REPLY: Is Platelet-Activating Factor the Missing Link Between COVID-19 and Atherosclerosis?

We appreciate the interest of Dr Demopoulos and colleagues in our recent review on the association between COVID-19 and atherogenesis.[1] We are thankful for the opportunity to elaborate further on the possible role of platelet-activating factor (PAF) in atherosclerosis and inflammation in COVID-19.

PAF is a potent pro-inflammatory phospholipid mediator known for its involvement in inflammation, immune response, atherosclerosis, and thrombosis.[2] PAF acts through the activation of the PAF receptor, expressed in various cell types, including monocytes, macrophages, platelets, and endothelial cells,[3] particularly in the presence of inflammation. PAF stimulates the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which facilitate monocyte adhesion and infiltration into the endothelium, an early step in atherosclerosis.[4] PAF also enhances the oxidative modification of low-density lipoprotein, facilitating its uptake by monocytes and foam cell formation, contributing to the progression of atherosclerosis and plaque instability.[5]

While the role of PAF in atherosclerosis is well reported, its specific involvement in COVID-19 pathophysiology is less understood. Antonopoulou et al[6] suggested that the spike protein of SARS-CoV-2 may stimulate the release of PAF from monocytes and can contribute to the dysregulated immune response with elevated pro-inflammatory cytokines seen in COVID-19 patients. By amplifying the inflammatory response, increasing the recruitment of immune cells to the endothelium, and worsening oxidative stress, PAF could contribute to vascular damage in COVID-19 patients, thereby accelerating atherogenesis. Furthermore, PAF interacts with other inflammatory mediators implicated in COVID-19, such as interleukin-6 and tumor necrosis factor-alpha, potentially creating a feedback loop that sustains chronic inflammation and endothelial damage.[7]

In conclusion, we acknowledge the evolving complexity of the interplay between inflammation, platelet activation, and atherosclerosis in COVID-19 and the emerging literature regarding the possibility of PAF's involvement in COVID-19-related cardiovascular complications, an important area for future exploration.

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