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EDITORIAL

Mast cell virus infection and inflammatory cytokines

P. Conti[1], G. Ronconi[2], A. Caraffa[3], C. Gallenga[4], I. Frydas[5], S. Kritas[6], V. Calvisi[7] and M. Trimarchi[8]

[1]Postgraduate Medical School, University of Chieti, Chieti, Italy; [2]University Polyclinic Foundation A. Gemelli IRCCS, Rome; [3]School of Pharmacy, University of Camerino, Camerino, Italy; [4]Department of Biomedical Sciences and Specialist Surgery, Section of Ophthalmology, University of Ferrara, Ferrara, Italy; [5]Aristotelian University, Thessaloniki, Greece; [6]Department of Microbiology and Infectious Diseases, School of Veterinary Medicine, Aristotle University of Thessaloniki, Macedonia, Greece; [7]Department of Orthopedics, University of L'Aquila, L'Aquila, Italy; [8]Division of Head and Neck, Otorhinolaryngology Unit, Vita Salute San Raffaele University, Milano, Italy

Mast cells (MCs) are hematopoietic cells developed from bone marrow progenitors in response to the ligand stem cell factor, a trans-membrane tyrosine kinase kit receptor. MCs are located virtually in all vascularized tissues and in proximity to neurons and play a decisive role in both innate and adaptive immune responses. Their activation is involved in oxidative stress correlated with infection and inflammation. Pro-inflammatory cytokines are secreted by MCs after physiologic and psychological stress due to virus infection, including SARS-CoV-2. MCs, along with macrophages and pulmonary alveolar epithelial cells, are the main targets attacked by the coronavirus. COVID-19 induced by SARS-CoV-2 causes inflammatory stress which activates MCs to secrete corticotrophin-releasing hormone (CRH), SP, IL-6, TNF, and IL-1. Toll-like receptor (TLR) virus activation in MCs leads to pro-inflammatory cytokine generation without degranulation, an effect that can be inhibited by IL-10, IL-4, IL-1Ra and IL-37. TLR has the ability to recognize extracellular PAMPs by causing the transcription of NLRP, pro-IL-1, and other pro-inflammatory cytokines. The multi-protein complex, comprising pro-caspase-1, activates caspase-1 which in turn activates pro-IL-1 that is transformed into highly inflammatory mature IL-1. In COVID-19, viral RNA is specifically recognized by TLR, followed by recruiting the signal transfer proteins MyD88, IRAK, IKK and TRAF6 which can activate the NF-κB, resulting in transcription of the pro-inflammatory cytokines IL-1 and TNF, responsible for the "cytokine storm" phenomenon. Meanwhile, a new variant of the coronavirus-19 called C.1.2. has been discovered in the United States in the past few days, the effects of which are unknown, and it is therefore of great concern. Researchers are now testing it on immune cells to see if they react and are comparing it to a delta variant. Thus, from the existing data in biomedical literature, we can conclude that the suppression of pro-inflammatory cytokines in viral infections (including COVID-19) mediated by MCs represents a promising therapy not only in this field of medicine, but also in autoimmune, allergic, and cardiovascular disorders, as well as tumor inflammation where MCs play a key role.

Key words: mast cell; virus; cytokine; inflammation; allergy; COVID-19; SARS-CoV-2; coronavirus; antinflammatory

Corresponding Author:
Dr. Pio Conti,
Professor of Immunology, Post Graduate School of Medicine,
University of Chieti-Pescara, University Zone,
Viale Unità d'Italia, 73 66013 Chieti, Italy,
Tel./Fax +39 0871 574136
e-mail: piocontieditor@biolifesas.org

