Managing SARS-CoV2 Infections Through Resolution of Inflammation by Eicosanoids: A Review

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Abstract: Severe Corona Virus Disease is characterized by angiocentric inflammation of lungs and cytokine storm leading to potentially fatal multiple organ failure. Several studies have shown the high levels of pro-inflammatory cytokines, indicative of a poor prognosis in COVID-19. Eicosanoids play an important role in the induction of inflammation and cytokine production, while anti-inflammatory and pro-resolving properties of some eicosanoic acid derivatives enable inflamed tissues to return to homeostasis through the resolution of inflammation by aiding the clearance of cell debris and downregulation of pro-inflammatory stimulants. This review attempts to provide an overall insight on the eicosanoids synthesis and their role in the resolution of inflammation in the context of Corona Virus infection.

Keywords: COVID-19, lipid mediators of inflammation, polyunsaturated fatty acids, cyclooxygenases, lipoxygenases, cytochrome P450, eicosanoids

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) causing Covid-19 pandemic has emerged as one of the global threats infecting millions of people and causing deaths of several millions around the globe. SARS-CoV-2 is the infectious form of human Coronavirus compared to SARS and Middle-East Respiratory Syndrome (MERS) coronaviruses that are known to have evolved as zoonotic diseases.1,2,3 Although the prognosis of Covid-19 is good where the recovery rate of infected persons is high, it causes serious illness in some individuals causing death. The prolonged 4–14 days of incubation period of Covid-19 with mean incubation period of 11 days results in delayed clinical manifestation of symptoms, thus, increasing the criticality of the disease. In critically ill patients, the severity of the infection is thought to be increasing with co-morbid conditions such as age, respiratory diseases like asthma, cardiovascular diseases and diabetes.

SARS-CoV-2 infects the upper and lower respiratory cells of humans causing severe lung inflammatory immunopathogenesis leading to pneumonia that can be fatal. At the organ level, the virus infects the type II pneumocytes of lung alveoli and gains entry into the cells by interacting with the host cell surface receptor, angiotensin converting enzyme 2 (ACE2) via its Spike (S) protein.4 ACE2 is required for the cleavage of the precursor angiotensin, I and II, into their active forms that regulate the cardiovascular and renal functions. At the system level, the virus-infected cell is recognized by the first-line defence system, the alveolar macrophages that elicit the immune response by secreting the cytokines and recruiting the neutrophils to the site of infection, alveoli, which cause an increase in reactive oxygen species (ROS) and proteolysis leading to acute inflammatory immune response.5

Inflammation is a protective immunological response that consists of immune cells, blood vessels and molecular mediators. Of the two types of inflammation, Acute inflammation starts as the first response by the injured tissue. It occurs by the movement of cells like plasma and leukocytes (granulocytes) from the blood into the damaged tissues followed by various biochemical events involving various cells within the injured tissue, the local vascular system and the immune system that finally leads to an inflammatory response.6 On the other hand, Chronic inflammation is the long-term type of inflammation that is caused due to the...
inability of the immune response to eliminate the cause of the acute inflammation and is characterized by the shift in the cells by simultaneous destruction and healing of the tissue.\(^7\)

The inflammatory response involves 3 different defence mechanisms.

1. Macrophages provide the first-line of defence mechanism. These are the phagocytic cells that engulf the pathogen and secrete chemical mediators, cytokines, that attract other immune cells.
2. The second line of defence mechanism is provided by the cytokines secreted by phagocytic cells. These cytokines are both pro- and anti-inflammatory in nature and the modulation of these cytokines decides the final outcome. The cytokines stimulate the mitotic effect in B and T lymphocytes that secrete antibodies and induce apoptosis of infected cells and finally eliminate the pathogen.
3. The third and most important mechanism is provided by Eicosanoid pathway, catalysing the conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes that play an important role in resolution of inflammation.

Inflammatory mediators can be classified majorly into 3 categories.\(^8\)

(i) **Preformed mediators** always exist even in the absence of the inflammatory stimuli. These are histamine, serotonin, lysosomal enzymes which are generated by the cellular sources such as mast cells, platelets, neutrophils, macrophages, etc.

(ii) **Newly synthesized mediators**, on the other hand, are formed in the presence of an inflammatory stimulus. These are eicosanoids such as prostaglandins, leukotrienes, platelet activating factors, cytokines, nitric oxide, etc., generated from cellular sources such as leucocytes, platelets, endothelium and macrophages.

