Aging, Male Sex, Obesity, and Metabolic Inflammation Create the Perfect Storm for COVID-19

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Coronavirus disease 2019 (COVID-19) is a novel threat that seems to result from the collusion between a new pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and an existing pandemic of metabolic disease driven by obesity. This Perspective explores the evolving epidemiological, clinical, biological, and molecular evidence to propose an unfolding paradigm in which old age, chronic metabolic disease (such as obesity, type 2 diabetes, and metabolic syndrome), and male biological sex produce a deadly symbiosis of dysregulated immunometabolism and chronic systemic inflammation that intensifies virally induced hyperinflammation associated with SARS-CoV-2 infection. It is intended to inspire new research directions and stimulate funding in this field.

The 1918 "Spanish" influenza A (H1N1) pandemic, which caused ~50 million deaths worldwide, was notable for being fatal to young and healthy subjects aged between 20 and 40 years (1). By contrast, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) and has already killed over 400,000 people worldwide in 4 months, is targeting older subjects with chronic medical comorbidities. This Perspective discusses a paradigm currently unfolding in which old age, chronic metabolic disease (such as obesity, type 2 diabetes, and metabolic syndrome), and male biological sex produce a permissive environment of dysregulated immunometabolism and chronic systemic inflammation that allows SARS-CoV-2 to unleash acute and deadly hyperinflammation. It is intended to highlight research gaps, inspire new research directions, and stimulate funding in this field.

Meta-Inflammation Creates a Permissive Environment for a Cytokine Storm

To determine why COVID-19 is especially lethal in those with metabolic disease and particularly impacts older males, we must first understand the pathogenesis of SARS-CoV-2 virally driven hyperinflammation. Our current understanding of the disease is that most of the critically ill and fatal cases did not develop severe clinical manifestations in the early stages. Rather, COVID-19 patients deteriorated suddenly in the later stages of the disease. What appears to be specific to SARS-CoV-2 is the host response that fails to launch a robust interferon-I and -III innate antiviral response to control virus replication (2). Instead, the immune response produces high levels of chemokines to recruit effector inflammatory cells (2). This inappropriate immune response with outpouring of inflammatory chemokines results in lung infiltration and hyperactivation of monocytes and macrophages producing proinflammatory cytokines (such as interleukin-6 [IL-6], IL-8, and IL-1β and tumor necrosis factor-α [TNFα]) and chemokines (such as CCL2, IFNγ-induced protein 10 [IP-10], and CCL3) (2–5). This increased local production of cytokines and chemokines, or "cytokine storm," attracts more inflammatory neutrophils and monocytes into lung tissue, producing edema and reduced gas exchange in the alveoli, leading to acute respiratory distress syndrome (ARDS) (3,6,7). Ironically, the cytokine storm is a result of well-intentioned but imbalanced efforts by the immune system to protect the host, which results in ARDS and ultimately multiorgan failure. Elevated IL-6 is believed to be central to the development of the cytokine storm (8,9). Notably, in mouse and primate models of severe acute respiratory syndrome coronavirus (SARS-CoV) infection (a closely related coronavirus), the cytokine storm is more severe and

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deadly in old animals than in young, despite similar virus replication (10,11). In the original series from Wuhan, China, patients developing ARDS exhibited biological features of a cytokine storm (5). Compared with moderate cases, severe cases exhibited higher serum levels of C-reactive protein (CRP), ferritin, and D-dimer as well as markedly higher levels of IL-6, IP-10, CCL2, and TNFα (4,5). As we will argue below, the chronic, low-grade systemic inflammation (e.g., meta-inflammation) with elevated IL-6 that characterizes older male subjects with obesity, type 2 diabetes, or hypertension in the context of metabolic syndrome provides a permissive inflammatory environment that intensifies the rapid development of this cytokine storm.

Metabolic Diseases Predispose to COVID-19

COVID-19 presents as a severe viral pneumonia with ARDS, but surprisingly, its severity and mortality are not more pronounced in subjects with chronic pulmonary disease or heart disease. Rather, it is especially pronounced in subjects with type 2 diabetes, obesity, and hypertension. Hypertension is not an isolated condition. It is usually part of a metabolic syndrome, which also includes abdominal obesity, fasting hyperglycemia, and dyslipidemia and predisposes to type 2 diabetes (12).

