Project title: „**Evaluation of the role of inflammasome in the pathogenesis of COVID-19- establishment of in vitro experimental platform.”.**
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The SARS-CoV-2 is a novel human coronavirus that cause severe pneumonia which in up to 20% cases leads to acute respiratory failure which often requires treatment in the intensive care unit. The illness has been termed the Coronavirus Disease 19 (COVID-19) and became the public health emergency concern all around the world. So far, no efficient treatment exists that would reduce the mortality or ease the symptoms of the disease. We hypothesize that the severe course of the disease is related to the excessive activation of one of the intracellular signaling pathway, namely the inflammasome complex. Forming of the inflammasome complex is early and potent mechanism of the cell's response to infection. Activation of inflammasome leads to the rapid release of strong acting inflammatory mediators like IL-1 and IL-18 and triggers cell death. Dysregulated activation of inflammasome has been shown to underlie severe course of other viral diseases such as influenza. SARS-CoV-2 can infect epithelial and endothelial cells in the lungs and presumably macrophages (which can also be activated by the mediators released by the infected epithelial and endothelial cells).

The primary aim of this project is to investigate whether the excessive activation of inflammasome in the lung cells plays critical role in the pathogenesis of COVID-19. Our hypothesis is that activation of the inflammasome triggers the lung cells death and drives the inflammatory response leading to acute respiratory failure. In order to verify this hypothesis, we designed a high-throughput platform enabling evaluation of the inflammasome activation by the selected viral proteins. Moreover, this model will be used to rapid assessment of the efficacy of clinically-available drugs with potent inflammasome inhibitory activity.

The SARS-CoV-2 proteins will be delivered to the human lung cells (epithelial and endothelial) by the molecular biology techniques. Analysis of the activation of inflammasome and cell death will be performed in real-time by the use of fluorescence- and luminescence-based imaging techniques. These experiments will be performed in both human cell lines and primary human cells. Because macrophages are major orchestrators of the lung immunity, it is also planned to investigate the effects of inflammasome-activated epithelial and endothelial released mediators on the human macrophage's activation. Importantly, we plan to test efficacy of two clinically-available drugs that are strong inhibitors of inflammasome pathway.

The proposed study will enable in-depth investigation of early phases of the lung cell's responses to the SARS-CoV-2 infection. The novel approach which combines molecular biology techniques to mimic aspects of the viral infection with the high-throughput methods of the analysis of inflammasome activation creates a unique opportunity to investigate interactions between the SARS-CoV-2 proteins and the host's cells and intercellular signaling. The findings of this project are expected to significantly increase the knowledge on the pathogenesis of SARS-CoV-2 infection. Moreover, we plan to use our platform to test the efficacy of pharmacological compounds that in case of positive results could launch a fast-track pre-clinical and clinical testing. Finally, our basic science results can be correlated with data obtained from clinical studies performed by our collaborators from the European Group on Immunology of Sepsis.