Infectious Disease Research
Viral Infection Publications by NanoString Customers

Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients

Hadjadj et al. MedRxiv. 2020.
Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases,
Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), Université de Paris.

Using the Nanostring® nCounter® Human Immunology Panel, the authors analyzed 574 immune genes from the blood of 50 COVID-19 patients with varied disease severity. Critically ill patients exhibited a profoundly impaired type I IFN response characterized by low interferon production and activity with consequent downregulation of IFN-stimulated genes. Low interferon was associated with persistent blood virus load, an exacerbated inflammatory response partially driven by NFκB, TNF-α, IL-6 production and signaling, and high inflammatory chemokines. These findings suggest that type-I IFN deficiency in blood is a hallmark of severe COVID-19 and could identify a high-risk population. The study also provides a rationale for testing IFN administration combined with adapted anti-inflammatory therapy targeting IL-6 or TNF-α in the most severe patients and raises concerns over the administration of IFN signaling-interfering drugs to critically ill patients.

A dynamic immune response shapes COVID-19 progression

Ong, EZ et al. Cell Host & Microbe. April 2020.
SingHealth Duke-NUS Academic Medical Center, Singapore
Singapore General Hospital

Using the nCounter® Human Immunology Panel, a team from the Viral Research and Experimental Medicine Center in Singapore conducted daily transcriptomic analyses on whole blood from three individuals infected with SARs-CoV-2 and compared them to healthy controls. The team found increased cytokine expression in severe cases, characterized by a peak in gene expression related to an inflammatory response after respiratory function had declined to its lowest level. An exception was the IL1 pathway. Parallel analyses of the expression of CD4 and CD8 cells suggested that the pro-inflammatory response may be intertwined with T cell activation, which could exacerbate disease or prolong the infection.

Inflammatory responses to a pathogenic West Nile virus strain.

Huang B et al. BMC Infect Dis. 2019 Oct 29;19(1):912.
Queensland Health Forensic and Scientific Services, Griffith University, University of Queensland.

Kunjin virus (WNVKUN), West Nile virus (WNV) originally isolated in Australia, has been considered more benign than other WNV strains circulating globally. In 2011, a more virulent form of the virus NSW2012 emerged during an outbreak of equine arboviral disease in Australia. In this study, host cell innate immune responses to WNVKUN isolates were measured in two in-vitro systems: the neuroblastoma cell line SK-N-SH and induced-pluripotent stem cells (iPSCs) derived from neuronal cells. Gene expression of 249 inflammation-associated genes was assessed using the NanoString nCounter Human Inflammation Panel. The NSW2012 isolate induced higher gene expression of IL-8 and CCL2 than cells infected with less pathogenic isolates. Pathway analysis indicated that inflammation-associated genes were highly activated in NSW2012-infected cells. Overall, NSW2012 appears to have unique genetic characteristics (e.g., upregulated expression of inflammatory genes) that contributed to the outbreak.

Lung transcriptional unresponsiveness and loss of early influenza virus control in infected neonates is prevented by intranasal Lactobacillus rhamnosus GG.

Kumova OK et al. PLoS Pathog. 2019 Oct; 15(10).
Drexel University College of Medicine, Erasmus University Medical Center.

Lactobacillus rhamnosus GG (LGG) is an immune modulator in respiratory viral infection, and this study showed that intranasal treatment of influenza virus infection with LGG considerably improved neonatal mouse survival. Transcription profiles of 753 immune-related genes were measured using the nCounter Mouse PanCancer Immune Profiling Panel. In the early stages of influenza infection, transcriptional responses in the lung of neonates were delayed, which subsequently increased mortality. However, LGG pretreatment resulted in improved immune gene transcriptional responses, similar to adult-like transcriptional signatures in the lungs, particularly upregulated type I IFN pathways. Also, protective activity of LGG was mediated by MyD88 through the Toll-like receptors-4 (TLR4). Taken together, LGG can improve both early control of the virus and transcriptional response to influenza infection.

A T164S mutation in the dengue virus NS1 protein is associated with greater disease severity in mice.

Chan KWK et al. Sci Transl Med. 2019 Jun 26;11(498).
Duke-NUS Medical School, Université de Montpellier, Monash University, National University of Singapore, Uniformed Services University of the Health Sciences, Bioinformatics Institute (A*STAR), and others.

