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# Interaction of Differentiated Cells and Their Progenitors (Type 1 and 2 Alveolar Epithelial Cells, AT1 and AT2, in Particular) May Contribute to COVID-19 Pathogenesis

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## Abstract

As type 1 alveolar epithelial cell (differentiated cells AT1, which are a component of the blood-air barrier) have considerably fewer ACE2 receptors than AT2 (a self-sustaining pool of AT1 progenitors), the latter seem to be far more injured by SARS-CoV-2 infection. In mild cases shortly after the onset of the infection the respiratory function may be provided by the intact or slightly injured AT1 epithelium, but later on, when a considerable amount of AT1 renewal by the virus-affected AT2 epithelium is needed, the symptoms of respiratory failure may become worse. This fact may explain (at least in part) a deferred dramatic deterioration of the respiratory function in Covid-19 patients. So at present an important aim of research is to study the distribution of receptors used by the virus to enter the host cells – both among more differentiated cells (which provide the functions of the tissue) and less differentiated (stem) cells which are responsible for the maintenance of this tissue. The concentration of such receptors and the degree of injury of the relevant cell types may be different, which, in its turn, may have an impact on the course of the disease and determine new approaches to its therapy. Data about successful therapy outcomes in severe Covid-19 cases using transplantation of Mesenchymal Stem Cells (MSCs) are of interest at this stage of research. MSCs have an immunomodulating ability and not only inhibit the virus-evoked excessive activation of the host immune system, but they are also capable of protecting alveolar epithelial cells due to the factors produced by them, thus improving lung function.

SARS-CoV-2 enters the human respiratory tract mainly by the air-borne way. The virus enters the airway lining cells and the lung alveoli. SARS-CoV-2 has been shown to require the ACE2 receptor (angiotensin converting enzyme-2) to enter the host cells [1]. The affinity of SARS-CoV-2 to this receptor is ten times as high as that of SARS-CoV, which is in line with a higher effectiveness of the SARS-CoV-2 infection [2]. So ACE2 is an important indicator both to assess the progression and to forecast the outcome of the COVID-19 disease.

All organs with a high degree of ACE2 expression are potential targets for the SARS-CoV-2 infection. That's why the distribution and number of ACE2 in the human organs may be closely related to the clinical symptoms of the COVID-19 disease. ACE2 receptors are widely distributed in various tissues of the human body, including the lungs, heart, kidneys, liver, enterocytes of the small intestine, vascular endothelium [3–5]. The main target organ for SARS-CoV-2 is the lungs. In fact, after the SARS-Cov-2 coronavirus enters the alveoli lining cells,

viral pneumonia (which is often bilateral) develops in the lungs of most patients. In this situation immune cell activation leads to fluid accumulation in the alveoli and to oxygen exchange disorders. X-ray focal changes may be found in the lungs even in asymptomatic cases. As the disease progresses, these focal changes become confluent and involve larger areas of the lung tissue, which leads to a significant deterioration of the respiratory function [6–8].

The alveolar epithelium is known to be heterogeneous; it is represented by cells of the following main types:

AT1 – flat (or respiratory) cells. They cover most (95–97%) of the alveolar surface and they are a component of the blood-air barrier. These cells are very sensitive to toxic substances and unable to replicate. AT1 are relatively long-living cells: 50% of their population is renewed within 3 months (i.e. 17% each month и ~ 4% each week if this process is linear) [9, 10].

AT2 – big (or granular) cells. Their number is roughly equal to the number of type 1 alveocytes, among which they lie as single cells or in small groups, but they cover only 2–5% of the alveolar surface area. AT2 cells produce surfactant, synthesize and release interferon and lysozyme, clear oxidants. They are also the progenitor cells for AT1 alveocytes, and this property determines their leading role as a key factor providing the lung epithelium function as well as the processes of lung tissue remodeling and repair after injuries. The AT2 population can proliferate and is self-sustaining [9, 10].

