
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

# Covid-19 management with inflammation resolving mediators? Perspectives and potential

## Introduction

COVID-19 is a new disease caused by coronavirus SARS-CoV-2. It was first described in 2019, developed into an epidemic in January 2020 and has spread the global to the present COVID-19 pandemic. It spreads mainly through droplet infection. On surfaces, virus particles remain infectious for hours to days, so that they can reach the mucous membranes of the mouth and nose from keyboards, tables, door handles and handles via the hands (lubricating infection). Infection via the conjunctiva of the eye is also possible [1,2].

The disease histories are non-specific and vary greatly. In addition to symptomless infections, mainly mild to moderate histories were observed, but also severe ones with pneumonia on both sides, including lung failure, multiorgan failure and death. Even as easily described disease histories can lead to long-term damage cannot be ruled out. Thus far, there are no specific therapeutic agents for coronavirus infections [3,4].

In the severe cases the acute respiratory distress syndrome is an example of excessive pulmonary inflammation that can be triggered by a range of insults, including pneumonia and sepsis, and describes the life-threatening hypoxic complication.

Some pathogens, such as the influenza virus and the Gram-negative bacterium Francisella tularensis, do trigger life-threatening “cytokine storms” in the host which can result in significant pathology and ultimately death. For these diseases, it has been proposed that down-regulating inflammatory immune responses may improve outcome [5].

Specialized pro-resolving mediators (SPMs) may play a new role in the management of this lung disease because SPM actively stimulate the resolution of infectious inflammation and are organ protective in animal disease models [6]. SPM are produced by cells of the innate immune, which are formed via the stereoselective enzymatic conversion of essential fatty acids that include arachidonic acid, eicosapentaenoic acid, n-3 docosapentaenoic acid and docosahexaenoic acid (DHA) [6]. SPMs are grouped into four families, lipoxins, resolvins, protectins, and maresins [6,7]. These endogenous mediators share basic physiologic properties in regulating host responses to actively enhancing resolution of inflammatory response mechanisms, such as reducing the hosts’ production of proinflammatory cytokines and chemokines, limit the neutrophils trafficking, stimulating the macrophages phagocytosis of apoptotic cells, bacterial killing, and cellular debris via G-protein coupled receptors (GPCRs) [7,8,9].

Experiments in mice have determined the amount and sort of exudate leukocyte trafficking and mediator metabololipidomics of murine peritoneal Escherichia coli infections with temporal identification of pro-inflammatory (prostaglandins and leukotrienes) and SPMs. For example, specific SPMs are temporally and differentially regulated during infections and that they are anti-phlogistic, enhance containment and lower antibiotic requirements for bacterial clearance [10].

The pro-resolution actions of these mediators are exemplified by their role in pulmonary inflammation. Resolvins, protectins and lipoxins each have a pro-resolution role in mouse models of allergic airway inflammation and infections both bacterial and viral [11].

Recent results [12] indicate that SPMs regulate the AFC in ARDS to protect lung function. Damage to the lung results in activation of the immune system, which not only leads to the release of several proinflammatory proteins and neutrophilic influx into the alveolar space but also leads to the local biosynthesis of pro-resolution lipids mediators, such as lipoxins, resolvins, protectins, and maresins [13]. Along these lines, Cilloniz et al. [14] used a mouse model to investigate influenza A virus virulence, comparing host transcriptional responses to infection with reconstructed 1918 H1N1 virus to avian H5N1 virus (Vietnam/1203). They found that extra-pulmonary dissemination was associated with down-regulation of genes involved in mediating the pro-resolution impact of lipoxin on leucocyte recruitment and counter-regulation of pro-inflammatory cytokine induction and that loss of lipoxin’s pro-resolution actions may be associated with greater influenza A virus virulence. These findings suggest a protective role for SPM in this infection, possibly related to the reduction and counter-regulation of pro-inflammatory cytokines that are up-regulated during viral infections.

If the beneficial actions of these mediators translate from pre-clinical studies into human clinical trials, they represent promising new strategies in the management of infectious disease. The pro-resolution, anti-inflammatory and antimicrobial-enhancing actions of SPM make these appealing candidates for further study in humans and specifically in COVID19 patients. From a therapeutic perspective it is important to note that these pro-resolution mediators have a substantial advantage over steroids for use in the treatment of infectious inflammation, or other systemic inflammatory states, as they are not immunosuppressive agents. Acetylsalicylic acid-triggered lipoxins and resolvins epimers share these pro-resolution actions and act by the same intracellular pathways. [15,16]. This effect is unique to aspirin, and is not shared with non-steroidal anti-inflammatory drugs, which do not trigger the endogenous biosynthesis of these mediators.

Morita et al. [17] reported that the SPM, protectin D1 (aka neuroprotectin D1) markedly attenuated influenza virus replication via RNA export machinery. Production of this SPM was reduced during severe influenza and PD1 inversely correlated with the pathogenicity of H5N1 viruses. Importantly, treatment with the SPM improved both survival and pathology of severe influenza in mice, even under conditions where known antiviral drugs fail to protect from death.

Together these results with SPM in animal disease models are promising and suggest a clinical trial be initiated to test their ability to activate resolution of lung inflammation and reduce tissue damage in COVID 19 patients to stop the cytokine storm; namely, the adjuvant management of the Covid-19 disease or the in the management of the cured humans for the improvement and resolution of chronic lung and heart inflammation in the post-acute phase of this disease. We should also consider means to increase endogenous production of SPM in these

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patients and test their association with outcomes of the disease. This pandemic brings urgent needs and suggest that we test whether activation of endogenous pro-resolving mechanisms in COVID 19 patients can expedite their recovery.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109813.

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Pedro-Antonio Regidor
*Pedro-Antonio Regidor, Centre for Womeńs Diseases, Bodenseestr. 7, 81241 München, Germany*
*E-mail address:* pedro-antonio.regidor@exeltis.com.