Acta Scientific Pharmacology

Volume 2 Issue 1 January 2021

Short Communication

Inflammation: Need for the Development of Novel Immunomodulators

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Received: December 02, 2020

Published: December 30, 2020

Inflammation refers to body's process of fighting things that harm it, such as infections, injuries, and toxins, -to heal the injured tissues. When cellular and tissue damage occurs, the injured cells and tissues, release chemical messengers that trigger, a host of responses from the immune system. Common feature of inflammation includes redness, swelling, heat, pain, and loss of function. Any kid of infection can induce inflammation. On the other hand, a variety of food ingredients can also cause inflammation. Inflammation can be either short-lived (acute) or long lasting (chronic). In this invited editorial, I will briefly describe two examples of inflammatory process,-one as an example of acute inflammation (COVID-19), and the other, as an example of chronic inflammation (Crohn's Disease). I will also describe the need for rapid development of disease specific biomarkers, as well as the immediate need, for the development of novel immunomodulators.

SARS-CoV-2, a novel killer virus has caused, an unprecedented syndemic worldwide. According to John Hopkins COVID-19 Tracker, global confirmed cases are over 62,875,460, global covid-related deaths are 1,461,763 (coronavirus.jhu.edu). In the US, COVID-19 positive cases are more than 13,393,166 and related deaths 266,932 (as of December 1st, 2020). Currently, more than 150,000 COVID-19 positive cases are reported every day, and a COVID-19 related death is reported every minute. In a recent article in Science, Jeffrey Brainard reports, on how researchers face hurdles to review, understand, evaluate, and synthesize COVID-19 evidence, at top speed (doi:10.1126/science.abc1761). The team analyzed more than 35,000 papers and reprints, about COVID-19 in a database called Epistemonikos. Despite the availability of such an overwhelming literature on COVID-19, there were no FDA approved drugs available to treat COVID-19 patients. Both National Institutes of Health (NIH) and the US Center for Disease Control (CDC), do not recommend any specific antiviral or immunomodulatory therapy for the treatment of non-hospitalized CIVD-19 patients. World Health Organization (WHO) has published a meta-analysis of studies on the steroid dexamethasone, which indicated that it reduces the severity of symptoms. Another review by the British Medical Journal (BMJ 2020:370:m2980), concluded with only low certainty, that the antiviral drug Remedesivir reduced the duration of hospital stays.

SARS-CoV-2 spreads like most respiratory viruses, through respiratory droplets, within a short range. Once the spike protein is attached to the host cell, the internalization of the virus is promoted by hemagglutinin cleavage, modulated by the TMPRSS2, a cell surface expressed protein by epithelial cells. Once the virions (viral particles), thus released fuse with the membrane, ACE 2 expression seems to get downgraded, resulting in excess production of angiotensin, and enhancing oxidative stress mechanisms. Of the total of 33 eligible studies, including 7673 infected patients, the most prevalent clinical symptom was fever (84.49%), cough (56.39%), fatigue (33.65%), dyspnea (22.34%), sputum production (22.34%), and myalgia (16.26%). Other symptoms reported include, shortness of breath, diarrhea, headache, chest pain, vomiting, sore throat, poor appetite, loss of smell and taste, and chills. The most prevalent comorbidity was hypertension (20%), cardiovascular disease (11.9%), and diabetes (9.8%). Other less know comorbidities include, excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease, and cerbrovascular diseases.

SARS-CoV-2 pandemic has introduced two very important but neglected areas of research, -'Cytokine Storm' and 'Warp Speed' Development of Interventions. The severity of the coronavirus disease seems to be associated with cytokine storm, most likely induced by the interleukin-6 (IL-6) amplifier, which is the hyperactivation machinery, that regulates the nuclear factor kappa B (NF-kB)