In severe dengue disease, the secreted form of the nonstructural protein 1 (sNS1) of dengue virus causes vascular leakage. In this study, NS1 was reverse engineered to include the T164S mutation in dengue virus serotype 2, mildly infectious strain. The T164S mutant virus correlated with increased disease severity in human PBMCs and mice as well as increased infectivity in mosquitoes. Gene expression profiling of 268 inflammation-associated human genes using a Panel Plus spike-in and the nCounter Human Inflammation Panel revealed that upregulated genes were induced in response to vascular leakage. MAPK genes were upregulated in the first 6 hours after infection with the T164S mutant virus. Infection of type 1 and 2 interferon receptor-deficient mice with the T164S mutant virus resulted in severe disease, which was associated with increased complement activation, tissue inflammation, and rapid mortality. The T164S mutation is predicted to form the unstable, hexameric NS1 that may cause more severe dengue disease.

Severe fever with thrombocytopenia syndrome phlebovirus non-structural protein activates TPL2 signalling pathway for viral immunopathogenesis.

Choi Y et al. Nat Microbiol. 2019 Mar;4(3):429-437.
University of Southern California, Chungbuk National University, National Institute of Biological Sciences, Beijing, Tuft Medical School, Chungnam National University, University of Glasgow, and others.

Severe fever with thrombocytopenia syndrome phlebovirus (SFTSV) is listed in the World Health Organization Prioritized Pathogens, due to the lack of therapies and vaccines. SFTSV non-structural protein (NSs) has been shown to block type I interferon pathway and facilitate disease progression. This study examined the effects of NSs on the expression of ~550 host immune genes in cells and mouse models using the nCounter Mouse Immunology Panel. The data, combined with the yeast two-hybrid screen, found that NSs interacted with A20-binding inhibitor of NF-κB activation 2 (ABIN2) and activated the formation of tumor progression locus 2 (TPL2) ternary complex and signaling, resulting in the upregulation of IL-10 expression. Activation of the TPL2 signaling pathway was required for the lethal phenotype. While SFTSV infection of wild-type mice led to rapid weight loss and death, Tpl2-/- mice or Il10-/- mice survived an infection. This study demonstrates that SFTSV-NSs targets the TPL2 signaling pathway to induce an IL-10 mediated immuno-suppressive environment that promotes viral pathogenesis.

Inflammation induced by influenza virus impairs human innate immune control of pneumococcus.

Jochems SP et al. Nat Immunol. 2018 Dec;19(12):1299-1308.
Liverpool School of Tropical Medicine, University of São Paulo, Royal Liverpool and Broadgreen University Hospital, University of Edinburgh, University Medical Center Utrecht, and others.

Following pandemic and seasonal influenza virus infection, secondary pneumonia is a main cause of mortality. This study demonstrated that influenza virus infection impaired the immunological control of nasal pneumococcus colonization, increasing susceptibility to S. pneumoniae. In a human challenge model, viral infection increased pneumococcus carriage load, which in turn induced early neutrophil degranulation and recruitment of monocytes to the nose. 594 genes expressed in blood neutrophils were analyzed using the nCounter Human Immunology Panel; levels of the cytokine CXCL10 were significantly increased by influenza virus infection, and CXCL10 could be used as a marker for increased susceptibility to S. pneumoniae. Taken together, nasal influenza virus infection induced inflammation, impaired innate immune function, and altered nasal gene responses to pneumococcus carriage.

Exploring Crimean-Congo Hemorrhagic Fever Virus-Induced Hepatic Injury Using Antibody-Mediated Type I Interferon Blockade in Mice.

Lindquist ME et al. J Virol. 2018 Oct 12;92(21).
US Army Medical Research Institute of Infectious Diseases.

Crimean-Congo hemorrhagic fever virus (CCHFV) can cause severe hepatic injury in humans. The only small-animal model in which CCHFV consistently induces severe liver damage has been mice lacking type I interferon (IFN-I) signaling. In this study, antibody-mediated blockade of IFN-I signaling in mice was used to investigate CCHFV-induced liver pathogenesis. When IFN-I blockade was administered within 24 hours after exposure to CCHFV, mice developed severe disease with > 95% mortality. Acute CCHFV infection resulted in a nearly complete loss of Kupffer cells, specialized macrophages in the liver. Transcriptional analysis of 687 genes in the liver using the nCounter Mouse Immunology and Inflammation Panels showed increased expression of proinflammatory cytokines, chemoattractants, and liver enzymes. Liver injury was caused by hepatocyte necrosis via activation of death receptor signaling pathways, independent of cytotoxic immune cells. Transcriptional and protein analyses revealed the activation of tumor necrosis factor superfamily members, implicating these molecules as key factors in liver cell death.

