Review

SARS-CoV-2 morbidity and mortality in racial/ethnic minority populations: A window into the stress related inflammatory basis of health disparities?

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A B S T R A C T

Health disparity related to race/ethnicity has been cited as *"the most serious and shameful health care issue of our time"* (Peterson et al., 2018). A portion of the now recognized disproportionate impact of the COVID-19 pandemic among Black, Indigenous and People of Color (BIPOC) communities is attributable to social determinants such as socioeconomic status (SES), physical living situation, health care access, and the psychosocial factors associated with socioenvironmental circumstances such as bias, victimization, trauma and toxic stress as well as structural factors that reduce the capacity to practice physical distancing (Agurs-Collins et al., 2019).

In this paper, we hypothesize that, prior to the COVID-19 pandemic, disproportionate socio-economic and environmental stressors in the BIPOC population promoted heightened stress-associated neurobiological activity (Stress-NbA). This chronic elevation in Stress-NbA results in down-stream complications of chronic stress including underactivation of anti-viral type I IFN pathway genes. This results in an increase in susceptibility to viral diseases, including coronavirus illnesses. Additionally, Stress-NbA chronically potentiates systemic inflammation (from hematopoietic system activation with myelopoiesis) increasing the prevalence of metabolic syndrome (MetS) and setting the stage for stress-related chronic non-communicable diseases (NCDs).

This process was propelled by overactivation of immune cell gene expression in the nuclear factor κ-light-chain-enhancer of activated B cells (NF-kB) activation pathway and underactivation of gene expression in the anti-viral type I interferon (IFN) pathway. The higher prevalence of MetS and NCDs in minority populations turned out to be predictive of the elevated risk they would face in the presence of a highly contagious viral pandemic. The stress-related generation of a chronic non-pathogen associated molecular pattern (non-PAMP) immunoactivation state led to decreased viral immune defense and increased susceptibility to SARS-CoV-2 infection with increased risk of severe illness induced by cytokine storm syndrome (CSS).

1. Introduction

A recent study suggests that approximately 97 million Americans (43% of adults) were at higher risk of illness from COVID-19 (Raifman and Raifman, 2020). Racial/ethnic risk disparities were found across all age groups for BIPIC communities when compared to White adults. By July 21, 2020, there were greater than 3.9 million cases in the US and over 142,000 COVID-19 related deaths according to the Johns Hopkins Center for Systems Science and Engineering (Johns Hopkins University, 2020). Data available through the end of May, based on over 600,000 cases, showed that 33 percent of cases were Hispanic despite making up only 18 percent of the U.S. population; 22 percent were Black despite comprising only 13 percent of the population; and 1.3 percent were Native American or Alaskan Natives, which is nearly twice their percentage of the population (Stokes et al., 2020).

Furthermore, data from the National Center for Health Statistics (NCHS) suggest that approximately one in four COVID-19 deaths take place among the 13% of Americans who are non-Hispanic Black (NCHS, 2020).

Health disparities are considered sequelae of social determinants, such as race/ethnicity and socioeconomic status (SES), intertwined with key factors such as the physical living situation, health care access, and the psychosocial factors associated with socioenvironmental circumstances such as bias, victimization, trauma and toxic stress (Peterson et al., 2018; Agurs-Collins et al., 2019; Williams and Cooper, 2020).

Certainly, part of the disproportionate impact of the COVID-19 pandemic on Blacks and other communities of color can be traced to structural factors that reduce the practice of physical distancing, disallow the luxury to work from home, or impair the ability to obtain proper health care and nutrition. In addition, minority populations in the US

disproportionally make up "essential workers who have the added risk burden of using public transportation to get to work" (Dorn et al., 2020).

However, another hallmark of the COVID-19 pandemic is that the hardest hit in terms of morbidity and mortality appear to be those suffering from MetS. Its characteristics include truncal obesity, systemic hypertension, and dyslipidemia as well as insulin resistance raising the specter of type 2 diabetes mellitus (McCracken et al., 2018). Stress-associated pathways may represent important pathobiological mechanisms leading to the excess prevalence of MetS among minority populations. Minority adults are overrepresented in high-stress groups, which have a 45% higher chance of having MetS than adults in the low-stress groups (Kuo et al., 2019). Prior epidemiologic studies have consistently shown that stress and stressful life events are more prevalent among Blacks and other minority groups compared to Whites. For instance, data from the Chicago Community Adult Health Study revealed that Blacks and U.S.-born Hispanic individuals of low SES report higher levels of stress (Sternthal et al., 2011). This study also found that members of racial and ethnic minority groups report high rates of exposure to discrimination (Sternthal et al., 2011). It is known that stress is associated with greater disease vulnerability and this includes infectious communicable diseases (CDs) as well as non-communicable diseases (NCDs) like cardiovascular disease and hypertension (Cohen et al., 2007).

On the basis of NCHS data on deaths in 2014, many of the largest gaps in life expectancy between Black and White Americans are attributable to MetS and stress related NCDs. The BIPOC population shares a high risk of both MetS and COVID-19 (Hall et al., 2003; Moore et al., 2017; Schumacher et al., 2008). The C.D.C. recently reported that close to 90 percent of severe COVID-19 cases occur in the context of underlying MetS related health conditions such as hypertension and cardiovascular disease, obesity, diabetes, and chronic lung disease (CDC, 2020).

