

## **The basic knowledge of cellular physiology at the core for the identification of anti-SARS-Cov2 drugs.**

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The recent outbreak of the SARS-Cov2 has challenged the scientific world to halt and/or to prevent the spread of this infectious agent with the aim to cure the Covid-19 disease. Integrated efforts of diverse disciplines have led to tremendous discoveries in a very limited amount of time since the initial recognition of this novel coronavirus and of its relative disease.

**1-The entry portal.** SARS-Cov2 enters the host cells through ACE2. ACE2 belongs to the renin-angiotensin endocrine system (RAS). Physiologically, the ACE1 converts angiotensin I (AngI) to AngII. AngII binds to two different GPCRs AGTR1 and AGTR2. While AGTR1 mediates the cardiovascular effects of AngII, activation of the AGTR2 counterbalances them. ACE2 limits the effects of AngII by transforming into Ang(1-7), which can be further transformed into alamandine. Ang(1-7) and alamandine binds to two additional GPCRs in the RAS system, which signaling contributes to limit the potential detrimental effects of AngI (e.g., cardiovascular diseases, immune system activation and inflammation) [1].

**2-The disease.** SARS-Cov2 virus binds to ACE2 through its spike protein in the envelope causing ACE2 internalization, which results in an imbalance of the RAS system towards an accumulation of AngII that leads to its detrimental effects [2]. In the lungs, it has been shown that ACE2 is expressed in the alveolar type II cells, which produce the surfactant and work as sort of lung stem cells. SARS-Cov2-induced deficit of this cellular pool is thought to be the cause of the lung damages, which lead to acute respiratory distress syndrome. In parallel to this processes, SARS-Cov-2 also affects the response of the immune system by determining its hyperactivation through increasing IL-6 production [2]. An hyperinflammatory state can then lead to disseminated intravascular coagulation (DIG) [3], which exacerbates the effects of the infection and cause multi-organ failure.

**3-Pharmacological approaches.** To date no specific treatment for SARS-Cov2 mediated Covid-19 disease is available. However, two different therapeutic approaches can be recognized that parallel with the development of different kinds of vaccines. On one hand, host reactions are being targeted by at least two already existing drugs (e.g., tocilizumab and heparin). Tocilizumab, a monoclonal antibody used for the treatment of rheumatoid arthritis, inhibits the pro-inflammatory effects of IL-6 [4] while heparin is used to buffer the consequence of the DIG [5]. On the other hand, several direct anti-viral have been tested but at the present the most promising one appears to be remdesivir. Remdesivir is a nucleoside analog RNA-dependent RNA polymerase inhibitor that has shown promising effects (i.e., hope) as both prophylactic and therapeutic agent toward SARS-Cov2 infection in monkeys [6] as well as in the most recent clinical trials [7].

**4-Beyond the Classical Pharmacological approaches.** Surprisingly, targeting the host (i.e., cellular) protein that interacts with the protein virus has been recently highlighted a third pathway. Gordon and co-workers have identified the interactome of all the SARS-Cov2 proteins produced in lung cells. More than 300 interactors have been discovered (i.e., 332) and the interactions mapped in the specific cellular processes each of the human protein belong to. In this way, the Authors have been able to pinpoint druggable human proteins that are required for virus infection and for which approved drugs are already available and, luckily, effective in stopping viral replication *in vitro* [8].

Overall, the daily accumulation of the knowledge regarding SAR-Cov2 and its relative COVID-19 disease while on one side underscores how shared theoretical and technical expertise is critical for the advancement of science on the other hand it firmly demonstrates how the basic knowledge of the physiological processes occurring at cellular and molecular levels requires unprecedented attention to define key physiological determinants of each human disease.

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