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Short Communication

Understanding the cytokine storm during COVID-19: Contribution of preexisting chronic inflammation

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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus can lead to clinical expression of the coronavirus disease (COVID-19). COVID-19 itself has a very heterogeneous clinical picture, ranging from asymptomatic to severe and deadly forms (1). It evolves into two phases with very distinct pathophysiology.

The first phase reflects the response to the virus with a clear respiratory tropism. This viral phase usually progresses favorably. The clinical picture is the result of the interaction of SARS-CoV-2 with respiratory epithelial cells (pneumocytes), with 10-20 times greater affinity than other coronaviruses for the cell surface protein angiotensin conversion enzyme 2 –the major cell receptor for this virus (2). This leads to local cell damage in the alveoli, with local and systemic inflammation. In most individuals, the nonspecific immune defense controls the disease. At the same time, a specific immune response of interacting T and B lymphocytes is established in response to viral antigens. Within a few days, specific neutralizing antibodies appear, which directly contribute to disease control and protective immunity.

In a small number of cases, a second phase appears, with diffuse systemic inflammation, clinically dominated by respiratory manifestations. The massive severity comes from an Acute Respiratory Distress Syndrome (ARDS), which may have a delayed onset. Hypoxia results from alteration of both sides of the alveolar-capillary barrier, with a massive inflammation secondary to the migration of activated neutrophils followed by monocytes and lymphocytes. These cells alter the alveoli membrane through the release of proteolytic enzymes, resulting in an inflammatory fluid leakage. This further amplifies the consequences on hypoxia. This respiratory presentation is just part of a pattern with a massive leak syndrome leading to cell infiltration and dysfunction of all the key organs. This systemic context has been referred to as the cytokine storm.

Cytokines are proteins that provide intercellular communication, inside and outside the immune system. The main proinflammatory cytokines Interleukin-6 (IL-6), IL-1, Tumor Necrosis Factor (TNF), and IL-17 play a major role in inflammation and, as such, are now targeted by many biologics. The mode of activation and the dynamic sequence of these cytokines occur in a well-defined order that has been clarified in vitro. First, IL-1 and TNF are produced in a large proportion by monocytes that subsequently induce the production of IL-6 by stromal cells. IL-6 is the key cytokine that induces the production of C-reactive protein (CRP) in the liver (3). All these effects are synergistically amplified by IL-17 produced by T cells and other lymphocytes. IL-17 is the key cytokine for protection against bacterial infections and fungi, infections that are controlled first by neutrophils. Thus, any disease in which neutrophils are involved suggests the contribution of the IL-17 pathway. Indeed, this pathway has been shown to be highly activated in patients affected by COVID-19 (4). Even more, through mimicry, the SARS-CoV-2 virus itself could activate the IL-17 receptor, increasing the inflammatory response massively (5).

The deregulation of this physiological inflammatory response in some patients with the SARS-CoV-2 infection is the cytokine storm with increased levels of these cytokines in the circulation (6). This syndrome was first described while treating some cancers with activated lymphocytes and/or large doses of cytokines (IL-2) (7). More recently, the same picture has been observed in patients treated with chimeric antigen receptor (CAR)T cells. Probably the best characterization was observed when normal individuals were exposed to a new agonistic anti-CD28 antibody; a very severe syndrome developed in a few hours (8). These examples show that the cytokine storm in COVID-19 results from inflammation, rather than from the virus itself. This information is critical when it comes to the selection of the treatments.

This systemic cytokine storm combines the massive elevation in the blood of CRP and all proinflammatory cytokines. Of these, because of its circulating levels, IL-6 is the easiest to detect, and CRP can be considered as

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a functional assay for IL-6. Through often synergistic interactions, these cytokines increase the production of Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Granulocyte colony-stimulating factor (G-CSF), two key cytokines that promote the formation and release of neutrophils from bone marrow precursors, and the production of IL-8, a key chemotactic factor, that attracts neutrophils. These cytokines, specifically TNF and IL-17, act together on the vascular endothelium and promote local thrombosis in small and large vessels (9). At the same time, they favor adhesion of migrating cells to the lung and other organs. On heart muscle cells, they cause, again through synergy, secondary cardiomyopathy that aggravates the prognosis (10, 11). All these effects are enhanced by hypoxia.

Some patients (with COVID-19) with preexisting chronic inflammation are at a high risk of ARDS and mortality. Advanced age combines dysfunction of major organs, especially cardiac functions. During the metabolic syndrome linked to obesity and diabetes, there is a massive storage of cytokines in adipose tissue. More importantly, in this context of infection, it is critical to take into account that any chronic inflammation leads to a cell-mediated immune defect that affects specifically the T helper 1 (Th1) pathway through inhibition of the expression of the IL-12 receptor (12). This further increases the risk and severity of infections.

In these high-risk patients, all it takes is another event that, again through synergy, will give this acute situation in a very short time. For instance, a bacterial infection, quite common after approximately a week of cough, would activate the Th17 pathway, the production of IL-17, and the attraction and activation of neutrophils. A common event with no consequence on a normal immune system may induce a much more severe presentation in individuals previously exposed to both chronic inflammation and an acute viral infection or just to the virus. This could explain the rare cases in young, apparently healthy subjects. For all these aspects, the contribution of genetic factors needs to be demonstrated to explain such high degree of heterogeneity.

In the field of rheumatology, most patients have been or still are under the influence of a chronic inflammation. As such, they could be at high risk of developing a severe case of COVID-19. It is too early to come to a conclusion. At this stage, these patients do not appear to suffer more from COVID-19. This impression results from my own practice, that of colleagues around the world, and a recent publication (13). The contribution of the same cytokines to the ARDS suggests that the control of chronic inflammation may even be protective, either from drugs with a large spectrum of effects such as methotrexate or hydroxychloroquine or from biologics with more selected effects on cytokines or cell subsets.

The control of the different phases of COVID-19 has yet to be made. The early phase would be the target of molecules with potential antiviral activity. Immunological interventions on the cytokine storm have an increasingly strong rationality. Currently, some of the inhibitors of TNF, IL-6, and IL-17 and of their signaling pathways already on the market are being evaluated in the various stages of COVID-19. Results of IL-6 inhibition were the first to be reported (14). As for the use of these inhibitors in chronic inflammation, the key objective is to identify markers to select patients with a potential of response. Even more important is the definition of the timing of their administration. As always, early immuno-intervention is probably the way to proceed.

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