pathway, -also stimulated by the simultaneous activation of IL-6 signal transducer, -activator of transcription 3 (STAT3) and NF-kB signaling, in non-immune cells including alveolar epithelial and endothelial cells [2]. Sinha and associates from the University of California, San Francisco, write, -Cytokine storm has no definition [3]. Cytokine storm implies, that the levels or released cytokines are injurious to host cells. They further explain, -that distinguishing appropriate from dysregulated inflammatory response in the pathophysiology of critical illness, however, has been a major challenge. With increased severity a parallel rise in markers of inflammation, - elevated levels of C-reactive protein, proinflammatory cytokines, - IL1B, IFNλ, TNFα, IP10 and MCP1 has been reported. Yang and associates followed a cohort of 53 clinically moderate and severe patients; they conducted a multiplex screen for 48 cytokines and correlated these results with lab results. They found a marked increase of 14 cytokines in patients with COVID-19, -high levels of three cytokines (CXCL10, CCL7, and IL-1) were associated with increased viral loads [4].

The inflammation of tissues, signals neutrophil recruitment, to contain infections by releasing oxidant enzymes, and neutrophil extracellular traps (NETs). When not properly regulated, NETs have the potential to propagate inflammation and microvascular thrombosis [5]. It is well known that primary tumors induce extracellular traps, with targetable metastasis promoting effect. They also are released in pathogen induced lung injury, systemic lupus erythematosus and several other inflammatory diseases. The effect of cytokine storm, specifically with interleukin- 6 and interleukin -8, seem to modulate platelet activation, neutrophil recruitment, and trapping, -and hypercoagulable state of the blood. Neutrophil extracellular traps (NETs) seem, to contribute to microthrombi, through platelet-neutrophil interactions in COVID-19 acute respiratory distress syndrome. Neonatal NET-inhibitory factor (nNIF) has been shown to block NET formation induced by COVID-19 plasma (31). It is well known that excessive inflammation from an overactive immune system response, can initiate the clot formation in severely ill COVID patients. Autoantibodies generated in response to the viral infection, instead of recognizing the foreign invader, seem to go after molecules that form cell membranes. Such attacks may prompt immune cells called neutrophils, to release a web of genetic material that traps the virus particles outside of the cells. Presumably, in the tissues this seems to be the way to control infections, but in the blood stream, it triggers thrombotic episodes [6].

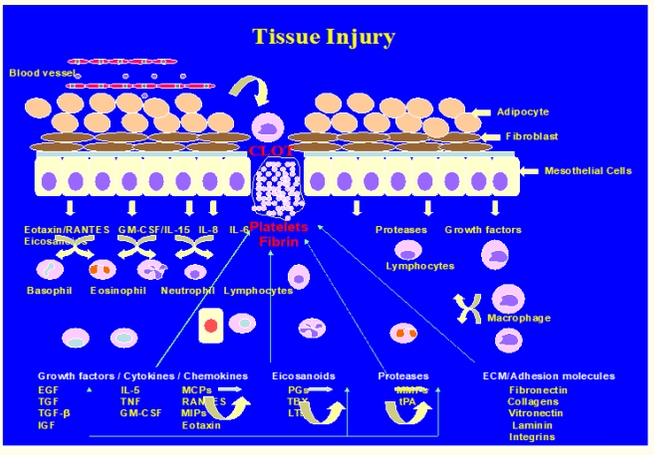

Figure 1

Cellular and Molecular Mechanisms Involved in Wound Healing (Courtesy: Dr. Gundu H.R. Rao), University of Minnesota.

Researchers at the prestigious Indian Institute of Science (IISc), Bengaluru, India, have discovered signaling pathways in wound healing, using fruit lies as models (Times of India 29th November 2020). According to them, all types of cells, sense invading microbes using specific signatures called, -microbe-associated molecular patterns. In addition, our body seems capable of detecting signatures associated with tissue damage. These signals are called, -damage-associate molecular patterns (DAMP). In their seminal study, they found that hydrogen peroxide helps home in the cells, needed on to the site of the damage, and initiate wound healing pathways. It has been well established that activation of toll like receptor (TLR) signaling pathways, can induce important wound mediators such as transcription factors, cytokines, chemokines, and growth factors in nearly all cell types involved in wound healing. Injury threatens organ function, cellular and tissue integrity, and induces a rapid, highly complex wound healing response which initiates inflammatory responses, extracellular matrix production, tissue engineering and restoration of the normal architecture (Figure 1).