Since the beginning of the SARS-CoV-2 outbreak, diabetes and hypertension were present in ∼25% and 35% of fatal cases in China (13,14) and 36.5% and 48% in Korea (15), respectively. In contrast, cardiac and chronic pulmonary disease were present in only 10% and 9% of fatal cases in Wuhan (13) and 16% and 17.5% in Korea, respectively (15). Diabetes was also present in 35% of fatal cases in Italy (16) and 58% of critically ill cases in Seattle (17). Although obesity rates were not reported in China, the BMI of critically ill patients transferred to intensive care was significantly higher than that of the general group (25.5 kg/m^2 vs. 22.0 kg/m^2) (18). Similarly, the BMI of individuals in the Seattle series was 33 kg/m^2 on average, suggesting that most patients were overweight or obese (17). A retrospective study of 5,700 patients hospitalized for COVID-19 in New York, the epicenter of the outbreak in the U.S., reported that obesity, diabetes, and hypertension were also predominant and present in 42%, 34%, and 57% of cases, respectively (19). In contrast, cardiac (coronary artery disease and heart failure) and chronic respiratory (asthma and chronic obstructive pulmonary disease) disease were present in only 18% and 14%, respectively (19). As of 12 May 2020, the New York State Department of Health reported that diabetes and hypertension were present in 36% and 55% of fatal cases, respectively, compared with only 23% for coronary artery disease and chronic obstructive pulmonary disease combined (20). In Louisiana, the epicenter of death rates per capita in the U.S. in April 2020, diabetes, obesity, and hypertension were present in 35%, 19%, and 57% of fatal cases, respectively (21). In contrast, cardiac and chronic pulmonary disease were present in only 18% and 11%, respectively (21). In a report not yet certified by peer review of over 4,000 patients from New York City, obesity was considered a more severe risk factor for hospitalization than the presence of chronic pulmonary or heart disease (22). In summary, among severe and deadly COVID-19 cases, diabetes, obesity, and metabolic syndrome are generally present in higher proportion than any other comorbidities.

Adiposity in Metabolic Disease Produces Meta-Inflammation

A question then arises: what makes metabolic diseases more fatal systemic environments for COVID-19 outcomes than severe chronic pulmonary or heart disease, in which lung and heart functions are already diminished? One possible explanation is that obesity, type 2 diabetes, and hypertension in the context of metabolic syndrome all share a common hallmark: an increased adiposity associated with chronic, low-grade systemic inflammation or meta-inflammation (23). Meta-inflammation develops following activation of resident macrophages in adipose tissue, promoting the recruitment of M1-polarized macrophages, which display a more proinflammatory phenotype (24), increasing the production of proinflammatory cytokines like TNFα, IL-6, and chemokines, locally and systemically. There are increases in white blood cell counts, acute-phase proteins such as CRP, and plasma levels of coagulation factors (fibrinogen, D-dimers) (25). This adipose inflammation is characterized by a type 1 immune response (Th1) that is usually activated acutely in response to infection. In the case of obesity, this immune response in adipose tissue is chronic and involves effector T cells, B cells, and natural killer (NK) cells that produce cytokines orchestrating the accumulation and activation of proinflammatory M1 macrophages (23). Additionally, obesity and Western diet also alter gut microbiota and increase intestinal permeability (26,27). This is associated with translocation of bacteria and lipopolysaccharide from intestine toward blood and adipose tissue, creating continuous metabolic endotoxemia, which fuels meta-inflammation (26,27). Meta-inflammation via IL-6 and other proinflammatory factors may skew the immune system to enable SARS-CoV-2 to unleash its deadly inflammatory complications, as will be discussed below.

Diabetes and Meta-Inflammation in COVID-19 Patients

In the past few decades, two other coronavirus outbreaks, the SARS-CoV outbreak of 2003 in Hong Kong and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak of 2013 in Saudi Arabia, have caused deadly pneumonias. In both outbreaks, diabetes was associated with increased mortality. Notably, in patients with MERS, diabetes was the strongest factor predicting mortality (reviewed in Drucker [28]). The impact of diabetes on COVID-19 outcomes has been reviewed based on studies available as of April 2020. Diabetes increases risk of intensive care requirement by two- to threefold, as well as

