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EDITORIAL

Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19

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SARS-CoV-2 virus is an infectious agent commonly found in certain mammalian animal species and today also in humans. SARS-CoV-2, can cause a pandemic infection with severe acute lung injury respiratory distress syndrome in patients with COVID-19, that can lead to patient death across all ages. The pathology associated with pandemic infection is linked to an over-response of immune cells, including virus-activated macrophages and mast cells (MCs). The local inflammatory response in the lung that occurs after exposure to SARS-CoV-2 is due to a complex network of activated inflammatory innate immune cells and structural lung cells such as bronchial epithelial cells, endothelial cells and fibroblasts. Bronchial epithelial cells and fibroblasts activated by SARS-CoV-2 can result in the up-regulation of pro-inflammatory cytokines and induction of MC differentiation. In addition, endothelial cells which control leukocyte traffic through the expression of adhesion molecules are also able to amplify leukocyte activation by generating interleukin (IL)-1, IL-6 and CXC chemokines. In this pathologic environment, the activation of mast cells (MCs) causes the release of histamine, proteases, cytokines, chemokines and arachidonic acid compounds, such as prostaglandin D2 and leukotrienes, all of which are involved in the inflammatory network. Histamine is stored endogenously within the secretory granules of MCs and is released into the vessels after cell stimulation. Histamine is involved in the expression of chemokine IL-8 and cytokine IL-6, an effect that can be inhibited by histamine receptor antagonists. IL-1 is a pleiotropic cytokine that is mainly active in inflammation and immunity. Alveolar macrophages activated by SARS-CoV-2 through the TLR produce IL-1 which stimulates MCs to produce IL-6. IL-1 in combination with IL-6 leads to excessive inflammation which can be lethal. In an interesting study published several years ago (by E. Vannier et al., 1993), it was found that histamine as well as IL-1 are implicated in the pathogenesis of pulmonary inflammatory reaction, after micorganism immune cell activation. IL-1 in combination with histamine can cause a strong increase of IL-1 levels and,

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consequently, a higher degree of inflammation. However, it has been reported that histamine alone has no effect on IL-1 production. Furthermore, histamine enhances IL-1-induced IL-6 gene expression and protein synthesis via H2 receptors in peripheral monocytes. Therefore, since MCs are large producers of histamine in inflammatory reactions, this vasoactive amine, by increasing the production of IL-1, can amplify the inflammatory process in the lung infected with SARS-CoV-2. Here, we have proposed for the first time an emerging role for histamine released by MCs which in combination with IL-1 can cause an increase in lung inflammation induced by the viral infection SARS-CoV-2.

Histamine [2-(4-imidazolyl)-ethylamine] is a molecule that has an imidazole ring linked to an ethylamine chain. Histamine is an organic neurotransmitter involved in the immune system and other physiological functions (1). It mediates inflammatory responses and plays a key role in allergic phenomena. Histamine is produced by various cells including mast cells (MCs) and is capable of increasing vascular permeability allowing the passage of microorganisms, fueling infection and inflammation (2). Histamine is stored in MCs which, after activation through the FcεRI receptor, releases (in seconds) the content of the granules into the tissues. Bacteria can also produce histamine through histidine decarboxylase (HDC) an enzyme responsible for catalyzing the decarboxylation of histidine to form histamine and participate in various inflammatory diseases (3-4).

MCs are immune cells that play a key role in allergies and anaphylaxis and possess a high number of affinity receptors (FcεRIs) for IgE antibodies (5). The isolated progenitors of human MCs are c-kit + CD34 + CD13 + FcεRI– capable of differentiating into mature cells (6). MCs are the main source of cytokines in the lungs and they are found in large numbers in the inflamed lung of patients with asthma and respiratory infections due to microorganisms, including the influenza virus (7). The recruitment process of MCs is mediated by innate immunity. In immune responses, MCs bind specifically stimulated IgE and through cross-linking they bind to the FcεRI receptor, inducing receptor aggregation and thus cellular activation, leading to secretion of biologically active mediators that play a key role in allergies and inflammation (2). Histamine can also be produced and released by other cells such as neutrophilic and basophilic granulocytes (8). This vasoactive amine is one of these mediators which is an important mediator of anaphylaxis difficult to detect in the blood as it has a very low half-life. In MC-mediated experimental models, MC-deficient mice do not produce histamine, proving that these cells are important sources of this biological mediator (9). The activation of H2 receptors and the synthesis of histamine causes an increase in cAMP which improves the production of caspase-1 and therefore of interleukin (IL)-1 in macrophages and also the synthesis of IL-6 induced by IL-1 (10). On the other hand, the activation of histamine