In this paper, we hypothesize that the disparity in BIPOC COVID-19 related outcomes may in-part be attributable to Stress-NbA associated immune perturbations. Specifically, we hypothesize that stress leads to a double hit on the inflammatory response: 1) reducing anti-viral actions and 2) enhancing pro-inflammatory immune activity. We posit that reductions in anti-viral actions increase risk of viral infections (including coronavirus infections), while the pro-inflammatory immune activity increases the risk of **CSS** (McGonagle et al., 2020). Additionally, chronic stress that results from socioeconomic disparities may increase the development of additional conditions (including MetS) which potentiate the risk of adverse outcomes during COVID-19 infection.

By interrogating this hypothesis, we may learn how to help BIPOC patients reduce their vulnerability to COVID-19 and other viral illness effects and at the same time learn more about the intricate relationship between the brain's psychosocial threat response system and its microbial threat response system.

Given the distinct experiences of racial/ethnic groups in the United State, our study has largely focused in the US. However, accumulating body of evidence shows that indigenous people around the world have an increased vulnerability to COVID-19 due to systemic inequalities and marginalization. This is now recognized globally and has led to a call to action (McLeod et al., 2020; Power et al., 2020; Zavaleta, 2020). Hence, the hypothesis presented here may also have implications in other countries.

1.1. Stress and immunoactivation

Toxic stress is associated with the development of MetS and socioeconomic and discrimination stress is known to exacerbate the precursor state of **allostatic overload** that predisposes to MetS (Laurencin and McClinton, 2020; Osei and Gaillard, 2017). **Allostasis** is the capacity to achieve stability through change (McEwen, 1998a; Sterling et al., 1998). It refers to biological mechanisms that protect the body by maintaining an internal physiological balance (McEwen, 1998a). It takes metabolic energy for the brain to maintain physiological parameters within a

normative range in response to external and internal environmental stressors and this can lead to the metabolic wear and tear referred to as **allostatic overload**. Chronic stress, early trauma, hypercortisolism and immune dysfunction contribute to allostatic overload and the development of MetS and NCDs (Furman et al., 2019; McGill, 2014).

Chronic stress initiates pathological changes by promoting Stress-NbA. Among neural tissues that react to stress, the amygdala plays a particularly prominent role (Ross et al., 2017). The amygdala is charged with keeping the organism safe and thus can be considered the brain's fear conditioning center (Jovanovic and Ressler, 2010). As part of its job, when threat is perceived in sensory information sent from the thalamus, the amygdala expresses the excitatory neurotransmitter glutamate, which alerts many brain regions including 3 hypothalamic nuclei. The tripartite stress response system, includes the paraventricular nucleus that will transmit downstream to the pituitary and the adrenal cortex–the so-called hypothalamic-pituitary-adrenal (HPA) axis– resulting in output of the stress hormone cortisol; the lateral hypothalamus, which, along with stimulation of the locus coeruleus, will stimulate catecholamines in the sympathetic nervous system (SNS), and the mediobasal hypothalamus, which will help to trigger an inflammatory response syndrome (IRS). The heightened SNS activity stimulates the production and release of leukocytes from the bone marrow niche, which primes the body for heightened chronic inflammation (Heidt et al., 2014).

Vertebrates evolved in challenging microbial environments so natural selection favored the development of a hair trigger innate immune response set in motion by peripheral blood mononuclear cells (PBMCs), which when activated can become macrophages. Through the intercession of the transcription factor, NF-kB, these cells produce pro-inflammatory cytokines, which in short order precipitate a non-specific inflammatory response, while also setting in motion the maturation of a specific adaptive immune response comprised of cellular and humoral arms that is carried out by lymphocytes (T cells and B cells). The humoral immune response in particular can take up to a month and is dependent on B cells specialized to produce antibodies to neutralize specific antigens of pathogens.

When these immune defenses are used acutely and then decommissioned, the organism maintains its mitochondrial energy balance and reserve capacity while also remaining safe.

When mammals evolved, another survival challenge joined the microbial threat. Since the hallmark of the mammalian survival strategy is secure attachment to parental and other social objects, largely mediated by a part of the paralimbic cortex called the anterior cingulate cortex (ACC), the fear of separation became the source of great amygdalar distress. A particular form of the acute stress response engendered by the amygdala became prominent in the life of mammals threatened with separation from social attachments. In the course of evolution, the acute stress response became entwined with the acute inflammatory response, which also relies on the tripartite stress response system for mediation and modulation (Raison and Miller, 2013).

An important component of the innate immune response involves the canonical pathway of the nod like receptor family pyrin domain containing 3 gene (NLRP3) inflammasome activation. This process is thought to involve two phases (Kelley et al., 2019). The initial priming phase involves pattern recognition signaling through toll like receptor 4 (TLR4) recognized pathogen associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS); or through signs of cell damage such as holes in the cell membrane. In the case of LPS, NF-kB is activated, which drives transcription of IL-1β and NLRP3 genes, leading to translation of pro-IL-1β and inflammasome components. When these proteins reach a certain level, the cell is primed. In the second phase, a second activating signal causes NLRP3 to form a complex, which recruits pro-caspase-1, which is then converted to the mature enzyme caspase-1. Caspase-1 is capable of catalyzing the conversion of pro-IL-1β to mature pro-inflammatory cytokine IL-1β (Frank et al., 2016). IL-1β can then start a cascade with the production of other pro-inflammatory cytokines and mediators, resulting in an amplified inflammatory response.

