Coronavirus 2019, Microthromboses, and Platelet Activating Factor

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ABSTRACT

Recent articles have reported elevated markers of coagulation, endothelial injury, and microthromboses in lungs from deceased patients with coronavirus 2019 (COVID-19). Platelets are critical in the formation of thrombi, and their most potent trigger is platelet activating factor (PAF). PAF is produced by cells involved in host defense, and its biological actions bear similarities with COVID-19 disease manifestations, including pulmonary microthromboses and inflammation, possibly via activation of mast cells. The histamine$_1$ receptor antagonist rupatadine was developed to have anti-PAF activity and inhibits activation of human mast cells in response to PAF. Rupatadine could be repurposed for COVID-19 prophylaxis. (*Clin Ther*. xxxx;xxx:xxx) © 2020 Elsevier Inc.

Key words: COVID-19, inflammation, mast cells, platelet-activating factor, thromboses.

Ackermann et al[1] recently reported the presence of severe endothelial injury and widespread pulmonary microthromboses accompanied with increased angiogenesis in lungs from deceased patients with coronavirus 2019 (COVID-19). These results support other recent publications from different centers reporting the presence of elevated coagulation markers[2–4] and microthromboses in the lung and other organs of patients with COVID-19.[5–8] Most recently, platelet activation and aggregation have been reported in patients with severe COVID-19,[9,10] but the triggers of these processes were not discussed.

The most potent trigger of platelet aggregation is platelet-activating factor (PAF), first discovered by Benvesiste in 1971.[11] Demopoulos et al[12] elucidated its structure as a glyceryl-ether lipid (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) and described its semisynthetic preparation in 1979. PAF is produced by cells involved in host defense, and its biological actions bear similarities with COVID-19 disease manifestations.[13] It was recently reported that platelets, via release of PAF, trigger perivascular mast cell activation, leading to inflammation.[14] Moreover, mast cell degranulation associated with interstitial edema and immunothrombosis was recently reported in alveolar septa of deceased patients with COVID-19.[15]

Mast cells are a rich source of PAF and are plentiful in the lungs,[16] where they may contribute to COVID-19.[17] We previously reported that levels of PAF were increased in allergic rhinitis[18] and chronic urticaria,[19] both of which involve activation of mast cells. Moreover, PAF appears to play a central role in inflammation.[20,21] In this context, innate immunity to COVID-19 appears to involve activated T cells and specific antibodies.[22,23] In addition, lung pathologic findings seen in severe acute respiratory syndrome (SARS) associated with COVID-19 are caused by a release of a storm of proinflammatory cytokines.[24,25] Mast cells are one of the richest sources of such cytokines, especially

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interleukin 6,[26,27] which has been implicated in COVID-19.[28] Because mast cells are involved in lung diseases, it makes sense that such patients would be even more susceptible to pulmonary complications of COVID-19.[29]

Given these findings, it would make sense to try to inhibit the action of PAF (Fig. 1). A number of PAF inhibitors have been synthesized but are not available for clinical use,[30–32] except for the histamine$_1$ receptor antagonist rupatadine, which was developed to specifically exhibit anti-PAF activity.[33] We reported that rupatadine also inhibits activation of human mast cells in response to PAF (Fig. 1).[34] Rupatadine could, therefore, be repurposed for at least COVID-19 prophylaxis. Interestingly, certain natural flavonoids also have anti-PAF activity,[35,36] in addition to their having anti-inflammatory actions and the ability to block COVID binding to target cells.[17]

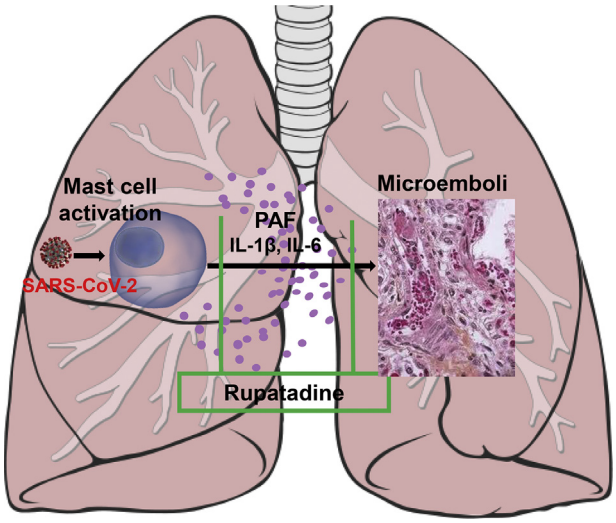

Figure 1. Diagrammatic representation of the release of platelet-activating factor (PAF), along with interleukin (IL) 1β and IL-6, from mast cells activated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent formation of microembolisms in the lungs of patients with coronavirus 2019 leading to SARS. Treatment with the dual histamine$_1$ and PAF-receptor antagonist rupatadine could limit or prevent this process.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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