Received: 26 July 2020 | Accepted: 9 September 2020

DOI: 10.1002/biof.1696

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REVIEW ARTICLE

Biofactors WILEY

COVID-19, microthromboses, inflammation, and platelet activating factor

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Abstract

Recent articles report elevated markers of coagulation, endothelial injury, and microthromboses in lungs from deceased COVID-19 patients. However, there has been no discussion of what may induce intravascular coagulation. Platelets are critical in the formation of thrombi and their most potent trigger is platelet activating factor (PAF), first characterized by Demopoulos and colleagues in 1979. PAF is produced by cells involved in host defense and its biological actions bear similarities with COVID-19 disease manifestations. PAF can also stimulate perivascular mast cell activation, leading to inflammation implicated in severe acute respiratory syndrome (SARS). Mast cells are plentiful in the lungs and are a rich source of PAF and of inflammatory cytokines, such as IL-1β and IL-6, which may contribute to COVID-19 and especially SARS. The histamine-1 receptor antagonist rupatadine was developed to have anti-PAF activity, and also inhibits activation of human mast cells in response to PAF. Rupatadine could be repurposed for COVID-19 prophylaxis alone or together with other PAF-inhibitors of natural origin such as the flavonoids quercetin and luteolin, which have antiviral, anti-inflammatory, and anti-PAF actions.

KEYWORDS

coagulation, COVID-19, flavonoids, inflammation, mast cells, PAF, rupatadine

1 | INTRODUCTION

The recent Coronovirus (severe acute pulmonary syndrome [SARS]-CoV-2) originated in China from where it spread rapidly,[1] and has reached pandemic proportions because of the high rate of infectivity, as well as high morbidity and mortality, known as COVID-19.[2] This coronavirus infects by binding to the ectoenzyme Angiotensin Converting Enzyme 2 (ACE2).[3–5] In addition, the serine protease TMPRSS2 is necessary for priming the viral "S" protein required for entry.[6] Defense against the virus apparently involves specific antibodies and activated T cells,[7,8] while the pulmonary sequelae result from release of multiple pro-inflammatory chemokines and cytokines that damage the lungs. [9,10]

Recent publications from different centers reported the presence of elevated coagulation markers[11–13] and microthromboses in the lung and other organs.[14–18] Most recently, platelet activation and aggregation has been reported in severe COVID-19 patients,[19,20] but the triggers of these processes were not discussed.

The most potent trigger of platelets known, is the lipid inflammatory molecule, platelet activating factor

Abbreviations: ACE2, angiotensin converting enzyme 2; OxPL, oxidized-phospholipid; PAF, platelet activating factor; SARS, severe acute respiratory syndrome; TLR4, toll-like receptor 4; TxA2, thromboxane-A2.

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(PAF) discovered in 1972.[21] In 1979, Demopoulos et al. elucidated its structure as a glyceryl-ether lipid (1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) and also described its synthetic preparation.[22] So far, only two articles have mentioned PAF with respect to COVID-19.[23,24] PAF is produced by many prokaryotic and eukaryotic cells, it is extremely short-lived, but has many potent biological effects on almost all tissues-organs (Figure 1).[25–27] Moreover, PAF appears to play a central role in inflammation.[28,29]

Most recently, platelets were reported to trigger degranulation of perivascular mast cells leading to inflammatory responses and tissue injury.[30] Moreover, mast cell degranulation associated with interstitial edema and immunothrombosis was just reported in alveolar septa of deceased patients with COVID-19.[31] Mast cells are unique tissue immune cells that can be activated by numerous triggers,[32–34] including viruses,[35] and can both secrete and be stimulated by PAF.[36] In fact, elevated PAF levels had been reported in allergic rhinitis[37] and chronic spontaneous urticaria,[38] both of which are known to involve activated mast cells. Mast cells are one of the richest sources of pro-inflammatory cytokines in the lungs[39] and have recently been implicated in COVID-19.[40]

2 | ROLE OF PAF IN COVID-19

The receptor for PAF has been implicated in the entry in H1N1 and H3N2,[41,42] as well as HIV,[43–46] and PAF inhibitors have been reported to confer including protection against neuroAIDS.[47] PAF and its receptor are also known to be involved in Dengue virus[48] and in respiratory syncytial virus.[49]

PAF appears to also affect the renin-angiotensin system,[50] including ACE2, which serves as the receptor required for SARS-CoV-2. For instance, Angiotensin II stimulates formation of PAF,[51] while PAF increases ACE2 activity.[52] Moreover, ACE and PAF acetylhydrolase gene polymorphisms have been reported to be involved in the progression of IgA-mediated disease.[53] Interestingly, mast cells also express the renin-angiotensin system.[54,55]

Many biological actions of PAF are similar to COVID-19 disease manifestations. In particular, PAF is implicated in the development of sepsis[56] and the most recently reported Kawasaki-like disease in children.[57] SARS-CoV-1 has the ability to induce production of compounds like oxidized-phospholipid (OxPL), which then induce cytokine production and acute lung injury via Toll-like receptor 4 (TLR4).[58] Oxidized lipids contain PAF and structural analogs of PAF that also show biological activity.[59] Oxidative stress and TLR4 signaling have been reported as key pathogenetic factors of acute lung injury.[60]

3 | TREATMENT CONSIDERATIONS

No effective COVID-19 treatments are presently available.[61,62] One approach would be to consider the use of PAF receptor inhibitors.[26,63] For instance, the Gingko biloba BN 52021 ginkgolide has been reported to inhibit Influenza virus activity[64] and has beneficial effects of in

