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Review

Isolation, social stress, low socioeconomic status and its relationship to immune response in Covid-19 pandemic context

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ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak was first reported December 2019, in Wuhan, China, and has since spread worldwide. Social distancing or isolation measures were taken to mitigate the pandemic. Furthermore, stress and low socioeconomic status in humans confer increased vulnerability to morbidity and mortality, what can be biologically observed. This condition tends to remain during the Covid-19 pandemic. Social disruption stress (SDR) raises important questions regarding the functioning of the immune system, and the release of several stress hormones. A molecular pattern, conserved transcriptional response to adversity (CTRA), is thought to have evolved to defend against physical injury during periods of heightened risk. Chronic CTRA activation could leave an organism vulnerable to viral infections, leading to increased pro-inflammatory gene expression and a suppression of anti-viral gene expression. The activation of such transcriptional status is related to conditions of social stress through either hostile human contact, or increased predatory vulnerability due to separation from the social group and also low socioeconomic status. This review aims to point out questions for government officials, researchers and health professionals to better target their actions during a pandemic and encourage studies for a better understanding of these characteristics.

1. Covid-19 pandemic and mitigation guidelines

The coronavirus disease 2019 (Covid-19) outbreak caused by the novel coronavirus SARS-CoV-2 was first reported December 2019, in Wuhan, China, and has since spread worldwide, causing thousands of deaths (WHO, 2020 - 1). The high infectivity of its etiological agent combined with the absence of previous immunity in the human population and the absence of a vaccine, makes the number of cases grow exponentially, if measures are not taken to stop its transmission (Kucharski et al., 2020). This situation led to a global public health campaign to slow the spread of the vírus, with recommendations for increasing hand washing, reducing face touching, wearing masks in public and physical distancing. There is a recommendation for restriction or prohibition on the functioning of schools, universities, places of community interaction, public transport, in addition to other places where people are crowded (Garcia and Duarte, 2020).

Such community mitigation guidelines, when adopted at the beginning of an epidemic period, are very important to preventing transmission, decreasing the spread of the disease, and consequently contribute to flatten the epidemic curve (Qualls et al., 2017). Notably, the process of social isolation can affect people's lives (World Health Organization (2), 2020). The application of social distancing or isolation measures in mitigating pandemic consists an important tool. However, it, in addition to stress situations, may influence the immune system in both humans and animals (Takahashi et al., 2018).

As the pandemic expands worldwide, following the restriction guidelines are a greater challenge. Specifically for vulnerable populations, such as residents of urban and peri-urban informal settlements. Space constraints, violence, and overcrowding in slums make physical distancing and self-quarantine impractical, and the rapid spread of an infection highly likely (Corburn et al., 2020). In particular, in these populations, which are the most economically vulnerable groups, there is a high rate of stress, which raises the need for special attention (Tadvi and Bandi, 2017; Lui et al., 2017; Chen and Miller, 2013).

The objective of this review is to point out questions about the effects of the Covid-19 pandemic in conditions such as isolation and low socioeconomic status, that is, how it relates to stress. With that, provide subsidies for discussions about attention and study of these effects,

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especially in this pandemic period. These data are of great importance for government officials, researchers and health professionals to better target their actions during a pandemic and a possible second wave and expand the research in the area.

2. Social disruption stress and immune system

It's well known that the immune system is influenced by neuronal interactions via feedback mechanisms and complex connections and interactions between immune cells and the central nervous system. This allows the immune system to engage the rest of the body in the fight against infection from pathogenic microorganisms and permit the nervous system to regulate immune functioning (Webster Marketon and Glaser, 2008; Dantzer, 2018). Particularly, the respiratory tract contains rich vasculature and autonomic nervous system innervation, specifically within the lung (Hoyle et al., 1998; Abelson et al., 2010).

Thus, in this context of a Covid-19 pandemic, social disruption stress (SDR) raises important questions regarding the correct functioning of the immune system. A stressor is defined as a threat or perceived threat against the body's homeostasis. The body reacts to stressors by activating conserved behavioral and physiological stress responses in an attempt to re-establish homeostasis. Some classical stressor examples are physiological difficulties such as injury or nutrient deficiency, perceived threats such as public speaking, and psychosocial burdens like social subordination or loneliness (Avitsur et al., 2006). Social stress is defined as feelings of discomfort or anxiety that individuals may experience in social situations, and the associated tendency to avoid potentially stressful social situations (Wadman et al., 2011). Cruces et al. (2014) showed in a review that the disruption of social bonds in social species constitutes a potent emotional stress. Social isolation is considered a risk factor for morbidity and mortality, and the response to isolation or loneliness can exert a significant influence on the three regulatory systems throughout the lifespan of the organism, which include characteristics of the stressor itself (e.g., duration), as well as those of the organism (e.g., biological age), in addition to external factors (e.g., environmental events).