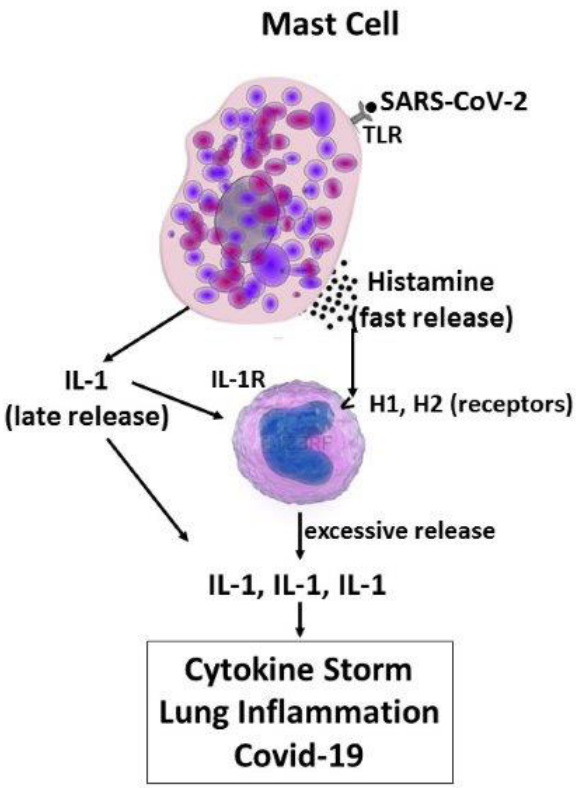

Fig. 1. *Activation of mast cell by SARS-CoV-2 causes an early release of histamine and late release of IL-1 which activate macrophage. Histamine potentiates the production of IL-1 which causes cytokine storm and lung inflammation in COVID-19.*

H2 receptors does not induce IL-1 synthesis. SARS-CoV-2 is a respiratory pathogen that causes COVID-19, a global pandemic that occurs in young and old with consequences that can be fatal (10). In COVID-19 there is a violent inflammatory response that can affect many vital organs, including the lung where severe tissue damage occurs. COVID-19 has a high morbidity and mortality due mainly to severe lung inflammation. (11). The pathological status of coronavrus-19 infection may be aggravated by subsequent bacterial infections (12). IL-1 is crucial in this inflammatory process and requires cleavage to be activated. Caspase-1 is an inflammasome protease capable of processing IL-1 (13). It is well known that in the lung infected by SARS-CoV-2, there is lymphopenia and a dominant neutrophilia which lead to the production of serine proteases such as cathepsin G, elastase and PR3, which also have the ability to process IL-1 (14). The generation of mature IL-1 causes a violent inflammation which can only be limited in part by the inhibition of neutrophilic granulocytes (15-16). SARS-CoV-2 infection can trigger the recruitment and accumulation of MCs in the lung, a process mediated by innate immunity and therefore by pro-inflammatory cytokines of the IL-1 family (17) (Fig. 1). The accumulation may be mediated by an increase in TLR and other innate receptors provoking the exacerbation of inflammatory symptoms in COVID-19 (18). In this study, we report that there is an important inter-relationship between MCs and IL-1β-mediated inflammation. In addition, here we emphasize that MCs activated by SARS-CoV-2 release histamine which increases IL-1 levels involved in cytokine storm and, therefore, excessive inflammatory reaction in COVID-19 (19).

In light of the above, we can conclude that the MCs stimulated by SARS-CoV-2 are involved in viral inflammation, contributing to the formation of the cytokine storm by producing histamine and IL-1 which is one of the most potent biological pro-inflammatory molecules with activity that can be lethal.

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