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Involvement of Platelet Activating Factor (PAF) in various Diseases

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SUMMARY: *Platelet Activating Factor (PAF) is a lipid compound, glyceryl ether analog of phosphatidylcholine. PAF through its binding to a well-characterized receptor initiates a multitude of cellular pro-inflammatory actions that are thus involved in the pathology of most chronic diseases, including cardiovascular and renal diseases, central nervous system (CNS) diseases and cancer. It has also played a role in several other chronic inflammation-related diseases, such as type I and type II diabetes, acute pancreatitis, liver damage, inflammatory eye diseases, vascular dysfunction during acute lung injury and autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease and Crohn's disease.*

I. INTRODUCTION

Platelet Activating Factor (PAF) is a lipid compound that belongs to the class of phospholipids. The IUPAC name of the compound is: 1-O-alkyl-2-acetyl-sn-glycero-3-phospho-choline and is a glycerol ether analogue of phosphatidylcholine (Figure 1). In October 1979 the structure of PAF was elucidated and proved by Demopoulos, Pinckard and Hanahan at the University of Texas at San Antonio (1). PAF biosynthesis occurs via two main pathways, the remodeling and the de novo pathway. The de novo synthesis pathway of PAF is believed to be responsible for the continuous production of PAF maintaining its levels in blood and various

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tissues. A central enzyme in this pathway is the DTT-independent CDP choline, alkyl acetyl glycerol phosphocholine transferase (PAF-CPT). The remodeling pathway is believed to be responsible for PAF production in inflammatory conditions. Its central enzyme is lyso-PAF acetyl-CoA acetyl transferase (lyso-PAF-AT). Regarding PAF catabolism, the most important enzyme involved is PAF-acetyl hydrolase (PAF-AH) which hydrolyzes short-chain acyl groups from the sn-2 position of PAF to form lyso-PAF.

Several studies have described the two biosynthetic pathways, while the cloning of acetyl-CoA lyso - PAF acetyltransferase (lyso-PAF - AcT) has significantly expands the PAF metabolism field (2). PAF through its binding to a well-characterized receptor initiates a multitude of cellular pro-inflammatory actions that are thereby involved in the pathology of most chronic diseases, including cardiovascular and renal diseases, CNS diseases and cancer.

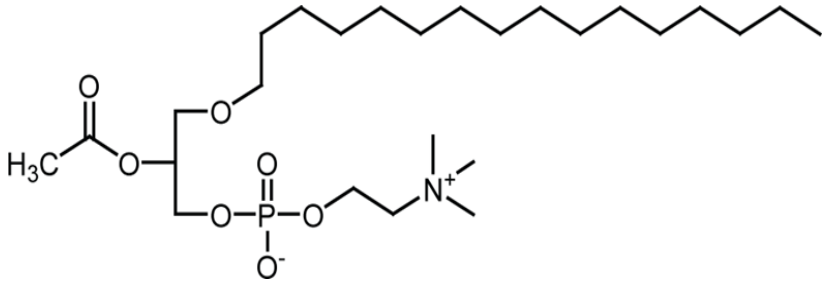

Figure 1: Structure of PAF

II. CARDIOVASCULAR DISEASES AND PAF

The key point of the atherogenesis mechanism involving PAF is the increase in its levels in the blood, the lack or deficiency of antioxidants and/or PAF inhibitors/agonists and the reduced activity of PAF-AH. High-density lipoprotein HDL, associated PAF-AHs have anti-inflammatory and antiatherogenic functions due to their inhibition of monocyte adhesion to the endothelium, their ability to attenuate phospholipid oxidation, and to inhibit the biological activity of low-density lipoprotein LDL (3). Hydrolysis of glycerophospholipids by PAF-AH generates lyso-PAF or lyso-phosphatidyl-choline (lyso-PC) and oxidized fatty acids, many of which tend to exhibit pro-inflammatory properties (4).

