Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(3): 36981
https://doi.org/10.31083/FBL36981

Editorial

Revisiting the Role of Platelet-Activating Factor in COVID-19-Induced Cardiovascular Complications

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Academic Editor: Graham Pawelec
Submitted: 9 January 2025 Revised: 27 January 2025 Accepted: 24 February 2025 Published: 17 March 2025

Since the onset of the COVID-19 pandemic five years ago, over 776 million cases have been reported, with 7.1 million deaths attributed to the virus. Additionally, 144.7 million individuals have experienced long-term effects (commonly referred to as "long COVID"), including persistent symptoms such as pulmonary, cardiovascular, neurological, and physical complications. Both the acute and chronic phases of COVID-19 are associated with severe cardiovascular complications, including a broad spectrum of arrhythmias. Several pathophysiological mechanisms have been proposed to explain this link, with inflammation, endothelial dysfunction, platelet activation, and immune hyperactivation emerging as the primary contributors [1].

Platelet-Activating Factor (PAF, 1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a highly potent pro-inflammatory and thrombotic mediator produced in response to various stimuli by cells such as endothelial cells, platelets, macrophages, monocytes, neutrophils, and mast cells. PAF activates platelets at extremely low concentrations (10^{-12} M) also leading to the secretion of other bioactive molecules from their granules. PAF exerts its biological effects through autocrine and paracrine mechanisms, by binding to its G-protein coupled receptor (PAFR), which is expressed in numerous cell types and tissues or by activating the inflammasome [2]. PAF induces hypotension, vasoconstriction, vascular permeability, and arrhythmias. At elevated levels, PAF causes a sustained decrease in cardiac index and triggers a tachycardic response. Furthermore, PAF plays a role in modulating T- and B-cell activation and proliferation and has been implicated as a mediator in pathological processes including atherosclerosis, one of the main causes of cardiovascular diseases. Elevated levels of PAF have been observed in nearly all conditions associated with inflammation and cellular damage and death.

The commonalities between the clinical manifestations of COVID-19 and the already known actions of PAF have led researchers to formulate its possible involvement as an important mediator of the thromboin-flammatory process in COVID-19 and prejudge the ascertained increased number of cardiovascular patients from the acute and chronic phase of COVID-19 [3]. Lipidomic studies upon coronaviruses highlighted the remodeling of host lipids including PAF, particularly following SARS-CoV-2 infection [4–8]. A previous *in vitro* study of host lipid differentiation on human cells following coronavirus infection revealed that the most elevated bioactive lipids were intermediates of phospholipase A2 (PLA2) metabolism, including PAF and metabolites of arachidonic acid. The authors proposed that the virus exploits specific host lipids that are essential for its replication [4]. In a recent study, the authors demonstrated that the *de novo* biosynthesis of glycerolipids (also known as Kennedy pathway) was a key pathway in SARS-CoV-2 infection. The study further confirmed that lung epithelial cells transfected with SARS-CoV-2 proteins exhibited consistent enrichment in ether- and vinyl-ether phosphatidylcholines (O-PC, plasmalogens), which serve as precursors in PAF biosynthesis [5]. The involvement of PLA2 in the pathogenesis and progression of COVID-19 has been underscored by lipidomic profiling of blood samples from COVID-19 patients that frequently revealed upregulation of lyso-phospholipids, as well as of fatty acids released from the *sn*-2 position of the glycerol backbone. Conversely, ether analogs of phosphatidylcholines and phosphatidylethanolamines, particularly plasmalogens, were found to be downregulated, suggesting that an interconversion pathway between plasmalogens and PAF may contribute to the regulation of pro- and anti-inflammatory signaling pathways [6,7]. The high activity of PAF, which corresponds to its particularly low levels, has not allowed its quantification in untargeted lipidomic analyses. However, targeted LC-MS/MS analysis has detected elevated PAF levels in the blood of patients with moderate COVID-19, while glucocorticoid therapy in individuals with severe/critical disease resulted in PAF decrease [8]. Additionally, it has been demonstrated that SARS-CoV-2 Spike protein stimulates PAF production in human monocytes and also enhances PAF-induced aggregation in platelet rich plasma from healthy individuals [9].

PAF catabolism is performed by three isoforms of PAF acetylhydrolase (PAF-AH), including two intracellular PAF-AHs (PAF-AH Ib and PAF-AH II) and its plasma isoform known as lipoprotein-associated phospholipase A_2 ($LpPLA_2$), encoded by the *PLA2G7* gene. These PAF-AHs hydrolyze the acetyl group from PAF, rendering it inactive. In patients with COVID-19, a significant increase in

both activity and protein levels has been observed for PAF-AHs. Furthermore, during the progression of COVID-19, the *PLA2G7* gene was found to be primarily expressed by pro-inflammatory macrophages in the patients' lungs and its expression was associated with the viral load. Additionally, SARS-CoV-2 ORF3a modifies PAF-AH Ib at protein level, leading to its characterization as an autoantigen. Increased levels of PAF-AHs are likely indicative of elevated PAF levels induced by SARS-CoV-2 and may provide a partial explanation for the commonly observed thrombotic complications and coagulopathies in COVID-19 patients [10].

Long COVID has been characterized as a coagulopathic and endothelial disease, with patients exhibiting increased markers of endothelial activation, platelet activation, inflammation, complement cascade activation and altered coagulation. While multiple overlapping causes of long COVID complicate the identification of a characteristic serum signature, angiopoietin-1 and P-selectin have been proposed as biomarkers, offering a high classification accuracy for long COVID status [11]. PAF plays a central role in this pathology by activating platelets and endothelial cells, inducing surface expression of P-selectin, and enhancing adhesive properties. This, in turn, creates a positive feedback loop, as P-selectin-mediated monocyte activation further amplifies PAF production, intensifying inflammatory and thrombotic responses. Furthermore, angiopoietin-1 has been reported to mediate PAF synthesis in endothelial cells. Notably, reduced levels of PAF-AH have been observed in long COVID patients six months post-infection. Additionally, a recent study identified a significant upregulation of the *PTAFR* gene in hospitalized COVID-19 patients [12].

These results indicate that PAF is involved in the pronounced inflammatory response characteristic of the acute and chronic phases of COVID-19, leading to disturbances in hemostasis and coagulation, and the emergence of thrombotic complications. Determining affordable monitoring approaches for PAF in various risk groups will support the management of cardiovascular disease in individuals with other chronic infections beyond COVID-19.

Combined therapeutic strategies that incorporate drugs with both anti-inflammatory/antiviral properties and the ability to inhibit PAF activity or lower its levels—such as corticosteroids [8] and Paxlovid [13]—alongside compounds that primarily act as PAF inhibitors (e.g., rupatadine, flavonoids, and polar lipids from olive oil) [14], could provide significant benefits for COVID-19 patients. Notably, this innovative integrative treatment approach has already been successfully implemented, leading to the full recovery of a severe COVID-19 patient [15].

Author Contributions

SA designed the study and wrote the manuscript. The author contributed to editorial changes in the manuscript. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author would like to thank the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest. Given her role as the Guest Editor member, Smaragdi Antonopoulou had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

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