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MINI-REVIEW

Eicosanoids

The Overlooked Storm in Coronavirus Disease 2019 (COVID-19)?

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Severe coronavirus disease 2019 (COVID-19) symptoms, including systemic inflammatory response and multisystem organ failure, are now affecting thousands of infected patients and causing widespread mortality. Coronavirus infection causes tissue damage, which triggers the endoplasmic reticulum stress response and subsequent eicosanoid and cytokine storms. Although proinflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes, are critical mediators of physiological processes, such as inflammation, fever, allergy, and pain, their role in COVID-19 is poorly characterized. Arachidonic acid–derived epoxyeicosatrienoic acids could alleviate the systemic hyperinflammatory response in COVID-19 infection by modulating endoplasmic reticulum stress and stimulating the resolution of inflammation. Soluble epoxide hydrolase (sEH) inhibitors, which increase endogenous epoxyeicosatrienoic acid levels, exhibit potent anti-inflammatory activity and inhibit various pathologic processes in preclinical disease models, including pulmonary fibrosis, thrombosis, and acute respiratory distress syndrome. Therefore, targeting eicosanoids and sEH could be a novel therapeutic approach in combating COVID-19. In this review, we discuss the predominant role of eicosanoids in regulating the inflammatory cascade and propose the potential application of sEH inhibitors in alleviating COVID-19 symptoms. We also discuss the host-protective action of omega-3 fatty acid–derived epoxyeicosanoids and specialized proresolving mediators in regulating anti-inflammation and antiviral response. Future studies determining the eicosanoid profile in COVID-19 patient or preclinical model are pivotal in providing the novel insight of coronavirus-host interaction and inflammation modulation. *(Am J Pathol 2020, ■: 1–7; https://doi.org/10.1016/j.ajpath.2020.06.010)*

Early in the coronavirus disease 2019 (COVID-19) pandemic, it was observed that morbidity and mortality were associated with a drastic systemic inflammatory response caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1–3] This was initially observed in the lung, with many patients experiencing respiratory distress, pneumonia, fever, and multi-organ failure. Severe pathologies are now widely appreciated in many organs throughout the human body, including the lung, heart, spleen, lymph nodes, brain, liver, kidneys, eyes, and vasculature, because of widespread inflammatory responses.[1,4,5] The proinflammatory cytokine storm is a critical driving force in severe COVID-19 infection and may lead to multisystem organ failure.[2,3,5,6] One of the first descriptions of the cytokine storm was detailed on graft-*versus*-host disease in 1993.[7] Since then, cytokine storms and associated hyperinflammatory mechanisms have been characterized in studies of viral infection [influenza, SARS-associated coronavirus

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(SARS-CoV), and SARS-CoV-2], macrophage activation syndrome, immunotherapy, chemotherapy, rheumatic diseases, traumatic injury, and acute respiratory disease and may thus be utilized as potential diagnostic markers of inflammatory disease progression.[8–12]

Both SARS-CoV and the influenza virus induce apoptosis and necrosis of various cell types, including T cells, endothelial cells, and epithelial cells, through proinflammatory cytokine- and chemokine-mediated vascular leakage and suboptimal T-cell responses.[6,13–16] Moreover, viral clearance may be impaired by a macrophage-derived proinflammatory cytokine storm and thus targeting viral replication may not be sufficient to promote host survival.[16] Locally and systemically elevated proinflammatory cytokines, including IL-1β, interferon-γ, IP-10, IL-1, IL-6, and monocyte chemoattractant protein 1, have been detected in select critically ill patients with COVID-19 and found to correlate with disease severity.[2,6] Interestingly, this hyperinflammatory innate host response to SARS-CoV may additionally correlate with death in large animal models (eg, primates) more directly than virus titers.[17] Thus, a therapeutic approach to stimulating the resolution of the host inflammatory response, including the cytokine storm, may be as critical as preventing viral replication for patient survival.[3]

