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REVIEWS

INFLAMMATION AT THE CROSSROADS: THE COMBINED EFFECTS OF COVID-19, AGEING, AND AIR POLLUTION

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Abstract: The global COVID-19 pandemic has highlighted different vulnerability profiles among individuals. With the highest mortality rate, the elderly are a very sensitive group. With regard to the main symptoms, a failure of the respiratory system, associated with deregulation of the immune system, has been observed. These symptoms may also be encountered in chronic exposure of susceptible populations to air pollution, including exacerbation of the inflammatory response. Is there a relationship between age, pollution exposure and the severity of COVID-19? Although it is unclear how these parameters are related, the same pathways can be activated and appear to find a common mechanism of action in inflammation.

Key words: Inflammation, COVID-19, ageing, air pollution.

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Introduction

Acute inflammation is an immediate, rapid response to an attack on the body. When as is usually the case the inflammation is not excessive, it resolves itself after the harmful agent or pathogen has been destroyed or eliminated. Essentially, acute inflammation comprises four phases (1): homing of immune cells to the tissue; immune cell differentiation and activation in situ; a "switch» to suppressive cells; and a return to homeostasis. In contrast, chronic inflammation persists over time, does not resolve itself fully, and may damage the tissues concerned. It is known that both acute and chronic lung inflammation contributes to the harmful effects of inhaled pathogens or toxicants, and constitutes a pathogenic pathway in many lung diseases (2). Lung inflammation is characterized by two successive steps. Firstly, activated macrophages, neutrophils and T lymphocytes infiltrate into the airways. Secondly, chemokines, oxygen radicals, proteases and pro-inflammatory cytokines are produced. Cytokines include interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), and interleukin 12 (IL-12) (2, 3). The lung damage caused by excessive acute inflammation can lead to pulmonary fibrosis and can interfere with gas exchanges. Unresolved lung damage and chronic inflammation are frequently observed in acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma. When inflammation cannot be resolved properly, its characteristics change as more macrophages are recruited and the adaptive system starts to respond. In the worst cases, this inflammation can evolve into an often lethal cytokine storm (also referred to as «cytokine shock» or «cytokine release syndrome»). Although the links between ageing, atmospheric pollution and COVID-19 are difficult to pinpoint, there is evidence for common pathways based on deregulation of inflammation in particular. Despite the increasing number of publications on the emerging disease COVID-19, only one author has considered the possibility of a cross impact between these different factors and focused its analysis on the treatment of inflammation and thrombotic states (4). Therefore we propose a review that considers the mechanistic aspect that would underlie this common pathway.

Inflammation and COVID-19

A cytokine storm is a massive inflammatory phenomenon in which cytokine production is both excessive and self-sustaining (5). This phenomenon has been described in a broad range of infectious and non-infectious diseases, including some human respiratory tract diseases caused by coronaviruses (6). With regard to coronaviruses that have emerged in recent years, it has been shown that infection by Severe Acute Respiratory Syndrome (SARS) coronaviruses can result in the massive production of TNFα, IL-6 and IL-8, and that infection by Middle East Respiratory Syndrome (MERS)-related coronavirus leads to the production of IL-6, IL-1β, and IL-8 (6). In severe cases of COronaVIrus Disease 2019 (COVID-19), elevated blood levels of IL-1β, IL-6, IL-8, IL-12, interferon gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNFα-induced cytokines have been evidenced (7). Furthermore, lymphopenia is a universal feature in patients with COVID-19, and an analysis of T lymphocyte subsets shows a significant decrease in CD4+ and CD8+ T cells counts. Among the various cytokines involved in the cytokine storm, IL-6 and GM-CSF appear to have the most harmful effects in the exacerbation of inflammation, with (among other things) high blood pressure, tachycardia progressing to

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bradycardia, hypoxia, and pulmonary fibrosis. The subsequent acute respiratory distress syndrome can lead to multi-organ failure and death. Even at the beginning of the pandemic, physicians suspected that a cytokine storm was involved in the expression of the most severe forms of COVID-19.