Margolis (2015) has proposed the "immunoactivation hypothesis" to explain the inter-relationship of MetS and the immune response. Diseases are triggered by various etiological agents including microbes (PAMPS) as well as non-pathogen factors (non-PAMPs). But disease progression requires immunoactivation (Margolis, 2015). While this immunoactivation can be caused by these agents and other factors, it may also precede the particular etiological agent in the context of significant stress and this then compounds the inflammatory disease process due to oxidative stress, impaired glucose and lipid metabolism, and disrupted neurohormonal modulation (Margolis, 2015).

The immune system is well integrated with the stress response system in large part due to the intercession of NF-κB (Bierhaus et al., 2004). Catecholamines from SNS fibres increase NF-kB DNA binding in immune cells, including the macrophage (Miller et al., 2009a). In addition, the high mobility groupbox-1 (HMGB-1) protein is a damage associated molecular pattern (DAMP) that signals cellular distress and stimulates an innate immune response. Indeed, macrophages, as master regulators of innate immunity, release HMGB-1 (Castiglioni et al., 2011). Once released into the extracellular space HMGB-1 initiates an IRS through effects at TLRs.

It is postulated that microglia release HMGB-1 in response to acute or chronic psychosocial stress (Frank et al., 2016). Microglia have receptors for stress hormones and IL-1β. In this way psychological stress can cause neuroinflammation via a non-PAMP stress related pathway. There are likely many other molecules (for example heat shock proteins) that signal in a similar manner.

With regard to severe COVID-19, it has been shown that an outburst of catecholamines accompanies the **CSS** (Konig et al., 2020). Catecholamines use a feed-forward loop employing alpha-1 adrenergic receptor (α_1-AR) signaling in immune cells to enhance the production of pro-inflammatory cytokines like IL-6 (Staedtke et al., 2018). This adds to the chronic Stress-NbA related generation of IL-6 (Kiecolt-Glaser et al., 2003). It has been noted that by interrupting this loop with an α_1-AR antagonist like prazosin, the chance of diminishing the CSS is improved and this has begun to prompt new research in COVID-19 patients (Konig et al., 2020; Vogelstein et al., 2020).

The effect of psychosocial stress, such as that caused by experiences of racism and discrimination among ethnic minorities and those with low SES, on glucocorticoids (GCs), HMGB-1 and the NLRP3 inflammasome provides a potential mechanism by which such stress exposure could prime neuroinflammatory and peripheral inflammatory processes. In response to stressors perceived as "*dangers*", GCs might precipitate the release of HMGB-1 by macrophages and in the brain by microglia. With respect to COVID-19, it is of interest that stress may induce inflammatory priming to subsequent immune challenges, such as SARS-CoV-2 infection, since macrophages and microglia are potential substrates for stress induced priming.

1.2. Stress, immunoactivation and gene expression

Recently much has been learned about the epigenetic control of gene activation through stress mechanisms. Indeed, there appears to be a transcriptomic signature of chronic stress (Miller et al., 2008). A consensus is building focused on the existence of what Cole and colleagues at UCLA have named the "**conserved transcriptional response to adversity (CTRA)**" (Cole, 2014, 2019; Robinson et al., 2008; Slavich and Cole, 2013).

When individuals face persistent threat, their gene expression status reflects an activation of certain innate IRS-related gene sets and an underactivation of others. The PBMCs from highly stressed individuals show up-regulated expression of proinflammatory NF-kB pathway genes and down-regulated expression of type I IFN response and antibody synthesis genes. Transcript origin analysis has identified monocytes, plasmacytoid dendritic cells (DCs), and B lymphocytes as primary cellular mediators of these effects. These gene expression outcomes are to some extent mediated by stress-related SNS stimulation effects on myelopoietic output.

An IRS is activated when extracellular signals prompt transcription factors to translocate from the cytoplasm into the immunocyte's nucleus. Here they activate genes leading to the production of pro-inflammatory cytokines that mediate the IRS. However, even in innate immune responses there is specificity that is based on the particular type of pathogenic exposure that is encountered (Amit et al., 2009).

Thus, if an individual is exposed to an extracellular pathogen such as a bacterium, the intracellular transcription factors NF-κB and activator protein 1 (AP-1) are triggered by bacterial PAMPs. A proinflammatory cascade with stimulation of immune response genes for *IL1β, IL6, IL8*, and *TNF*, results in increased output of these proinflammatory cytokines.

On the other hand, if a person encounters an intracellular viral pathogen such as SARS-CoV-2, then transcription factors such as IFN regulatory factors are designed to activate resulting in amplification of antiviral immune response genes such as type I IFN genes and IFN stimulated genes (ISGs). The type I IFN pathway will set in motion the production of other pro-inflammatory cytokines when this type of PAMP is sensed (Irwin and Cole, 2011; Slavich and Cole, 2013).

Type I IFN-stimulated gene responses are highly regulated by epigenetic control mechanisms, including methylation and acetylation processes that modulate the transcriptome (Menachery et al., 2014). During H1N1-09 or SARS-CoV infection, when these viruses were recognized by the host, type I IFN pathways were stimulated, and chromatin modification complexes were induced to remove certain deactivating histone marks such as H3K27me3 and place activating ones such as H3K4me3. This resulted in a strong anti-viral response with activation of certain transcription factors such as phosphorylated signal transducer and activator of transcription 1 (*STAT1*) and IFN regulatory factor 7(*IRF7*).

