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Stem Cells as Potential Therapeutics and Targets for Infection by COVID19 – Special Issue on COVID19 in Stem Cell Reviews and Reports

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We are still at the beginning of understanding the pathogenesis of COVID19 or SARS-Cov2 virus infection, and different experimental therapeutic strategies, including cell therapeutics, have been proposed to control this unfortunately so often fatal infection. Therefore, during an outbreak of this pandemic at the time when vaccines were still not available, there were proposed different types of cell-based therapeutics, including mesenchymal stem cells. The idea behind the application of these cells was based on a well-known fact that a secretome from these cells, enriched both in soluble factors and extracellular microvesicles, has immunosuppressive effects. As an example, these cells are applied in the clinic to ameliorate Graft versus Host Disease (GvHD) in patients after hematopoietic transplantations. To highlight better mesenchymal stem cell-based strategies employed to fight COVID19 infection, this February special issue on COVID19 contains several review papers discussing the rationale and summarizing therapeutic effects of mesenchymal stem cells as well as other types of cells that were employed for treatment. This data is also important as it sheds more light on the rationale to employ immunomodulatory effects of mesenchymal stem cells in other disorders driven by uncontrolled response of immune system.

It has been postulated that a significant pathological pathway triggered by COVID19 infection is systemic induction of a so-called "cytokine storm" initiated by hyperactivation of Nlrp3 inflammasome [1], and indeed hyperactivation of Nlrp3 inflammasome in response to COVID19 proteins has been recently confirmed. While physiological activation of intracellular Nlrp3 inflammasome immune complex regulates several aspects of stem cell biology, its pathologic hyperactivation may lead to cell death in mechanisms of pyroptosis. This Nlrp3 inflammasome triggered cell-damaging reaction may explain why mesenchymal stem cells show some beneficial effects, as they may ameliorate immune response in COVID19 infected patients. This phenomenon, however, requires further studies.

COVID19 infection is well known to damage primarily cells in the respiratory tract, lungs, vasculature, brain, and other organs. However, a crucial and still not very well studied aspect of COVID19 infection is the potential damage of the stem cell compartment. In an elegant review, Dr. Smadja addressed hematological complications of COVID19 infection [2]. Moreover, in this special issue, there are published two experimental papers demonstrating the consequences of the presence of COVID19 entry receptor ACE2 on hematopoietic stem progenitor cells (HSPCs) [3, 4]. What is important is that expression of this receptor, as demonstrated, increases with more primitive phenotype of stem/progenitor cells [3]. It is why it is not surprising why ACE2 is highly expressed on very small embryonic-like stem cells that, as reported by several laboratories, may correspond to very primitive stem cell population residing in adult tissues [5]. In addition, Drs. Virant-Klun's and Strle's paper shows ACE2 receptor presence on the surface of oocytes and cells in developing blastocyst [6]. This may explain some problems with miscarriages observed during the COVID19 infection. Overall, COVID19 infection may negatively affect innate immunity cells as well as several types of somatic cells including stem cells (Fig. 1).

What is also very important, Dr. Broxmeyer's group demonstrated that exposure of HSPCs to recombinant COVID19 spike protein results in a decrease of clonogenicity of progenitor cells in all major hematopoietic lineages [3]. The specificity of this effect on clonogeneic growth of HSPCs has been demonstrated by preincubation of spike protein with human recombinant ACE2 protein or anti-ACE2 blocking antibodies [3]. In addition, Dr. Kucia et al. provided evidence that spike