(iii) **Complement Factors**: Under the influence of an inflammatory stimulus certain proteins in the plasma like complement undergo chain reactions releasing intermediary substances like C3a, C5a and C5b – 9. A plasma protein known as Hegeman factor, on the other hand, activates, complement-clotting-kinin cascades resulting in blood clotting and pain.

Among the three inflammatory defence pathways, the Eicosanoid pathway is considered as primary inflammatory immune response during infection. Eicosanoids are formed by oxidation of arachidonic acid (AA) and other polyunsaturated fatty acids (PUFAs) majorly by 3 enzymes – cyclooxygenases (COX), lipooxygenases (LOX) and cytochrome P450 enzymes.\(^9\) Of these, COX and LOX pathways are primarily involved in production of lipid mediators of inflammation – prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs) and are responsible for regulating a diverse set of homeostatic and inflammatory processes.

**Eicosanoid Synthesis: The COX, LOX, and CYP Pathways**

Arachidonic acid, once released from the membrane phospholipids by the action of phospholipases, is subsequently metabolized to an unstable prostaglandin G2 (PGG2), which is reduced to prostaglandin H2 (PGH2) by the COX enzymes. PGH2 is then metabolized to a variety of tissue-specific prostaglandins (PGs) by specific PG synthases. COX exists in two distinct isofoms; COX-1 is the dominant source of prostanoids that performs housekeeping functions and is continuously expressed in most cells. COX-2 is assumed to be the most important source of prostanoid formation in inflammation and critical proliferative diseases and is induced by inflammatory stimuli, hormones, and growth factors. The non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, indomethacin, etc. inhibit both COX-1 and COX-2 non-specifically while the COXIBs such as celecoxib, valdecoxib, etc are COX-2 specific inhibitors.

The LOX enzymes insert molecular oxygen into AA and depending on the position of insertion they are classified as 5-LOX, 8-LOX, 12-LOX, and 15-LOX which generate four types of hydroperoxyeicosatetraenoic acids (HPETEs; 5-, 8-, 12-, and 15-HPETE). Peroxides reduce HPETEs into monohydroxy eicosatetraenoic acids (HETEs). HPETEs are also converted to biologically active compounds such as leukotrienes (LTs), lipoxins (LXs), and hepoxilins.

The third AA-metabolizing pathway is the cytochrome P450 (CYP) pathway. The hydroxylase activity of CYP enzymes converts AA to hydroxyeicosatrienoic acids (HETrEs). The epoxygenase activity of CYP enzymes, such as the CYP2J and 2F families, generates AA epoxides or epoxyeicosatrienoic acids (EETs; 5,6-EET, 8,9-EET, 11,12-EET, and...
The EETs are mainly metabolized by soluble epoxide hydrolases (sEHs) to the corresponding diols or dihydroxyeicosatrienoic acids (DHETrEs). The physiological roles of the so formed lipids differ in different cells. For example, autocrine signalling by PGE2 through its receptor, EP, in macrophages downregulates TNF alpha and up-regulates IL-10 production leading to reduced inflammatory signals while the binding of PGE2 to its cognate GPCR receptors in neurons causes the pain associated with inflammation.

**Inflammation: Initiation and Resolution**

The primary goal of the inflammatory response is to maintain homeostasis by identifying and eliminating the cause of imbalance. A typical inflammatory response consists of four components: inflammatory inducers; the detecting sensors; downstream mediators; and the target tissues that are affected.

The type and degree of activated inflammatory response depend on the nature of the inflammatory trigger and its extent. Once detected, pathogens induce the production of inflammatory cytokines, chemokines, and proinflammatory lipid mediators such as prostaglandins and leukotrienes to establish an effective inflammatory response and clearance of the debris of dead and dying pathogen and host cells by pro-resolving lipid mediators. Pro-inflammatory mediators, such as interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and PGE2 are produced locally in the inflamed tissues.

Proinflammatory cytokines in the circulation induce leukocytosis and acute-phase proteins. With continued exposure, soluble antigens react with circulating specific antibodies to form immune complexes that further amplify inflammation at deposition sites. Sensing of the inflammatory response by innate immune cells and resident cells triggers the production of mediators to modulate the inflammation. Macrophages, neutrophils, dendritic cells, and mast cells produce cytokines that control the initiation of inflammation and its maintenance and regulate its amplitude and the duration of the response. Thus, a set of Lipid mediators acts as pro-inflammatory mediators that turn on inflammation, while some lipid mediators act as endogenous agonists to activate termination of inflammation by stimulating resolution.