However, it is known that viruses can exploit natural epigenetic deactivation processes to modulate and control host IFN response (Menachery et al., 2014). Research suggests that coronaviruses have evolved ways to delay recognition and impair IFN induction until after peak viral loads have embedded resulting in a limitation of the type I IFN inflammatory defense. For example, reports have demonstrated the ability of coronaviruses to inhibit IFN production in the course of SARS. It is clear that coronaviruses, despite generation of significant amounts of type I IFN inducing dsRNA, are able to suppress early IFN induction (Spiegel et al., 2005; Versteeg et al., 2007).

Furthermore, viral immunomodulatory nonstructural proteins have the capacity to inhibit IFN responsiveness in a cell specific manner. Macrophages express angiotensin converting enzyme-2R (ACE-2R), the receptor exploited by SARS-CoV-2 for entry to cells (Wan et al., 2020). Macrophages and conventional dendritic cells (cDCs) with deficient IFN responses to coronaviruses, appear to be dependent on the supply of type I IFN from plasmacytoid DCs (pcDC) if there is to be protection for infected cells. Coronaviruses like SARS-CoV-2 may interfere with regulation of the type I IFN system by disrupting the cross-talk of pcDCs with macrophages and cDCs (Cervantes-Barragan et al., 2009). Interestingly, the lack of the type I IFN receptor (IFNAR) on macrophages in LysM-Cre ± ifnar1fl/fl mice exposed to murine hepatitis coronavirus leads to completely uncontrolled viral replication and death in only 4 days. Thus, type I IFNs provide important protection for macrophages under conditions of coronavirus infection and therefore facilitate removal of the virus from the circulation through the cooperation of macrophages and DCs.

High rates of viral replication leading to excess production of NF-kB related pro-inflammatory cytokines by infected cells plus delayed stimulation of anti-viral IFN responses pursuant to viral escape mechanisms are increasingly recognized as major factors in the development of severe COVID-19 infections contributing to excessive morbidity and mortality (Merad and Martin, 2020). Researchers have been surprised that such diminished IFN protection can be persistent despite a massive innate NF-kB based immune response. There is some suggestion that SARS-CoV-2 attachment to ACE2Rs on the surface of macrophages enable the virus to gain cytoplasm access leading to activation of the NLRP3 inflammasome with production of IL-1β. While IL-1β can amplify macrophage activation of the innate immune response, it can also

dampen type I IFN production (Mayer-Barber et al., 2014).

A recent study looked at an integrated immune analysis of 50 COVID-19 infected patients with varying degrees of illness severity (Hadjadj et al., 2020). The researchers found a persistent viral load and a pronounced IRS at least partially driven by NF-kB pathway hyperactivation in severely ill COVID-19 patients. But they also found a significantly underactive type I IFN response reflected in no IFN-β and low IFN-α production and activity. This profile suggests that severe COVID-19 disease stems from an enormous IRS kindled by both PAMPs and DAMPs in the context of high viral load related to an impaired type I IFN anti-viral response. Risk factors for severe COVID-19 infections would therefore be expected to include MetS comorbidities that are prevalent in BIPOC communities and are associated with an NF-kB innate immune response and an impaired type I IFN immune response, compounded by the ability of the SARS-CoV-2 virus to impair the generation of an anti-viral IFN response. Indeed, metabolic diseases have been found to be prominent risk factors for adverse outcomes among individuals with COVID-19 infection (Costa et al., 2020). It is also suspected that patients with pre-morbid coronavirus risk factors like hypertension, type 2 diabetes, hyperlipidemia and obesity will experience oxidative stress-driven induction of tissue factor (TF) (Merad and Martin, 2020). This will set in motion inflammatory processes that trigger endothelial cells to attract macrophages, which bind and then activate the NF-kB pathway. This contributes to the endotheliitis, cytokine storm and diffuse intravascular coagulation challenges patients with severe COVID-19 face.

Another way to think of stress, immunoactivation and gene expression is to examine how a person can impact gene activation states through behavioral change. Buric et al. (2017) reviewed clinical and non-clinical studies using a variety of research designs that have studied gene expression analysis in relaxation response eliciting mind body interventions (MBIs) (i.e., mindfulness and other meditation techniques, yoga, Tai Chi, Qigong, and breath regulation) (Buric et al., 2017). Eighteen relevant studies were analyzed. Overall, the studies indicate that MBIs are associated with a downregulation of the NF-kB gene ontology pathway. Thus, it appears that MBIs may attenuate the adverse impact that chronic stress has on gene expression, with implications for health promotion and illness prevention (particularly during the pandemic), notably among individuals with heightened chronic stress, including marginalized racial or ethnic groups or individuals of low SES.

To summarize, if the BIPOC population exposed to chronic stress-induced non-PAMP inflammation were to exhibit a type I IFN anti-viral handicap during a coronavirus pandemic, in which the virus can exploit epigenetic strategies to further disrupt host type I IFN anti-viral defenses, one might expect the excess morbidity and mortality we are seeing in racial and ethnic minorities during the COVID-19 crisis. Explicating the assortment of mechanisms that contribute to delayed type I IFN defense and to the different phases of inflammatory response will be crucial to understanding COVID-19 disease risk and outcome. It appears there is enough evidence suggesting chronic discrimination stress is one driver we must consider.