mortality rates, compared with the overall population (29). The mechanisms by which diabetes aggravates COVID-19 outcome are still unclear. Indirect evidence suggests that uncontrolled hyperglycemia could to play a role (29), and improved glycemic control is associated with better outcomes in Chinese patients with COVID-19 and preexisting type 2 diabetes (30). In contrast, in a French multicenter observational study of over 1,300 patients with diabetes and hospitalized for COVID-19, long-term glycemic control (HbA_{1c}) was not associated with disease severity (intubation or mortality at day 7) (31). In contrast, obesity was independently associated with COVID-19 severity. Additionally, systemic inflammation (measured by CRP) was also independently associated with early death (31). Thus, the influence of meta-inflammation in individuals with diabetes could play an important role in COVID-19 severe outcomes. A case series from China reported that hospitalized COVID-19 patients with diabetes as the only comorbidity exhibited uncontrolled systemic inflammation characterized by elevated leukocyte-to-lymphocyte ratio, CRP, ferritin, and IL-6, as well as a state of hypercoagulability with elevated D-dimer and fibrinogen, compared with those without diabetes (32). Importantly, IL-6 is a strong predictor of disease severity and evolution toward a cytokine storm (8,9). Elevation in ferritin also indicates the activation of the monocyte-macrophage system, which is a crucial part of the inflammatory storm (9,33). This suggests that the meta-inflammation characteristic of patients with type 2 diabetes produces a permissive, dysregulated inflammatory support that facilitates the development of the inflammatory cytokine storm, thus accelerating the deterioration of COVID-19 patients. Studies are needed to determine the individual contribution of inflammation driven by hyperglycemia, insulin resistance, or obesity in the enhanced mortality of COVID-19 patients with type 2 diabetes.

Obesity and Meta-Inflammation in COVID-19 Patients

The influence of obesity in fatal SARS-CoV-2 infection is clearly documented and reinforces the hypothesis that excess adiposity and associated meta-inflammation are central to COVID-19 evolution toward a cytokine storm. In a study involving 3,615 COVID-19 patients in New York City, obese patients aged <60 years with a BMI between 30 and 34 kg/m^2 were two times more likely to be admitted to the intensive care unit for ARDS compared with individuals with a BMI <30 kg/m^2. Likewise, severely obese patients with a BMI >35 kg/m^2 were three times more likely to be admitted to intensive care compared with patients in the same age category with BMI <30 kg/m^2 (34). In a Chinese cohort of 383 COVID-19 patients from Shenzhen, those who were overweight (BMI 24.0–27.9 kg/m^2) and obese (BMI ≥28 kg/m^2) exhibited 1.84-fold and 3.40-fold odds, respectively, of developing severe COVID-19 (respiratory failure) compared with normal-weight patients (BMI 18.5–23.9 kg/m^2) after adjustment for age, sex, and multiple comorbidities (30). In another Chinese study involving 150 patients with COVID-19, obesity was associated with a threefold increased risk of disease severity after multiple adjustments. A nearly linear relationship between higher BMI and severe illness was shown with each 1-unit increase in BMI associated with a 12% increase in the risk of severe COVID-19 (35). Further, in a French cohort of 126 patients from Lille, COVID-19 severity (defined by respiratory failure requiring mechanical ventilation) was directly correlated with BMI. This pattern was not observed in 306 obese control subjects with severe acute respiratory disease unrelated to SARS-CoV-2 (36). Taken together, these studies suggest that the increase in adipose tissue mass in obese individuals with SARS-CoV-2 infection specifically aggravates COVID-19 pneumonia compared with other causes of severe acute respiratory disease. The effect of obesity is likely to be correlated to the amount of adipose tissue, independently from reducing lung capacity and ventilation and probably via increasing circulating factors. Consistent with a systemic role of adipose tissue in COVID-19 mortality, and as discussed above, the BMI of critically ill patients in Wuhan was higher than that of control subjects but below the obese range, even for Asian standards (25.5 kg/m^2 vs. 22.0 kg/m^2) (18), further arguing for a systemic role of adipose tissue. Obese individuals exhibit a state of meta-inflammation, which, as discussed for type 2 diabetes above, may exacerbate SARS-CoV-2–induced immune-inflammatory reaction. Additionally, obese subjects exhibit hyperleptinemia. Elevated leptin levels in obese people may contribute to worsening of ARDS. Leptin has structural similarities with IL-6, and the leptin receptor, OBR, is a member of the class I cytokine receptor family, which includes the receptor for IL-6 (37,38). Leptin acts as a potent inflammatory cytokine and stimulates innate immune responses by promoting the activation of monocytes/macrophages and chemotaxis and activation of neutrophils (38). Leptin also stimulates the production of IL-6 by cultured human airway epithelial cells, thereby exacerbating inflammation. Finally, leptin acts on the leptin receptor in cultured human lung fibroblasts to increase production of proinflammatory cytokines such as IL-6, chemokines involved in airway inflammation (i.e., CCL11/eotaxin, CCL2/MCP-1, CXCL8/IL-8, and CXCL10/IP-10), and the soluble vascular cell adhesion protein 1 (soluble VCAM-1), an important adhesion molecule in the process of recruitment of inflammatory cells (39). Notably, in humans and mice with pneumonia unrelated to COVID-19, hyperleptinemia is associated with rapid progression toward a cytokine storm with ARDS compared with control subjects with pneumonia but without evolution to ARDS (40,41). Thus, hyperleptinemia in severely obese individuals may act as a proinflammatory cytokine in the lung and add to meta-inflammation to facilitate the development of a cytokine storm.