Inflammation and ageing

Ageing and age-related diseases share some basic mechanistic components, many of which result in inflammation. The development of a chronic, sterile, low-grade inflammatory state contributes to the pathogenesis of age-related diseases (8). Biological ageing is the result of an accumulation of genetic and epigenetic changes that lead progressively to cell damage, impaired tissue function, vulnerability to stressors, low physiological reserves, and a more limited ability to maintain homeostasis (9). Although a single mechanism for the causes and progression of biological ageing has not been established, the most frequently cited etiologies are redox stress, immune system deregulation, mitochondrial dysfunction, glycation, hormonal changes, epigenetic modifications, and telomere attrition (10). The environment may also have a role in biological ageing by disrupting the homeostatic balance (11). Even though the involvement of the afore-mentioned factors is widely accepted, the cellular and molecular details of biological ageing have yet to be determined. Some studies have suggested that chronic inflammation accelerates biological ageing (12). Although the immune response that is characteristic of acute inflammation subsides within a few days, chronic inflammation is characterized by the release of elevated levels of pro-inflammatory cytokines in response to physiological and environmental stressors. This essentially shifts the immune system into a state of low-level activation (8). The chronically active immune system activity associated with advancing age has been termed "inflammatory ageing" or "inflammaging" (13–15). Although the detailed mechanisms have yet to be characterized, the pro-inflammatory cell phenotype associated with the upregulation of the inflammatory response with age has been found to have a role in the initiation and progression of age-related diseases such as cardiovascular disease, type II diabetes, frailty, sarcopenia, Alzheimer's disease, osteoporosis, and cancer (16, 17).

Ageing and COVID-19

The COVID-19 pandemic is having a major impact on populations worldwide. Although all age groups are at risk of contracting COVID-19, older adults are the most at risk of severe disease as a result of age-related physiological changes and possible pre-existing conditions (18–20). A very recent report showed that the mean ± Standard Deviation (SD) age of patients with severe and critical forms of COVID-19 was 59.38 ± 16.54, with more than 50% over the age of 60 and a predominance of males (64.60%) (21). Similarly, over 50% of the deceased patients are aged 60 or over (21). A study published in The Lancet Infectious Diseases estimated that the proportion of infected people likely to be hospitalized increases with age, up to a maximum of 18.4% [95% confidence interval: 11.0-37.6] among people aged 80 or over (22). In Wuhan (China), patients over 65 years of age had a greater number of co-morbidities at baseline and displayed more severe symptoms (including multisystem failure and death) than younger patients did (23). Eight out of 10 deaths reportedly occur in people with at least one co-morbidity - particularly cardiovascular disease, hypertension, and diabetes, but also a range of other pre-existing chronic conditions that often appear with age (24). One explanation for this may be that immunosenescence in the older adult is associated with greater susceptibility to infectious disease (25). Hence, "inflammaging" can accentuate the harmful effects of SARS-CoV-2 infection. Conversely, an acute SARS-CoV-2 infection may worsen any chronic, age-related, pro-inflammatory conditions. When combined with immune senescence and the age- and sex-specific distributions of angiotensin-converting enzyme II (ACE 2) in the airway epithelium, this situation may accentuate the antiviral response to inflammation (53).

Air pollution and inflammation

As mentioned above, environmental factors can have a role in the occurrence of disease. Air pollution constitutes one of the best known environmental risk factors, and is thought to cause about 3.3 million premature deaths per year worldwide (26). Air pollution is composed of particles, gases, and bio-aerosols containing pollen and airborne microorganisms (viruses, bacteria, fungi, spores, etc.). A large number of studies have shown that exposure to air pollutants is associated with cardiovascular adverse events (27). Inflammation is very frequently cited as a cause of cardiovascular disease; it is not always associated with an infection and may be triggered by other "danger signals" referred to collectively as danger-associated molecular patterns. These patterns come from damaged or altered cells (e.g. cancer cells), chemical irritants (e.g. pollutants) and even physical disturbances (e.g. mechanical forces). This sterile inflammation may be associated with oxidative conditions that are potentially triggered or exacerbated by exposure to air pollution (28, 29). Oxidative stress is generally defined as a chronic shift in the intracellular redox balance towards oxidative conditions. It is initiated by reactive oxygen species (ROS) and reactive nitrogen species, and has a central role in many adverse health effects - particularly in the respiratory tract (3). High levels of ROS may exceed the cells' antioxidant capacity and trigger a cascade of events closely associated with inflammation and, at higher concentrations, apoptosis and genetic and epigenetic alterations. Thus, increased activation of the transcription factor nuclear factor - kappa B by oxidative stress is involved in the regulation of a large number of genes controlling the inflammatory

response (30). Furthermore, environmental exposure has been shown to increase levels of pro-inflammatory cytokines (e.g. IFNγ, IL 6, IL 8, IL 12, IL-1β, and TNFα) (31). The release of these cytokines into the lung and the peripheral blood leads to systemic inflammation and immune disorders (32–35). Exposure to air pollutants also increases the numbers of immune cells (neutrophils, lymphocytes and macrophages) that infiltrate into the lungs (36). Neutrophil recruitment to the lungs increases the inflammatory response and the resulting damage. During this pollutant-induced phase of inflammation, the number of macrophages also increases via differentiation of the infiltrated monocytes into M1 macrophages (37). Chronic exposure to pollutants such as fine particles ($PM_{2.5}$) can raise levels of inflammatory markers such as C-reactive protein, which is directly involved in the development of cardiovascular disease (38). This can also lead to the development of chronic inflammatory diseases, such as asthma and COPD (39).