Cell death, including apoptosis, is induced by host defense mechanisms in response to infections.[18] However, cell death (debris) can trigger an eicosanoid and cytokine storm in inflammatory diseases.[10] Virus-induced inflammatory proteins and cell debris trigger a cellular endoplasmic reticulum (ER) stress response, which mediates the virus-host interaction in infected cells.[19] Normally, an ER stress response down-regulates global protein synthesis to diminish further viral replication in infected cells. However, prolonged responses initiate proinflammatory and later proapoptotic programs of ER stress in host cells, which cause elevated cytokine production during infection. The spike protein, which mediates SARS-CoV binding to angiotensin-converting enzyme 2 for cellular entry, has been shown to activate ER stress transducer X-box binding protein 1 and up-regulate ER-resident protein Herpud1 and chemokine Cxcl2 in infected murine fibroblast L cells.[20] In addition, overexpression of SARS-CoV ORF8b protein elevates ER stress effector CHOP, which leads to cell apoptosis in HeLa cells.[21] Coronavirus-induced tissue damage and accumulation of cellular debris (ie, cell fragments and proteins) has further been implicated in stimulating cell apoptosis and boosting inflammation by regulating other cellular pathways (JNK/p38, Bcl2/Bax, inflammasome, and NF-κB) with specific ER stress sensor arms.[19] Manipulations of the coronavirus-induced ER stress response upstream of the devastating cytokine storm could be a powerful approach in combating COVID-19 pathogenesis in patients with severe pneumonia or multi-organ failure (Figure 1).

Arachidonic acid–derived lipid autacoids, including prostaglandins (PGs), thromboxanes, and leukotrienes, generated by cyclooxygenases and lipoxygenases are collectively termed eicosanoids and are critical mediators of inflammation, resolution, and tissue homeostasis.[22] Eicosanoids play pivotal roles in a broad range of physiological processes, such as inflammation, fever, allergy, and pain.[22,23] On activation by cell debris or infection, the inositol-requiring enzyme 1α–X-box binding protein 1 branch of the ER stress pathway up-regulates expression of microsomal prostaglandin E synthase-1 and prostaglandin-endoperoxide synthase 2 [cyclooxygenase 2 (COX-2)], and accelerates the biosynthesis of prostaglandins (PGE_2, PGD_2, and $PGF_{2\alpha}$) and thromboxane B_2 from arachidonic acid.[24,25] This ensuing eicosanoid storm may be associated with production of a cytokine storm.[10,26] Indeed, activated ER stress signaling alone only slightly increases the level of IL-6, whereas the presence of PGE_2 and/or other cytokines (interferon-γ) with an activated ER stress response greatly enhances IL-6 production in glial cells.[27] More important, this eicosanoid surge has not been adequately evaluated in the setting of COVID-19 infection.

Although elevated cytokine levels in COVID-19 have been identified as a major factor contributing to morbidity and mortality, the role of eicosanoids in COVID-19 as key mediators of both inflammation and its active resolution remains poorly characterized.[3,28–30] More important, not all eicosanoids are proinflammatory as arachidonic acid and related fatty acids are also metabolized into anti-inflammatory and proresolution docosanoids in certain temporal situations.[22,31–33] Infectious processes often activate inflammasome formation and the subsequent formation of an eicosanoid storm consisting of both proinflammatory and anti-inflammatory mediators, thereby disrupting the temporal progression of inflammation and its resolution.[34] Namely, phospholipase A_2 regulates eicosanoid class switching during inflammasome and caspase activation, triggering arachidonic acid to generate proresolution mediators, such as lipoxins.[34,35] As increased proinflammatory cytokines may be a driving force in severe COVID-19, the balance of proinflammatory/anti-inflammatory eicosanoids and proresolution lipid mediators during the initiation and resolution of infection can regulate the cytokine storm.[34] Thus, we hypothesize that SARS-CoV-2 may trigger a temporal production of an eicosanoid storm, including an imbalance of both proinflammatory and proresolution mediators.[3,22]

