EDITORIAL

MAST CELLS CONTRIBUTE TO CORONAVIRUS-INDUCED INFLAMMATION: NEW ANTI-INFLAMMATORY STRATEGY

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Coronavirus, which can cause respiratory syndrome, to date has affected over seventeen thousand individuals, especially in China. Coronavirus is interspecies and can also be transmitted from man to man, with an incubation ranging from 1 to 14 days. Human coronavirus infections can induce not only mild to severe respiratory diseases, but also inflammation, high fever, cough, acute respiratory tract infection and dysfunction of internal organs that may lead to death. Coronavirus infection (regardless of the various types of corona virus) is primarily attacked by immune cells including mast cells (MCs), which are located in the submucosa of the respiratory tract and in the nasal cavity and represent a barrier of protection against microorganisms. The virus activates MCs which release early inflammatory chemical compounds including histamine and protease; while late activation provokes the generation of pro-inflammatory IL-1 family members including IL-1 and IL-33. Here, we propose for the first time that inflammation by coronavirus may be inhibited by anti-inflammatory cytokines belonging to the IL-1 family members.

Viral infections are certainly increasing globally; they can cause an epidemic spread, but also a pandemic one in different countries, as was the case with the avian influenza virus H5N1 (mortality 35%), as well as severe acute respiratory syndrome (SARS) (mortality 10%) (1). Middle East respiratory syndrome caused by coronavirus first appeared in 2012, and since then over seventeen thousand patients have been infected worldwide (especially in China) of whom about 900 have died (a number destined to increase), according to the World Health Organization (WHO) (2). There are several types of coronavirus, they can be transformed and become interspecies and have an incubation ranging approximately from 1 to 14 days (1). They are of unknown origin, although may originate from various animals such as snakes, bats, pigs, or dromedary camels, which are the main host, and in these animals can cause acute diarrhea, gastroenteritis, villous atrophy, poor absorption and death (2). Human-to-human virus transmission also occurs in healthcare facilities and communities. Coronaviruses often have highly pathogenic activity in animals, but today it has been seen that, with their particular pathogenic proteins, they can cause

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more or less serious respiratory diseases both in adults and in children. Moreover, it has now come to the fore that coronavirus is one of the major respiratory pathogens causing serious inflammatory outbreaks of acute pneumonia in individuals (3). Therefore, human coronavirus infections can induce not only mild to severe diseases, but also systemic inflammation, high fever, cough, acute respiratory tract infection and dysfunction of internal organs that can lead to death. Coronavirus is classified as a RiboNucleic Acid (RNA) virus, with a genome that can often escape the innate immune system, especially if it is malfunctioning (4). Regardless of the various types of coronavirus, the entry of the virus into the organism activates innate immunity, which intervenes in the first instance to engulf the invader. The severity of the disease lies in the ability of innate immune cells to stem viral infection (5). The stronger the innate immune system, the less the ability of the virus to replicate itself, suppress the immunity and, therefore, to induce the pathological state. In the case of innate immune suppression by the virus, adaptive immunity is also inhibited. The coronavirus is capable of producing viral enzymes and proteases that damage the immunity and inhibit the signaling pathways of type I interferon (IFN), along with the nuclear factor-κB, facilitating innate immune evasion (6).

