Platelet-activating factor acetylhydrolase and premature ovarian failure

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Summary

Premature ovarian failure (POF) appears to be a complex disease entity with several underlying etiopathogenic contributions including the possibility of multiple distinctly different autoimmune mechanisms, in which inflammatory autoimmunity targeted to ovarian-specific germline antigens (e.g., zona pellucida proteins or Mater) or differentiation/regulatory factors (e.g. inhibin-alpha) were regarded as one of the most crucial factors. Platelet-activating factor (PAF) and PAF class oxidized phospholipids stimulate the occurrence and development of inflammation and atherosclerosis. PAF acetylhydrolase (PAF-AH) can hydrolyze PAF and PAF class oxidized phospholipids and eventually prevent the body from the damage of these inflammatory mediators. These findings indicate a potential relationship between PAF-AH and POF thus have major implications for the future health of women who suffer with premature ovarian failure.

Key words: Premature ovarian failure (POF); Platelet-activating factor (PAF), PAF acetylhydrolase (PAF-AH).

Introduction

Premature ovarian failure (POF), generally described as irreversible cessation of menses before the age of 40, has a torturing influence on both women's physical and mental health. It is characterized by hyper-gonadotrophic and hypoestrogenic amenorrhea and regarded as the final step in the process of aggravation of ovarian dysfunction. Previous population-based studies estimated that about 0.3% ~ 1% adult women experienced POF. The total incidence varied from 1% to 3% due to different ethnicity. Almost 20% ~ 25% patients of primary amenorrhea and 10% ~ 20% of secondary amenorrhea eventually diagnosed as having POF.

Many factors are considered to be correlated with POF. Besides smoking, pelvic radiotherapy, pelvic chemotherapy and operation on pelvis, many hereditary diseases including absence of X chromosome, translocation between X chromosome and autosome, absence of gonadotropin or its receptor gene, mutations in FOXL2 gene and premutations in fragile X gene are considered correlating to POF. However, one-third to one-half of the cases are idiopathic and the identifiable aetiology of POF are still elusive. Ovarian biopsy of POF patients showed infiltration of lymphocytes and the characteristics of autoimmune oophoritis. Autoimmune ovarian disease (AOD) is considered one of the reasons leading to POF, but the immunological mechanism is still poorly understood due to short of specific clinical symptoms in the early stage of POF and lack of diagnostic features of ovarian inflammatory or autoimmune disease. Auto-reactive T cell-mediated autoimmune oophoritis is characterized by the limited or diffused inflammation and accumulation of mononuclear cells in the stroma of ovary. Although ovarian inflammation does not affect the ovarian function, it can lead to infertility in female mice. T cell-mediated inflammation is the prerequisite in the pathogenesis of ovarian atrophy induction and infertility. Both of the follicular and interstitial regions can be involved, the interstitial inflammation may be restricted to the hilus of ovary, to the region around the follicles or to the entire ovary. Clinical manifestations are closely related with the range of damage, from asymptomatic ovarian inflammation to menstrual disorders, POF, and infertility.

The current study found that platelet-activating factor (PAF), a kind of phospholipid with a wide range of biological activity, can affect the disorder of cardiovascular, respiratory, digestive, reproductive, skin, and other tissues or systems through mediating inflammation. In order to ensure the role of PAF in inflammation, PAF receptor antagonist was involved in many researches in recent years, which can resolve and inactivate PAF and related phospholipids. PAF and PAF class oxidized phospholipids stimulate the occurrence and development of inflammation and atherosclerosis. PAF acetylhydrolase (PAF-AH) can hydrolyze PAF and PAF class oxidized phospholipids and eventually prevent the body from the damage of these inflammatory mediators.

It is currently well known that POF is closely related with autoreactive T cell-mediated autoimmune oophoritis. Since PAF and PAF-AH are linked with inflammation of ovary, it is wondered if there are any changes in the expression of PAF and PAF-AH in premature ovarian failure patient. How about the relationship between the expression of PAF and PAF-AH and the incidence of premature ovarian failure? Can we use PAF and PAF-AH as the future prediction factors of POF diagnosis and targets of POF treatment?

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However, until now, there is no satisfied answer and further research in the field is required currently.

PAF and biological effects of oxidized phospholipids

In 1972, a kind of soluble phospholipid released by rabbit tropic alkaline granulocyte was reported by Benveniste, which was named PAF because of its platelet aggregation function [1]. Subsequent studies found that PAF is a mediator of inflammation with a wide range of biological activity and involved in various physiological and pathological processes [1].

