Received: 4 October 2022 | Accepted: 5 October 2022

DOI: 10.1002/biof.1908

EDITORIAL

Biofactors WILEY

Platelet activating factor: Have we been missing the forest for the trees?

This special issue includes papers that address how immunity may be influenced by platelet-activating factor (PAF).

PAF was discovered in 1972 and its structure was elucidated in 1979 as a glyceryl-ether lipid (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine).[1] PAF exists in very low concentration and is extremely short-lived due to its degradation and inactivation by PAF acetylhydrolases including lipoprotein-associated phospholipase A_2 (Lp-PLA_2). All the above make its routine measurement difficult and the existing ELISA kits quite unreliable.[2] PAF is the most potent trigger of platelet aggregation known, is produced by endothelial cells, macrophages, monocytes, neutrophils, and platelets[3,4] and is critical for the development of microthromboses.[5,6] PAF exerts its autocrine and paracrine actions mostly by binding to the its G-protein-coupled receptor (PAF-R) located on the plasma and nuclear membrane and is expressed by a variety of cells and tissues. PAF-R apart from PAF, also interacts with PAF-like oxidized phospholipids (Ox-PLs) that are produced in vivo under oxidative stress and exert PAF-like action.[7] In addition, PAF-R recognizes components of the bacterial wall, such as lipoteichoic acid (LTA) and lipopolysaccharides (LPS) supporting the idea that PAF-R acts as an alternative system for innate immunity.[8] It should be noted that PAF-R stimulates PAF biosynthesis and PAF activates monocytes leading to increased PAF-R expression demonstrating a self-feedback activation loop.[9]

PAF has many potent biological effects,[10,11] including promotion of inflammation.[6,11–14] PAF induces IL-6 production[15–17] and then IL-6 stimulates production of PAF.[18,19] PAF has also been implicated in activation of the brain-specific macrophages, microglia,[20] as well as in cancer.[21,22]

PAF stimulates mast cells[23] and eosinophils,[24–26] and has been implicated in allergic conditions[27] such as anaphylaxis,[28–30] chronic spontaneous urticaria (CSU),[31–33] immediate and late cutaneous reactions,[34] and rhinitis.[35–39] Elevated PAF levels were strongly associated with severe anaphylaxis, more so than histamine or tryptase.[28] Moreover, combination treatment blocking both PAF and histamine markedly reduced the severity of peanut-induced anaphylaxis.[40] Elevated blood PAF levels have been reported in patients refractory to treatment with antihistamines.[31] PAF can also be secreted from mast cells,[23] unique tissue immune cells that can be activated by numerous triggers.[41] A number of recent papers have highlighted the importance of PAF in COVID-19.[5,6,42] In fact, it was recently reported that the coronavirus spike protein can modulate PAF production and also enhances in vitro PAF-induced platelet aggregation in non-vaccinated individuals.[43]

There are no clinically available PAF inhibitors, except for the histamine-1 receptor antagonist rupatadine which was developed to also have anti-PAF activity.[44] Rupatadine at 40 mg/day inhibited histamine- and PAF-induced flares and ex vivo platelet aggregation in normal male subjects.[45] In a network meta-analysis comparing the efficacy of second-generation antihistamines in CSU, rupatadine was superior to other antihistamines with respect to change from baseline in pruritus and wheal scores.[46] This superiority may be due, not only to its ability to block the action of PAF, but also due to the fact that rupatadine could also inhibit histamine[47] and TNF release from human mast cells in response to PAF,[23] and the release of histamine and IL-6 from human mast cells stimulated by different triggers.[48] Co-administration of PAF inhibitors has been shown to significantly improve the therapeutic effect of specific drugs in inflammatory or viral diseases where PAF is involved, such as cancer[49,50] and AIDS where some antiviral drugs have a pleiotropic PAF inhibitory effect It is worth mentioned that the drug Paxlovid, recommended for COVID-19, consists of the antiviral PF-07321332/Nirmatrelvir and the antiretroviral drug Ritonavir, which has also potent anti-PAF activity.[51,52]

It was recently reported that certain bionylated peptides could inhibit PAF activation in vitro and in vivo.[53] Plasmalogen analogs have also been proposed as PAF antagonists.[54] The existence of specific polar lipids that modulate PAF action and metabolism has been

Abbreviations: Lp-PLA_2, lipoprotein-associated phospholipase A_2; LPS, lipopolysaccharides; LTA, lipoteichoic acid; OxPLs, oxidized-phospholipids; PAF, platelet-activating factor; SARS, severe acute respiratory syndrome.

demonstrated in typical Mediterranean Diet foods such as virgin olive oil, yogurt, and wine.[55,56] Consumption of yogurt enriched with polar lipids from olive oil by-products reduced platelet sensitivity and subclinical inflammation in human subjects.[57]

Certain natural naturally occurring phenolic flavonoids,[58] commonly found in fruits, green plants, and seeds, have been reported to modulate the synthesis of PAF.[59] Such flavonoids, especially the flavone luteolin, inhibit activation of both mast cells[60,61] and microglia.[62–65] Luteolin formulated in olive pomace oil[66] to increase absorption (e.g. BrainGain®, FibroProtek®, NeuroProtek®, and PureLut®) inhibited neuroinflammation,[67–70] was neuroprotective[67,69,71,72] and reduced cognitive dysfunction,[73–76] especially brain fog.[77,78] Such flavonoids have also been proposed as prophylaxis or treatment for COVID-19.[79–82]

It is apparent that PAF is involved in many biological processes other than platelet aggregation and may serve as a common pathogenetic factor for many complex diseases involving perivascular inflammation. There is an urgent need to develop a rapid, reliable assay for PAF that would help in the diagnosis and understanding of complex diseases, as well as in the discovery of new therapeutic approaches.

AUTHOR CONTRIBUTIONS

Theoharis C. Theoharides, Smaragdi Antonopoulou, and Constantinos A. Demopoulos contributed equally to the concept, literature review, and writing of the manuscript.

CONFLICT OF INTEREST

The authors have no conflict to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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