Although eicosanoids, such as prostaglandins and leukotrienes, are best known as products of arachidonic acid metabolism by cyclooxygenases and lipoxygenases, arachidonic acid is also a substrate for another enzymatic pathway, the cytochrome P450 system. This eicosanoid pathway consists of two main branches: ω-hydroxylases, which convert arachidonic acid to hydroxyeicosatetraenoic acids; and epoxygenases, which convert it to four regioisomeric epoxyeicosatrienoic acids (EETs; 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET).[36] EETs regulate inflammation and vascular tone and are produced predominantly in the endothelium.[36] More important, the epoxides

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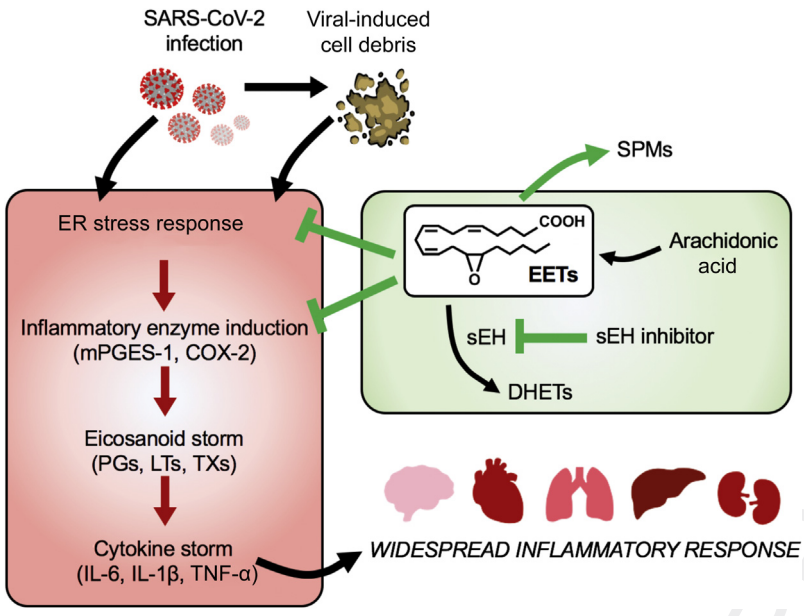

Figure 1 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to severe tissue damage, which releases cell debris. Both primary infection and the accumulation of cell debris initiate the endoplasmic reticulum (ER) stress response and up-regulate inflammatory enzymes, including microsomal prostaglandin E synthase-1 (mPGES-1) and prostaglandin-endoperoxide synthase 2 [cyclooxygenase 2 (COX-2)], which subsequently produce eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs). These proinflammatory lipid autacoids induce cytokine storms that mediate widespread inflammatory responses and organ damage in severe coronavirus disease 2019 (COVID-19) patients. By contrast, epoxyeicosatrienoic acids (EETs), which are stabilized by inhibition of their metabolizing enzyme, soluble epoxide hydrolase (sEH), are anti-inflammatory and proresolving mediators that promote the termination (resolution) of inflammation by suppressing the ER stress response, inflammatory enzyme induction, and proinflammatory cytokine production. EETs also shift arachidonic acid metabolism to favor the production of specialized proresolving mediators (SPMs), which initiate downstream anti-inflammatory and proresolving programs. EETs and sEH inhibitors may counterregulate the unabated systemic inflammatory response and organ failure associated with COVID-19 infection. DHET, dihydroxyeicosatrienoic acid; TNF-α, tumor necrosis factor-α.

of EETs are rapidly converted into dihydroxyeicosatrienoic acids by the soluble epoxide hydrolase (sEH) enzyme (Figure 1). Soluble epoxide hydrolase inhibitors, which raise endogenous EET levels, exhibit potent anti-inflammatory activity, including inhibiting proinflammatory cytokines in various pathologic diseases, including inflammatory bowel disease, atherosclerosis, pancreatitis, diabetes, hypertension, stroke, cerebral ischemia, dyslipidemia, pain, immunologic disorders, ocular diseases, neurologic diseases, renal disease (eg, acute kidney injury), organ damage, vascular remodeling, ischemia-reperfusion, lung disease (chronic obstructive pulmonary disease), fibrosis (eg, pulmonary and cardiac fibrosis), graft stenosis, and other medical conditions.[37–39] Although EETs and sEH signaling play a key role in hyperinflammatory diseases, their role in COVID-19 should be explored.

