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QIAGEN® Ingenuity® Pathway Analysis (IPA®) for viral research

Reveal the biological mechanisms driving antiviral host response

Sample to Insight

In the 21st century we have experienced major epidemics, including some that qualify as pandemics. These were caused by old diseases such as cholera, the plague and yellow fever, as well as emerging ones, such as severe acute respiratory syndrome (SARS), Ebola, Zika, middle-eastern respiratory syndrome (MERS), human immunodeficiency virus (HIV), influenza A (H1N1)pdm/09 and, most recently, COVID-19. These viral epidemics and pandemics can greatly increase morbidity and mortality over a wide geographic area and cause significant economic, social and political disruption. For these reasons, researchers are challenged with understanding the complex molecular mechanisms and signaling pathways underlying mammalian antiviral responses and aim to devise strategies to modulate host immune function via the development of antiviral therapeutics and management of clinical cases. These are precisely the viral research applications that QIAGEN IPA enables, helping viral researchers quickly and easily gain novel insights to accelerate their discoveries.

QIAGEN Digital Insights is the leading provider of genomic content, based on advanced curation methods to ensure relevance and accurate insights. QIAGEN Ingenuity Pathway Analysis (IPA), a QIAGEN Digital Insights solution, is used by thousands of researchers worldwide and cited extensively in studies on host response to viruses. The QIAGEN Knowledge Base, upon which QIAGEN IPA is built, is an industry-leading database comprised of biomedical content that has been aggregated, integrated and curated for the last 20 years and is updated weekly. QIAGEN IPA is powered by over 7 million findings from the QIAGEN Knowledge Base, and provides over 700 curated signaling and metabolic pathways. It has been used by thousands of researchers and hundreds of pharmaceutical companies and has been cited in over 25,000 scientific publications. For viral research specifically, IPA has been cited over 2000 times in multiple journals. Moreover, in the last few months, IPA has been referenced in over 70 publications and pre-prints on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), highlighting its applicability for emerging critical human disease research.

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Dr. Daniel Todt, postdoctoral researcher in the Department of Molecular and Medical Virology at Ruhr University Bochum

With QIAGEN IPA, virologists, as well as life science and public health lab researchers, can easily analyze interactions of host molecular mechanisms during viral infection. Built on evidence from thousands of curated publications from biomedical literature, IPA networks are constructed to predict gene and drug effects on selected biological processes, diseases or pathways. IPA can analyze differential expression profiles to identify impacted functions, pathways in viral infection datasets, generate hypotheses about novel regulatory networks and gain additional insights about single-cell biology.

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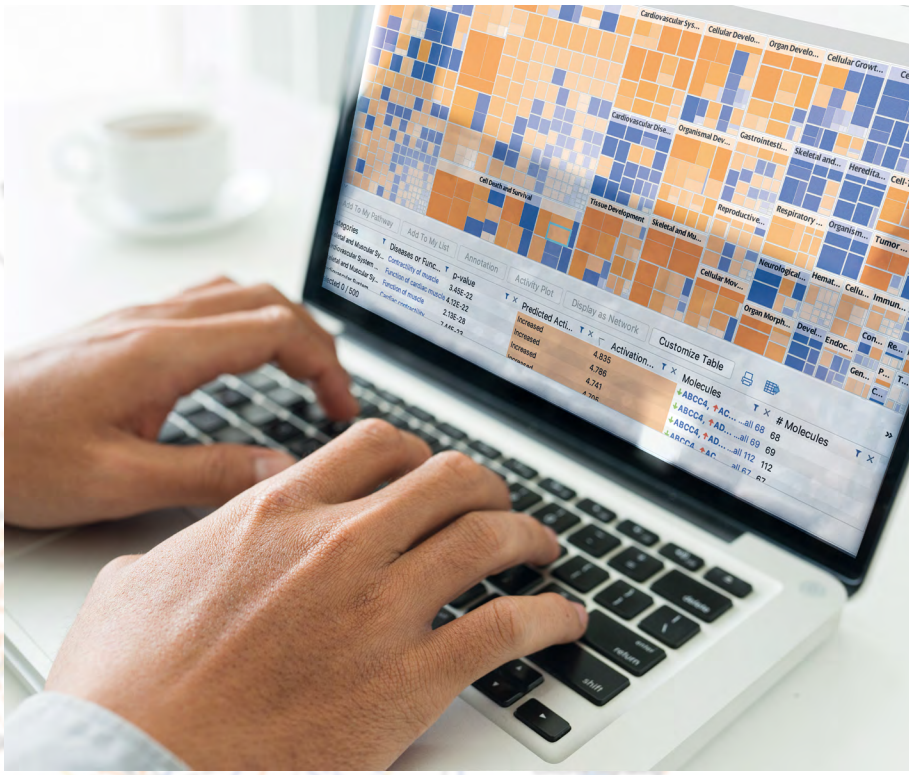
QIAGEN IPA is for all researchers interested in the biology of mammalian host response to viruses — from graduate students to immunologists to data scientists with no expertise in immunology or viral research. What's great is that bioinformatics skills are not necessary to use IPA. The software allows you to branch out from specific viruses of interest to easily compare to various other research avenues in just a few clicks. You can analyze whether antiviral responses are similar across viruses, identify potential key upstream regulators and biological processes triggered in these infections, and identify differentially expressed isoforms that could potentially be used as biomarkers for key pathological endpoints. You can also discover potential therapeutic targets or compounds to inhibit.