It has been reported that SDR leads to several immune response alterations in both humans and animals. Using a rhesus monkey model, Capitanio and Cole (2015) demonstrated that social instability adversely impacted metabolites of epinephrine and norepinephrine, and expression of immune response genes, as well as behavior. Additionally, the authors used sympathomimetic drugs to challenge the sympathetic nervous system. It was demonstrated that the responses in lymph nodes tracked the social, and not the drug, condition: social instability upregulated the density of sympathetic nervous system fibres in lymph nodes and downregulated Type I interferon gene expression, which is related to induce protection against viruses. This demonstrates the sympathetic nervous system is extremely sensitive to social conditions, altering the expression of this gene.

Human studies shows that individuals with high aggression traits display heightened inflammatory cytokine levels and dysregulated immune responses such as slower wound healing. Psychological stress can trigger cytokine release, and growing evidence has shown an important role for the immune system in regulating negative emotional states as well as personality (Takahashi et al., 2018). For example, hostile marital relationships are associated with slower wound healing and dysregulated cytokine production at wound sites. Proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor (TNF-a) and C-reactive protein (CRP) are positively related to behavioral aspects of aggression traits and acute episodes of anger (Kiecolt-Glaser et al., 2003).

In addition to aggression, depression, which is associated with social isolation, both in the elderly and in young people (Domènech-Abella et al., 2017; Ge et al., 2017) can alter levels of key cytokines in the inflammatory process. Increased circulating IL-6 has been observed in humans suffering from major depression (Maes et al., 1997; Kiecolt-Glaser et al., 2003; Hodes et al., 2014; Kiraly et al., 2017).

Stress is also known to cause the release of several stress hormones - primarily glucocorticoids through activation of the hypothalamic–pituitary–adrenal (HPA) axis and catecholamines through the sympathetic nervous system (Marketon and Glaser, 2008). It has been shown that social disruption stress increases plasma corticosterone (Padgett et al., 1998).

Loneliness, also termed Perceived Social Isolation (PSI), has become of worldwide concern, impacting on health, and affecting all groups from adolescents to especially the elderly. Self-isolation and social distancing are necessary and a recommendation during the Covid-19 pandemic, but may increase the loneliness levels, what may have a negative impact on health (Baker and Clark, 2020; Berg-Weger and Morley, 2020; Holt-Lunstand et al., 2015). It has been demonstrated in different animal models. Plasma corticosterone levels correlated significantly with plasma ACTH and with adrenal corticosterone levels in socially isolated (caged) rats (Prelló et al., 2006). In a zebrafish model, neurochemical analyses showed that serotonin levels increased when fish were exposed to social stimulus after acute isolation, but its metabolite 5HIAA decreased in response to social stimulus following both acute and chronic isolation. Dopamine levels were also reduced in fish exposed to social stimulus after acute and chronic isolation (Shams et al., 2017).

Moreover, stress and low socioeconomic status in humans confer increased vulnerability to morbidity and mortality, what can be biologically observed. Lower socioeconomic status individuals have restricted autonomy and opportunities that could lead to more stress and consequently increase in stress hormones, such as cortisol, catecholamines, glucagon and growth hormone (Volaco et al., 2018). Socioeconomic disadvantage was also associated with greater accumulation of cortisol in hair in both parents and children, and that both perceived and biological markers of stress in a study with socioeconomically diverse samples of 35 parents and 26 children (Ursache et al., 2017). Another study evaluated 108 men and 94 women. Low socioeconomic status was associated with heightened ambulatory blood pressure and cortisol output over the working day, which may reflect stress-related activation of biological pathways (Steptoe et al., 2003).

Additionally, worldwide, disadvantaged socioeconomic position (SEP) is widely associated with disease and mortality, what tends to remain during the Covid-19 pandemic (Khalatbari-Soltani et al., 2020). Taken together, this data raises concern to vulnerable populations in this pandemic scenario.

3. Transcriptional profile related to adversity and its impact on immune response

A field of research, related to the established field of behavioral genetics, seeks to identify the genes that influence social behavior, to understand the influence of these genes on the underlying neural and endocrine mechanisms and to explore the effects of the environment, especially the social environment, in the action of genes. Social genomics research field has been demonstrating that humans and other vertebrates activate a conserved pattern of gene transcriptional responses when they experience extended periods of threat or uncertainty (Cole et al., 2015a, b; Slavich and Cole, 2013). A molecular pattern was observed, the conserved transcriptional response to adversity (CTRA), which is mediated by the sympathetic nervous system "fight-or-flight" response and is thought to have evolved to defend against physical injury during periods of heightened risk. The CTRA pattern involves up-regulated transcription of genes related to pro-inflammatory responses (such as *IL1B*, *IL8*, and *IL6*), which play a key role in immune responses to wounding injuries and related bacterial infections. It also involves a complementary down-regulation of antiviral genes (e.g., *IFI*- and *ISG*-family genes) and genes involved in antibody synthesis (e.g., *IGJ*). The CTRA supposedly evolved to fight against physical threats. However, among humans, it may also be triggered by non-physical threats, including threats to the symbolic self, such as social isolation (Cole et al., 2007; Slavich and Cole, 2013).

