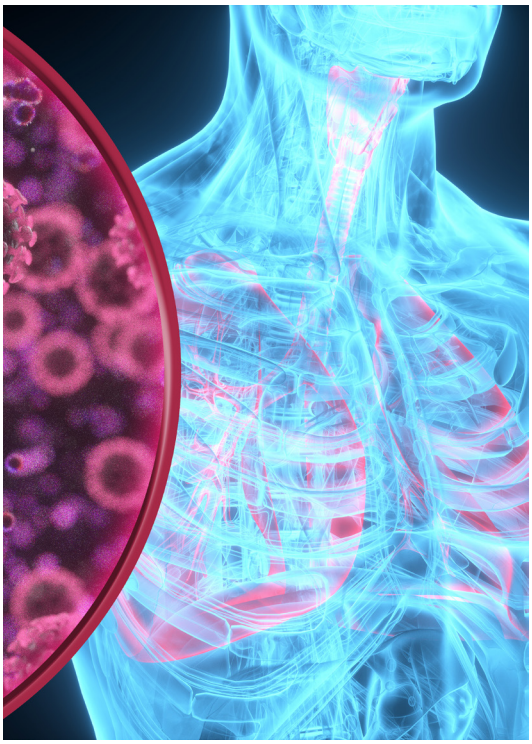
Case Study

Investigation of the transcriptional host response to SARS-CoV-2 identifies an imbalance in the host response which drives the development of COVID-19



Problem: SARS-Cov-2 is a deadly novel coronavirus that causes different degrees of morbidity and mortality host response.

Coronaviruses are a group of single-stranded RNA viruses with a wide range of hosts[1]. Recently, three highly pathogenic human coronaviruses have emerged from animal to human transmission, they are SARS-CoV-1, MERS-CoV and most recently, SARS-CoV-2[2]. The first two viruses have a fatality rate of 10% and 36 % respectively while the current global fatality rate of SARS-CoV-2 infection remains unknown[3]. SARS-CoV-2, the name of the virus that causes Coronavirus Disease 2019 (COVID-19) is characterized by a range of symptoms including fever, cough, and malaise in the majority of cases[4]. More severe cases of COVID-19 involve the development of acute respiratory distress syndrome followed by acute lung injury, both of which can cause injury to alveolar lumen, leading to inflammation and pneumonia[5].

The typical physiological response, after viral infection, begins with cellular detection of replication, which is largely mediated by a family of intracellular Pattern Recognition Receptors (PRRs) that sense aberrant RNA structures, often formed during virus replication. Detection of these virus specific RNA structures initiates downstream transcription factors which results in the activation of two antiviral programs, IFN-I/IFN-III which acts to control viral replication and chemokine and interleukin secretion which activate the adaptive immune response[6]. This antiviral response puts a selective pressure on viruses which in turn has encouraged the evolution of countless viral countermeasures[7]. Because of this, the host response to each virus is not uniform and infections can cause different degrees of morbidity, ranging from asymptomatic to fatal.

Solution: Comparison of the transcriptional response to multiple respiratory viruses reveals response to SARS-CoV-2 differs via inactivation of the IFN pathway

In an effort to understand the body's transcriptional response to COVID-19 and to determine the differences from other known viruses, Blanco-Melo et al., took a two-pronged approach. First, in an effort to compare the transcriptional response (using RNA Seq) of SARS-CoV-2 to other respiratory viruses the authors infected a variety of lung cell lines, including cells originating from both normal and neoplastic lung tissue with six known respiratory viruses, including MERS-CoV and SARS-CoV-1 and 2. Second, they sought to correlate these results with natural infections by analyzing both Ferret and human response to infection.

