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Review

Mediterranean diet and platelet-activating factor; a systematic review

Tzortzis Nomikos, Elizabeth Fragopoulou, Smaragdi Antonopoulou, Demosthenes B. Panagiotakos*

School of Health Science and Education, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

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ABSTRACT

Platelet-activating factor (PAF) is a glycerylether lipid and one of the most potent endogenous mediators of inflammation. Through its binding to a well-characterized receptor it initiates a plethora of cellular pro-inflammatory actions participating by this way to the pathology of most chronic diseases, including cardiovascular and renal diseases, CNS decline and cancer. Among the variety of prudent dietary patterns, Mediterranean Diet (MD) is the dietary pattern with the strongest evidence for its ability to prevent the same chronic diseases. In addition, micronutrients and extracts from several components and characteristic food of the MD can favorably modulate PAF's actions and metabolism either directly or indirectly. However, the role of this traditional diet on PAF metabolism and actions has rarely been studied before. This systematic review summarizes, presents and discusses the outcomes of epidemiologic and intervention studies in humans, investigating the relationships between PAF status and MD. Seventeen full-text articles trying to interlink the components of MD and PAF are found and presented. The results are inconsistent due to the variability of the measured indices and methodology followed. However, preliminary results indicate that the characteristic "healthy" components of the MD, especially, cereals, legumes, vegetables, fish and wine can favorably modulate the pro-inflammatory actions of PAF and regulate its metabolism. Larger, well-controlled studies are necessary to elucidate whether the attenuation of PAF actions can mediate the preventive properties of MD against chronic diseases.

1. Introduction

1.1. Platelet activating factor (PAF) – Metabolism and actions

Platelet activating factor (PAF) is one of the most potent, pro-inflammatory, phospholipid mediators. Actually, PAF refers to a group of molecular species with the general chemical structure of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine [1]. They are glycerylether analogues of phosphatidylcholine with two unique structural features which determine their biological properties. The first one is the ether bond at the *sn-1* position of the glycerol moiety and the second one is the acetyl-group esterified in the *sn-2* position of the glycerol backbone (Fig. 1). The molecular species of PAF differ in the structure of the alkyl-moiety at the *sn-1* position of glycerol backbone with 16:0, 18:0 and 18:1 alkyl-moieties being the most abundant [2]. (See Table 1.)

PAF is synthesized by almost all cell types, either at basal conditions or under specific stimuli. The main cellular sources of PAF are platelets, macrophages, monocytes, eosinophils, basophils, endothelial cells and renal cells [3]. The intracellular and extracellular levels of PAF are determined by the relative rates of its synthesis and degradation. PAF is synthesized by two distinct biosynthetic pathways. The first pathway, or *de novo* pathway, is responsible for the basal synthesis of PAF and involves a three step metabolic route including acetylation of 1-*O*-alkyl-2-lyso-*sn*-glycero-3-phosphate to 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphate which is dephosphorylated by a phosphohydrolase to 1-*O*-alkyl-2-acetyl-*sn*-glycerol. The latter is transformed to PAF accepting a phosphocholine group from CDP-choline by the action of CDP-choline cholinephosphotransferase (PAF-CPT) [4]. In the remodeling pathway, membranous ether analogs of phosphatidylcholine are hydrolyzed by a cytoplasmic phospholipase A_2 to lyso-PAF, which is then acetylated to PAF by the action of two isoforms of acetyl-CoA:lyso-PAF acetyltransferases (lyso-PAF ATs), namely lysophosphatidylcholine acyltransferases 1 and 2 ($LPCAT_1$ and $LPCAT_2$). $LPCAT_2$ is activated under inflammatory conditions while LPCAT1 is calcium independent and

Abbreviations: AT, acetyltransferase; BMI, body mass index; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LPCAT1,2, lysophosphatidylcholine acyltransferases1,2; LpPLA2, Lipoprotein-Associated Phospholipase A2; Mediterranean Diet, MD; PAF, Platelet-activating factor; PAF-CPT, CDP-choline cholinephosphotransferase; PAFR, PAF receptor; PBMC, peripheral blood mononuclear cells; PRP, platelet rich plasma; RBC, red blood cells; T2DM, Type 2 Diabetes Mellitus

* Corresponding author at: 70 El. Venizelou Ave., Kallithea, Harokopio University, Attica 176 71, Greece.
E-mail address: dbpanag@hua.gr (D.B. Panagiotakos).

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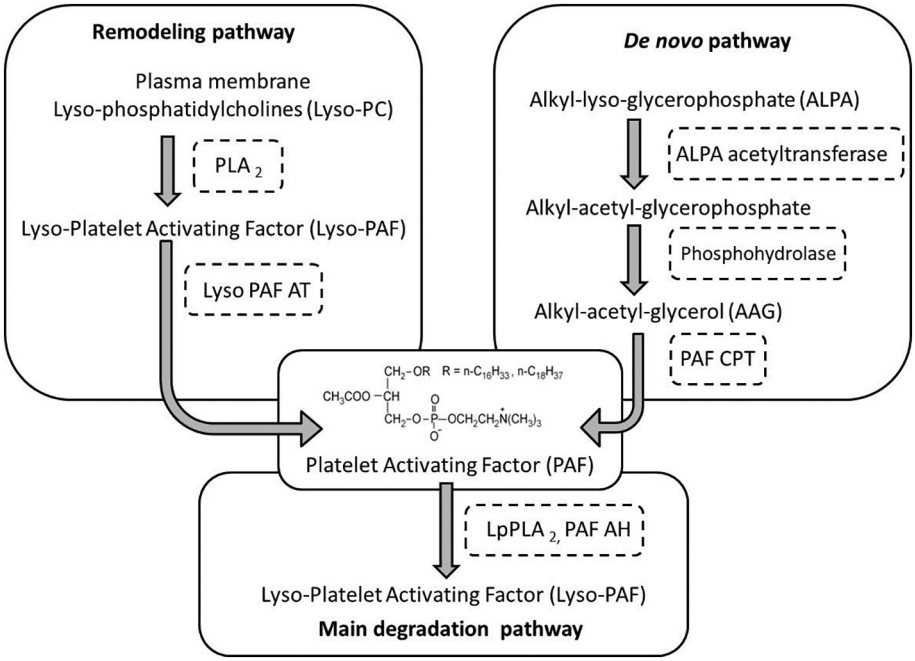