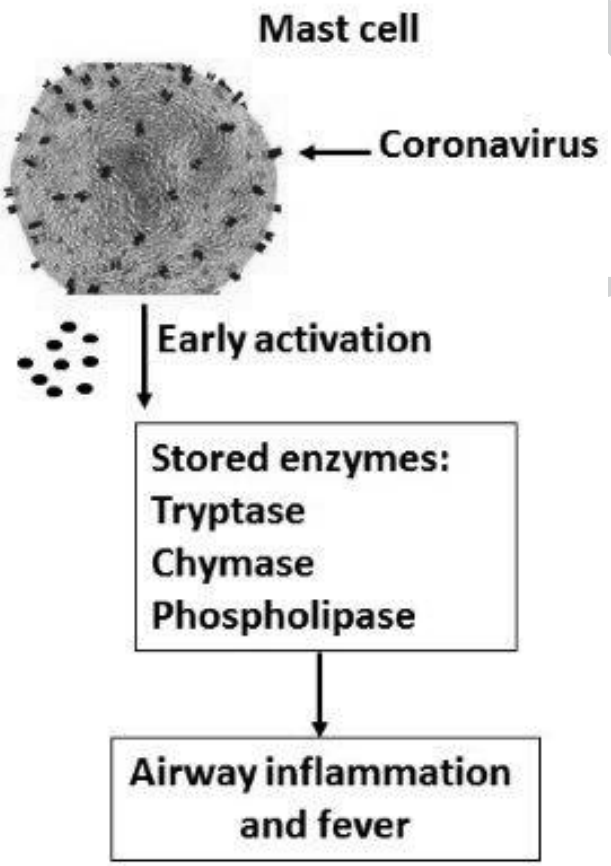

Fig. 1. *Coronavirus activating mast cell which early releases proteases and other compounds, and late release IL-1 family members, which both contribute to airway inflammation and fever.*

In light of all the above, new anti-coronavirus strategies are needed to fight the disease, in order to avoid infection. Laboratory experiments on rodents show that inoculating various different types of coronavirus, all induce an innate and adaptive immune response, but also an acute encephalomyelitis with invasion of the virus throughout the brain (7). Therefore, the virus mainly settles in the white matter, causing chronic neuroinflammation and demyelination. The disease causes the activation of T and B cells which are attracted to the place of infection by specific chemokines (8). Coronavirus infection is primarily attacked by immune cells, but the virus has developed viral proteins over time that counteract the innate immune system (9). Some viral proteins antagonize interferon (IFN) and stimulate inflammatory proteins. including IL-1 family member cytokines (10). The abnormal production of cytokines aggravates the inflammatory state and pathogenesis of the disease, which also takes place in SARS. There are several types of coronaviruses with variable morphogenesis of the envelope and production of different proteins (11). The protein E of the envelope is very small but capable of influencing the replication of the viral genome, accentuating the pathogenicity, and may cause strong inflammation and even death of the patient. In addition, protein E activates the inflammasome in the tissues and causes increased edema, with lethal results for humans. Immune Treg cells expressing IL-2 receptor, CD4 receptor and FoxP3 transcription factor, are cells that regulate immune status tolerance in humans and are generated in the thymus (12). Corona virus-

induced type 1 Treg cells produce anti-inflammatory IL-10, protecting the body from the most aggressive forms of infection. The development of therapeutic anti-viral agents based on strengthening the immune system has been one of the main objectives of modern medicine. The immune response to the virus can be enhanced with the administration of antigens, adjuvants and vaccines. The vaccines that normally protect us from bacterial and viral infections, in the case of coronavirus, are not currently available and the experimental ones have not proved to be effective, although some vaccines have exerted a slight protective effect (13). We believe that coronavirus infection, as well as other pathogenic microorganism infections, can be combatted by preventing contagion and boosting the immune system.

Mast cells

Mast cells (MCs) are immune cells derived from hematopoietic precursor cells (bone marrow $CD34^+$), which mature and reside in virtually all vascularized tissue (14). MCs are located perivascularly in proximity to neurons, and their differentiation and proliferation are regulated by the stem cell factor (SCF), which binds the surface kit-receptor. After activation, MCs produce inflammatory mediators, including proteases and pro-inflammatory cytokines, participating in host response, for example, in skin diseases, and asthma (14). MCs are involved in the innate and adaptive immune systems, playing a role in autoimmunity, infections, tissue damage, and inflammatory signals (15). MCs express TLR which can be quickly recognized by pathogens, including viruses that activate them in the airways and respiratory tract, causing serious damage. When properly activated, MCs generate biologically active substances including chemokines and cytokines without degranulation. MCs are responsible for