1.3. Stress, and the evolutionary convergence of social and inflammatory biases

Mounting a threat-provoked premonitory immune response, would be evolutionarily advantageous. In fact, this kind of precautionary response occurs when immune response genes respond to psychosocial brain signals suggesting that a non-pathogen social danger is present with wounding and concomitant bacterial infection potential (Slavich and Cole, 2013). The innate IRS can indeed be activated in a non-PAMP fashion when someone is subjected to adverse interpersonal conditions such as social conflict, rejection, isolation, or exclusion and low SES. This may relate to the extraordinary importance social attachment and its survival advantage plays in our mammalian evolutionary history (MacLean, 1990;Fricchione, 2011).

A large literature has documented associations between low SES in both childhood and adulthood with inflammation in later life (Pollitt et al., 2007). Neighborhood, family, individual and biological factors provide key pathways between SES and health effects (Chen and Miller, 2013). Additionally, several factors including discrimination as well as perceived stress, depression, and distrust have all been associated with altered inflammatory processes (Lewis et al., 2010). Inflammatory processes have in turn been associated with chronic NCDs such as cardiovascular disease and diabetes (Chen and Miller, 2013).

The link between social determinants and inflammation may relate to gene expression and a recent study provided the first large-scale assessment of this **social genomics hypothesis** in an epidemiological cohort (Brown et al., 2019). It provides preliminary evidence for the hypothesis that the levels of gene expression from various immune and metabolic pathways covary with social factors such as loneliness, discrimination, chronic stress burden, and adult SES (Lewis et al., 2010). One early social risk factor study focused on the effects of loneliness on gene expression in a group of high loneliness vs. low loneliness subjects (Cole et al., 2007). Those subjects with high loneliness showed up-regulation of NF-kB driven innate immune response gene sets and down-regulation of type I IFN and humoral response gene sets. This may represent a signature gene expression profile for those with the chronic social isolation stress known to increase risk of MetS and inflammatory disease (Cole et al., 2007). The social isolation challenge of COVID-19 might compound this risk.

Acute stress has been found to enhance antiviral defenses (Phillips et al., 2009; Powell et al., 2013), but chronic stress has been more associated with diminished antiviral immune responses (Irwin and Cole, 2011). Assuming a chronic activation of non-PAMP social adversity pathways, as theorized to occur in racial/ethnic minority groups, Irwin and Cole (2011) have hypothesized that the innate IRS response to contemporary social adversity involves hyper-activation of the NF-kB regulated genes driving pro-inflammatory protection against bacterial extracellular pathogens, along with a parallel hypo-activation of antiviral immune response genes, designed to combat viral intracellular pathogens (Irwin and Cole, 2011). This scenario may help explain the intense effect of chronic stress in lowering the threshold for viral illnesses (Miller and Cohen, 2005).

Thus, it has been proposed that this increased bacterial IRS and reduced viral IRS signature represents our CTRA *basal transcriptome* (Irwin and Cole, 2011 ; Antoni et al., 2012; Cole et al., 2012; Powell et al., 2013). While adaptive in the face of acute threats, such a programmatic IRS defense strategy may put people at risk of severe viral disease when anticipated or perceived non-PAMP related social dangers are persistent, as we may surmise they are in under-resourced and discriminated against minority populations (Slavich and Cole, 2013). Indeed, it has been shown that low social class early in life, a condition more prevalent in members of marginalized racial and ethnic minority groups, confers a heightened pro-inflammatory state as a lasting biomarker (Miller et al., 2009b). Studies have also shown that the elderly have greater levels of pro-inflammatory cytokines and acute phase proteins in their blood and, in addition, greater activation of the NF-kB and its downstream regulated genes responsible for the IRS (Franceschi et al., 2017; Furman et al., 2017; Ferrucci and Fabbri, 2018). The high morbidity and mortality we see in the elderly COVID-19 positive population may reflect the fact that a viral insult in an older patient, whose chronic IRS is primed to protect against bacterial assault but also characterized by a susceptibility to viral disease, may be overburdened not only by metabolic wear and tear (allostatic overload) but also by a handicap in the battle against the SARS-CoV-2 virus (Furman et al., 2017; Ferrucci and Fabbri, 2018). It was recently speculated that premorbid immune response deficiency in the aging population impairs successful control of viral load early in COVID-19 infection, increasing the morbidity and mortality observed in the elderly (Blanco-Melo et al., 2020).

If the hypothesis, in which there exists a transcriptional landscape that includes specific inflammatory non-PAMP genes that correlate with the adversity of psychosocial stress, is correct, there could be a biological

underpinning that adds to the social determinants of worsened disease that we are seeing in this COVID-19 pandemic. Under conditions of chronic psychosocial stress and in the case of exposure to SARS-CoV-2, we might expect to see what we are seeing in this pandemic–a more intensive risk for COVID-19 as well as a greater risk for severe morbidity and mortality. Severe complications emerge when the pre-morbid innate IRS, that has become chronic, compounds the physiological challenge patients face when stricken with the highly contagious SARs-CoV-2 virus.

This unholy alliance of a severe pathogen-associated immune response secondary to the COVID-19 virus and a persistent non-PAMP CTRA immune response related to psychosocial stress in minority populations and the elderly, may be expected to increase the morbidity and mortality of these patients.