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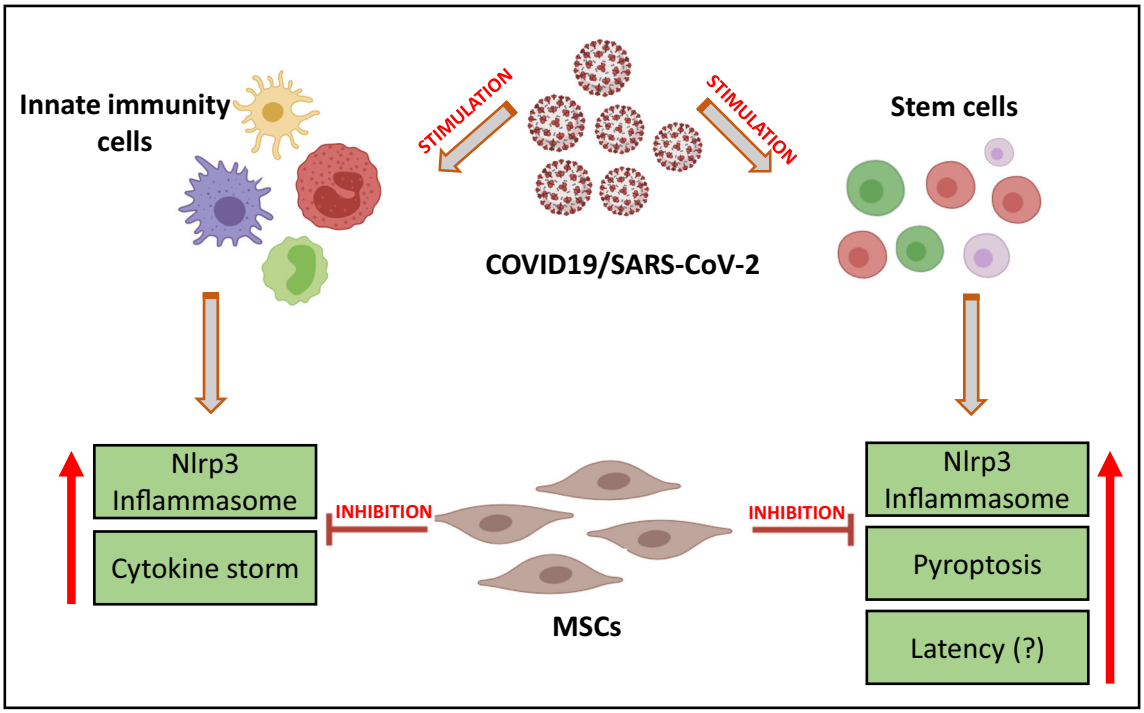

Fig. 1 SARS-Cov-2/COVID19 and stem cells. The virus can damage cells in the course of productive infection. On the other hand, as depicted at the Figure, the virus can stimulate innate immunity cells and stem cells and hyperactivate Nlrp3 inflammasome to induce cytokine storm or cell death by pyroptosis. Several papers in this issue special issue demonstrate that mesenchymal stem cells (MSCs) may ameliorate these effects by secreting several immunomodulatory soluble factors and extracellular microvesicles. The remaining problem is that if in the case of abortive infection, can the virus survive in a latent form in long living stem cells?

protein interaction with HSPCs as well as with endothelial progenitor cells hyperactivates Nlrp3 inflammasome [4]. All this together suggests that stem cells are damaged as a result of the pathological immune response. Furthermore, it is important to realize that in addition also several mediators released in the course of "cytokine storm", in particular some pro-inflammatory cytokines, may also impair the proper function of stem cells.

The presence of ACE2 receptor for COVID19 entry on HSPCs also raises another important question: if after entering stem cells COVID19 lead to productive or unproductive infection of these cells? Productive infection after virus entry would lead to lysis of infected cells. This still, in the case of HSPCs, has to be demonstrated with an alive virus. However, in parallel, we have also to consider another alternative scenario. Since COVID19 may enter stem cells that are long-living cells, it may survive in the stem cell compartment for a prolonged time and become activated again if the immune system becomes compromised. If this could be a case, COVID19 may become a latent virus. Therefore, a potential late effect of COVID19 on the stem cell compartment is still hard to predict, and more studies are needed to address all these alternative effects.

Another important aspect is that stem cells, in addition to ACE2, may express other potential COVID19 entry receptors such as toll like receptor 4 (TLR4) and CD147. Therefore, more studies are needed to address if, in addition to ACE2, spike protein may also activate Nlrp3 inflammasome in TLR4 or CD147-dependent manner. A recent report supports this possibility in the case of TLR4 [7]. In conclusion let's hope that next months will bring answers to all these outstanding yet questions. The current armamentarium of scientific tools and the ability to rapidly communicate between different research groups will lead to dethroning of this treacherous virus, with its stolen crown (corona). Therefore, we hope to soon banish this usurper from the realm along with its all of its relatives.

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