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Research Summary

Modulation of proinflammatory responses by SARS-CoV-2 host shutoff

The ongoing worldwide COVID-19 pandemic requires expanded research efforts for the discovery of preventative and therapeutic measures to combat the disease. To develop effective vaccines and antivirals against SARS-CoV-2, a better understanding is needed of the basis of its pathogenesis to identify key targets for new therapies. The development of novel drugs for clinical use takes years because most of the promising candidates, while efficacious in laboratory settings, often underperform or have side effects in clinical trials. However, medications that are already approved for use in humans against other, often unrelated conditions, have the potential to be rapidly re-purposed for the treatment of new diseases (old drug/new use paradigm). If proven effective against COVID-19, these drugs would have a much more rapid transition from bench to bedside. Viruses rely on their host cells for most of their metabolic needs, which makes repurposing of existing drugs to targeting specific cellular processes an attractive approach. One viral protein that is important in SARS-CoV-2 pathogenesis is non-structural protein 1 (nsp1). This protein is responsible for shutting down a subset of immune responses to the virus by destroying cellular messenger RNA (mRNA) – the process known as host shutoff. In addition to blunting antiviral responses in infected cells, host shutoff lessens competition from cellular mRNAs for resources needed by the virus to synthesize its own proteins. Thus, nsp1 helps SARS-CoV-2 to block host defences and to multiply efficiently in human lungs and other tissues. At present, the mechanism of nsp1 action and the cellular genes that help SARS-CoV-2 host shutoff remain unknown. In addition, several other viral genes have been proposed to act as inhibitors of antiviral responses. This research investigates the mechanism of host shutoff by the nsp1 protein and identifies cellular co-factors that are necessary for nsp1 function. In addition, a library of 2,188 FDA-approved drugs will be screened for molecules that can inhibit nsp1 and weaken the virus' ability to evade the immune system. Studies performed using other coronaviruses that had the nsp1 gene artificially deleted showed that these viruses were unable to grow efficiently and, most importantly, were unable to cause disease in laboratory animals. Therefore, it is believed that targeting nsp1 with drugs will be effective in treating COVID-19.