Oxidative stress and inflammation are like the first responders, for both physiological and pathological processes. Inflammation is a part of the normal physiological process. Whenever a tissue is injured, blood vessels open around the wound, to allow more blood flow, bringing more oxygen and nutrients to the injured area. Platelets and white blood cells arrive on the scene, to close the

wound, to help clean the debris, and facilitate the healing process. Cellular signals promote mechanisms, that build the needed scaffold with fibrin, collagen, and extracellular matrix components, for cell recruitment and tissue growth. Final stages involve, tissue engineering and maturation of the healing surface. It looks like a simple straight forward mechanism if everything goes smoothly. As mentioned earlier, distinguishing appropriate from dysregulated inflammatory response in the pathophysiology is harder. Every time there is a cut or an injury in the vasculature, the same cellular mechanisms are involved in the tissue engineering and repair process. If the response goes out of control hardening of the vessels may develop, with subclinical atherosclerosis and formation of micro thrombi, resulting in acute vascular events such as heart attack and stroke.

SARS-CoV-2, brought to our attention the severity of cytokine storm, and the role of immunomodulators, in the management of inflammatory disorders. If one searches inflammatory diseases on the Internet, the following definition shows up: Inflammatory diseases include a vast array of disorders and conditions that are characterized by inflammation. Examples include, allergy, asthma, autoimmune diseases, coeliac diseases, glomerulonephritis, hepatitis, inflammatory bowel disease, Crohn's disease, atherosclerosis, perfusion injury and transplant rejection. Having said that, the biomarkers that are routinely used to characterize these diseases are quite different and, in some cases, not necessarily disease specific. Same can be said about the therapeutic options. For instance, a collaborative study between Italian and US researchers found, high levels of (IL)-1B, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-18, tumor necrosis factor (TNF-alpha), granulocyte stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor, fibroblast growth factor, and macrophage inflammatory protein1 [7]. The therapeutic approaches include, use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and the use of single, specific, anti-cytokine agents like, - Anakinra, an IL-1 receptor antagonist infusion, canakinumab, an IL-1B antibody (Novarits), IL-6 antagonists (tocilizumab), Sarilumab, sirukumab, siltuximab or cocktails of such therapeutics. There are clinical trials in progress testing combination of anti-cytokine drugs. Since viral Spike protein seems to induce TNF-a-converting enzyme (TACE)-dependent alteration of ACE-2, -TNF-a blocker, -adalimumab is also undergoing clinical testing. Researcher from Santiago, Chile, have published their first report on the use of Tocilizumab, an interleukin 6. Based on their results they hypothesize, that the use of Tocilizumab in COVID-19 patients, not only inhabits exaggerated inflammatory response, but also restores cellular immunity [8].

The National Institutes of Health has launched an adaptive Phase 3 clinical trial, to evaluate the safety and efficacy of three immune modulator drugs in hospitalized COVID-19 patients. This is a part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) initiative, -the Trump administration's 'Operation Warp Speed (OWS)' goal. The ACTIV public-private partnership, has selected three agents from a pool of over 130 immune modulators initially reviewed. What this shows us is, that even the most advanced country like the US, did not have an FDA approved immunomodulator for managing the 'cytokine storm', that was a common clinical condition in severe COVID-19 patients. On 16th of June 2020, investigators on the CIVID-19 RECOVERY trial revealed, that participants with severe COVID-19 (2014) given 6 mg dexamethasone once daily, had an 8-26% lower mortality, than 4321 participants given standard care [9]. Even though dexamethasone worked, it is not clear whether corticosteroids are the best option for all patients in the second phase of illness. Guidance from the US Centers for Disease Prevention and Control (CDC) recommends, against corticosteroid therapy in coronavirus infections, because steroids are known to 'prolong viral replication' in patients with Middle East Respiratory (MER) syndrome. Despite this observation, when the US President was found positive for COVID-19, the clinicians at Walter Reed Medical Center, treated (VIP Syndrome) him with Regeneron cocktail of antibodies, dexamethasone, Vitamin D, Zinc, Famotidine, and aspirin.