1.4. Socioeconomic and environmental stressors, amygdalar activation, and the immune response

Because social attachment is so central to our evolutionary survival strategy, when it is threatened, our amygdalae erupt with alarm (MacLean, 1990; Fricchione, 2011). Amygdalar overactivation in the face of stress leads to SNS overdrive, which can produce transcriptional alterations in differential gene expression (Irwin and Cole, 2011).

Recently a model has been developed to help explain the stress-related cascade that can lead to PBMC changes commensurate with the CTRA response and downstream morbidity. When the amygdala perceives environmental threats, it will produce excitatory glutamatergic signals in axonal flow from the central amygdala nucleus. This will lead to hypothalamic and brainstem stimulation that results in hormonal, autonomic, and behavioral changes reflective of the fear and stress response. In stressed medical ICU physician trainees for example, it has been shown that chronic stress induces monocytosis and neutrophilia (Heidt et al., 2014). In mice, stress activates upstream hematopoietic stem cells when heightened sympathetic drive releases norepinephrine. Norepinephrine stimulates the β_3 adrenergic receptor to activate bone marrow niche cells to increase hematopoietic stem cell proliferation resulting in output of neutrophils and inflammatory monocytes (Heidt et al., 2014).

A longitudinal cohort study using positron emission tomography/computerized tomography (PET/CT) and psychometric testing showed that amygdala activation (AmygA) in stressed subjects correlated with increased bone marrow activation and myelopoiesis as well as with arterial wall inflammation and was predictive of future cardiac events (Tawakol et al., 2017). This suggests that heightened AmygA is associated with hematopoietic overactivity and arterial inflammation, and that activation of this neural-hematopoietic-arterial network predicts the development of future major adverse cardiovascular events (MACE).

In a follow up PET/CT study, Dar and colleagues (2020) were able to show that individuals with lower AmygA, despite chronic exposure to socioeconomic or environmental stressors, enjoyed relative protection from cardiovascular disease (i.e. a > 50% decreased MACE risk within 5 years of imaging) (Dar et al., 2019). This protective effect may be secondary to reduced production of bone marrow derived immune cells and less atherosclerotic inflammation. The authors suggest that enhancing neurobiological resilience, defined as lower AmygA despite chronic stress exposure, may decrease the risk of cardiac disease.

In another recent study, lower SES was associated with higher AmygA; and independently predicted MACEs presumably through a cascade that includes heightened AmygA, bone marrow activation, and arterial inflammation (Tawakol et al., 2017). These findings illuminate a Stress-NbA mechanism by which SES disparities may potentiate adverse health outcomes.

The results of this study may directly relate to the disparities seen with COVID-19 because chronic stressors, known to be associated with AmygA and cardiac disease risk, were quantified using individual home addresses reflecting differential stress exposure due to neighborhood median household income, and crime rate. Subjects living in the lowest-

income neighborhoods had 4 times the risk of a MACE over the next 5 years when compared to subjects living in the highest-income neighborhoods (Tawakol et al., 2019).

It has also been demonstrated that experimental inflammatory challenge can selectively increase AmygA to socially threatening images determined with fMRI. Interestingly, this activity correlated with feelings of social disconnection (Inagaki et al., 2012). With regard to COVID-19 infection, minority perception of threat signals in the context of inflammatory challenge may exacerbate vulnerability to morbidity and mortality from an AmygA cascade that leads to bone marrow activation of hematopoiesis and arterial inflammation associated with NF-kB transcriptional overactivation and the CSS.

1.5. Stress, immunoactivation and mitohormesis

Psychosocial stress modulates mitochondrial functioning through physiological and behavioral effects. This implies that the brain provides one level of analysis of psychosocial stress signals while mitochondria serve as monitors of stress at the cellular level.

Mitochondria provide energy as well as signals that mediate the organism's capacity to adapt to stress. Psychosocial stress can get translated into metabolic activation and processed at the cellular level as *oxidative stress* (McEwen, 1998b). As mentioned, it takes metabolic energy input for the brain to maintain physiological parameters within a normative range in response to external and internal environmental stressors and this can lead to allostatic loading under chronic stress conditions.

A process called *"mitohormesis"* offers an intracellular framework with the potential to help us understand the severity of the COVID-19 experience of disadvantaged minorities. In mitohormesis, small amounts of stress tend to enhance capacity to deal with future stress challenges through mitochondrial remodeling and priming of antioxidant pathways (Cox et al., 2018). In what is referred to as the *"mitonuclear matching process"*, Tumor Necrosis Factor Receptor-Associated Protein-1 (TRAP-1) inhibition in mitochondria under tolerable stress activation can lead to reactive oxygen species (ROS) generation in amounts that cause retrograde stress signaling from mitochondria (mtDNA) to nuclear DNA (nDNA) with induction of Forkhead box O (FOXO) mediated transcription of cell protection antioxidant genes. These nuclear antioxidant gene products travel back to mitochondria in a process of retrograde stress signaling to activate a mitochondrial antioxidant defense and remodeling process that protects cells from future insults. Such positive stress exposures will be processed at the mitochondrial level as *"protective embedding"* with the tendency to enhance mitochondrial reserve capacity and resilience.

