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editorial

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Extracellular vesicles from mesenchymal stem cells as a Covid-19 treatment

One of the hallmarks of coronavirus disease 2019 (COVID-19) is the so-called 'cytokine storm' in response to the presence of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) in the lungs. In an effort by the body to step up and protect itself against the virus, immune cells are recruited, release cytokines and, via a positive feedback loop, activate more immune cells that release more proinflammatory cytokines. This acute cytokine release typically includes a cocktail of interleukin (IL)-2, IL-6, IL-7, inducible protein 10 (IP10), interferon γ (INFγ), monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1α (MIP1α), granulocyte-colony stimulating factor (GCSF), and tumor necrosis factor (TNFα). So, ironically, the cytokine storm is a result of well-intentioned, but misplaced, efforts by the immune system and it induces pulmonary edema, interrupted air exchange, infection, and acute respiratory distress syndrome (ARDS). Respiratory failure from ARDS is the leading cause of mortality from COVID-19 [1].

Throughout the world, efforts are being made to prevent the spread of SARS-Cov-2 by timely reverse-transcriptase PCR testing for SARS-Cov-2 RNA from swabs taken from individuals where there is reason to believe that they might have been infected and then self-isolating individuals who test positive. Associated with this is contact tracing, to warn others who might have had contact with the infected individual to also self-quarantine; requesting those in society who are most vulnerable to cocoon; and varying degrees of lock-down of the population at large. In parallel, scientists and clinicians are working to optimize and/or repurpose pharmacological interventions (with >300 clinical treatment trials for COVID-19 underway) [2] and to develop new therapies. including an effective prophylactic vaccine as the Holy Grail.

Mesenchymal stem cells (MSCs), because of their immunomodulatory and anti-inflammatory capabilities and restorative properties associated with their stemness, could contribute, as cell-based therapies, to the arsenal of treatments for COVID-19. Leung *et al.* reported on a pilot clinical trial that accrued seven patients with COVID-19-related pneumonia and who were each administered a single intravenous infusion of MSCs (1×10^6/Kg body weight) [3]. The health of all the individuals had substantially improved within 2 days, inflammatory cytokine levels were significantly decreased, the level of anti-inflammatory IL-10 had increased, and overactivated cytokine-secreting T cells and natural killer (NK) cells had disappeared by 3–6 days post treatment. No adverse effects resulted [3]. A similar outcome was achieved from a case study in Baoshan, China. As of 28 April 2020, a search of clinicaltrials.gov showed 24 such trials specific to COVID-19, several of which are actively recruiting in China (NCT04288102, NCT04252118, NCT04336254, NCT04339660, and NCT04269525), France (NCT04333368), Iran (NCT04366063), Ireland (NCT03042143), Jordan (NCT04313322), and the USA (NCT04349631, NCT04348435, and NCT04355728). The MSCs being investigated in these single or multicenter trials are from a range of allogenic sources, including bone marrow, umbilical cord/Wharton's jelly, adipose tissue, and dental pulp. A search of the Chinese Clinical Trial Registry (www.chictr.org.cn) also showed at least 20 MSC trials for COVID-19 registered there.

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Extracellular vesicles (EVs) encompass exosomes and ectosomes [4] and can be described as mini-maps of their cells of origin. There is increasing evidence that many, if not all, of the beneficial effects of MSCs can be attributed to their paracrine action via the release of EVs, rather than cellular engraftment and response at the site of injury [5,6]. This suggests that MSC-EVs can produce any of the therapeutic benefits of MSCs. For this reason, MSC-EVs from a broad range of sources, including bone marrow, adipose tissue, peripheral blood, umbilical cord, amniotic fluid, placenta, periodontal ligament, and gingival tissues, are currently under investigation for many conditions and areas of regenerative medicine [7]. For one arm of the above-mentioned NCT04366063 trial currently recruiting in Iran and with an estimated primary completion date of 6 June 2020 and overall completion date of 10 December 2020, MSC-EVs are being administered after MSCs; as the other intervention arm, MSCs are administered without additional EVs; and conventional therapy for virus treatment and supportive care for ARDS is the control arm. Time will tell how the addition of MSC-EVs contributes to this treatment of ARDS. Another pilot clinical trial of MSC-EVs in COVID-19, intended to take place in Ruijin, China (NCT04276987), is registered at clinicaltrials.gov, although, as of 28 April 2020, it has not yet recruited patients.