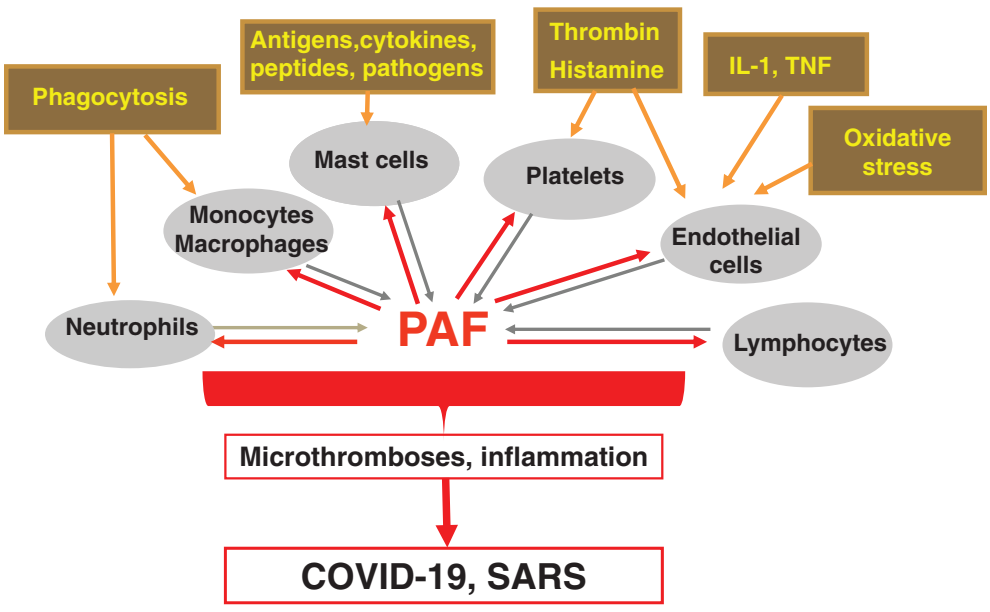

FIGURE 1 The main sources of and biological responses orchestrated by PAF. A variety of triggers (brown boxes) stimulate release of PAF from different cell types (gray ovals). PAF then acts back to stimulate the cells of its origin (autocrine action) leading to microthromboses and inflammation that contribute to the pathogenesis of COVID-19 and SARS

HIV-infected patients.[44] The histamine-1 receptor antagonist rupatadine was specifically developed to have anti-PAF activity[65] and also inhibits activation of human mast cells in response to PAF.[36]

A number of laboratories have used molecular docking software to identify the best potential COVID-19 inhibitors of SARS-CoV-2 binding to its ACE2 receptor on host cells.[66–70] In addition to a number of drugs that may be repurposed, these high-throuput screening for small molecules interacting with the human ACE2 receptor ranked three flavonoids[71] among the best *potential* inhibitors: quercetin (3,3′,4′,5,7-pentahydroxyflavonol), luteolin (3′,4′,5, 7-tetrahydroxyflavone), and eriodictyol (5,7,3′,4′-tetrahydroxyflavanone).[66–70,72,73]

It is interesting that polar lipid fractions[25] of natural origin (eg, from olive oil, wine, and fishes), as well as flavonoids in general[74] and quercetin in particular[75] have been reported to inhibit PAF synthesis and platelet aggregation.[76,77] They also inhibit mast cell activation and have been shown to be more potent inhibitors of mast cell release of pro-inflammatory cytokines that the "mast cell blocker" cromolyn.[78,79] Recent reviews have focused on the potential use of polyphenolic compound for COVID-19.[80,81] In fact, quercetin has recently been mentioned as a potential treatment of COVID-19.[82,83] However, mounting evidence indicates that luteolin alone, or in combination with quercetin, may offer a number of advantages.[40]

Luteolin has been shown to have broad anti-viral properties.[84–87] Luteolin specifically binds to the surface spike protein of SARS-CoV-2 and inhibits entry of the virus into host cells.[88] Furthermore, luteolin inhibits serine proteases, including the SARS-CoV 3CL protease, [9,89] required for viral infectivity. Moreover, luteolin inhibits release of pro-inflammatory cytokines,[79,90] especially from mast cells, which are one of the richest sources of pro-inflammatory molecules.[91,92] A novel structural analog of luteolin, tetramethoxyluteolin has been shown to be an even more potent inhibitor of pro-inflammatory cytokine [79,93–95] and chemokine[96] release from human mast cells. These flavonoids are generally considered safe.[80,97,98]

There have been publications showing that the steroid dexamethasone can inhibit PAF formation[99] and potentially COVID-19.[100] However, use of dexamethasone may be detrimental because it could inhibit innate immunity.[101] In addition to PAF, there are additional mechanisms that promote platelet aggregation and thromboses.[102] When the blood vessel wall is damaged or the endothelium is disrupted, collagen, and tissue factor initiate the formation of a thrombus. In addition, thromboxanes also promote clotting via platelet aggregation.[103] A recent article reported that IL-1 can induce both inflammation and microthromboses via thromboxane-A2 (TxA2) that could be inhibited by the IL-1 receptor antagonist (IL-1Ra).[104]

4 | CONCLUSION

Recent evidence points to presence of pulmonary microthromboses and pro-inflammatory cytokines in COVID-19 patients. A common pathogenetic factor may be PAF that could act on the endothelium, platelets, and mast cells, leading to COVID-19 and SARS. Rupatadine and other anti-PAF drugs, alone or together with quercetin and luteolin, could be used prophylactically or in mild cases of patients infected with SARS-CoV-2.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The authors contributed equally to the concept, literature review, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research

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How to cite this article: Demopoulos C, Antonopoulou S, Theoharides TC. COVID-19, microthromboses, inflammation, and platelet activating factor. *BioFactors*. 2020;1–7. https://doi.org/10.1002/biof.1696