**Pro-Inflammatory Lipid Mediators**

In response to acute triggers, both chemical and mechanical stimuli, membrane-derived arachidonic acid is rapidly acted upon by cyclooxygenases and lipoxygenases to generate various lipid mediators in leukocytes and other immune cells. Prostaglandins and leukotrienes are widely known for their pro-inflammatory properties (Figure 1).

**Prostaglandins**

There are 10 subclasses of Prostaglandins, of which D, E, F, G, H and I are crucial in inflammatory settings. Prostaglandin D2 (PGD2) exerts both pro-inflammatory and anti-inflammatory properties depending on the receptor to which it binds. It has been shown that PGD2 promotes viral-induced bronchiolitis via binding to DP2 receptor and is elevated by more than 10-times in asthma patients. On the other hand, PGD2 exerts anti-inflammatory activity via DP1 signaling and ameoriolates lung inflammation. Prostaglandin D2 is also found to increase intracellular cyclic AMP levels in certain cell types and have anti-inflammatory actions and its non-enzymatic degradation products such as 15-deoxy-delta-12,14-prostaglandin J2 (PGJ2) and cyclopentenones enhance resolution by promoting leukocyte apoptosis and macrophage clearance by inhibiting nuclear factor-xB (NF-xB) activity. Prostaglandin E2 (PGE2), generated via prostaglandin E synthase (PGES) in leukocytes and other inflammatory cells regulates stress responses, immunity, and inflammatory pathways by increasing vascular permeability, vasodilation, blood flow and local pyrexia via four G-protein-coupled receptors (EP1, EP2, EP3, and EP4). PGE2 inhibits TH1 response and elicits TH2 response that is ineffective in mounting antiviral immune response. PGE2 was found to interact with viral transcriptions and translations in infections such as cytomegalovirus (CMV), respiratory syncytial virus (RSV), herpes simplex virus (HSV), coxsackie B virus (CVB2), enterovirus 71 (EV71) and influenza A virus (IAV) enabling increased replication and viral dissemination. Recent studies have also identified the role of PGE2 in impaired immune response to Covid-19 infection.

Both prostaglandin E2 and prostaglandin D2 promote a switch in the expression of biosynthetic enzymes by exciting the neutrophils that change their phenotype to a pro-resolution phenotype by a process known as lipid-mediator class switching. PGF2α synthesized from PGH2 by PGF synthase, leads to edema due to increased vascular permeability resulting in pain and acute inflammation. Elevated levels of PGF2 have been indicated as a risk factor for rheumatoid arthritis and cardiovascular
PGI2 is one of the most prostanoids involved in cardiovascular homeostasis and is a potent vasodilator and inhibitor of platelet aggregation. Inhibition of PGI2 leads to thrombosis. Thromboxanes

While PGI2 is involved in vasodilation, inhibition of platelet aggregation and leukocyte adhesion, Thromboxane A2 (TXA2) is involved in vasoconstriction and platelet aggregation. Thus, a delicate balance in the levels of PGI2 and TXA2 is very critical in the maintenance of proper vascular biology. Increased levels of TXA2 have been identified in Covid-19 patients.

The tissue-specific formation of these eicosanoids, formed in response to stimuli, physiological or pathological, help in responding adequately to maintain normal cellular homeostasis. However, these responses sometimes go beyond the control and result in the damage of the tissues and resulting in the onset of various inflammatory disorders.

Leukotrienes

Leukotrienes are autocoids formed in myeloid cells by the 5-lipoxygenase pathway. There are five biologically active leukotrienes namely leukotriene A4, B4, C4, D4, and E4. The 5-HPETE formed by the action of 5-LOX is further converted to the epoxide leukotriene A4 by the same enzyme, which is metabolized to either leukotriene B4 (LTB4) by LTA4 hydrolase or LTC4 by LTC4 synthases. LTB4 regulates chemotaxis of neutrophils and leukocyte adhesion to endothelial cells. It binds to its receptor (BLT1) in dendritic cells and increases the production of the inflammatory cytokines IL-1β, IL-6, IL-12 and TNFα. It also induces release of lysosomal enzymes and reactive oxygen species. LTB4 activates peroxisome proliferator activated receptor α (PPARα) to regulate the duration of the inflammatory response. LTC4 in turn is metabolised into LTD4, LTE4, and LTF4 by specific enzymes and are called cysteinyll or peptido leukotrienes due to the presence of the cysteine or peptides in their structure. They regulate the migration of dendritic cells and vasopermeability and are also responsible for the synthesis of several cytokines such as IL-5 and TNF α. In view of
their role in the mediation of allergy and asthma the 5-LOX inhibitors like Zileuton or leukotriene receptor antagonists such as Montelukast are being used in the treatment of the above symptoms.