However large amounts of chronic toxic stress cause mitochondrial distress with structural consequences (mitochondrial fission), loss of the matching of mtDNA and nDNA interests required for cellular health, and overproduction of free radical ROS, which can lead to cellular distress and eventual death by apoptosis. Persistent negative exposures result in what is called *"negative embedding"* with intensive health consequences due to the cellular pathophysiology of mitoallostatic loading (Picard et al., 2018).

The consequences of stress and mitoallostatic loading include mtDNA damage and decreased mitonuclear matching, telomere shortening, altered gene expression (CTRA), cell stress, fatigue, and chronic immunoactivation via NF-kB induction and inflammasome activation (Jo et al., 2016). This latter effect owes itself to the intimate relationship between DAMP, PAMP and non-PAMP stimulation of mitochondrial ROS with promotion of NLRP3 inflammasome production of pro-inflammatory cytokines in activated macrophages (Jo et al., 2016) · Furthermore, Van den Bossche et al. (2016) have shown that inflammatory M1 macrophage activation dampens healthy mitochondrial function, impairing the capacity of mitochondria to repolarize macrophages to an anti-inflammatory M2 phenotype (Van den Bossche et al., 2016).

Switching macrophage polarization states is an emerging idea for managing inflammatory diseases and could be conceptualized as a

therapeutic target to arrest the kind of CSS that has overtaken many patients with severe COVID-19 infections. Mitochondrial manipulation would constitute an approach of choice to facilitate macrophage repolarization and reduce the harmful effects of chronic toxic stress in racial and ethnic minority populations at risk.

1.6. Treatment effects on COVID 19 disease progression and mortality in BIPOC

Another point that merits discussion is what current evidence says about treatment effects on COVID-19 disease progression and mortality in BIPOC communities. It is of interest that early administration of IFN-a2b in one study appeared to be associated with reduced in-hospital mortality as opposed to late IFN therapy, which was associated with increased mortality and delayed recovery. This suggests that the timing of IFN therapy is key for favorable responses in COVID-19 patients and also suggests that, in BIPOC patients, whom we hypothesize are starting from a lower IFN-based anti-viral immune response, early IFN based therapy for COVID-19 may be especially beneficial (Wang et al., 2020). This is because it is increasingly recognized that starting out with an imbalanced IFN response may contribute greatly to the pathophysiology of COVID-19 (Acharya et al., 2020).

It is also of interest that preliminary data from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial suggest that dexamethasone, which as a treatment can be expected to dampen an over-active NF-kB dominated cytokine storm response, appears to be beneficial for those participants treated well into the symptomatic phase, with the onset of hypoxemia. There was, however, possible harm when dexamethasone was used to treat participants without severe COVID-19 symptoms. Therefore, although not conclusive, the early findings from the RECOVERY trial do not support use of dexamethasone for patients with milder disease (Johnson and Vinetz, 2020).

According to our hypothesis, BIPOC patients with COVID-19 may be at excess risk due to their chronic stress related activation of the NF-kB pro-inflammatory pathway. Therefore, since they start from a primed baseline, they may be more susceptible to quickly progress to a severe COVID-19 precipitated IRS. It will be interesting to see whether expeditious use of dexamethasone in BIPOC patients, under conditions of severe COVID-19, is particularly therapeutic.

This discussion suggests to us that the BIPOC population, who we hypothesize to be at risk both from too little Type I IFN pathway activation early in their exposure to COVID-19 and an overly robust NF-kB pathway activation that eventually leads them to severe status, may especially require early treatment with IFN therapy, with a steroid like dexamethasone at the ready if and when severe symptoms emerge. As treatment trial data accumulates, it will be important to tease out relative response rates in BIPOC subjects with an eye toward this hypothesis.

2. Summary

The interaction between social conditions and communicable diseases is being illuminated by the SARS-CoV-2 pandemic. The evolutionary relationship between the inflammatory bias of our heritage in a dirty microbial world and our social attachment bias as mammals represents our bimodal survival strategy.

The necessary bidirectional communication between the central nervous system (CNS) and the immune system is the product of these evolutionary selection biases, but it has become a conditional handicap in the modern world of chronic stress, especially for individuals of marginalized racial or ethnic groups or individuals of low SES (Irwin and Cole, 2011). Macroaggressions and microaggressions in our society may contribute to inflammation-related NCDs, while dampening innate anti-viral immunity. In other words, acute PAMP immunoactivation on top of chronic non-PAMP innate immunoactivation (with decreased viral immune response) may have led to increased COVID-19 related morbidity and mortality among the BIPOC population. This double immunological

hit has conceivably predisposed to the tragic outcomes we are witnessing in what has been called an NCD–COVID-19 co-pandemic (Ahmed et al., 2020).

Prior studies have shown the impact of chronic stress on viral diseases Cohen and colleagues (1991) observed that higher levels of perceived stress correlate with greater risk of developing coronavirus infection after nasal inoculation (Cohen et al., 1991). Psychological stress also predicts a greater expression of illness and an increased production of IL-6 in response to an upper respiratory infection (Cohen et al., 1999). The present viral pandemic emphasizes the double jeopardy at risk populations face from the combination of stress immunoactivation and diminished anti-viral immune response.

What is to be done? Structural racism creates an enormous toll of psychosocial stress with vulnerability to NCDs and to viral communicable diseases (CDs). Sociopolitical movements to dismantle structural racism may benefit from a deeper understanding of the physical consequences of maltreatment of racial and ethnic minorities as illuminated in the multifaceted impacts of the COVID-19 syndemic (Horton, 2020).

