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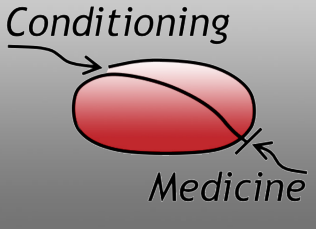

EDITORIAL | OPEN ACCESS

Laboratory and clinical research on COVID-19: focus on non-lung organs

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Coronavirus disease 2019 or COVID-19 has wreaked havoc on the world, killing 1.3 million and infecting 53 million globally to date (https://coronavirus.jhu.edu/map.html). In the US alone, there are about 245,000 deaths and 10.8 million infections (https://coronavirus.jhu.edu/map.html). COVID-19's highly infectious spread across populations involves acute and chronic debilitating symptoms. Initially thought a purely respiratory virus, COVID-19 has now been recognized as a multi-organ disease, infecting the heart and the brain, among other vital organs. Co-morbidity factors have also been identified in the severity of COVID-19's manifestations. The use of immunomodulatory and anti-inflammatory drugs has met some success but not to the extent of eradicating the virus. Putting an end to this pandemic through widespread vaccination may be many months away, despite the recent news on Pfizer's effective vaccine. Until then, limiting the transmission of COVID-19 will rely heavily on the implementation of the Centers for Disease Control and Prevention recommendations on practicing public health measures, such as social distancing, hand washing, and wearing a face mask.

This special issue assembles recent progress in COVID-19 laboratory and clinical research detailing our current understanding of the consequential disease pathologies and treatments. The overarching goal of these studies is to guide the public discourse of COVID-19 based on scientific and clinical evidence.

Our colleagues (Borlongan et al., 2020; Hess et al., 2020; Jarrahi et al., 2020; Park et al., 2020) and others, recently reported the neurological consequences of COVID-19. In particular, increased incidence of stroke has been reported in patients suffering from COVID-19 (Avula et al., 2020; Bridwell et al., 2020). Here, we raise the hypothesis that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the etiological agent of COVID-19, is neurotropic (Hess et al., 2020, this issue). Although SARS-CoV-2, a positive-sense single-stranded RNA virus, targets epithelial cells and the respiratory system, it appears that SARS-CoV-2 is also neurotropic, allowing the virus to infect the central nervous system. Such neurotropism also provides insights on how the virus may be treated. Indeed, we reported that cannabidiol may have some potent effects against acute respiratory distress syndrome induced by simulated viral infection (Salles et al., 2020; Khodadadi et al., 2020). However, the use of cannabidiol as prophylaxis for SARS-CoV-2 and COVID-19 warrants further investigations (Brown, 2020).

Next, in further exploring treatment strategies designed to sequester the virus as it spreads from the respiratory system to other organs, Dr. Maevsky hypothesizes the potential utility of so-called "hypoxic conditioning" to activate hypoxia-inducible factor 1 alpha (HIF-1α)-induced cytoprotective signaling for reduction of illness severity and improvement of vital organ function in patients with COVID-19 (Maevsky, 2020 this issue). Dr. Maevsky also introduces the potential application of small doses of succinate, as one of hypoxia's and ischemia's key signaling products with a track record of being an effective antihypoxic agent. Coincidentally, two recent papers allude to this HIF-1α-mediated hypoxic conditioning for use in COVID-19 (Codo et al., 2020; Serebrovska et al., 2020).

Building on reported COVID-19-related strokes but paradoxical decline in stroke patient admissions during this pandemic, Dr. Liu and co-workers embarked on clarifying the status of stroke patients before and after COVID-19 (Liu et al., 2020, this issue). Interestingly, several patients were reported "missing" in emergency departments (ED) around the world. For example, while an abrupt change to triage procedures and managements accompanied the uptrend in COVID-19 patient ED admission, there was a noticeable drop in the ED admission for non-COVID-19 patients (Giamello et al., 2020; Rai et al., 2020). International surveys suggested a drop of 42% of stroke admissions. The likely cause was an unwillingness of stroke patients to come to the hospital and risk becoming infected with COVID-19. Clearly, stroke education needs to be increased during this time as many patients may miss the opportunity for thrombolysis and mechanical thrombectomy, two proven therapies for stroke.

As seen in the brain, equally devastating pathological consequences are observed in the heart following COVID-19. Dr. Hausenloy and collaborators provide an update on the cardiac manifestations of COVID-19 (Chan et al., 2020, this issue). A challenge in the cardiac field is that non-COVID patients with symptoms of ischemia/heart failure presenting as dyspnea and chest discomfort overlap with those COVID-19 patients (Tavazzi et al., 2020). Nonetheless, the persistence of viral RNA and pneumocyte syncytia may provide differential diagnosis for COVID-19 patients presenting with coronary thrombosis (Bussani et al., 2020). As for treatment of cardiac consequences in COVID-19, Dr. Hausenloy's long-standing interest in ischemic conditioning may offer novel applications for this indication (Hausenloy et al., 2020).

Finally, the recognition of COVID-19 neurological and

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cardiac manifestations may be embedded in our understanding of co-morbidity factors of the disease. Here, Kingsbury and colleagues focus on aging, obesity, and gender (i.e., male) that worsen the clinical outcomes of COVID-19 (Kingsbury et al., 2020, this issue). Similar reports have implicated these co-morbidity factors in COVID-19 (Białas et al., 2020; Hazeldoine and Lord, 2020; Iaccarino et al., 2020), which not surprisingly accompany brain and heart diseases (Beyene et al., 2020; Nordström et al., 2020). That specific pre-existing co-morbidity factors may increase susceptibility and worsen the outcome of COVID-19 suggests management and/or treatment of one or a combination of the co-morbidity factors may alleviate COVID-19 symptoms. Along this line of developing treatments, Kingsbury and co-authors also discuss the progress of vaccines for COVID-19.

The articles in this special issue elucidate the pathology and treatments of COVID-19's consequential diseases, such as stroke and cardiac ischemia/failure. One of the concerns is possible long-term neurological and cardiovascular sequela of COVID-19. In Georgia, we are establishing a longitudinal neurological cohort study of COVID19 positive subjects (CONGA Study), half of whom are African American, as we know African Americans have higher mortality than whites. Novel directions in our understanding of COVID-19 and its management and treatment require the acknowledgement of the devastating pathological manifestations within and outside the lungs.

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