**Pro-Resolving Lipid Mediators**

Restoration of tissue homeostasis through resolution pathways is initiated by an active class switch in the production of mediators, such as classic prostaglandins and leukotrienes, to the immunoresolvent endogenous lipid mediators such as resolvins, protectins, lipoxins, and maresins collectively known as Specialized Pro-resolving Lipid Mediators (Figure 2).29

Lipoxins are synthesized from endogenous fatty acids such as arachidonic acid, while resolvins, protectins, and maresins are derived from dietary fatty acids such as ω-3 fatty acids.

Lipoxins A4 and B4 were isolated and identified initially as inhibitors of polymorphonuclear neutrophil infiltration and as stimulators of nonphlogistic recruitment of macrophages. Sequential oxygenation of arachidonic acid by 15-lipoxygenase, and 5-lipoxygenase, followed by enzymatic hydrolysis, leads to the production of lipoxin A4 and lipoxin B4 in human mucosal tissues. Also, 5-lipoxygenase and 12-lipoxygenase are involved in the synthesis of lipoxin A4 and lipoxin B4 in platelets and blood vessels.30

Resolvins are biosynthesized from the precursor essential ω-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid (Figure 2). The two major groups of the resolvin family are E-series, derived from eicosapentaenoic acid; and D-series, derived from docosahexaenoic acid. Interaction between resolvins and specific receptors modulates the fate of innate immune cells and counter-regulates active inflammation by prevention of neutrophil penetration, phagocytosis of apoptotic neutrophils to clear the lesion, and enhancing the clearance of inflammation within the lesion to promote tissue regeneration.31,32

Protectins are also biosynthesized via a lipoxygenase-mediated pathway which converts docosahexaenoic acid into a 17S-hydroxyperoxide-containing intermediate and finally converted into 10,17-Dihydroxydocosahexaenoic acid, known as protectin D1 or neuroprotectin in the leukocytes (Figure 2). They are found to reduce tumor necrosis factor-alpha and interferon-gamma secretion, block T-cell migration and promote T-cell apoptosis. Protectins reduce polymorphonuclear neutrophil transmigration

![Figure 2](https://doi.org/10.2147/JIR.S355568)

**Figure 2** The role of eicosanoids in the mediation of inflammation and resolution through class-switching and thus in the maintenance of homeostasis.
through endothelial cells and enhance the clearance of apoptotic polymorphonuclear neutrophils by human macrophages and is found to have crucial roles in managing diseases Alzheimer’s Disease, Parkinson’s disease, and other neuro degenerations.19,33–35

Resolution of Inflammation Through Arachidonic Acid Derived Epoxycosatrienoic Acids (EETs)
EETs are generated from arachidonic acid by cytochrome P450 enzymes. They are found to promote the resolution of inflammation through mitigation of the cytokine storm.36 Increased EET biosynthesis in endotoxemia mouse models was observed to shift arachidonic acid metabolism to suppress the endotoxin-induced surge of proinflammatory cytokines (IL-6 and IL-1β), chemokines (monocyte chemoattractant protein 1 and epithelial-derived neutrophil-activating peptide), adhesion molecules (E-selectin), and NF-κB activation in lungs and aids in the clearing of cellular debris.37,38

The activation of endoplasmic reticulum (ER) stress effectors (phosphorylated eukaryotic initiation factor 2 alpha, CHOP, and glucose-regulated protein) by cigarette smoke extracts was found to be inhibited upon treatment with 14,15- EET in human bronchial epithelial cells.39 EETs are rapidly converted into dihydroxyeicosatrienoic acids by the soluble epoxide hydrolase (sEH) enzyme. Soluble epoxide hydrolase inhibitors raise endogenous EET levels and therefore exhibit potent anti-inflammatory activity, including inhibiting pro-inflammatory 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 remodelling, ischemia-reperfusion injury, lung disease (chronic obstructive pulmonary disease), fibrosis (eg, pulmonary and cardiac fibrosis), graft stenosis, and other medical conditions.40–42