Use cases: How QIAGEN IPA can support your viral research

Transcriptomic analyses of SARS-CoV-1 and SARS-CoV-2 from in vitro infected Calu-3 cells

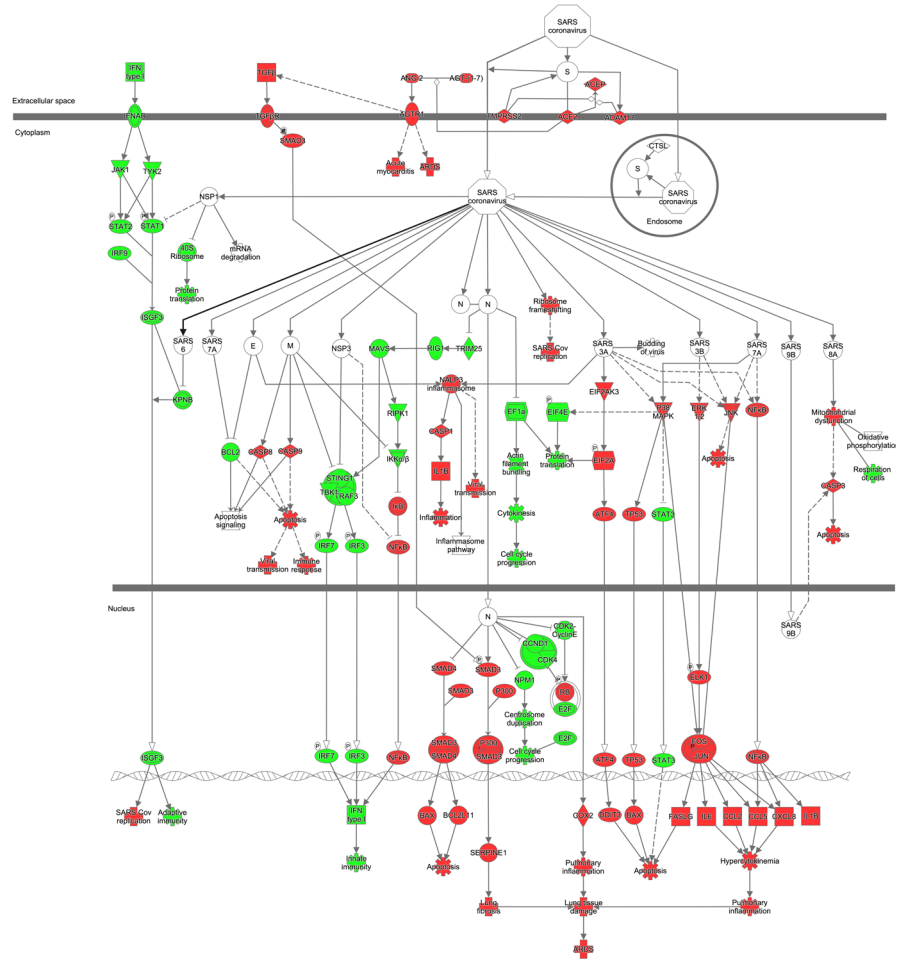


Figure 1. Coronavirus Pathogenesis Pathway. The Coronavirus Pathogenesis Pathway in IPA shown here is overlaid with colors that indicate the likely node activity pattern in the case of overall pathway activation, e.g., when pathogenesis by coronavirus is occurring. Red represents likely increased activity for the node (as determined by the pathway curators based on the underlying literature). Green indicates that the node is likely to have decreased activity in the activated state of the pathway (as determined by the pathway curators).

Predicting the host responses induced by coronaviruses is key to understanding disease mechanisms and to identifying potential therapeutics. QIAGEN IPA enables you to examine the coronavirus pathogenesis pathway in host cells (Figure 1). When using IPA to compare SARS-CoV-1 and SARS-CoV-2 infection in host cells, you can detect pathway differences, as well as detect important networks to drive hypotheses and investigate which drugs or antivirals are predicted to decrease SARS-CoV-2 infection. Using the upstream regulator analysis, QIAGEN IPA shows you drugs predicted to reverse the effect of SARS-CoV-2 on specific genes and pathways, to counteract infection. Another angle you can pursue is to identify transcript variants linked to SARS-CoV infection-induced responses. You can look beyond biological data related to viral infection using QIAGEN IPA with Analysis Match to develop new hypotheses on inhibitors of SARS-CoV-2 infection. QIAGEN also recently developed Coronavirus Network Explorer (https://digitalinsights.qiagen.com/coronavirus-network-explorer/)—a free web-based resource on a predicted set of networks identified using the ▷

extensive QIAGEN Knowledge Base with machine learning to infer new connections between SARS-CoV-2 and the host response. This shows predicted interactions between SARS-CoV-2 virally-encoded proteins and host proteins that ultimately drive host responses. For example, you can examine the network displaying interrelations between key host molecules involved in the coagulation cascade (Figure 2).

