



**SPOT
LIGHT**

Extending a global understanding of COVID-19

DR. DEXI CHEN, PHD, MD



Achieving multi-omic insights with microfluidics and CyTOF technology

“The host’s immune response to a pathogen is an ongoing theme in infectious disease research, contributing to disease progression and a patient’s symptoms and outcome,” says Dr. Dexi Chen, PhD, MD, of the Beijing Institute of Hepatology and You’an Hospital. “As such, our current research focuses on patients’ immune response to 2019-nCoV in the lungs of severe COVID-19 patients.”

In December 2019, an outbreak of COVID-19 was reported in Wuhan, Hubei Province, China. The disease spread in China, followed by reports of increasing cases globally. Initially, most patients who died in the hospital died of severe pneumonia and acute respiratory distress syndrome (ARDS). Chen and his team worked quickly to understand COVID-19 pathology in critical patients, determined to help direct treatments for the disease. To date, this prolific lab has published four studies using mass cytometry to investigate COVID-19.

While their initial pathological findings from a COVID-19 patient who had developed ARDS showed the characteristic diffuse alveolar damage and obvious mononuclear cell infiltration in the lung, the types and subsets of infiltrating immune cells in the lung tissues were not clear. The group used Imaging Mass Cytometry™ (IMC™) to analyze the immune cell clusters in lung tissue after biopsy of two patients with COVID-19: one who had died from ARDS and the other of severe pneumonia (Zhang et al.).

Results showed that ARDS in the first patient was the result of an increased infiltration of immune cells—specifically T cell lymphocyte and macrophage subsets—as well as more focal infiltration of natural killer cells. The added complication of bacterial pneumonia in the second patient led to a different distribution, shown by cluster infiltration of neutrophils and macrophages, diffuse infiltration of T cell subsets and scattered infiltration of natural killer cells and dendritic cells. This newfound data suggests the specific cell types that play a major role in lung injury.

“Imaging Mass Cytometry with CyTOF® technology is our method of choice for these studies because the limited samples are very valuable. CyTOF allows more than 30 markers in one panel, and we don’t have to worry about color compensation or background autofluorescence issues,” explains Chen.

Moving forward with these new findings, the team examined gene expression levels associated with the modified immune response observed during disease progression. With the need to move swiftly to determine the immune response of COVID-19 patients before and after treatment, they chose the Biomark™ HD system and 96.96 Dynamic Array™ integrated fluidic circuits (IFCs) for gene expression (GE) (Ouyang et al.). Chen adds that in a short period of time, one 96.96 IFC for gene expression can process 9,216 reactions from 96 samples and assays, using less sample and reagent to achieve high-quality, consistent results. “This is critical for us to answer these questions quickly,” he says.

Using Juno™ and Biomark HD to examine the innate immune status and immune-related gene expression levels in 11 patients, the group found decreased T cell proportions and down-regulated gene expression involved in T cell activation and differentiation in severe COVID-19 patients, indicating suppression of the T cell immune response.

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The team then applied mass cytometry to analyze PBMC from patients with different disease progression, observing obvious differences in composition of immune cells in severe patients (Wang et al.). CyTOF technology revealed a disturbed immune system homeostasis with dysfunction in T cell subsets, dendritic cells and macrophages that were excessively activated at first and became exhausted as the disease progressed to critical stages. Further study with CyTOF

and cytokine assays on additional patients confirmed these findings, showing a decrease in T cells, B cells and NK cells along with a progressive decrease of interleukin-2 (IL-2) in plasma (Shi et al.). Association of immune cell suppression with IL-2 could serve as a warning of disease deterioration in patients with COVID-19 pneumonia.

Such a combination of approaches to uncover the diverse mechanisms activated in the COVID-19 response strengthens our understanding of the disease and its progression. These studies demonstrate the unique changes in immune response across varying disease progression as well as patient response to treatment. Further experiments could be performed to support this data, increasing patient numbers and expanding the antibodies used to discern more targeted cell type behaviors.

SARS-CoV-2 has displayed distinct properties throughout this pandemic, yet it also shares some similarities with SARS-CoV and MERS-CoV. These findings have helped extend global understanding of the SARS-CoV-2 infection mechanism, and they provide a basis for future novel immune therapeutic strategies.

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