These transcriptional changes indicate a down-regulation of antiviral

defenses and a corresponding up-regulation of proinflammatory wound-healing and antibacterial defenses (Irwin and Cole, 2011; Cole, 2013). CTRA facilitates an adaptive response to acute threats that could result in injury. However, chronic CTRA activation could leave an organism vulnerable to viral infection and subject to collateral damage from systemic inflammation, ultimately leading to disease, disability, and death (Belsky and Snyder-Mackler, 2017). Studies in animal and cell culture systems have also shown that activation of fight-or-flight signaling pathways in the sympathetic nervous system (SNS) plays a major role in evoking CTRA gene expression profiles, whose activation is mediated by receptors that stimulates transcription factors such as NF-κB, GATA, and cAMP response element-binding protein to selectively up-regulate transcription of proinflammatory genes (e.g., *IL6*) (Cole et al., 2010) while simultaneously inhibiting the activity of transcription factors, such as the interferon response facstor family, that control transcription of Type I interferon genes (e.g., *IFNB*) (Collado-Hidalgo et al., 2006). This increased pro-inflammatory gene expression and a suppression of anti-viral gene expression would happen because in conditions of social stress, the up-regulation of pro-inflammatory gene expression prepares the body to better deal with bodily injury and bacterial infection which is more likely under conditions of social stress either through hostile human contact, or increased predatory vulnerability due to separation from the social group. However it contributes to a paradoxical increase in inflammation-related diseases (cardiovascular disease and depression, caused by excessive proinflammatory immune response gene expression), and vulnerability to viral infections such as the common cold, caused by insufficient antiviral immune response gene expression, as shown in Fig. 1. Thus, what evolutionarily served to respond to an imminent physical threat, today seems to be activated by social threats, whether real or imagined (Cole et al., 2007; Miller et al., 2008; Miller et al., 2009; Slavich and Cole, 2013; Cole, 2014).

Interestingly, a transcriptome representation analysis showed relative expansion of the immature proinflammatory monocyte transcriptome in peripheral blood mononuclear cells from people subject to chronic social stress (low socioeconomic status) and non-human (mice) subject to repeated social defeat. Mouse cell transcriptome confirmed these results, and promoter-based bioinformatic analyses indicated increased activity of transcription factors involved in early myeloid lineage differentiation and proinflammatory effector function (notably PU.1, NF-κB, EGR1, MZF1, NRF2). Myeloid lineage immune cells and their innate effector molecules, such as proinflammatory cytokines and type I interferons, are regulated by β-adrenergic signaling and adverse socioenvironmental

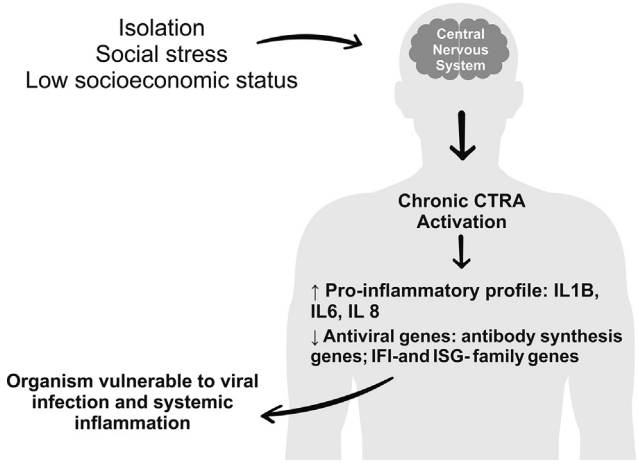

Fig. 1. Chronic CTRA stimulation (due to isolation, social stress or low socioeconomic status i.e.) may lead to stimulation of pro-inflammatory profile (such as IL1B, IL6, or IL8 gene expression) and inhibition of antiviral genes, such as Interferon inducible (IFI) and Interferon stimulated (ISG) gene families. This may leave organisms more vulnerable to viral infections due to insufficient antiviral immune response gene expression.

conditions. The authors suggest that sympathetic nervous system-induced up-regulation of myelopoiesis mediates the proinflammatory component of the leukocyte CTRA dynamic and may contribute to the increased risk of inflammation-related disease associated with adverse social conditions (Powell et al., 2013).

