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Commentary

The multiple sclerosis (MS) drugs as a potential treatment of ARDS in COVID-19 patients

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ABSTRACT

We encourage studies on the effectiveness of multiple sclerosis drugs for the treatment of ARDS in COVID-19 infection. These drugs, through the inhibition of the RhoA/actin-dependent expression of virus receptors in the macrophages and macrophage recruitment to the lungs, have the potential to inhibit cytokine storm of lung macrophages, reduce or eliminate ARDS and improve the outcome of COVID-19 infection.

The main and most deadly symptom of the SARS-CoV-2 infection is acute respiratory distress syndrome (ARDS) in the lungs of COVID-19 patients. ARDS is caused by the hyperactive immune response and the production of cytokine storm by the lung macrophages. The entry of the virus to the lung epithelial cells and lung macrophages depends on the ACE2 receptor expressed on the surface of these cells. The immune factors (cytokines and chemokines) released from the infected cells recruit additional immune cells, including monocytes and macrophages from the bone marrow and blood, to join the fight against infection. This avalanche (cytokine storm) of immune factors is extremely damaging for the lung tissues and, ultimately, leads to lung failure (Hu and Christman, 2019; Joshi et al., 2018; Hussell and Bell, 2014; Ye et al., 2020; Chen et al., 2017; Wang et al., 2020; Yan et al., 2020). Thus, the potential drugs which could reduce or eliminate ARDS should be targeting the ACE2 receptors and macrophage response.

Research in our laboratory has been, for years, focused on the prevention of long term (chronic rejection) of transplanted organs. During these studies, we showed that chronic rejection depends on the macrophage entry into the allograft and that the application of the inhibitors of small GTPase RhoA pathway prevents macrophage infiltration and inhibits chronic rejection (Liu et al., 2017a; Liu et al., 2017b; Chen et al., 2018a). The RhoA pathway regulates actin cytoskeleton in all eukaryotic cells, and as such also regulates actin-dependent cell movement and recycling and expression of macrophage receptors, which home macrophages to the graft. In our search for clinically applicable RhoA pathway inhibitors we found that drugs clinically approved for the treatment of multiple sclerosis (MS), Fingolimod and Siponimod, also inhibit RhoA and RhoA/actin-dependent macrophage receptors recycling, and expression, and can be potentially used as an anti-chronic rejection therapy in human transplantation (Chen et al., 2018b; Uosef et al., 2020). Our center is initiating the clinical trial on the effect of Fingolimod in kidney transplantation patients. Because these clinically approved drugs inhibit, via RhoA/ actin pathway, macrophage movement, and expression of macrophage receptors, they have also a potential to inhibit ACE2 receptors expression and the recruitment of macrophages to the lungs of the COVId-19 patients, which in turn would decrease cytokine storm and attenuate ARDS. This hypothesis is also supported by the recent Through Gene Ontology (GO) and MetaCore analyses of gene expression profile in the SARS-CoV/SARS-CoV-2 infection (Liu et al., 2020). These analyses showed that the upregulation of actin/cytoskeleton remodeling/cell migration pathways is crucial for the SARS-CoV-2 infection. Based on all these data we strongly encourage the studies on the effectiveness of the RhoA inhibitors such as Fingolimod and Siponimod for the treatment or prevention of ARDS in COVID-19 infection.

CRediT authorship contribution statement

Malgorzata Kloc: Conceptualization, Writing - original draft. **Rafik M. Ghobrial:** Writing - review & editing.

Declaration of Competing Interest

Authors do not have any conflicts of interest.

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