Johns Hopkins All Children's Researchers Help to Explain Extreme Levels of Inflammation, Especially in Lung Diseases

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Laszlo Nagy, M.D., Ph.D. (center), and Laszlo Halasz, Ph.D. in the Nagy Lab in the Institute for Fundamental Biomedical Research at Johns Hopkins All Children's
By Randolph Fillmore

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"How cells decide what to do, and how they carry out different 'jobs' in response to signals, is a fascinating study," says Nagy, a professor in the Division of Endocrinology, Diabetes and Metabolism in the Departments of Medicine and Biological Chemistry at the Johns Hopkins University School of Medicine.

That lifelong fascination has provided the foundation for decades of work aimed at unraveling the mysteries of cell activity in the immune system.

One aspect of his how-do-cells-work pursuit has been in investigating the activities of specialized white blood cells in the immune system called "macrophages." Macrophages play a key role in defending against disease by helping clear the body of bacteria, viruses, fungi and parasites. Their "dedicated job" is to track down and engulf the body's "foreign invaders" and to initiate a response from the immune system to eliminate them.

Why Study Macrophages?

Nagy's years of focus on macrophages has led to a better understanding of how they work, and he and his colleagues have published many studies.

For example, the researchers found that a specialized transcription factor, regulating gene activity, called "Early Growth Response 2" (EGR-2) can trigger a long-term response to macrophage activity resulting an anti-inflammatory, pro-regenerative phenotype.

They also have discovered how a damaged muscle can begin healing when macrophages rush in and secrete growth factors, including growth/differentiation factor-15 (GDF-15).

In their most recent investigations into macrophage activity, researchers in the Nagy lab in the Johns Hopkins All Children's Institute for Fundamental Biomedical Research in St. Petersburg, Florida, have found that an imbalance in macrophages can compromise their healing response to inflammation.

New Study Reveals "Extended Synergy" Role for Macrophages

Under Nagy's direction, and as part of a broad collaboration, an international team of researchers recently published a paper outlining their findings regarding macrophages. Researchers discovered a link between pro- and anti-inflammatory factors and macrophages resulting in the production of high levels of inflammatory mediators and inflammation, especially if present in diseases affecting the lungs.

The research team's results were reported in a paper titled "The epigenetic state of IL-4-polarized macrophages enables inflammatory cistromic expansion and extended synergistic response to TLR ligands." Their report was published in November in the prestigious journal *Immunity*.

The research team found that inflammatory mediators (cytokines), specifically Interleukin-4 (IL-4), a repair-type macrophage-polarizing factor, and a number of receptors called Toll-like receptors (TLRs), can "enhance" each other. Their synergistic relationship can lead to hyperinflammatory response from the immune system and create "super inflammation," especially in diseases affecting the lungs.

The finding surprised the researchers because previous research into the same signaling mechanisms did not suggest that the two pathways (IL-4 and TLR) had any positive influence on each other.

Nagy and his team, however, discovered a process through which very high levels of inflammation can occur when macrophages become "polarized" by the cytokine IL-4 and subsequently exposed to proinflammatory signals from bacteria for example. This new mechanism may contribute to disease processes by inducing high levels of inflammation.

The Nagy-led team also found that when a transcription factor (proteins that help turn specific genes "on" or "off" by binding to nearby DNA) became involved, things turned out differently. In this case, a transcription factor called "Early Growth Response 2" (EGR-2) contributed to the process through what the researchers called "extended synergy." Synergy, or a "synergistic relationship," means that when two or more factors work together, they become stronger than either one individually.

In this case, IL-4, TLR, and EGR-2, working together in extended synergy, promoted a hyperinflammatory response by the immune system. Given this new information, the researchers concluded that their findings "established that IL-4-induced genetic reprogramming is responsible for the development of hyperinflammatory responsiveness to TLR activation through extended synergy, and contributes to lung pathologies."

What Do Their Findings Mean?

Nagy explains the phenomenon they discovered through a simple example using hot and cold water as explanatory "stand-ins" for IL-4 and TRL receptors.

"If you mix hot and cold water you would expect to get 'lukewarm' water as a result," he says. "However, we found that when the two signals were mixed (one cold and one hot) the result was extremely hot water — or, in this case, high levels of inflammation."

The surprising findings may have groundbreaking implications by providing an appropriate "target" for developing a strategy to prevent the development of extended synergy and the resulting high levels of inflammation. That research is now in its early stages, Nagy says.

Technological Contributions to the Study

According to Nagy, immune systems are very complicated and difficult to study in the body. So, one aspect of the study carried out by researchers in the Nagy lab was to use bone marrow-derived macrophages (BMDM) from both human and mouse cells to focus on the interaction between cytokines (white blood cells) and transcription factors.

"The immune responses by each individual are determined by natural genetic variations, prior experience, disease state, pathological or physiological exposures, including earlier infections and aging," Nagy says. "Therefore, we investigate interactions between isolated signaling events at the genetic and transcription levels using tissue resident macrophages."

The Nagy lab includes bioinformatics experts, such as study co-author Laszlo Halasz, Ph.D., who works with the data. Nagy credits the bioinformatics experts and the new technology that allowed them to use very large data sets in reaching their conclusions.

"These data sets are available to any researcher," Nagy comments. "Whenever we publish a study, we deposit these datasets so others can use them as well."

More on "Super Inflammation"

Nagy and the researchers noted in their report that high levels of inflammation often occur in the lungs with diseases such as asthma. And while they were not studying COVID-19 and their findings are not related to the SARS-CoV-2 virus that can cause COVID-19, hyperinflammatory responses — called the result of a "cytokine storm" — are often a COVID-19 complication. It is that kind of hyperinflammation that the researchers investigated.

According to Nagy, extended synergy operates in the alveoli, the many tiny air sacs in the lungs that allow for rapid gaseous exchange, and where airway inflammation occurs and drives enhanced inflammation. Macrophages line the internal lung surfaces and guard the lungs.

"Our next step is to find an appropriate target and develop a way to stop the hyperinflammatory response by interfering with extended synergy," Nagy says. "That work is underway."