Omega-3's to Stay Healthy and Avoid the Cytokine Storm of Covid-19

In the May 2020 issue of the journal, Cancer and Metastasis Reviews, a group from the University of California, Davis, and Harvard Medical School describe a two-pronged approach to averting the hyper inflammation that occurs in the lungs which are fatal to many of the victims that die from the virus. The article titled, *Inflammation Resolution: A Dual-Pronged Approach to Averting Cytokine Storms in COVID-19*, discusses the effect that eicosanoids, a group of 100 powerful hormone-like substances that control virtually all physiological actions in your body. The most important thing about eicosanoids is to keep them in balance. These eicosanoids are totally controlled by the diet.

Medical researchers from the Harvard Medical School, University of California, Davis, Virginia Commonwealth University, and Institute for Systems Biology, Seattle have discovered that chemical molecules called **Resolvins**, could help prevent the cytokine storms caused by the COVID-19 disease. The study was led by assistant professor Dr. Dipak Panigrahy and Dr. Molly Gilligan, both from Harvard Medical School.

Dr. Gilligan notes, "We are now recognizing the importance of controlling this robust inflammatory response in COVID-19 infection in order to reduce associated organ damage and mortality. Finding new ways to dampen the body's inflammatory response to COVID-19 will likely be as important as finding effective antiviral therapies to control COVID-19 infection and reduce life-threatening organ damage. Moreover, these Resolvins have been found to be non-toxic and non- immunosuppressive in ongoing clinical trials for other inflammatory diseases, making them even more promising candidates for rapid clinical translation."3

Severe coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus is frequently characterized by pulmonary inflammation. Severe coronavirus disease (COVID-19) is characterized by pulmonary hyper-inflammation and potentially life-threatening 'cytokinestorms'. Life-threatening 'cytokine storms' involving the release of pro-inflammatory cytokines may contribute to the rapid systemic organ failure observed in select critically ill COVID-19 patients. Controlling the local and systemic inflammatory response in COVID-19 may be as important as anti-viral therapies.

Eicosanoids play a critical role in the induction of inflammation and pro-inflammatory cytokine production. SARS-CoV-2 may trigger a cell death ('debris')-induced 'eicosanoid storm', including prostaglandins and leukotrienes, which in turn initiates a robust inflammatory response. SARS-CoV-2 causes massive cell death and cellular debris that activates inflammasomes, which in turn trigger a macrophage-derived 'eicosanoid storm', a surge of pro-inflammatory bioactive lipid mediators, such as prostaglandins and leukotrienes, that fuels local inflammation.

A paradigm shift is emerging in our understanding of the resolution of inflammation as an active biochemical process with the discovery of Resolvins which "resolve" inflammatory eicosanoids. Resolvins counter pro-inflammatory cytokine production, a process called inflammation resolution. Resolvins and their lipid precursors (omega-3s) exhibit anti-viral activity at nanogram doses in the setting of influenza without being immunosuppressive. Resolvins "also promote anti-viral B cell antibodies and lymphocyte activity, highlighting their potential use in the treatment of corvid-19. Resolvins and other eicosanoid derived molecules attenuate pathological thrombosis and promote clot removal, which is emerging as a key pathology of COVID-19 infection. This resolution of inflammation in COVID-19 may reduce acute respiratory distress syndrome (ARDS) and other life-threatening

complications associated with robust viral-induced inflammation. These anti-inflammatory strategies (stimulating inflammation resolution) may benefit COVID-19 management via debris clearance and inflammatory cytokine suppression.

Resolvins are lipid mediators derived from omega-3 fatty acids and serve as the body's natural "stop" signals to inflammation. These medical researchers found that increasing levels of these resolvins or lipid mediators in the body could be a new therapeutic approach to preventing life-threatening inflammation caused by SARS-CoV-2. What is exciting for us is that these lipid mediators that 'turn off,' or resolve, inflammation are already in clinical trials for other inflammation-driven diseases, such as eye disease, periodontal disease, and pain. The mediators can quickly be applied to turn off inflammation in COVID-19 patients. What makes resolvins ideal is that there are basically derived from omega-3 fatty acids that are already proven safe for human consumption, are inexpensive, easily available and consumed.

The resolution of inflammation is an active biochemical process, and hyper- inflammation may result from a deficit in the active anti-inflammatory biochemical process. Endogenous pro-resolution lipids [omega-3 fatty acids] can terminate the inflammatory response. To sum up this point, these anti-inflammatory compounds decrease the bad eicosanoids and increase the good ones.

Specialized pro-resolving inflammatory mediators including resolvins and other eicosanoid derived molecules mediate endogenous resolution by stimulating macrophage phagocytosis of cellular debris and countering the release of proinflammatory cytokines/chemokines. Loss of these inflammation resolution mechanisms will sustain pathologic inflammation.

Resolvins promote anti-viral B lymphocytic activity in influenza, suggesting they may be a promising therapy for COVID-19. Resolvins also protect against primary influenza infection and promote adaptive immunity.

Resolvins and other eicosanoid derived molecules "down-regulate the transcription regulator NF-κB1, the center of eicosanoid-induced cytokine storms, which promotes the induction of pro-inflammatory cytokines and prostaglandin synthesis via cyclooxygenase(COX). Resolvins and other eicosanoid derived molecules terminate self-sustaining inflammatory processes, such as those induced by COVID-19, by broadly inhibiting proinflammatory cytokine production and promoting a return to tissue homeostasis.

Resolvins and other eicosanoid derived molecules "act at significantly lower doses and are not immunosuppressive." In contrast "conventional anti-inflammatory agents such as NSAIDs and COX-2 inhibitors, while limiting the eicosanoid storm, maybe 'resolution toxic' as they indiscriminately inhibit eicosanoid pathways that produce resolution mediators and thereby prevent active resolution, meaning they also inhibit the good omega-3 eicosanoid pathways. Inhibiting the resolution mediator pathway with conventional anti-inflammatory agents such as NSAIDs and COX-2 inhibitors "may potentially facilitate COVID-19-induced tissue injury and progression of the infection." A critical point, NSAIDs and COX-2 inhibitors may worsen the tissue injury and the progression of infection, which would include risk of death.

As demonstrated in many inflammatory disease models, selectively promoting endogenous inflammation resolution mechanisms clears inflammatory exudates more effectively and promotes a return to tissue homeostasis compared with classic anti-inflammatory agents (drugs). Thus, activating

endogenous resolution pathways, with omega-3 fatty acids, may be a novel therapeutic approach to limit severe organ damage and improve outcomes in COVID-19 patients.

This article adds that adequate levels of omega-3s may reduce the adverseness of the COVID-19 “eicosanoid and cytokine storms,” reducing symptoms, improving clinical outcomes, and possibly reducing deaths. The bottom line is that this is another reason to take omega-3s, as eicosanoid balance is an important factor in optimizing host health.