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MAST CELLS, VIRUS AND INFLAMMATORY CYTOKINES

Mast cells (MCs) are hematopoietic cells that reside in virtually all vascularized tissues and play an important role in both innate and adaptive immune responses (1). Furthermore, they intervene in infections caused by microorganisms, aggravating the inflammatory process (2). MCs, terminally differentiated, are ubiquitous and try to oppose viral infection by collaborating with other immune cells (3). They are major effector cells in allergic reaction but also, by expressing Toll-like Receptors (TLRs), they can be activated by bacterial and viral antigens (4). In innate immunity, MCs support TH1 responses by mediating resistance to pathogens (including SARS-CoV-2), while anti-inflammatory cytokines, such as IL-10, contribute to TH2 responses by increasing immune activity and contributing to virus and parasite elimination. In chronic fatigue syndrome mediated by SARS-CoV-2 MC activation, cytokine levels are also elevated (2). The increase in pro-inflammatory cytokines in COVID-19 causes the "cytokine storm" with complement activation, excessive recruitment of neutrophils due to the increase of CXC1,2,3,5,8 chemokines, injuries of the vascular system and pulmonary thrombosis. These effects may result in a high degree of morbidity and potential lethal consequences. IL-1 receptor antagonist (IL-1Ra) a member of the IL-*1* family that binds to IL-*1 receptors* but does not act intracellularly, performs an immunoregulatory function and intervenes in TH2 responses (5). The protective role of T cells from the pathogenesis of SARS-CoV-2 infection has not yet been established. However, memory SARS-CoV2-specific T-cell response occurs as result of virus infection. $CD8^+$ T cells, after infection, are very important in clearing the virus from lung, thus preventing or decreasing lung complications. $CD4^+$ T cells polarize to Th1 profile with IFNγ, TNF, and IL-1 which can be detected in infected SARS-CoV-2.

Furthermore, coronavirus-19 with its RNA is specifically recognized by TLR; this reaction leads to recruit signal transfer proteins MyD88, IRAK, IKK and TRAF6 which can activate the NF- κB that is followed by the transcription of the pro-inflammatory cytokines such as IL-1 and TNF.

MCs with their TLRs respond to a wide variety of cytokines, microbes and microbial products, producing pro-inflammatory cytokines without degranulation. In viral infections, cytokines secreted by immune cells can trigger the activation of MCs which can also be activated by IL-1, IL-6, IL-33 and other cytokines, proving their effectiveness in inflammation, while they can be inhibited by IL-10, IL-4, IL-1Ra and IL-37 (6). The production of cytokines by MCs is an inflammatory reaction tending to stem and inhibit viral replication, but in some cases this reaction can become very harmful and sometimes lethal.

We have previously reported that the MC reaction against SARS-CoV-2 viral infection is mediated by cytokines and other extracellular stimuli, including stress (7). Coronavirus-19 seems to increase the risk of psychological factors which have been shown to influence COVID-19 severity. MCs activated by stress release corticotrophin-releasing hormone (CRH), an important central nervous system mediator of the stress response that is also elevated in the brain and cerebrospinal fluid (8). CRH can stimulate the release of vascular-endothelial growth factors from MCs and can increase vascular permeability. In addition, CRH provokes blood brain barrier damage through MC activation. Infection with pathogenic viruses can cause stress and fatigue syndrome, where levels of substance P (SP) are increased and induce MC activation with production of CRH implicated in brain inflammation and pathophysiology of pain.

In the past 20 years, considerable progress has been made in the field of IL-1 stimulation and inhibition, influencing therapeutic interventions. Cytokine IL-1 released by macrophages, MCs and other immune and non-immune cells, mediates almost all physiological and pathological processes including microorganism infections. Moreover, IL-1 stimulates itself in an autocrine manner as well as other cytokines that intervene on the efficacy of the vaccine and on the allergic response by influencing inflammatory and immunological processes (9). Cytokines, including IL-1, with the NALP3 (Nod-like receptor pyrin3) gene mutation, are known to impact COVID-19 pathogenesis, lymphocyte

trafficking and inflammation. The TLR, which is similar to that of IL-1, recognizes microbial products, mediating the host response to SARS-CoV-2 infection. Mature IL-1 beta derives from its immature precursor IL-1 which is activated by the active caspase-1 generated by the pro-caspase-1, which in turn is activated by the inflammasome, a complex of interacting intracellular proteins (5). Viral genomes encode molecules homologous to cytokines to prevent the host's immune response against viral infection. Blocking these genes inhibits viral infection with improved immune response. There are some viral genes that can code for anti-inflammatory cytokines, such as IL-10 which is a regulatory cytokine produced by almost all immune cells and is expressed to suppress the high IFN-γ that is generated in the infectious process as an immune response. Corticosteroids also reduce IL-1 transcription and translation by inhibiting allergic inflammation, decreasing the ability of blood immune cells to synthesize this potent pro-inflammatory cytokine, but can block the synthesis of antibodies useful against the virus. Thus, by neutralizing pro-inflammatory cytokines, such as IL-1, significant therapeutic progress can be achieved.