Stabilizing EETs by using sEH inhibitors (sEHIs) has been shown to have promising results in various preclinical models and human trials, including obesity-induced hypertension and obesity- diabetes-induced cardiomyopathy and epithelial dysfunction.43 From studies using murine models of endotoxin-induced acute respiratory distress syndrome, sEHIs were found to decrease pulmonary inflammation and associated edema by suppressing cytokine expression and neutrophil infiltration.44,45 sEHIs reduce NF-κB induction of inflammatory enzymes (ie, COX-2) and the downstream production of proinflammatory mediators, such as PGE2.46

Managing Cytokine Storm in Covid-19 Patients: Eicosanoid Approach
Bronchoalveolar lavages (BALs) from severe COVID-19 patients were characterized by increased fatty acids and inflammatory lipid mediators with a predominance of thromboxane, prostaglandins, leukotrienes notably LTB4, LTE4, and monohydroxylated 15-lipoxygenase metabolites derived from linoleate, arachidonate, eicosapentaenoate, and docosahexaenoate.44 Specialized pro-resolving mediators (SPM), notably lipoxin A4 and the D-series resolvins which are responsible for restraining inflammation were also found to be increased indicating a lipid mediator storm occurring in severe COVID-19 patients, involving pro-inflammatory lipids.3,47

Targeting eicosanoid metabolism to reduce inflammation and associated complications during Covid and other related infections, therefore, is a promising therapeutic approach. Promoting endogenous resolution has shown better outcomes when compared to conventional administration of anti-inflammatory agents in disease models including influenza in achieving tissue homeostasis.48

However, current interventions focus on limiting eicosanoid storms with anti-inflammatory agents such as NSAIDs and COX inhibitors, or steroidal anti-inflammatory drugs that may hamper the resolution of inflammation.49 Inhibition of resolution mediators would result in infection progression and associated damage.50

Randomized clinical trial studies and retrospective analysis of corticosteroid therapies in SARS infections are inconclusive and their application is not advised with the risk of potential harm.51 Corticosteroid therapies were found to decrease circulating dendritic, and T cells,50 suppress cytokine release leading to potential local immunosuppression, and high doses of glucocorticoids were linked to long-term lipid metabolic alterations and elevated risk of avascular necrosis.52,53

However, methylprednisolone and dexamethasone pulses were reported improved clinical prognosis and reduced mortality rates for severe SARS CoV 2 patients at the pulmonary phase receiving supplemental oxygen,54,55 while the
recent meta-analysis studies indicate that the steroidal treatment is associated with increased mortality, and delayed RNA clearance and a higher rate of acute respiratory distress syndrome among COVID 19 patients.

Lowering the levels of PGE$_2$ through the inhibition of human microsomal prostaglandin E synthase-1 (mPGES-1) is hypothesised to improve the host immune response against COVID-19. Additionally, mPGES-1 inhibition has the advantage of not disrupting rest of the prostaglandin levels as it allows basal biosynthesis of PGE$_2$ by the two other constitutive synthases, cPGES and mPGES-2. Selective inhibition of mPGES-1 was found to suppress Influenza A Virus (IAV) infection and the expression of pro-inflammatory genes in lung epithelial cells.

SPMs and EETs are also shown to have promising results in crucial antiviral strategies such as debris clearance and were also found to attenuate pathological thrombosis, promote clot removal and downregulate NF-kB, hence may prevent cytokine storms. Autopsy studies in COVID-19 patients had shown increased angiogenesis by approximately 2.7 times compared with influenza patients. Inhibition of sEH was shown to prevent angiogenic diseases, such as diabetic retinopathy.

SPMs were found to promote antiviral B lymphocytic activity during infections such as influenza. Precursors of SPMs such as 17-hydroxy docosahexaenoic acid (17-HDHA) are also identified as potential vaccine adjuvants as they enhance adaptive immune responses against primary influenza. Hence, supplementing SPMs or their precursors during covid treatment or combining them with covid vaccine as a prophylactic measure could be an effective approach for the treatment of Covid-19 patients. However, the target receptors of most SPMs are yet to be identified and further research is required to characterize the signalling pathways underlying their functions. A thorough understanding of the interplay of pro- and anti-lipid mediators during SARS CoV-2 infection, as presented in Figure 3, is very critical for coming up with strategies for the management of SARS CoV-2 infection.

**Future Perspective**

Although steroidal or non-steroidal anti-inflammatory agents show a slight decrease in the all-cause mortality rate of seriously ill Covid-19 infected patients, the long term post-covid effects have become increasingly unpredictable.
including death. Therefore, strategic inhibition of pro-inflammatory eicosanoids with NSAIDs and simultaneous activation of anti-inflammatory eicosanoids with EETs as supplements might be a promising approach for the treatment of Covid 19.

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