The potential advantages of MSC-EVs over MSCs as a treatment for COVID-19 could be many. These include the fact that EVs do not need to be administered systemically (where many would be lost and not arrive in the airways and lungs) but can be delivered intranasally or by inhalation. EVs cannot self-replicate, eliminating some safety concerns sometimes voiced in relation to cell therapy, such as uncontrolled cell division. Scientists in academia and industry are already working together to develop the optimal and most efficient way to scale-up and produce functional MSC-EVs by current good manufacturing practice (cGMP) standards for their contribution to regenerative osseointegration by improving endoprosthesis and so reduce the risk of inflammation of hip revision prostheses (i.e., hip replacements) (www.evpro-implant.eu/). There is also evidence that MSC-EVs could be scaled up, for example, in stir-tank or hollow-fiber bioreactors; potency tested to ensure that they have the desired activities; and stored as an 'off-the-shelf' treatment until required (although substantial efforts are now needed to ensure that there is an appropriate robust, reliable, and reproducible potency tests for any MSC-EVs being considered as a therapeutic option for COVID-19. Considering that MSCs are heterogeneous and EVs are heterogenous, it cannot be assumed that all MSC-EVs would act in the same way). There is also the possibility to pay-load useful MSC-EVs with other therapeutic molecules, such as antiviral drugs, that could be considered beneficial to have delivered to the site of required intervention.

Another consideration when making the case for MSC-EVs as a potential treatment for COVID-19 is the fact that, when SARS-Cov-2 targets cells in the human body through viral structural spike (S) proteins, which bind to the angiotensin-converting enzyme 2 (ACE2) receptor, it uses this host cell receptor and its endosomes to enter cells. A possibility, as yet unexplored, might be to decorate MSC-EVs, which span the size range of viruses, with spike proteins so that they can compete with SARS-Cov-2 for cellular uptake. Again, these EVs could be pay-loaded with a molecule(s) of choice, such as a small interfering (si)RNA, miRNA, or protein, depending on what is considered most relevant to interrupt the activities of the virus in the cell and so protect the airways and lungs. Furthermore, because SARS-Cov-2 appears to hi-jack at least part of the cellular endosomal pathway in its efforts to replicate [i.e., the pathway by which naturally occurring exosomes (which are a subclass of EVs) are made], temporarily blocking the endosomal pathway with therapeutic inhibitors [8], possibly delivered into these cells by MSC-EV, might also prove beneficial.

As with all potential treatments for COVID-19, further research is essential to determine how beneficial and safe MSC-EVs will be and in what role(s) they would be of most use; be that as packages of naturally occurring immunomodulatory/anti-inflammatory molecules; competitors to SARS-Cov-2; and/or as souped-up delivery vehicles carrying a useful payload. However, as MSC-EVs apparently bear the benefits of MSCs and then some, research focused on their exploitation as a therapeutic option in COVID-19 is warranted, while giving due consideration to the fact that they might also exacerbate some of the symptoms. Until further preclinical research is completed, this is an unknown.

During a pandemic that is causing hardship, morbidity, and mortality to escalate throughout the world, there might be temptation to take short-cuts and progress unproven therapies rapidly to patients, especially if there appears to be no other useful options. However, due consideration to evidence-based science, ethics, safety, good clinical practice, and oversight by relevant regulatory authorities is essential and must never be compromised in our fight against SARS-Cov-2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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