Research data have shown that the more ACE2 receptors the tissue has and the more susceptible it is to infection, the higher the viral load and the worse its injury are. A high viral load (identified by the serum viral RNA, RNAaemia) in critically ill Covid-19 patients was associated with a drastically elevated interleukin 6 (IL-6) level (up to 10 times the normal limit) and a bad outlook in critically ill COVID-19 patients, including a possible cytokine storm and multiple organ dysfunction. Besides, its level correlated with the degree of tissue injury identified by blood biomarkers [11]. Of 6.4% human lung cells having the ACE2 receptor, 84% are on the AT2 epithelial cells, as research has shown [1]. Other cell types, including the AT1 epithelial cells, airway cells, endothelial cells and macrophages, also expressed ACE2, but at a substantially lower level than AT2 [1, 12]. These results show that it is the AT2 cells that seem to be the main target for SARS CoV-2 in the lungs. It should be noted that AT2 are the progenitor (stem) cells for the AT1 respiratory epithelium which needs a timely renewal. So there is the issue of the consequences resulting from damage of tissue stem cells and the associated untimely and limited (or even impossible) renewal of differentiated cells in cases with a severe course of the infection caused by immune deficiency and inability of the host organism to limit viral replication, which leads to the death of the relevant target cells. There is a possibility that this suggestion may also apply to other organs besides the lungs: the ACE2 receptor is widely distributed in the human body and was found in 72 types of human tissues [3, 4]. In fact the majority of complications in Covid-19 patients affect the lungs, heart, kidneys and brain; however the disease may affect any organ of the human organism in severe cases. It should be noted that even a mild course of the Covid-19 disease fails to guarantee that there are no complications; such complications may be not immediate, and serious lung or heart problems may develop only after a while in some patients. So Covid-19 patients need a long-term follow-up: even after the first symptoms disappear new symptoms may appear or disappear during 30 days [11, 13, 8]. Thus, the lung function is 20–30% decreased during the first months after coronavirus is not detected any longer (i.e. negative test results). There is a possibility that the long-term lung consequences of the COVID-19 disease may be explained (at least in part) by the fact that the deficiency of the AT1 pool and their progenitors (AT2) may have its impact not immediately, but as ineffective AT1 renewal due to AT2 injury is manifested. Besides, ACE2 is also present on the AT1 epithelial cells in a certain concentration (which is small as compared to that on AT2), so AT1 cell death may accelerate the required substitution of AT2 for the AT1 differentiated cells.

So, as AT1 have considerably fewer ACE2 receptors than AT2 [9, 10, 1] the latter seem to be far more injured, but their injury has an impact on the respiratory function later – when their reduced ability to renew AT1 becomes evident. In this situation the worse AT1 are injured, the sooner (and in a larger extent) they will need AT2 substitution. Some patients who carry the virus may feel

all right because their respiratory function is provided by the intact or slightly injured AT1 epithelium, but later on, when a significant amount of AT1 renewal by AT2 is needed, the symptoms may appear and become worse.

From the above it is clear that at present an important aim of research is to study the distribution of receptors used by the virus to enter the host cells – both among more differentiated cells (which provide the functions of the tissue) and less differentiated (stem) cells which are responsible for the maintenance of this tissue. The concentration of such receptors and the degree of injury of the relevant cell types may be different, which, in its turn, may have an impact on the course of the disease and determine new approaches to its therapy.

Besides the antiviral and anti-inflammatory medications used to treat Covid-19 patients today, other medications and methods which help maintain tissue stem cell populations should be developed and used. Data about successful therapy outcomes in severe Covid-19 cases using transplantation of mesenchymal stem cells (MSCs) are of interest at this stage of research. MSCs have an immunomodulating ability and not only inhibit the virus-evoked excessive activation of the host immune system, but they are also capable of protecting alveolar epithelial cells due to the factors produced by them, thus improving lung function [14].

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