PAF was produced by various cells such as neutrophils, basophils, macrophages, and vascular endothelial cells in many physiological or pathological conditions such as thrombosis, oxidative stress, and inflammation [1]. There are mainly two ways: one is the modified route, the hemolytic PAF (lyso-PAF) turn into PAF under the action of acetyltransferase. The other is the re-synthesis route, which is catalytic and synthesis in the basis of 1 - O - alkyl-S nonglycerol phosphate-3, through acetyltransferase, phosphatase and phosphorylcholine transferase. Re-synthesis pathway is the main way under physiological conditions; the modified pathway is mainly involved in allergic reaction and other pathological reactions. PAF plays the biological role by activating G protein-coupled PAF receptors. It can cause platelet aggregation which can make neutrophils release oxygen free radicals, promote cell adhesion, and cause smooth muscle cells contract. It can also act on vascular wall endothelial cells to increase the permeability of vascular walls or emerge cascade amplifying function [2]. PAF receptors are widely distributed in human body, its increased generation or reduced degradation lead to the accumulation of PAF in body, and then its physiological role is magnified, which can cause pathologic situation. PAF participate in asthma, cerebral thrombosis, atherosclerosis, and the development of other diseases; it especially plays an important role in atherosclerosis.

PAF oxidized phospholipids, belonging to the super PAF family, is stimulated by oxidative stress. Because of similarity to PAF, PAF oxidized phospholipids can produce similar biological activity of PAF when combined with PAF receptor [3].

Biological activity of PAF-AH

PAF is synthesized and secreted by cells when stimulated, and then quickly eliminated through metabolism, which exist in vivo with dynamic equilibrium. The acetyl group at the sn-2 position of its glycerol backbone is essential for its biological activity and involves a variety of physiological responses. Deacetylation induces loss of activity of PAF. PAF-AH can hydrolyze the acetyl group on the Sn-2 position of PAF, which determine the level of PAF in the plasma and tissue.

PAF-AH in the International Classification of the Commission as: EC3.1.47 belongs to hydrolase - esterase hydrolysis - carboxylic acid hydrolase class. The extensive research of PAF-AH began from about 1980, firstly in rabbits, then cattle and reptiles, and then fishes. PAF-AH has the following characteristics: 1) independent on Ca2 + ; 1) its substrate is acetyl group at the C2 position of glycerol backbone or short chain (including oxidated) fatty acids. This feature allows phospholipids and lipoproteins of the cell membrane not to be hydrolyzed and only hydrolyze the harmful substances such as PAF and oxidized phospholipids. PAF-AH belongs to phospholipase A2 family. It can be divided into two types in the body; one is plasma PAF-AH, also known as lipoprotein-associated phospholipase A2, which exist in the plasma in the form of lipoproteins. Plasma PAF-AH is primarily bound with low-density lipoprotein (low density lipoprotein, LDL) (L-PAF-AH) and about 20% is bound with high-density lipoprotein (high density lipoprotein, HDL) (H-PAF-AH). The other is intracellular PAF-AH, which can be divided into IB and IIB type. Different from other phospholipase A2, this type of PAF-AH has higher hydrolytic activity on the phospholipids with short-chain acyl ester at the sn-2 position. Therefore, it can specifically hydrolyze PAF and PAF-like oxidized phospholipids to induce the loss of biological activity, which determine the level of PAF and PAF-like oxidized phospholipids in plasma and tissue. In addition, in vivo/vitro experiments confirmed that the plasma-type PAF-AH can also regulate the inflammatory response by blocking the signal transduction commenced by PAF and PAF-like oxidized phospholipids.

The relationship between PAF and disease

PAF is a phospholipid with potent, diverse physiological actions which is involved in various physiological and pathological processes, such as asthma, sepsis, atherosclerosis, and hypertension [4-6]. When encountered with inflammation and oxidative stress, the level of PAF is increasing which is synthesized and secreted by macrophages, endothelial cells, neutrophils, and other cells that are involved in inflammation and vascular system [1], and then PAF exerts its biological activity by binding and activating G protein-coupled PAF receptor. PAF-like oxidized phospholipids is a class of oxidized phospholipids production that generated in the process of lipid oxidation and share the similar structure with the PAF and generate PAF-like biological action by binding with PAF receptor [7]. PAF and PAF-like oxidized phospholipids can increase the permeability of capillary blood vessels and the contraction of smooth muscle cells, and activate platelets, polymorphonuclear leukocytes, neutrophils macrophages, and other cells, and also have a strong pro-inflammatory action.

The relationship between PAF-AH and inflammation and cardiovascular disease

Endothelial injury and chronic inflammation play an important role in the occurrence and development of atherosclerosis, and even in the process of rupture at athero-

sclerosis site [8, 9]. Hyperlipidemia, particularly hyperlipidemia of increased oxidized LDL (Ox-LDL) can promote the development of atherosclerosis [10]. Because of their oxidation lipid and apolipoprotein (apo), Ox-LDL with pro-inflammatory reaction can activate white blood cells, platelets, and endothelial cells to produce the oxidation of lipids, including PAF. PAF can promote the inflammatory response and further the development of AS [11].