This transcriptional profile has also been related to socioeconomic status. In a study, 53 CTRA candidate genes were evaluated. Both down-regulation in response to stress (antiviral-response genes) and up-regulation in response to stress (proinflammatory genes) were related to low socioeconomic status participants compared to higher status individuals. In the same work, the authors conducted a hypothesis-free genome-wide screening of the roughly 35,000 transcripts assayed for association with socioeconomic status. They observed a group of 141 unique genes as being differentially expressed in the low-versus higher-socioeconomic status groups. Of these genes, enriched for binding sites of 3 transcription factors implicated in CTRA gene regulation, including the proinflammatory NF-κB family of transcription factors, which is a key regulator of the biological response to stress (Levine et al., 2017).

As the epidemics grow exponentially, the health-care systems may become overloaded. In China, non-pharmaceutical interventions, including social distancing have substantially reduced transmissibility of Covid-19 across the country. However, a second wave of Covid-19 transmission is possible because of viral reintroduction, which has been exponentially increasing since March 2020. There are potential consequences of premature relaxation of interventions to mitigate the epidemic, which may lead to a second wave of the disease (Leung et al., 2020). Given that, governments should act and prepare immediately to ensure that the health-care system has adequate labour, resources, and facilities to minimise the mortality risk of Covid-19 (Xu and Li, 2020).

Particularly, in this pandemic period, a fact that draws our attention is that some of the stress-generating factors related to the activation of CTRA are social isolation and socioeconomic status, as well as mourning and chronic stress (Cole et al., 2007; Levine et al., 2017; O'Connor et al., 2014; Slavich and Cole, 2013; Uchida et al., 2018). Recent research has begun to identify the CNS processes that regulate peripheral CTRA activity, define its implications for disease, and explore the role of positive psychosocial factors in buffering such effects (Cole, 2019). The reduced activity of threat-related gene expression programs may contribute to the health effects associated with optimism.

In this sense, dispositional optimism has been linked to better physical health (Carver et al., 2010; Tindle et al., 2009) and has impacts on health at the biological level. For example, reduced activity of threat-related gene expression programs may contribute to the health effects associated with optimism. Positive psychological factors contribute to reduced CTRA activity (Fredrickson et al., 2013; Kitayama et al., 2016; Kohrt et al., 2016; Nelson-Coffey et al., 2017). Uchida et al. (2018) observed a group of 114 male Japanese workers. Dispositional optimism was accessed with a 6-item Life Orientation Test–Revised (Scheier et al., 1994). The authors showed that optimism was inversely linked to CTRA after controlling for age, BMI, and indices of well-being.

It has been demonstrated that purpose in life (eudaimonic well-being) is successful against the adverse effects of loneliness in predicting leukocyte gene expression profiles. For example, the relationship between eudaimonia (a well-being status that includes happiness, virtue, morality, and a meaningful life) (Baumeister et al., 2013), and a social perceptual dynamics underlying loneliness, may play a key role in engaging the biological signaling pathways that regulate CTRA gene expression in immune cells (Cole, 2014; Cole et al., 2015a,b). Together, this is useful to provide a rationale for the development of new intervention strategies to mitigate the health risks associated with loneliness not by directly targeting social interaction per se, but rather by promoting social well-being indirectly via the development of pro-social eudaimonic well-being. And also raises the possibility that psychological resilience factors can, at least in some circumstances, outweigh the effects of a well-established and quantitatively robust psychological risk factor such as perceived social isolation (Cole et al., 2015a,b).

Powell et al. (2013) suggests specific molecular strategies (e.g., β-blockade) and cellular biomarkers (e.g., CD16$^-$ monocytes) that could potentially be harnessed in future studies to develop health-protective interventions. Other alternatives could be considered with potential for application in clinical and health settings, such as meditation, yoga, praying, or tai-chi (Holmes et al., 2019; Boyle et al., 2019; Mañas et al., 2010).

4. Conclusion

The Covid-19 pandemic and interventions to mitigate the transmission of the virus bring public health issues related to social isolation, stress and vulnerable and low socioeconomic status groups. The possible change in the pattern of immune responses related to stress, as well as the gene expression profile, the CTRA, resulting from these situations are of concern, especially with regard to the immune response to viruses. Understanding the mechanisms through which social disadvantage, isolation and stress becomes biologically embedded and understanding this embedding may address social gradients in health, and allow better strategies to understand and deal with these issues. Thus, the present review aims to raise questions related to the effects of these conditions in patients infected or susceptible to contamination by Covid-19 to provide support to government officials, health agents and researchers so that they can consider these facts and direct their actions during the pandemic, as well as encourage studies to better understand these characteristics.

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