaizumi T, Kawamura Y, Yoshida H, Takamatsu S, Mizuno S: Activity of platelet-activating factor (PAF) acetylhydrolase in plasma from patients with ischemic cerebrovascular diseases.

Prostaglandins 1988; **35:** 685–698
103. Satoh K, Yoshida H, Imaizumi T, Takamatsu S, Mizuno S: Platelet-activating factor acetylhydrolase in plasma lipoproteins from patients with ischemic stroke. *Stroke* 1992; **23:** 1090–1092
104. Graham RM, Stephens CJ, Sturm MJ, Taylor RR: Plasma platelet-activating factor degradation in patients with severe coronary artery disease. *Clin Sci* 1992; **82:** 535–541
105. Stephens CJ, Graham RM, Sturm MJ, Richadson M, Taylor RR: Variation in plasma platelet-activating factor degradation and serum lipids after acute myocardial infarction. *Coron Artery Dis* 1993; **4:** 187–193
106. Yamada Y, Ichihara S, Fujimura T, Yokota M: Identification of the $G^{994}\rightarrow T$ missense mutation in exon 9 of the plasma platelet-activating factor acetylhydrolase gene as an independent risk factor for coronary artery disease in Japanese men. *Metabolism* 1998; **47:** 177–181
107. Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; **362:** 801–809
108. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull Jr W, et al: A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol* 1995; **15:** 1512–1531
109. Tew DG, Southan C, Rice SQJ, Lawrence GMP, Li H, Boyd HF, et al: Purification, properties, sequencing, and cloning of a lipoprotein-associated, serine-dependent phospholipase involved in the oxidative modification of low-density lipoproteins. *Arterioscler Thromb Vasc Biol* 1996; **16:** 591–599
110. Hattori M, Arai H, Inoue K: Purification and characterization of bovine brain platelet-activating factor acetylhydrolase. *J Biol Chem* 1993; **268:** 18748–18753
111. Hattori K, Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K: Purification and characterization of platelet-activating factor acetylhydrolase II from bovine liver cytosol. *J Biol Chem* 1995; **270:** 22308–22313
112. Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K: Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase. *Nature* 1994; **370:** 216–218
113. Reiner O, Carrozzo R, Shen Y, Wehnert M, Faustinella F, Dobyns WB, et al: Isolation of a Miller-Dieker lissencephaly gene containing G protein β-subunit-like repeats. *Nature* 1993; **364:** 717–721
114. Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K: The catalytic subunit of bovine platelet-activating factor acetylhydrolase is a novel type of serine esterase. *J Biol Chem* 1994; **269:** 23150-23155
115. Adachi H, Tsujimoto M, Hattori M, Arai H, Inoue K: cDNA cloning of human cytosolic platelet-activating factor acetylhydrolase γ-subunit and its mRNA expression in human tissues. *Biochem Biophys Res Commun* 1995; **214:** 180–187
116. Hattori M, Adachi H, Aoki J, Tsujimoto M, Arai H, Inoue K: Cloning and expression of a cDNA encoding the β-subunit (30-kDa subunit) of bovine brain platelet-activating factor acetylhydrolase. *J Biol Chem* 1995; **270:** 31345–31352
117. Ho YS, Swenson L, Derewenda U, Serre L, Wei Y, Dauter Z, et al: Brain acetylhydrolase that inactivates platelet-activating factor is a G-protein-like trimer. *Nature* 1997; **385:** 89–93
118. Hattori K, Adachi H, Matsuzawa A, Yamamoto K, Tsujimoto M, Aoki J, et al: cDNA cloning and expression of intracellular platelet-activating factor (PAF) acetylhydrolase II. *J Biol Chem* 1996; **271:** 33032–33038
119. Stafforini DM, McIntyre TM, Zimmerman GA, Prescott SM: Platelet-activating factor acetylhydrolase. *J Biol Chem* 1997; **272:** 17895–17898