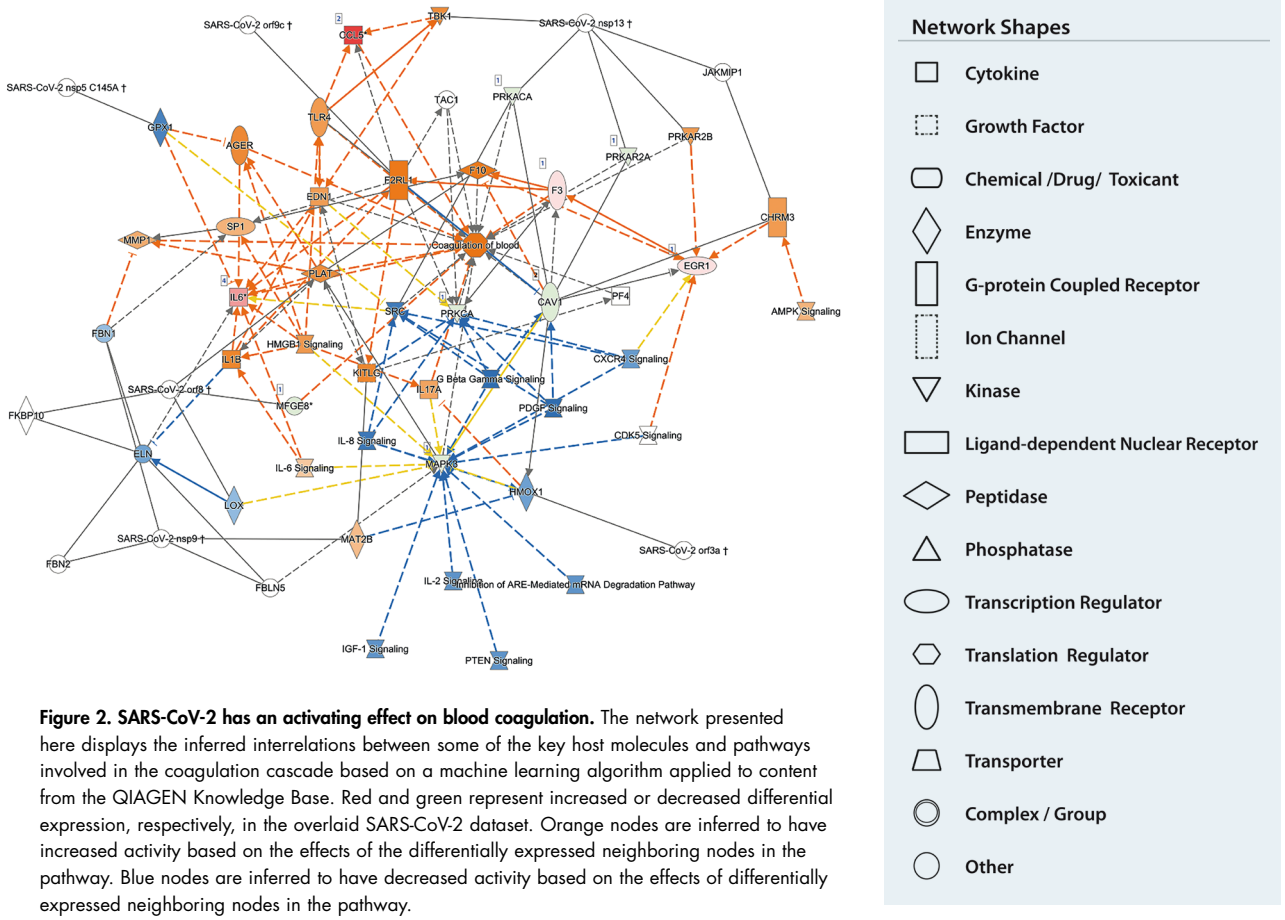


Figure 2. SARS-CoV-2 has an activating effect on blood coagulation. The network presented here displays the inferred interrelations between some of the key host molecules and pathways involved in the coagulation cascade based on a machine learning algorithm applied to content from the QIAGEN Knowledge Base. Red and green represent increased or decreased differential expression, respectively, in the overlaid SARS-CoV-2 dataset. Orange nodes are inferred to have increased activity based on the effects of the differentially expressed neighboring nodes in the pathway. Blue nodes are inferred to have decreased activity based on the effects of differentially expressed neighboring nodes in the pathway.

Network Shapes

- Cytokine
- Growth Factor
- Chemical /Drug/ Toxicant
- Enzyme
- G-protein Coupled Receptor
- Ion Channel
- Kinase
- Ligand-dependent Nuclear Receptor
- Peptidase
- Phosphatase
- Transcription Regulator
- Translation Regulator
- Transmembrane Receptor
- Transporter
- Complex / Group
- Other

Causal and upstream regulator network analysis of Calu-3 cells infected by SARS-CoV-2

The continuous and rapid emergence of new viral strains calls for a better understanding of the fundamental changes occurring within the host cell upon viral infection. A paper from earlier this year used QIAGEN IPA to analyze RNA-seq transcriptome data from Calu-3 human lung epithelial cells infected with SARS-CoV-2 compared to five other viruses and characterized their coding and noncoding

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RNA transcriptional portraits (1). Canonical pathway analyses in IPA of SARS-CoV-2-infected cells highlight a higher degree of enrichment in pathways related to dendritic cell (DC) maturation. Causal network analysis provides further insights into the pro-inflammatory environment upon viral infection, highlighting several toll-like receptors, interferons, NFkB subunits and tumor necrosis factors (TNFs) that are significantly activated in SARS-CoV-2 infection, positively correlating with disease severity. These findings serve as the basis for future research and understanding of host response to SARS-CoV-2 and other viruses.