PAF and PAF-like oxidized phospholipids can induce the PAF-AH production [4, 5]. In 2000, Packard *et al.* first proposed that reduced PAF-AH, new coronary heart disease risk factors, can independently predict coronary events [7]. The expression of PAF-AH in the arterial wall of rabbit can reduce ox-LDL accumulation in the artery wall to achieve anti-inflammatory, antithrombotic, and anti-proliferation of smooth muscle cell [13]. The study found that the PAF-AH gene G994 mutation led to the reduction or loss of PAF-AH activity and the occurrence of coronary heart disease and cerebral infarction [7, 14]. Another study showed that activity of plasma PAF-AH in acute myocardial infarction decreased [14]. Recent study indicated LDL in the patients with PAH-AH defects is more prone to oxidation comparing with control group and has a stronger role in stimulation of adhesion molecules [15]. These studies suggested that plasma PAF-AH has the role of anti-inflammatory, anti-oxidation, and anti-atherosclerosis [11, 12].

Recently, however, some studies found that concentration and activity of PAF-AH increased in the patients with coronary heart disease. A large case-control study in Europe found that patients with decreased activity of PAF-AH accompanying V397 homozygous alleles have low coronary heart disease risks, which suggested that PAF-AH has a direct role in promoting atherosclerosis [16]. These studies suggested that lysophosphatidylcholine (lyso-PC), oxidized free fatty acids (OX-FFA) and other substances, which are produced by PAF-AH hydrolysis on PAF and PAF-like oxidized phospholipids, are pro-inflammatory mediators, can stimulate the production of adhesion molecules and cytokine, and promote the formation of atherosclerosis [7]. Considered together, the impact of PAF-AH on the atherosclerosis and cardiovascular disease is dual [17, 18]. Chen proposed that the advantages and disadvantages of the PAF-AH in plasma affecting on the body depends on the final effects of PAF-AH hydrolysis [8].

More and more studies have shown that the increase of LDL-PAF-AH activity is risk factors of atherosclerosis and cardiovascular disease [3]. Oxidative stress increased plasma levels of Ox-LDL, LDL-PAF-AH activity and lyso-PC, which may have a negative impact on the body.

PAF-AH is stored in the body as HDL-associated PAF-AH which can degenerate extra PAF or PAF-like oxidized phospholipids [19]. HDL-associated PAF-AH plays a protective role against inflammation and oxidation and is considered a protective factor against atherosclerosis [5]. With adenovirus-mediated gene transfer of PAF-AH in ApoE-deficient mice, the level of oxidized LDL decreased, however, HDL-associated plasma PAF-AH and PAF-AH activity in plasma increased, and vitro antioxidant of various lipoproteins also increased. In addition, the ability that HDL promotes cholesterol spilling from cultured macrophage and inhibits foam cell formation was enhanced [20].

Some studies found that in the cholesterol-fed rabbits, PAF-AH activity in plasma increased through augmenting the secretion of PAF-AH activity from macrophages. Meanwhile, lyso-PC was increased. Simvastatin treatment reduces PAF-AH and LDL-associated PAF-AH activity in plasma in the cholesterol-fed rabbits by decreasing the level of plasma LDL [14]. In the patients with familial hypercholesterolemia, both PAF-AH and LDL-associated PAF-AH activity were increased, while HDL-PAF-AH/LDL-PAF-AH ratio was significantly decreased [7]. Caslake and Packard stated that the increase of HDL-PAF-AH / LDL-PAF-AH ratio may contribute to preventing the formation of atherosclerosis [17].

The relationship between PAF-AH and POF

Plasma PAF-AH, especially HDL-associated PAF-AH, may be a hydrolytic enzyme against inflammation, oxidative stress and atherosclerosis [21]. 1/3~ 1/2 of the POF are idiopathic. Studies have shown that idiopathic POF was related with autoimmune oophoritis. The inflammation of ovaries induced the damage of ovarian tissue, consequently affecting follicular development elicit follicular atrophy, finally leading to POF. In addition, inflammation leads to the collection of inflammatory mediator PAF and the increase of relevant PAF-AH. Because PAF-AH, as receptor antagonist of PAF, can transfer PAF to inactivated form, hence the relationship of PAF-AH and PAF is converse. If PAF-AH is not sufficient to be against PAF; the increase of PAF might lead to pathological change of ovaries through excessive accumulation of PAF. The hypothesis of treatment of POF through improving the level of PAF-AH in patients to eliminate the accumulation of PAF in the ovarian tissue needs more laboratory data to confirm. Plasma PAF-AH, especially HDL-associated PAF-AH, may be a hydrolytic enzyme against inflammation, oxidative stress, and atherosclerosis [21]. One-third to one-half of the POF are idiopathic. Studies have shown that idiopathic POF is related with autoimmune oophoritis. The inflammation of ovaries induce the damage of ovarian tissue, consequently affect follicular development, elicit follicular atrophy, and finally leading to POF. In addition, inflammation leads to the collection of inflammatory mediator PAF and the increase of relevant PAF-AH. Because PAF-AH, as receptor antagonist of PAF, can transfer PAF to inactivated form, the relationship of PAF-AH and PAF is converse. If PAF-AH is not sufficient to be against PAF, the increase of PAF might

lead to pathological change of ovaries through excessive accumulation of PAF. The hypothesis of treatment of POF through improving the level of PAF-AH in the patients to eliminate the accumulation of PAF in the ovarian tissue needs more laboratory data to confirm.

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