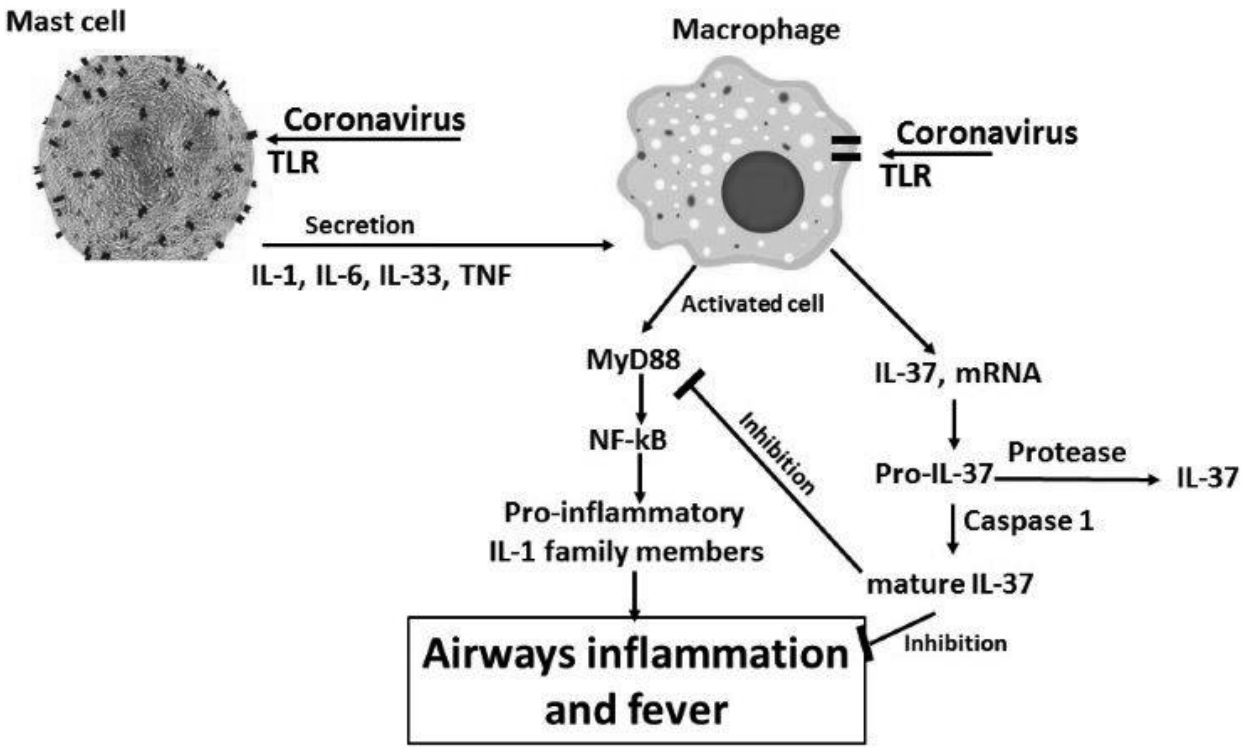

Fig. 2. *Coronavirus binding Toll-like receptor, activating mast cell which secretes IL-1 family members (IL-1, IL-33), IL-6 and TNF. These cytokines along with coronavirus activate macrophages. This stimulation provokes dual effects: one being airway inflammation and fever, and the other production of IL-37 which inhibits airway inflammation and fever.*