A population-based approach to the public health problems of racial and ethnic minority groups is mandatory. At the turn of the 20th century, poor people succumbed at alarming rates to CDs. In light of public health advances like water chlorination and vaccination later in the century, annual death rates dropped by more than 90% to approximately 50 per 100,000 people from 800 per 100,000 (Centers for Disease and Prevention, 1999). The development and implementation of community-based interventions are now needed to reduce the secondary effects of the social, behavioral, and economic determinants of illness (Borja, 2020). A trans-NIH working group on the social, behavioral, and economic impact of COVID-19 has recommended looking at such interventions. We would add the challenge of homelessness, a condition overrepresented in racial and ethnic minorities, to the list of potentially modifiable risk factors since people experiencing homelessness have been estimated to be twice as likely to be hospitalized, two to four times as likely to require critical care and twice as likely to die as the general population (Culhane et al., 2020).

Population based scalable MBIs designed to mitigate stress-related risk and promote resilience or recovery in high-risk populations, when combined with the structural community-based interventions suggested above, could help improve our long-term response to the pandemic and help prepare at-risk communities more effectively for future public health emergencies. In addition to the extensive acute care medication and vaccine trials that are underway, there is a need to study the potential of certain medications, such as melatonin, minocycline, prazosin, and metformin, along with behavioral and MBI approaches, to manipulate the bidirectional CNS–immune regulatory system by affecting gene expression changes in stress and the immune response.

Finally, opportunities may exist for Big Data to help reduce health care disparities (Zhang et al., 2017). Machine learning and natural language processing (NLP) could use coded demographic and social determinant data extant in electronic medical records to improve longitudinal approaches to evidence-based care for the most discriminated against groups in our society. Strengthening surveillance by connecting geographical and social determinant variables for minority populations residing in certain zip codes to clinical outcomes would be of assistance. If carried out ethically, we may be cautiously optimistic that this enhanced level of understanding can improve our chances of effectively intervening in a future viral pandemic to both prevent illness and treat it when it occurs.

There are challenges to the hypothesis presented here indicating the need for more research. While there is growing consensus that chronic social stress triggers a pro-inflammatory state marked by elevated antibacterial gene expression pathways along with reductions in antiviral defense, and that social subordination has the power to affect the gene expression response to microbial challenges, there is countervailing research available (Snyder-Mackler et al., 2016). For example, in research on female rhesus macaques, low social status drives more

exaggerated cell expression of both NF-κB and IFN-associated genes after exposure to the viral surrogate Gardiquimod (Sanz et al., 2020).

In addition, IFN-induced gene expression has been found to be higher in African American systemic lupus erythematosus (SLE) patients than in European American patients (Ko et al., 2013). Nuclear breakdown debris and subsequent antibody complexes lead to over-activation of the innate immune response through TLR and type I IFN activation in Black SLE patients.

Perhaps most challenging is work from the UCLA group in which discrimination stress and racial differences in WBC gene expression were examined (Thames et al., 2019). In one study, they found greater activation of pro-inflammatory NF-kB and AP-1 pathways in African Americans versus European Americans but also found elevated transcription of innate antiviral response type I IFN factors. There did not appear to be the kind of deficit in antiviral response gene activation seen in other socially challenging contexts in previous studies. The authors speculate that differences in viral disease background (some subjects were stable chronic HIV + patients) or in SES or other environmental circumstances may have played a role. It is notable however, that the Log 2 transcription factor-binding motifs ratio, when discrimination stress was considered, did show that antiviral response transcription factors (IRFs) were in the negative range while NF-kB and AP-1 were in the positive range relative to Caucasians.

Recent SARS-CoV-2 studies using cell and animal models of infection, as well as transcriptional and cytokine and chemokine profiling of COVID-19 patients, support the importance of an imbalanced immune response characterized by severity-associated upregulation of the NF-kB gene expression pathway and downregulation of the type I IFN gene expression pathway, as the key vectors that drive morbidity and mortality (Blanco-Melo et al., 2020; Bost et al., 2020; Hadjadj et al., 2020). But in order to advance our hypothesis, more transcriptomic gene expression research designed to focus on toxic stress and particularly social discrimination stress in a large sample of the BIPOC population at risk for COVID-19 is essential (Bost et al., 2020; Hadjadj et al., 2020). We need to know whether segments of the BIPOC population are particularly vulnerable to the CTRA, compounding their risk of failing to mount an adequate type I IFN defense when exposed to a COVID-19 viral load. Furthermore, single cell analysis would be useful for looking at some of the pathways described and enhance our understanding of specific immune processes that may increase relative risk for SARS-CoV-2 infection.

We have learned the hard way that to ignore the ample scientific warnings of our lack of preparedness for a pandemic in our country was pure folly. Sadly, this failure has fallen hardest on our disadvantaged minorities. Their social determinants of illness vulnerability may reflect, to some extent, a combination of stress response and immune response related factors aligned against them, leading to excess morbidity and mortality in this COVID-19 pandemic. We hope the hypothesis presented here will prompt studies designed to confirm or reject it. And if confirmed we hope it will help society be better prepared to help these at-risk populations in the future.

Declaration of competing interest

The authors have no competing interests to declare.

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