Pathway analyses of hepatitis E virus from in vitro infected hepatoma cell lines and primary cells

The hepatitis E virus (HEV) is a long-neglected RNA virus and the major causative agent of acute viral hepatitis in humans worldwide. However, the mechanisms of liver pathology and clinical disease remain poorly understood for HEV infection. For these reasons, Dr. Daniel Todt and his colleagues developed a robust and improved cell model of the pathogen and used QIAGEN IPA to identify HEV host cell interactions and novel host components required for the viral life cycle, as well as restriction factors. "We wanted to interrogate which cell lines are susceptible to HEV infection, such as hepatoma cell lines, primary human hepatocytes, and also primary porcine hepatocytes, because HEV has a big reservoir in animals, especially pigs and wild boar," said Dr. Todt. "So, we infected these primary hepatocytes or primary cell cultures and we asked what host response is triggered in these cell types, as well as what the kinetics are behind HEV infection. Using RNA-seq and QIAGEN IPA, we identified quite a few pathways that were frequently regulated upon HEV infection and how these pathways were altered over time." Understanding these interactions will provide insight into the viral life cycle of HEV and might further help to devise novel therapeutic strategies and antiviral targets.

Analysis of signaling pathways in neural progenitor cells infected by Zika virus

Zika virus (ZIKV) infection is a serious public threat with cases reported in about 70 countries and territories. One of the most serious consequences of ZIKV infection is congenital microcephaly in babies and has been suggested to result from infection of neural progenitor cells (NPCs) in the developing fetal brain. Raman et

al. employed quantitative proteomics to determine the protein expression profile during viral replication in NPCs (2). Analysis of the protein expression changes using IPA resulted in the identification of a wide range of cell signaling pathways, including pathways involved in neurogenesis and embryonic development, as well as cell cycle, apoptosis, lipid metabolism and oxidative stress. Notably, the differential regulation of the ephrin receptor and PPAR signaling pathways, as revealed by quantitative proteomics and validated by qPCR array, underscores the need to explore these pathways in disease development. Collectively, these findings could help shed light on the mechanisms underlying ZIKV-induced microcephaly and ZIKV replication in NPCs.

Transcriptome analysis of the HSV-1-infected trabecular meshwork cells

Herpes simplex virus type 1 (HSV-1) is causative for hypertensive anterior uveitis, and trabecular meshwork (TM) cells, the key cells regulating intraocular pressure (IOP), are considered to be the site of inflammation. Choi et al. explored the profiles of genes expressed in human TM primary cells upon HSV-1 infection using IPA (3). Analysis in IPA showed that genes involved in organismic injury and abnormalities, cellular development, cellular growth and proliferation, cellular movement, cell death and cell survival were significantly enriched. IPA revealed that HSV-1 induced transcriptional suppression of many components related to fibrosis. Choi and colleagues also used IPA upstream regulator analysis and found that the most significant upstream regulator was TGF-β1, and one of the activated regulators was PDGF-BB. This study may provide a novel mechanism for the pathogenesis of HSV-1 infection in human TM cells

Transcriptome and pathway analysis of the *P. leucopus* brain response to Powassan virus

Powassan virus (POWV) is a tick-borne Flavivirus that infects small-to-medium-sized mammals and is responsible for life-threatening encephalitis in North America and some regions of Russia. To characterize the mild encephalitic response in *P. leucopus* mouse brains, Mlera et al. used RNA-seq to profile the differential transcriptome changes associated with POWV infection in the brains of *P. leucopus* mice, and then employed IPA to interrogate the canonical

pathways responding to POWV infection and infer upstream regulators (4). Their results indicate that POWV induces the differential expression of many genes and the *P. leucopus* mice mount a robust interferon response against the virus in a tightly regulated manner. The *P. leucopus* mouse brain transcriptome sequencing results showed the upregulation of RIG-like receptors RIG-I, MDA5 and LGP2, as well as genes encoding toll-like receptors TLR1-TLR4, TLR6 and TLR7, suggesting that POWV-associated molecular patterns were also detected by these membrane-bound pathogen recognition receptors. These results will be useful for the identification of factors that have a role in restricting POWV.

Paving the way for antiviral host response research

QIAGEN IPA is used by virology labs around the world for basic research in studies of the host response to viruses. This valuable tool accelerates the understanding of 'omics data from organisms and viruses to help assess interactions between the two, and reveal where therapeutics could potentially come into play to help modulate host response.

References

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