Male Sex Is a State of Relative Meta-Inflammation

Men with COVID-19 have a uniformly more severe outcome than women. Previous coronavirus outbreaks exhibited

the same apparent male predominance. During the first SARS-CoV outbreak, among 1,755 hospitalized patients in Hong Kong, the case fatality rate was 21.9% in men compared with 13.2% in women, with a relative risk of 1.66 (95% CI 1.35, 2.05) for men compared with women (42). During the MERS-CoV outbreak in Saudi Arabia, among 425 reported cases, disease occurrence was higher among men (62% of cases) (43). The case fatality rate was also higher for men (52%) than for women (23%).

Today, in China, Europe, and the U.S., COVID-19 mortality is consistently 1.5- to 2-fold higher in men than in women (13,15,16,19,44,45). The Global Health 50/50 research initiative website at University College London provides real-time sex-disaggregated data on COVID-19 mortality from most countries worldwide (46). It is well documented (although underestimated) that females exhibit heightened innate and adaptive immune response to viral infections compared with males (47), which may help them clear SARS-CoV-2 faster than males. There are multiple biological reasons why females enjoy a more robust immune response to infections than males, including gene dosage in X-linked immune-response genes and the different concentrations of sex steroids between females and males (47). Sex-biased immune responses, however, extend to meta-inflammation. Men exhibit a predominant visceral adipose tissue distribution compared with women, which is associated with a more proinflammatory circulating cytokine profile (48,49). Following ingestion of a high-fat meal, obese men exhibit a significant and prolonged elevation in IL-6 and TNFα (50). As discussed above, activation of myeloid cells (monocytes, macrophages, and neutrophils) is a hallmark of obesity, both in peripheral tissues such as adipose and systemically, which produces meta-inflammation (23,25). In mice, diet-induced obesity elicits a much greater inflammatory response in adipose tissue of males than females, which is only partially reduced by ovariectomy and is therefore only partially mediated by estrogens (51). Notably, when exposed to obesogenic diet, mice from both sexes gain weight, but males develop more meta-inflammation than females, which is related to cell-intrinsic properties of male leukocytes and adipose tissue macrophages (52). Accordingly, cultured peripheral blood mononuclear cells (PBMCs) from men produce more TNFα than PBMCs from women following lipopolysaccharide stimulation (53). The propensity to adipose inflammation in males also relates to androgens' effects on immune cells (54). Therefore, the higher propensity to meta-inflammation of obese men compared with women is dependent on sex hormones as well as on the cell-autonomous characteristics of male immune cells and may increase their risk of cytokine storm compared with women. In a mouse model of SARS-CoV infection (the coronavirus of 2003), female mice exhibited lower pulmonary inflammatory cell infiltration, producing fewer inflammatory cytokines and chemokines, and resulting in milder pulmonary damage and lower female mortality compared with males (55). Importantly, ovariectomy in female mice resulted in the same mortality rate as in males, suggesting that ovarian sex hormones protect female mice from SARS-CoV inflammatory cytokine storm. Evidence suggests that the inflammatory immune responses in COVID-19 patients might be more elevated in men and associated with worse outcomes than in women (45). In a series of 168 patients hospitalized for severe COVID-19 in Wuhan, blood neutrophil-to-lymphocyte ratio, CRP, and ferritin concentrations were higher in men compared with women as well as in patients who died compared with those who were discharged (not disaggregated by sex) (56). These data suggest that inflammatory immune responses to SARS-CoV-2 are more elevated in men and associated with more lethal outcomes than in women. In the study by Cai and colleagues (30), men who were obese were at 5.66 increased odds of severe COVID-19 outcomes compared with men who were normal weight, even after multiple adjustments. In contrast, obese women exhibited no increased risk of severe disease, although the study lacked statistical power to draw definitive conclusions for women. In future studies, investigators should analyze and report data pertaining to COVID-19 comorbidities disaggregated by sex. Studies are needed to determine the role of biological sex and sex steroids in the immune response to SARS-CoV-2 and the mortality from COVID-19 in relation to various comorbidities.

