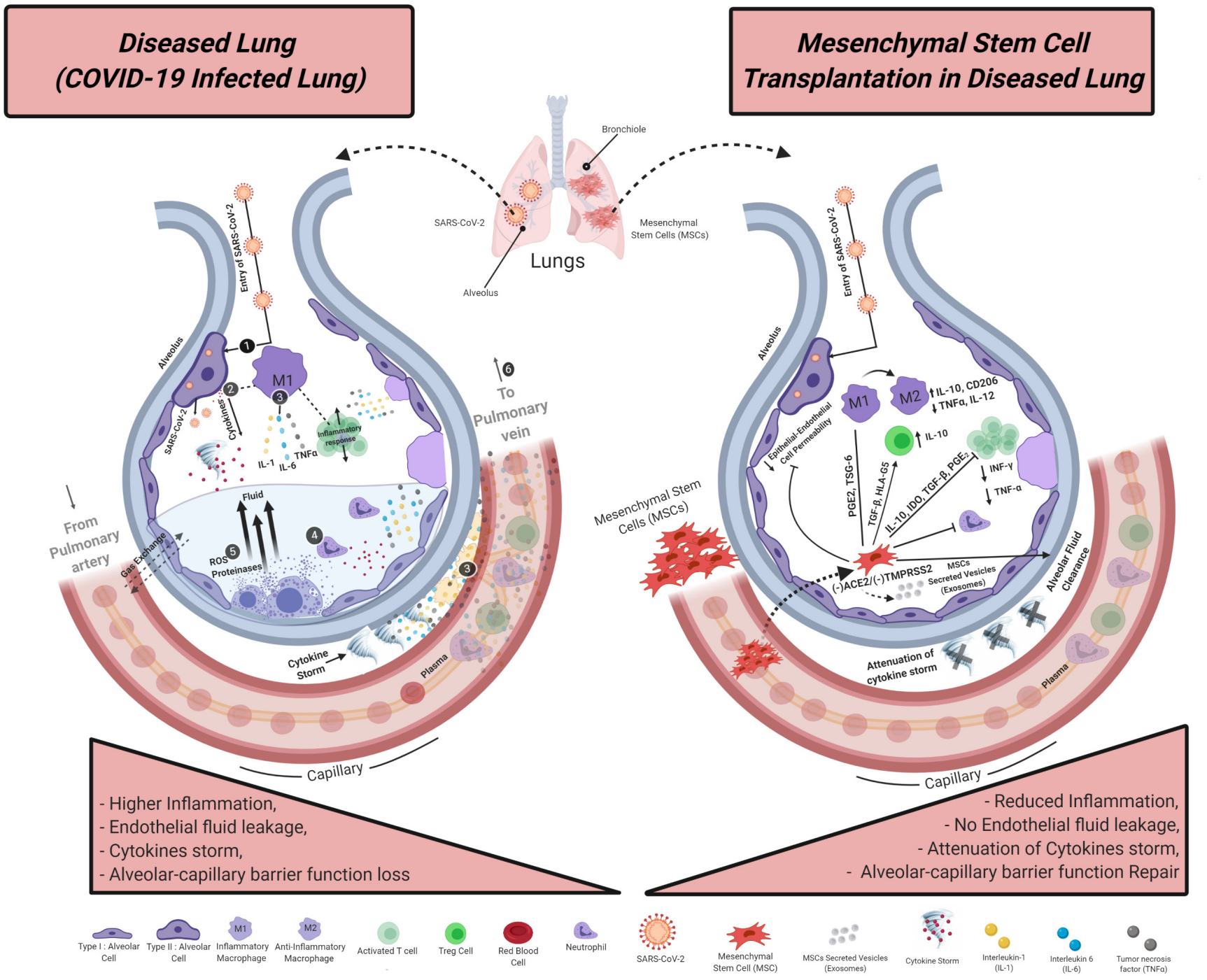

Figure S1 Diseased lung (COVID-19 infected lung): (I) when the SARS-CoV-2 enters the alveolus, it starts to infect the alveolar type II cells and replicates, (II) the alveolar type II infected cells tend to release pro-inflammatory cytokines, which further signals the body's immune system to respond, which leads to mild symptoms like cough, body ache and fever in COVID-19 infected patients, (III) IL-1, IL-6 and TNF-α released by macrophages causes vasodilation which permits more immune cells to travel to the alveolus. It further causes an increase in capillary permeability, which results in the plasma leakage into the alveolus and interstitial space, (IV) parallelly, neutrophils release proteinases and reactive oxygen species (ROS), which destroy infected cells, (V) these infected or dead cells pool with the plasma to form a protein-rich fluid that remains collected within the alveolus, causing pneumonia and shortness of breath. Accumulation of fluid and dilution of surfactant lining the alveolus causes collapse of alveolar, which reduces the gas exchange and can lead to acute respiratory distress syndrome, (VI) overdrive of the immune system, causes inflammation spread throughout the circulatory system leading to cytokine storm (systemic inflammatory response syndrome), this storm can drastically drop the blood pressure (septic shock) leading to multi-organ failure or death as organs can no longer be perfused. Created with BioRender.com. Mesenchymal stem cells (MSCs) transplantation in the diseased lung: MSCs and their secreted extracellular vesicles (Exosomes) potentially modulate the immune cells (T cells and dendritic cells) and epithelial cells, which are involved in the airway inflammation. The mesenchymal SCs function their modulatory effects via promoting anti-inflammatory cytokine, chemokines, cell-cell contact, mitochondrial transfer and genomic regulation, which could attenuate inflammation and regenerate lung damage caused by nCOVID-19. It has been studies that SARS-CoV-2 can infect angiotensin I converting enzyme 2 (ACE-2) receptor-positive cells, however MSCs lack ACE-2 receptors and TMPRSS2. Thus, when SARS-CoV-2 enter and infect the alveolar type II cells, MSCs inhibits epithelial-endothelial cell permeability. Further PGE2, TSG-6 secreted by MSCs influence the macrophage switch from M1 (an inflammatory) into M2 (an anti-inflammatory) state. This MS macrophage expresses high levels of Interleukin-10 and CD206, additionally reduces Interleukin-12 and TNF-α levels, and demonstrates elevated phagocytic activity. Further MSCs support and trigger the development of Treg populations via immunomodulatory factors (TGF-β, and HLA-G5) and expresses higher Interleukin-10 level, thus collectively modulate and balance Treg. During an inflammatory environment created by activated cells, MSCs recruit effector T cells and local helper (Th). The inducible NO synthase (iNOS) and intracellular enzymes indoleamine-2,3-dioxygenase (IDO) produced by MSCs are some of the mediators of T cell suppression, that further promotes their polarity shift from a Th1 state (pro-inflammatory) to Th2 state (anti-inflammatory). Lipid mediator prostaglandin E2 (PGE2), interleukin-10 (IL-10), and transforming growth factor β (TGF-β) secretion by MSCs inhibit the production of tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and Th17 cell differentiation. MSCs secreted IL-6, diminishes respiratory burst from neutrophils, the suppression of peroxidase and protease (releasing destructive enzymes) save neutrophils from apoptosis. Thus, through the anti-inflammatory mechanism, MSCs results into an attenuation of cytokine storm, alveolar fluid clearance and maintain alveolar-capillary barrier function. Created with BioRender.com.

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