Fig. 1. Main enzymatic pathways of PAF metabolism.

does not participate in inflammatory processes [5,6]. Oxidized phospholipids, recognizing PAF receptor and exerting similar actions with PAF can also be produced, non-enzymatically, by the oxidative modification of LDL [7]. Both PAF and oxidized phospholipids with short *sn-2* chain can be degraded by intracellular and extracellular PAF-acetylhydrolases which hydrolyze the acetyl- or oxidized acyl- moiety of the *sn-2* position producing the inactive metabolite lyso-PAF. The extracellular isoform of PAF-acetylhydrolase circulates bound to lipoproteins, mainly LDL, and is called Lipoprotein-Associated Phospholipase A_2 ($LpPLA_2$) [8,9] **(**Fig. 1**)**.

PAF exerts its actions by binding to a specific G-protein coupled receptor (PAFR) at concentrations ranging from pM to nM in an autocrine, paracrine or juxtacrine fashion. The binding of PAF to its receptor triggers multiple intracellular signaling pathways specific for the cell type. Its main cellular targets are leukocytes, platelets and endothelial cells but PAFR has also been found in lungs, brain, kidney, adipose tissue [10,11]. A nuclear receptor has also been identified leading to the activation of MAP kinases and NF-kB [12].

PAF mediates several physiological processes of the human body such as regulation of blood pressure and immune system, fetal implantation, lung maturation and initiation of parturition [3]. However, when its production and secretion is, either acutely or chronically, raised it mediates several pathological processes through its cellular actions **(**Fig. 2**)**. Initially recognized as a mediator of IgE-induced anaphylaxis [13,14], it is now known that PAF is involved in almost every pathological condition with an inflammatory background. It participates in the initiation and propagation of the endothelial inflammation by triggering leukocyte adhesion, chemotaxis, respiratory burst, increased vascular permeability, platelet activation, expression of adhesion molecules on both leukocytes and endothelial cells and secretion of pro-inflammatory mediators [15]. In addition, PAF dysregulates myocardium contraction, electrophysiology and hemodynamics playing a crucial role for heart failure progression [16]. Apart from its well known role in atherosclerosis, cardiovascular and renal pathology, recent data imply a crucial role of PAF in malignant transformation, tumor growth and metastasis, immunesuppression and chemoresistance [17,18]. Moreover, a role of PAF for CNS disorders (Alzheimer's Disease, Multiple Sclerosis, spinal cord injury) [19], comorbidities associated with HIV infection [20] and autoimmune diseases [21] has also been proposed. Finally, PAFR of epithelial cells serves as a binding site for phosphorylcholine, expressed on the bacterial cell wall surface, facilitating by this way the adhesion, colonization and invasion of bacterial pathogens [22]. Taking into account the established role of PAF in atherosclerosis, bacterial infection and allergy and its emerging roles on renal diseases, tumor progression, CNS diseases and autoimmunity, as well as the crucial and established role of healthy diets in the management of the aforementioned disorders, the study of PAF metabolism through dietary means deserves further attention.

1.2. Mediterranean diet and health

Among the variety of prudent dietary patterns, Mediterranean Diet (MD) is the dietary pattern that has received the most attention the preceding years. Originated early after the end of the 2nd World War, in late 1940s and 1950s, mainly in the rural areas of countries of the upper Mediterranean region, MD is characterized by a variety of foods consumed, as well as moderate alcohol consumption, mainly wine. A large-scale study conducted in the late 1960's by Cresta et al., reported that diets in the Mediterranean areas were mainly characterized by a high consumption of cereals, vegetables, salads, fruits and fish, accompanying by high intake of olive oil as the principal source of fat, and a much lower intake of potatoes, meat and eggs, dairy and sweets [23]. Since then, several epidemiological studies and clinical trials have been developed and established the scientific interest in the health benefits of the MD. Ancel Keys from the Seven Countries Study, was the one who first summarized the major contribution of the MD on heart disease incidence, in the following words: "*My concern about diet as a public health problem began in the early 1950s in Naples, where we observed very low incidences of coronary heart disease associated with what we later came to call the 'good Mediterranean Diet*' [24]. The recent joint scientific statement from the American Heart Association and the American Diabetes Association recommended that a Mediterranean-style dietary pattern may improve glycemic control and cardiovascular risk factors, through its anti-inflammatory and anti-oxidative properties [25]. Moreover, on November 16, 2010, as an acknowledgement of the importance of MD for human health, UNESCO approved the inscription of the Mediterranean diet in the list of the intangible cultural heritage of human kind. According to that inscription, "*The Mediterranean diet*