Other sex-related factors may participate in the male bias in COVID-19 morbidity and mortality. The first deadly coronavirus of 2003 (SARS-CoV) used the angiotensin-converting enzyme 2 (ACE2) as receptor for cell entry, which is also the receptor for SARS-CoV-2 (57). SARS-CoV-2 also requires the transmembrane serine protease TMPRSS2 for S protein priming (57). Notably, ACE2 is located on the X chromosome. Since women have two copies compared with one in men, ACE2 may be regulated differently in men than in women. Additionally, TMPSS2 is a direct androgen receptor target gene and its expression is increased by androgens (58), which could also have an impact on TMPSS2 expression in men. Together, ACE2 and TMPSS2 are likely to be regulated differently in men and women, which may affect virus entry and pathogenicity. Additional studies are needed to address these questions.

Old Age Is a State of Meta-Inflammation

COVID-19 morbidity and mortality are higher in older people. Overall, in Asia, Europe, and the U.S., 80% of deaths associated with COVID-19 were observed among adults aged ≥65 years, with the highest percentage of severe outcomes among persons aged ≥80 years (13–16,19,59).

Aging is associated with a progressive decline and dysregulation in immune functions and produces a systemic, chronic, and low-grade proinflammatory response called inflammaging (60). The accumulation of senescent cells during aging is one of the contributors to inflammaging, owing to their acquisition of a proinflammatory senescence-associated secretory phenotype whose goal is to promote the immune-mediated clearance of senescent

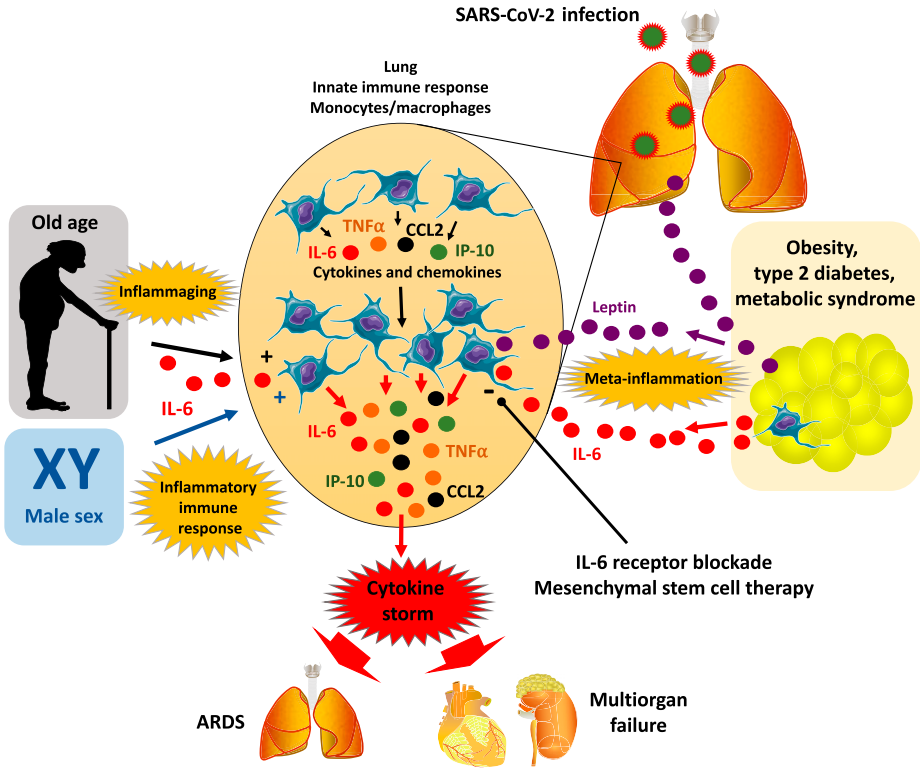

Figure 1—Age, male sex, and excess adiposity interact with SARS-CoV-2 infection to produce the perfect cytokine storm. Obesity, type 2 diabetes, and metabolic syndrome are characterized by excess adipose tissue leading to meta-inflammation with production of proinflammatory cytokines like IL-6 that dysregulate innate immune cells of the lungs. In obesity, hyperleptinemia also acts as a proinflammatory cytokine on lung airway epithelial cells, immune cells, and fibroblasts creating a local inflammatory state. Aging is associated with dysregulation in immune functions and inflammaging with increased systemic proinflammatory cytokines, including IL-6. Male sex is also characterized by an intrinsic propensity to meta-inflammation. Upon SARS-CoV-2 infection, the cumulative effects of old age, male sex, and excess adiposity produce a state of heightened meta-inflammation, which skews immune cells to produce more chemokines and inflammatory cytokines, attracting more inflammatory cells, ultimately leading to a cytokine storm.