These expedited clinical trials (OWS) may help us find a host of immune modulators, that can be used to treat inflammatory diseases such as asthma, autoimmune diseases, and inflammatory bowel disease. Crohn's disease is a chronic (long-term) disease that causes inflammation in the digestive tract. It belongs to a larger group of illnesses, -called inflammatory bowel disease. One cause of inflammation seems to be, excess production of TNF -alpha. As mentioned earlier, oxidative stress and inflammation, are body's normal reaction to protect itself from pathogens. But when there's excess inflammation that does not go away, it can trigger chronic inflammatory bowel disease. Like COVID-19, there is no cure for Crohn's disease. Identification of markers of biomes, as well as disease specific biomarkers, will enable us to develop, appropriate interventions and better manage these chronic diseases. Furthermore, such biomarkers, will help us to identify and follow the progression or regression of these inflammatory diseases. For instance, understanding the interactions between circulating mRNAs and clinical phenotypes, can enhance our knowledge of such complex diseases and help us develop better interventions [10]. Advances in genom-

ic, and metabolomic array-based technologies, will yield new and useful diagnostic capabilities, to follow the progression or regression of the inflammation [11]. Despite widely available circulating biomarkers such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), sensitivity and specificity of these assays as markers of IBD, remains low since correlation with disease activity is poor. The only broadly recognized biomarker for IBD is fecal calprotectin (FC), and fecal lactoferrin (FL). Fecal miRNAs seem to show strong correlation to disease activity. Especially miR-16, miR-21, miR-155 and miR223 show differential miRNA expression level in IBD patients [12].

Coronavirus disease as well as Crohn's disease, -currently have no cure. In the absence of a cure, much of what is done, is treating, and managing the clinical symptoms, related to these inflammatory diseases. Biomarkers can sometimes help following the efficacy of a drug better, than conventional clinical symptoms presented by the diseases. In view of these observations, it is essential to determine disease specific biomarkers, that can be used to follow, the progression or regression of the disease, as well therapeutic efficacy of treatments. The challenge in this area is, that biomarkers should allow the early detection of the progression of a disease, and it should be specific, so that these markers could provide a more robust drug safety and efficacy measurements. A recent study by the researchers at the Albert Einstein College of Medicine and Mount Sinai Hospital, report the results of a study, that was done to assess the prognostic capability of the inflammatory markers in predicting the clinical outcomes. Based on the results of their studies, they conclude, "Laboratory values drawn within 48 hours of Emergency Department presentation, though often correlated with clinical outcomes, are not individually highly predictive of which COVID-19 patients in a predominantly older minority population, will die or require endotracheal intubation, renal replacement therapy, or ICU admission. This was a retrospective study with some serious limitations. Earlier studies for instance, have shown that C-Reactive Protein level was associated with severity of the disease [13] and elevated D-dimer with increased mortality [14]. Neutrophil-Lymphocyte Ratio (NLR) is yet another convenient marker for monitoring the severity of the inflammation [15].

COVID-19 has killed more than 1.5 million individuals globally and over 270,000 in the US alone. Majority of deaths (74%) occurring in people over the age of 65. When it comes to the body's ability to fight infection, the immune system should perform four main tasks: 1) recognize the pathogen or the injury. 2) alert the immunomodulatory system or wound healing mechanisms, 3) destroy the invader pathogen or initiate the healing process and 4) clear the invader or restore the regulatory mechanisms [16]. According to experts these mechanisms are known to be dysfunctional in older people. The authors of a seminal article on this topic hypothesize, that during aging, immune system changes in two major ways; 1) a gradual decline in immune function called immunosenescence, which hampers pathogen recognition, alert, and clearance, 2) a chronic decrease in systemic inflammation called inflammaging, which arises from an overactive alert immune system. These observations reveal the complexities of immune modulation. Having said that, it also provides a great opportunity and a challenge for researchers and entrepreneurs. Just the two examples, that we have discussed to illustrate the similarities and differences in the inflammatory processes, and the resulting immune response in acute and chronic phases, clearly demonstrate the need for the development of disease specific, or mechanism specific markers, and a variety of immunomodulators, -including both inhibitors as well as stimulators of this mechanism.

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