EETs, which are generated from arachidonic acid by cytochrome P450 enzymes, promote the active termination (resolution) of inflammation through mediating a broad array of anti-inflammatory and proresolving mechanisms, including mitigation of the cytokine storm.[3,40,41] In an endotoxemia mouse model, increased EET biosynthesis suppresses the endotoxin-induced surge of proinflammatory cytokines (IL-6 and IL-1β), chemokines (monocyte chemoattractant protein 1 and ENA-78), adhesion molecules (E-selectin), and NF-κB activation in lung.[42] Similarly, treatment with 14,15-EET inhibits activation of ER stress effectors (p-eIF2α, CHOP, and GRP78) by cigarette smoke and suppresses injury-induced oxidative stress and cell apoptosis in human bronchial epithelial cells.[43] Reduction of the ER stress response by EETs and promoting the activity of anti-inflammatory, proresolving mediators may represent a promising new therapeutic avenue in COVID-19 treatment.

Although inflammation can induce sEH expression,[36,37] COVID-19 infection may further stimulate sEH levels throughout the body in various tissues. Stabilizing the anti-inflammatory, proresolving EETs by using sEH inhibitors (sEHIs) has been shown to have a valuable therapeutic application in various preclinical models and human trials, including sepsis, cardiovascular disease, neuroinflammatory disease, and cancer.[44–46] More important, administration of sEHIs suppresses pulmonary cytokine expression and neutrophil infiltration, thereby alleviating pulmonary inflammation and edema and decreasing mortality in murine models of endotoxin-induced acute respiratory distress syndrome.[47] Similar anti-inflammatory activity has been observed in other models of chronic obstructive pulmonary disease, asthma, and pulmonary fibrosis.[48] In addition, sEHIs dramatically reduce NF-κB induction of inflammatory enzymes (ie, COX-2), as well as the downstream production of proinflammatory mediators, such as PGE_2.[24]

These omega-3 fatty acid–derived epoxyeicosanoids exhibit anti-inflammatory activity in various inflammatory diseases, including in the lung, heart, ocular angiogenesis, and pain.[49] Omega-3 supplementation may also synergize with sEH inhibition to suppress inflammation.[50] Omega-3 epoxides, stabilized via inhibition of sEH, are important regulators of inflammation and autophagy in metabolic diseases.[51] Dietary eicosapentaenoic acid/docosahexaenoic acid supplementation causes a profound shift of the endogenous cytochrome P450–eicosanoid profile from arachidonic acid– to eicosapentaenoic acid– and docosahexaenoic acid–derived metabolites, increasing, in particular, the

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plasma and tissue levels of 17,18-epoxyeicosatetraenoic acid and 19,20-epoxydocosapentaenoic acid. COVID-19 is characterized by increased angiogenesis demonstrated in autopsy samples of lungs from patients who died from COVID-19 compared with influenza patients.[52] Inhibition of sEH prevents angiogenic diseases, such as diabetic retinopathy.[53] Cytochrome P450−derived lipid metabolites epoxydocosapentaenoic acids and epoxyeicosatetraenoic acids also dampen choroidal angiogenesis.[54]