During harmful inflammatory SARS-CoV-2 lung infection, treatment with IL-1 inhibitors such as IL-37 could cause suppression of NLRP3 with a reduction in the number of inflammatory granulocytes that in COVID-19 prevail over other immune cells (3).

SARS-CoV-2 INDUCES INFLAMMATION IN COVID-19

Coronaviruses (CoVs) are a large family of zoonotic RNA viruses commonly circulating globally among humans. As has already been seen, CoVs can mutate and recombine rapidly to form new CoVs that can spread between individuals. SARS-CoV-2 (severe acute respiratory syndrome coronavirus-19) pandemic, spread around the world, has killed thousands of people every day, causing a severe outbreak of disease crisis that has never been seen before (2). Now, we hope that this unpleasant event is teaching us to better defend ourselves against another possible pandemic.

Most viruses, including those that cause flu and COVID-19, do not travel only in the air but can be contained at higher concentrations in the so-called respiratory droplets that the people emit when sneezing or coughing. Masks can block most droplets, especially the larger ones. If both the person sneezing and the people nearby are wearing masks the likelihood of transmission is much lower. Without the shadow of a doubt, vaccinations have supported the general well-being of the world population and have been recognized as an important means in public health.

The spreading of the SARS-CoV-2 pandemic has accelerated the rapid production of virus-neutralizing vaccines in the scientific world, a process that in the past took several years. The most widely used vaccines today are those with mRNA with lipid nanoparticle technology (mRNA1273 Moderna and mRNA BNT162b2 Pfizer-BionTech) and the viral vector one (AstraZeneca). mRNA vaccines give the body's cells instructions to mount a strong defense against a virus. To create the new mRNA in the laboratory, a large library for different pathogens was built. This system could also be used to create an HIV vaccine.

mRNA vaccine consists in encapsulating this molecule in nanoparticles and injecting them into the body by stimulating the cells to produce antigenic proteins which activate the production of antibodies. The high concentration of certain natural antibodies in the blood can mean that patients have encountered the virus and could potentially face COVID-19.

Anti-SARS-CoV-2 antibodies bind to the receptor-binding domain (RBD) and neutralize the virus. After infection the immune system takes time to build a sufficient number of neutralizing antibodies and by that time the coronavirus has done considerable damage. The mRNA vaccine represents the first generation of lifesaver vaccines that work by introducing spike protein information into the human body in order to instruct the immune system to recognize the spike protein receptor RBD. But this receptor often gets hidden by other parts of the spike protein, preventing antibodies from binding to it. The spike protein of the vaccine, not being the whole virus, does not stimulate the immune system

as it does with SARS-CoV-2; therefore to have an effective reaction, a large dose of the vaccine must be administered. When the dose of the vaccine is too high, strong side effects can be created with harmful consequences for the host. To avoid this, a vaccine with the RBD receptor alone should be created, even if it would be too small to induce an immune response and also technically difficult to implement.

Recent data published (10) report that the coronavirus-19 vaccine produces reduced but acceptable short-term immunogenicity in patients with rheumatic diseases, demonstrating a good safety profile. The vaccine, in these patients who presented inflammatory rheumatoid arthritis and axial spondyloarthritis, although immunogenic, was however less effective. Coronavirus vaccination does not cause significant adverse events even if it results in reduced but sufficient short-term immunogenicity.

SARS-CoV-2 tends to multiply and therefore genetically mutate, creating variants, as recently happened with the delta variant, which is more contagious, severe and weakens the vaccine response. Therefore, to combat the formation of variants, the majority of individuals must be vaccinated in order to achieve herd immunity. The effectiveness of the variant vaccines is unclear, especially on the new lambda variant which has currently only infected about two thousand individuals in the US.

Meanwhile, the research continues and world-renowned scientists are working hard on a simple, yet scientifically complicated, oral drug that can fight COVID-19 while avoiding hospitalization.

In this article we can conclude that, by targeting pro-inflammatory cytokines produced by MCs such as IL-1, IL-6, IL-33 and TNF after viral activation, it is possible to hope that their inhibition will give a better and novel therapeutic effect, including life expectancy. The concepts reported here are in agreement with the existing biomedical literature which tells us that in pathological states, such as infectious ones caused by pathogenic viruses, blocking pro-inflammatory cytokines generated by various immune cells, including MCs, can prevent, improve and successfully treat inflammatory diseases.

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