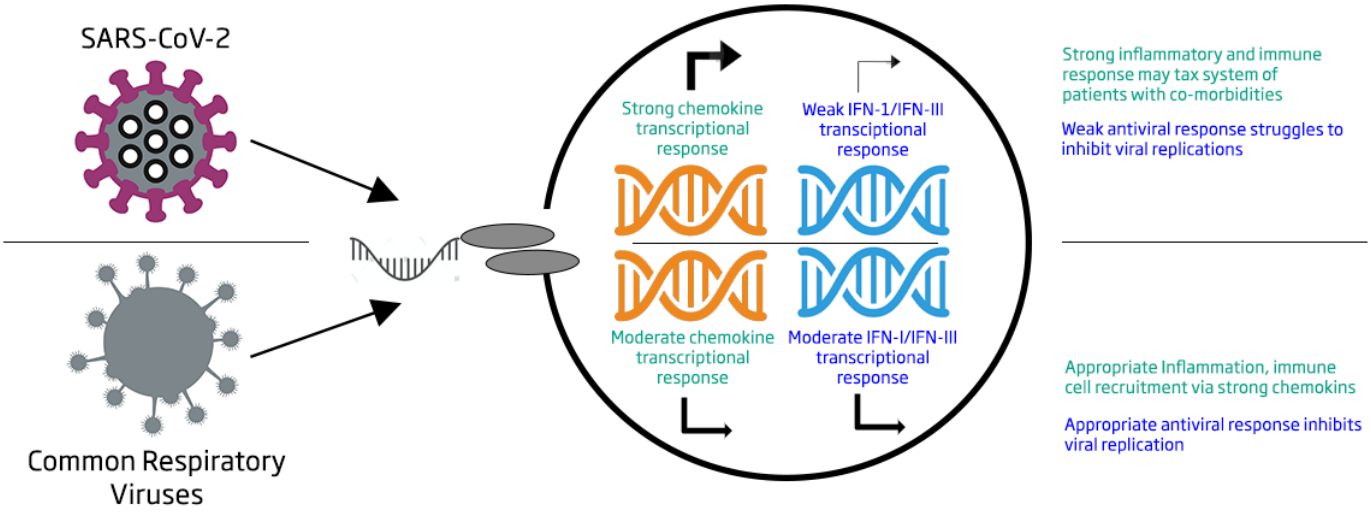


Figure 1: In contrast to other common respiratory viruses, which typically have moderate immune and antiviral transcriptional response, SARS-CoV-2 infection generates a weaker antiviral response and stronger immune response.

Overall, Blanco-Melo et al., were able to show that the transcription footprint of SARS-CoV-2 infection was distinct in comparison to the other viruses tested here, including Respiratory syncytial virus (RSV), Human parainfluenza virus 3 (HPIV3) and Influenza A (IAV). While the authors noted that SARS-CoV-2 infection showed a robust chemokine signature it failed to launch a robust IFN-I/-III response (Figure 1). These findings may explain why serious cases of COVID-19 are more frequently observed in individuals with co-morbidities, as a waning immune response would enable sustained viral replication.

Significance: Further investigation into the host immune response to SARS-CoV-2 could facilitate treatment of COVID-19.

The results of this study suggest an immune imbalance in response to SARS-CoV-2 viral infection where low levels of interferons reduce a cell's ability to limit viral replication and the activation of less-specific immune response promotes inflammation. Given this dynamic, treatments for COVID-19 have been more focused on controlling the bodies inflammation response. The study by Blanco-Melo et al., is the first of its kind to describe the transcriptional response to infection by SARS-CoV-2. The HTG EdgeSeq Immune Response Panel was specifically designed to monitor the bodies transcriptional response to disease that activate the body's immune response.

The HTG EdgeSeq Immune Respose Panel contains over 80% of the genes used to monitor immune response by Blanco-Melo et al., and contains an additional 1,957 genes intended to monitor immune response including 95 genes that are known targets of Ruxolitinib. In conclusion, the HTG EdgeSeq Immune Response Panel has the potential to function as an important tool in understanding the body's response to viral infection including SARS-CoV-2.

References

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