Moreover, EETs shift arachidonic acid metabolism to stimulate the production of specialized proresolving mediators, such as lipoxins, which stimulate clearance of inflammatory cellular debris and counter proinflammatory cytokine production without being immunosuppressive.[24,48] Pharmacological enhancement of resolution via resolvins at nanogram doses per day or omega-3 fatty acid supplementation restores endogenous specialized proresolving mediators.[55−57] Stimulation of resolution of inflammation by immunoresolvent agonists, including resolvins, is host protective during infection and sepsis.[58−61] The anti-inflammatory agent dexamethasone may have activity in COVID-19 patients.[62] Dexamethasone stimulates specialized proresolving mediators to stimulate resolution of airway inflammation.[63] The ER stress response can be reduced by dexamethasone by promoting protein folding and degradation of misfolded proteins from the ER.[64]

Targeting eicosanoid metabolism could be a promising new approach in COVID-19 infection given the critical role that eicosanoids play in both the initiation and resolution of inflammation.[22] Although current therapeutic strategies are aimed at inhibiting individual inflammatory cytokines (ie, IL-1 and/or IL-6) or viral cell entry and intracellular processing, these strategies neglect the critical upstream role that ER stress and eicosanoids play between generation of cell fragments and proteins released during viral-induced death (debris) and the downstream cytokine production in coronavirus infection (Figure 1). Nonsteroidal anti-inflammatory drugs (NSAIDs), the pan-COX inhibitors that block prostaglandin biosynthesis, are a routine and effective choice for the relief of influenza-caused fever and pain.[23,37] There may be minimal to no benefit for severe SARS-CoV-2 infections with NSAIDs, which also increase the risk of gastrointestinal and cardiovascular complications.[65] Initially during infection, the classic mediators of inflammation, including prostaglandins and leukotrienes, are produced, leading to the initiation of inflammation.[66] Subsequently, prostaglandin E_2 and prostaglandin D_2 induce a lipid mediator class switching of eicosanoid production by neutrophils from leukotriene B_4 and 5-lipoxygenase pathways to lipoxins, resolvins, and protectins to promote resolution.[33,66−69] Thus, NSAIDs should be used with caution as they may block subsequent activity of prostaglandins, which are essential for the resolution of inflammation.[22] NSAIDs are currently recommended to be on an individual basis because of the insufficient evidence in clinical trials and their well-known gastrointestinal and cardiovascular toxicities.[70]

Interestingly, sEHIs synergize with COX inhibitors in reducing inflammation and blocking the gastrointestinal erosion and cardiovascular events associated with these drugs.[40,71,72] Shifting arachidonic acid metabolism via sEH inhibition also alters the ER stress response toward a more homeostatic role in cell maintenance and promotes the production of anti-inflammatory, proresolving lipids, thus representing an attractive new approach to controlling inflammation in COVID-19. Indeed, sEHIs have been demonstrated to suppress the inflammatory response and inflammation-driven diseases in lung, heart, liver, kidney, and vasculature in numerous preclinical models.[37,40] Recently, sEHIs have proved nontoxic at high doses in clinical development (phase 2A trials) and synergistic with other well-established anti-inflammatory medications, such as NSAIDs, to promote anti-inflammatory programs and reduce the gastrointestinal adverse effects.[71] Interestingly, risk factors for COVID-19 are similar to idiopathic pulmonary fibrosis, and previous coronavirus outbreaks have been characterized by fibrosis.[73] Pharmacologic or genetic inhibition of soluble epoxide hydrolase prevents inflammation and liver fibrosis in various tissues, including lung, heart, liver, and kidney.[74−80] Thus, the antifibrotic activity of sEHIs may additionally be useful in speeding recovery after COVID-19 infection.[40] Temporal data on eicosanoid levels in patients are critical to further establish the role of a putative eicosanoid storm in COVID-19, and additional preclinical and clinical studies are needed to test the safety and efficacy of sEHIs in COVID-19 patients. Herein, we propose sEHIs alone or in combination with other agents, such as COX inhibitors or omega-3 lipids, are envisioned to be of benefit in blocking or moderating the inflammatory cascade when the patient's condition first appears to be deteriorating in COVID-19.

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