Bioactive lipids, such as PAF, PAF-like derivatives and oxidized phospholipids OoxPLs, have been identified in atherosclerotic plaque. PAF-like molecules are formed when cell membrane phospholipids undergo oxidative damage, and form smaller oxidized residues on the second carbon which mimic PAF action. OxPLs have important roles in angiogenesis, endothelial barrier function, regulation of innate and adaptive immunity, thrombosis, and are best known for their role as inducers of systemic inflammation and atherosclerosis. PAF-AH degrades pro-inflammatory OxPLs and plays a key role in the generation of lyso-PC and oxidized fatty acids (5,6,7,8). Also, PAF as well as other vasoactive compounds (arachidonic acid metabolites, histamine, cytokines, chemokines and proteolytic enzymes) can also be released from mast cells that accumulate in mesenteric arteries during atherosclerotic plaque exacerbating atherogenesis. (9). Cytokines produced by mast cells can be activated by proinflammatory stimuli, such as hypercholesterolemia and hyperglycemia, and induce the endothelial expression of adhesion molecules such as P-selectin, Vascular Cell Adhesion Molecule-1 (VCAM-1) and chemokines such as PAF that mediate neutrophil migration (9).

III. NEUROLOGICAL DISEASES AND PAF

PAF alters blood-brain barrier permeability, which effects the inflammatory disorders of the CNS (10). It is involved in the development of brain dysfunction after traumatic brain injury (10) and may influence postsynaptic hippocampal damage in encephalomyelitis (11). It is also involved in neurodegenerative diseases such as amyotrophic lateral sclerosis (12), an acute cerebrovascular disease with high morbidity, disability and mortality is stroke, where PAF is implicated in its pathogenesis through platelet aggregation.

IV. RENAL AND URINARY DISORDERS AND PAF

PAF is considered one of the main inflammatory mediators in renal physiology (13). It is synthesized in various renal cells, including mesenchymal cells, does not accumulate in renal cells, but is secreted and affects mesenchymal cells, neighboring podocytes causing glomerulosclerosis and proteinuria. It can also play a role in the hemodynamics of the kidney (14,15).

V. PAF AND CANCER

PAF plays an important role in cancers that are particularly difficult to treat. Melanoma, for example, is characterized as the most dangerous form of skin cancer due to its rapid metastasis, as a result of proinflammatory signaling mediated by PAF and its receptor PAF-R (16). It appears that pro-oxidant agents can suppress the host immune response through their ability to produce oxidized lipids and PAF-R agonists. PAF and PAF-like molecules are produced by cells of the skin upon exposure to UV light, contributing to the pathology of melanoma. Indeed, it seems that PAF and PAF-like molecules are also generated by cancer cells in patients with melanoma, after their exposure to radiation therapy (17,18,19). Increased production of PAF has also been found in various types of cancer, such as cancer of esophagus, lung, pancreas, breast, colon. All the above reinforce its special role in cancer (20,21,22).

VI. PAF AND ALLERGY

Elevated PAF levels correlate with the severity of allergic systemic reactions. PAF has been found to be involved in various allergic and anaphylactic reactions, bronchial asthma and bronchoconstriction of asthmatic patients, mucus hypersecretion, allergic rhinitis and the pathogenesis of urticaria. Several studies have shown that PAF can enhance bronchial obstructive changes by stimulating allergic inflammation of the airway epithelium, and can also increase skin capillary permeability inducing the development of inflammatory reactions in the skin (23). Anaphylaxis, especially in children, is a severe allergic reaction that can be life-threatening. PAF levels were elevated in 20% of patients with allergic skin reactions, in 67% of anaphylactic reactions without hypotension or severe respiratory involvement, and in 100% of patients with severe anaphylactic symptoms (24). This suggests that PAF is likely involved in the pathogenesis of anaphylaxis.

VII. PAF AND DIABETES

Type 1 Diabetes Mellitus, T1DM, is caused by autoimmune destruction of β-cells in the pancreas, which begins years before the clinical presentation of the disease. PAF levels in the serum of patients with newly diagnosed T1DM are significantly higher than in the healthy group, indicating that PAF plays a role in its development. Similarly, high levels of PAF were found in Type 2 Diabetes Mellitus T2DM2, but a little reduced compared to DM1 (25,26,27,28). The above shows that PAF is maybe related to the development of diabetes.

PAF has also been implicated in several other chronic inflammation-related diseases such as acute pancreatitis (29), liver injury (30), inflammation associated with gut dysfunction such as necrotizing enterocolitis (31), inflammatory eye diseases (32), vascular dysfunction during acute lung injury, and autoimmune disorders, such as rheumatoid

arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, and Crohn's disease (33).

VIII. CONCLUSIONS

Platelet Activating Factor (PAF) is a lipid compound involved in many pathological conditions. Future clinical research could focus on the prognostic characteristics of PAF and thus clarify its role.

Conflicts of Interest: The author declares no conflicts of interest regarding the publication of this paper.

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