Air pollution and COVID-19

In recent years, a large number of research groups have examined the interaction between airborne particles and viruses. For example, the risk of pneumonia caused by respiratory syncytial virus (RSV) in children is increased by the penetrate of particulate pollutants ($PM_{2.5}$ and PM_{10}) deep into the respiratory tract (40). Similar results have been reported for measles, the incidence of which was significantly amplified by an increase in $PM_{2.5}$ of 10 $\mu g/m^3$ (4). In Europe, the epidemiological data show that the regions known to be the most polluted by $PM_{2.5}$, PM_{10}, and NO_2 (Lombardy and the Po valley in northern Italy) were also the most affected by the spread of SARS-CoV-2 (42, 43). In the United States, the results of an ecological study of 98% of the American population (currently under review) suggested a strong association between elevated particulate matter concentrations and mortality rates due to COVID-19 (44). A slight increase in long-term exposure to $PM_{2.5}$ leads to a large increase in mortality associated with COVID 19. A study conducted in 120 Chinese cities determined a significant association between a 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, NO_2 and O_3 and the number of new positive cases (2.24%, 1.76%, 6.94% and 4.76%, respectively) (45). Thus, several research groups have looked at whether or not the presence of SARS-COV-2 RNA on particulate matter in outdoor air samples is a potential early indicator of the spread of COVID-19 (43). Thus, an RT-qPCR analysis of RNA extracted from 34 PM_{10} samples showed the presence of the E gene (which is specific for SARS-like viruses) and RdRP genes (which are highly specific for SARS-CoV-2) (46). However, it is not known whether virus-carrying particles are contagious. There are several possible explanations for the impact of air pollution exposure on the severity of COVID-19. One of them would be that chronic exposure to air pollution has been implicated in many cardiopulmonary diseases. The oxidative stress due to exposure to pollutants leads to the production of free radicals, which damage the respiratory system and reduce resistance to viral and bacterial infections. Pollutants might both directly impair the lungs' ability to eliminate pathogens and indirectly exacerbate any underlying cardiovascular or pulmonary diseases (47, 48). The presence of co-morbidities leads to inflammation, and pollutant-induced oxidative stress and cell damage may worsen the prognosis (49, 50). Chronic exposure to $PM_{2.5}$ leads to the overexpression of alveolar ACE-2 receptors; this increase might amplify the viral load, deplete ACE-2 receptors, and weaken host defenses. Moreover, NO_2 acts as a pro-oxidant by depleting the anti-oxidant pool and thus impairing tissue defenses (especially phagocytic activity) and increasing inflammation and cell damage. Exposure to NO_2 causes a severe form of COVID-19 in ACE-2-depleted lungs and thus worsens the outcome (51).

Inflammation at the crossroads?

The most severe forms of COVID-19 increase in prevalence with age; as described above, the oldest people have the highest mortality rate and the greatest risk of cytokine shock. The analysis of patients with COVID-19 patients shows that younger individuals are less affected by the disease (52). This can be explained by the immature immune system in children, who are much less affected by this epidemic (53, 54). Moreover, it is now well known that the effects of air pollution are exacerbated among the elderly, with effects on the immune, respiratory and cardiovascular systems (55, 56). The cytokine storm sometimes seen in COVID-19 is particularly damaging for older adults (57); in particular, myocardial injury can be amplified by exposure to particulate pollutants. Indeed, $PM_{2.5}$ exposure is known to increase the risk of heart diseases like as acute myocardial injury and infarction (58). One of SARS-CoV-2's first targets is the respiratory tract, which is continuously exposed to external stressors. Activation of the immune system in the lungs during exposure to gaseous or particulate pollutants has already been demonstrated - especially in sensitive individuals like older adults (56). Moreover, the aggravation of chronic inflammatory respiratory diseases (e.g. asthma) by air pollution has been widely described (59, 60). Thus, COVID-19 may have more serious outcomes (e.g. cytokine shock) when the respiratory tract has already been sensitized by chronic exposure to air pollution.

Conclusion

In conclusion, one can legitimately hypothesize that COVID-19 is synergized by age and exposure to air pollution via an exacerbation of inflammation. Further research is needed to determine the infectious potential of SARS-CoV-2 on particulate matter and the latter's potential role in spreading disease. Public health policies in populations such as older adults (e.g. reducing their exposure to atmospheric pollution)

may now be especially important. Furthermore, disparities in socioeconomic factors and elevated prevalences of diabetes, heart disease, and chronic airway diseases (e.g. lung cancer and COPD) are likely to accentuate the mortality rate among older populations (47). The presence of common pathways (including inflammation and repeated exposure to air pollutants) may have contributed to the disproportionate impact of COVID-19 on older adults.

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