Diagnostic accuracy of digital RNA quantification versus real-time PCR for the detection of respiratory syncytial virus in nasopharyngeal aspirates from children with acute respiratory infection.

Bouzas ML et al. J Clin Virol. 2018 Sep;106:34-40.
Federal University of Bahia School of Medicine, Fundação Oswaldo Cruz (FIOCRUZ), Rega Institute for Medical Research, University Hospitals Leuven.

To diagnose viral respiratory tract infections, multiplex digital RNA quantification using the NanoString nCounter® analysis system was used to identify the presence of different respiratory viruses in a single reaction. This study investigated the accuracy of using a Custom CodeSet to detect respiratory syncytial viruses (RSV), subgroups RSV-A and RSV-B, in nasopharyngeal aspirates from children with acute respiratory infection. Using quantitative RT-PCR data as a reference, accuracy of the nCounter data was 95.2% for RSV-A and 95.3% for RSV-B, and the results from both methods significantly correlated for RSV-A and RSV-B in nasopharyngeal aspirates. Thus, the authors concluded, the robustness and high-throughput multiplexing capacity of the nCounter system is suitable for large-scale epidemiological studies.

Distinct Gene Profiles of Bone Marrow-Derived Macrophages and Microglia During Neurotropic Coronavirus-Induced Demyelination.

Savarin C et al. Front Immunol. 2018 Jun 11;9:1325.
Lerner Research Institute, Cleveland Clinic Foundation.

This study investigated the gene expression profiles of bone marrow-derived macrophages (BMDM) vs. microglia, which was associated with demyelination induced by infection with a gliatropic coronavirus JHMV strain in a murine model. To analyze major myeloid cell types including M1/M2 polarization, the nCounter Mouse Myeloid Innate Immunity Panel (754 targets) was used. Results revealed that the central nervous system-infiltrating BMDM established a characteristic profile, including M1 and M2 markers throughout infection. In contrast, microglia expressed a dynamic gene profile with repressed M2-markers and upregulated pro-inflammatory and phagocytic features, which coincided with demyelination after viral control. Overall, these data support a pro-inflammatory and pathogenic role of microglia during JHMV-induced demyelination, whereas the gene expression profile of BMDM was independent of the tissue environment.

Nonstructural proteins nsp2TF and nsp2N of porcine reproductive and respiratory syndrome virus (PRRSV) play important roles in suppressing host innate immune responses.

Li Y et al. Virology. 2018 Apr;517:164-176.
Kansas State University, Ohio State University, Lawrence Livermore National Laboratory, University of Cambridge, Leiden University Medical Center.

Porcine reproductive and respiratory syndrome virus (PRRSV) has a ribosomal frameshift mechanism to yield two truncated nonstructural protein (nsp)-2 variants, nsp2TF and nsp2N, of the nsp2 region of the viral replicase. Importantly, nsp2, nsp2TF, and nsp2N all include the PLP2 domain, which has been implicated in disrupting type I interferon signaling, leading to suppressed cellular innate immune responses. In this study, the expression levels of 579 immunological genes were evaluated using the nCounter Human Immunology Panel. Gene expression analysis identified significant upregulation of host innate immune genes in cells infected with nsp2TF/nsp2N-deficient viruses. Also, nsp2TF/nsp2N-deficient viruses were less capable of counteracting the innate immune response in infected pigs. These results suggest that nsp2TF and nsp2N can suppress the host innate immune responses against PRRSV infection.

A conserved transcriptional response to intranasal Ebola virus exposure in nonhuman primates prior to onset of fever.

Speranza E et al. Sci Transl Med. 2018 Mar 28;10(434).
Boston University, US Army Medical Research Institute of Infectious Diseases.

This study investigated the host response to Ebola virus after intranasal exposure in nonhuman primate (NHP) models. RNA-seq and a Custom CodeSet targeting 769 NHP genes was used to monitor the host response over time. During acute Ebola infection, innate immune pathways were activated. The timing of the host response was associated with clinical presentation: a predictable pattern over time with interferon genes being upregulated early, followed by fever and the expression of cytokine genes, and ending with excessive immune dysregulation. The authors also found that, once started, lethal Ebola infection has a predictable host response to infection, regardless of the timing of the onset of symptoms. Moreover, expression of a subset of genes was associated with disease development before other indications of infection. These data allowed the authors to map the NHP response to infection during both the symptomatic and asymptomatic phases.

To learn more about NanoString technologies visit nanostring.com

APR 2020 MK2406