allergic reactions, but also participate in inflammation and defend the body against bacterial helminthic and viral infections. MCs can be classically activated by IgE and specific antigen, but also by bacteria and viruses. IgE stimulates MCs via FcεRI high-affinity receptor (1 x $10^{10}M^{-1}$), which bind to the FcεRI and cause receptor aggregation and a series of biochemical events (14). Activated MCs immediately release chemical mediators and/or late production of pro-inflammatory proteins such as cytokines and chemokines (16). Therefore, virus-activated MCs may provoke the release, after seconds, of stored chemical mediators such as histamine, tryptases and chymase. In addition, after hours of incubation, activated MCs secrete synthesized inflammatory cytokines including IL-6, IL-1, IL-31, IL-33 and TNF, and chemokines CC5, CCL2, MCP-1 and CXCL8 which attract white blood cells to the inflammatory sites (16). All these compounds have a major role in inflammation. MCs produce, store and synthesize highly inflammatory TNF, both intra-cellular and extra-cellular. MC innate immune cells are real sentinels of the human body, ready to immediately attack the external invaders which can be harmful to cells, tissues and organs. MCs release IL-33, a member of the IL-1 family of cytokines, which is considered a cytokine called "alarmin". MCs are peripherally located near dendritic cells, in communication with sensory nerves that cross-talk with brain cells, including microglia. MCs protect the body from infections caused by bacterium and viruses (17). These cells, communicating with the external environment, neutralize various pathogens, but in doing so they also produce pro-inflammatory compounds which can be harmful for the body. Stressful and chronic conditions predispose humans to pathogenic infections including those caused by coronavirus. In fact, neurotransmitters, including substance P, that are generated in stress, can activate immune cells such as MCs to produce pro-inflammatory cytokines and chemical mediators of inflammation (18).

Experiments with coronavirus in mice have shown that this pathogenic RNA microorganism can activate the cells of both innate and adaptive immune systems, including MCs. These cells are located in the submucosa of the respiratory tract and in the nasal cavity and represent the protective cells that are at the forefront in fighting viral and bacterial agents (19). They are involved in many biological processes where they induce the secretion of a broad spectrum of cytokines and chemokines. In addition, viruses activating MCs cause the release of some specific chemokines, such as the ligand 5 (CCL5), which attracts the CD8 T immune cells that defend the lung tissue and fight viral infection (20). Epithelial cells represent a physical barrier to the entry of microorganisms including viruses. The cross-talk between viruses and epithelial cells causes the production of immune mediators in order to defend the body. Viruses develop particular mechanisms to invade the body and immune cells including MCs. The host response to RNA virus invasion activates TLR3 on MCs with an anti-viral IFN production (positive effect) (21); but often the virus only causes sensitization of MCs with the synthesis of IgE that bind to the FcεRI receptor and trigger a violent inflammatory reaction (negative effect). Therefore, the function of MCs towards viral infections is not yet clear. However, RNA viruses stimulate MCs to produce IFN gamma e CXCL8 chemokines, resulting in the recruitment of NK cells that also produce type I interferons (IFNs) which are anti-viral cytokines. In addition, type I IFNs enhance the cytotoxic activity of NK cells against virus-infected cells (22). So, in this case, MCs are anti-viral immune cells through the above mechanism. On the other hand, viruses stimulate mucosa MCs to release pro-inflammatory cytokines such as TNF, IL-1, IL-6 and proteases, which aggravate the inflammatory state.

Virus-activated MCs produce histamine, prostaglandin D2 (PGD_2), and leukotriene C4 (LTC_4) which induces acute bronchoconstriction and lung inflammation. Therefore, we can conclude that viral infections can activate MCs which respond with dual effects, a positive one helping the immune system to fight infection, and a negative one causing the release of chemical mediators of inflammation and the secretion of pro-inflammatory cytokines such as IL-1, IL-33, IL-18, and TNF, aggravating the pathological state of the patient.

IL-37 is a member of the IL-1 family of cytokines,

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which is activated by caspase-1 and suppresses transcription of pro-inflammatory genes and immune responses. Since IL-37 is an inhibitor of IL-1, a potent pro-inflammatory cytokine (23), we believe that this anti-inflammatory cytokine may suppress fever and inflammation provoked by coronavirus, so as to reduce the number of deaths.

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