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Commentary Article

Dynamic meta-analysis guided by evidence for the prioritisation of host genes involved in COVID-19

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Description

There are different sources of evidence associating host genes with viral replication of SARS-CoV-2, subsequent host immune response, and subsequent pathophysiology. Integrating these information sources may provide more comprehensive proof that certain genes and proteins are associated with main processes underlying disease mechanisms. In order to make educated judgements on novel treatments for use in model experiments and clinical trials, this is important.

SARS-CoV-2 is a 30 kb single-stranded positive-sense RNA genome betacoronavirus and is genetically related to other human coronaviruses: SARS-CoV, MERS-CoV and 229E, OC43, HKU1 and NL63 seasonal 'common cold' coronaviruses. As other viruses, SARS-CoV-2 depends on replicating host machinery. Host abuse factors are an attractive target for novel treatments, as opioid resistance growth is projected to be slower for host-directed therapies than for viral-directed therapies.

Care that targets viral replication specifically may target viral proteins (e.g. remdesivir) or host proteins that the virus relies on. In general, host-targeted therapies can play an important role in infectious diseases, and the only therapy used so far to minimize COVID-19 mortality is dexamethasone. By targeting host immune-mediated organ damage,5 it is likely to respond. Such host-directed therapies, repurposed from other indications (e.g., anakinra, tocilizumab, sarilumab, mavrilimumab), are currently under review.

In this study, current evidence from human beta-coronavirus research were systematically identified and combined to produce a detailed ranked list of host genes involved in COVID-19. We comment on the use of this resource to advise more studies on the pathogenesis of COVID-19 and prioritise host therapeutic objectives. We performed a systematic review of published studies and pre-print manuscripts relating to host gene involvement in human beta-coronavirus infection and related disease to classify current literature that could include informative databases for host gene prioritisation. Results from established studies were combined using meta-analysis by information content (MAIC) in the form of lists of implicated host factor genes, an approach we previously developed to classify host genes required for replication of the Influenza A virus (IAV). We have previously shown that from an unknown potential trial, the MAIC algorithm effectively forecasts fresh experimental outcomes.

Consistent with the emerging definition of COVID-19 pathogenesis, core genes are heavily expressed in the top 100 genes in the inflammatory response to SARS-CoV-2 infection. This include genes involved in viral identification (TLR3, IFIH1), inherent immune system activation (OAS2, HERC5, S100A9), chemotaxis (S100A9, CXCL10, CXCL8, CCL20, SAA2) and pro-inflammatory cytokinesis (S100A9, CXCL10, CXCL8, SAA2) (IL1A, IL18). The endosome-associated pathogen-associated molecular pattern receptor, Toll-like receptor 3 (TLR3), is signaling pathway in the respiratory tract and many inflammatory responses. TLR3 detects viral double-stranded RNA and induces Type I interferons and other pro-inflammatory cytokines, such as IL6 (rank 104) and TNF alpha (rank 182), to be generated by IRF3 and NF-11BB.

Systematic evaluation and meta-analysis are routine components of clinical evidence appraisal and certain genomics areas, but they have become less commonly used in mechanistic biology. We have extensively analysed and meta-analysed host gene-level data from studies that answer a variety of complementary questions about human beta-coronavirus infection using a

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versatile and intuitive process. This offers external validation of various host genes involved in both the viral life cycle and the immune response, and recognises multiple possible therapeutic targets with large multi-source support. We assume that the accuracy of MAIC can increase with each iteration as more and larger datasets become usable.