cells (61). As in the case of meta-inflammation, inflammaging is characterized by increases in systemic proinflammatory cytokine levels, namely IL-1β, IL-6, and TNFα (60). Inflammaging is influenced by changes in body composition, such as decreased lean muscle mass and increase in adiposity (62). Sex steroids are important modulators of immune cells (47). Testosterone and progesterone are generally anti-inflammatory, suppressing immune responses involved in inflammation, whereas estrogens are proinflammatory at low concentrations but anti-inflammatory at high concentrations (47). Sex steroid concentrations decline rapidly in women and more gradually in men after midlife, which may explain why sex differences in inflammaging decrease in older age. Therefore, in young people with a healthy immune system, COVID-19 is usually mild or asymptomatic (63). In old people, however, inflammaging constitutes another permissive environment for the development of a cytokine storm. In fact, in mice, the combination of aging, male sex, and increased adiposity produces a lethal cytokine storm following systemic administration of stimulatory immunotherapy (64).

Race, Ethnicity, and Meta-Inflammation

Minorities are also disproportionally affected by COVID-19 mortality. In New York, Black and Hispanic individuals represent 22% and 29% of the population, respectively, yet represented 28% and 34% of fatalities (21). In contrast, non-Hispanic White people represent 32% of the population but represented only 27% of fatalities (21). In Louisiana, non-Hispanic Black people represented 56% of fatalities compared with 41% for non-Hispanic Whites. One explanation for the higher prevalence of COVID-19–related deaths among minority groups could be that the prevalence of obesity, metabolic syndrome, and type 2 diabetes is disproportionally high in Black and Hispanic individuals compared with Whites (65,66). However, meta-inflammation could also play a role. A study of the transcriptional response of primary macrophages to pathogens found a stronger inflammatory response in individuals of African versus European ancestry, most of which was under genetic control (67). In a cross-sectional study of over 1,000 participants, Black individuals exhibited higher concentrations of inflammatory markers such as IL-6 and fibrinogen compared with White individuals, even after

adjusting for socioeconomic status and demographic factors (68). A retrospective study of over 1,300 patients hospitalized for COVID-19 in Louisiana reported that non-Hispanic Black patients were more likely than non-Hispanic White patients to exhibit increased inflammatory biomarkers such as CRP and procalcitonin (69). Further, the Family and Community Health Study, spanning over a 20-year period and including data from over 400 Black Americans, reported that race-related stressors such as discrimination and segregation in juvenile years predicted systemic inflammation in adults (70). Therefore, biological and social factors may also predispose minorities to systemic inflammation and therefore to COVID-19 storm.

The Perfect Inflammatory Storm

Acute inflammation is a fundamental immune response to cope with stresses (60). In young and healthy individuals, this acute and regulated response is necessary and efficient in protecting against infectious diseases, like SARS-CoV-2 infection, which can be asymptomatic. In later life, however, it can be detrimental. Aging and chronic metabolic disease like obesity, type 2 diabetes, and metabolic syndrome are characterized by dysregulated immune function leading to chronic meta-inflammation. Male sex is also characterized by an intrinsic propensity to meta-inflammation compared with female sex. The cumulative effect of old age, male sex, and excess adiposity is likely to produce a state of heightened meta-inflammation that dysregulates and skews the immune system toward a perfect inflammatory cytokine storm (Fig. 1). In agreement with this concept, therapeutic strategies targeting the inflammatory response such as IL-6 blockade (71) or the transplantation of mesenchymal stem cells (72) are showing some promising preliminary results in preventing the cytokine storm.

In conclusion, between the appearance of COVID-19 in December 2019 and the time of writing of this Perspective, the story unfolding is suggestive of a collusion between a new pandemic of SARS-CoV-2 and an existing pandemic of metabolic disease combined with other factors predisposing to meta-inflammation including older age, male sex, and socio-biological factors in minority groups. Funding for research in this area is needed.

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