Scientists solve decades long mystery of NLRC5 sensor function in cell death

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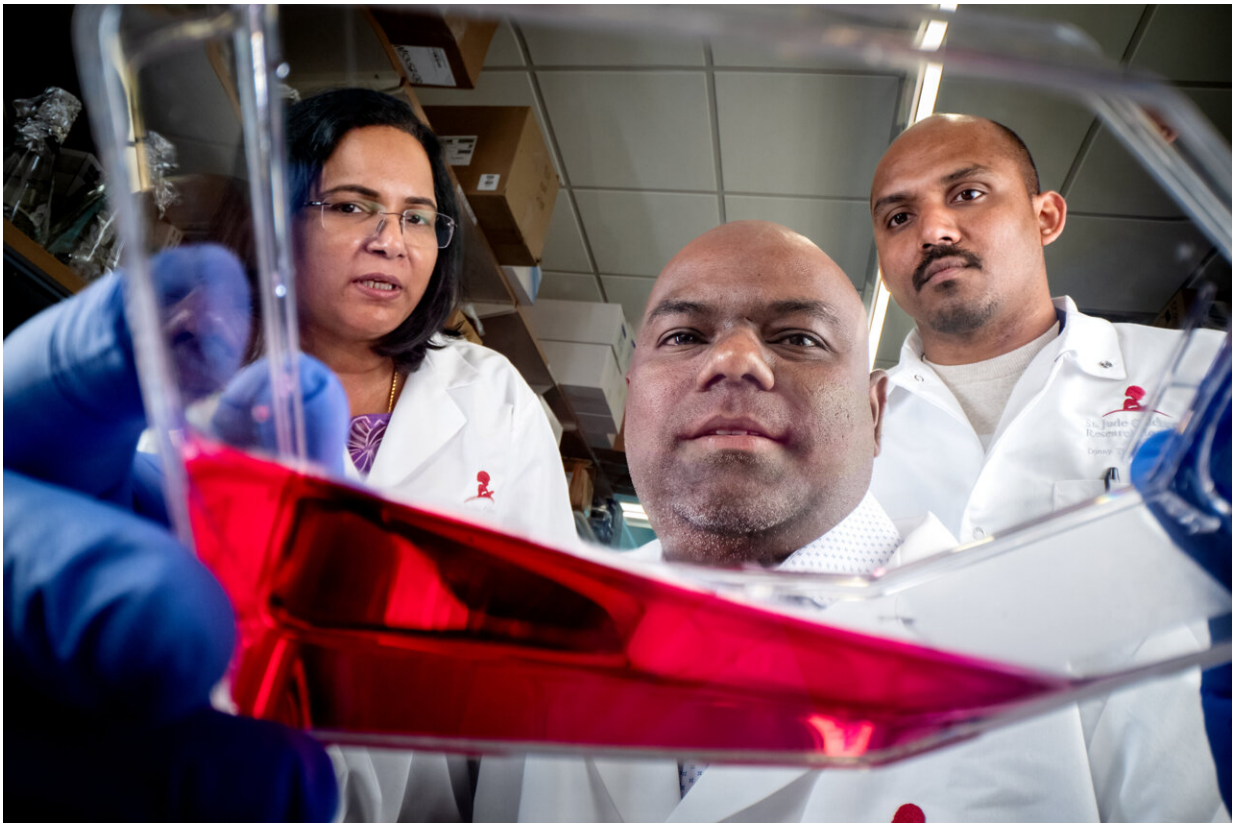

Thirumala-Devi Kanneganti, Ph.D., Balamurugan Sundaram, Ph.D., and Nagakannan Pandian, Ph.D., recently published research revealing the function of the innate immune sensor NLRC5 in cell death. Credit: St. Jude Children's Hospital

The innate immune system is responsible for protecting the human body

from threats that could cause disease or infection. The system relies on innate immune sensors to detect and transmit signals about these threats. One of the key innate immune strategies to respond to threats is through cell death. New research from St. Jude Children's Research Hospital discovered that NLRC5 plays a previously unknown role as an innate immune sensor, triggering cell death. The findings, published in *Cell*, show how NLRC5 drives PANoptosis, a prominent type of inflammatory cell death. This understanding has implications for the development of therapeutics that target NLRC5 for the treatment of infections, inflammatory diseases and aging.

Depending on the threat, innate immune sensors can assemble complexes such as inflammasomes or PANoptosomes. The inflammasome can be thought of as an emergency broadcast system that is activated quickly, while the PANoptosome is more like an emergency response unit that generally integrates more signals and components to respond to the threat. How innate immune sensors work—what triggers them to act—has been a mystery, which researchers have been chipping away at for decades.

Nucleotide-binding oligomerization domain-like receptors (NLRs) are a large family of important molecules involved in inflammatory signaling. They are generally thought to function as innate immune sensors that detect threats. However, the specific roles of several NLRs in sensing are not yet understood. Scientists at St. Jude conducted a large screen, testing a specific NLR, NLRC5, to see what threats activate it. Through their efforts, they discovered that depletion of nicotinamide adenine dinucleotide (NAD), a molecule essential in energy production, triggers NLRC5-mediated cell death through PANoptosis.

"One of the biggest questions in the fields of immunology and innate immunity is what the various members of the NLR family are sensing, and what their functions are," said corresponding author Thirumala-Devi

Kanneganti, Ph.D., St. Jude Department of Immunology vice chair. "NLRC5 was an enigmatic molecule, but now we have the answer—it is acting as an innate immune sensor and cell death regulator, driving inflammatory cell death, PANoptosis, by forming a complex."

Identifying the NLRC5 trigger

Scientists in the Kanneganti lab conducted a rigorous screen to get to the bottom of what threats trigger NLRC5. This included looking at pathogens such as bacteria and viruses, as well as pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) that can be released by or mimic an infection or the cause of an injury or illness, as well as other danger signals such as cytokines (immune signaling molecules).

The researchers also looked at heme, the component of hemoglobin responsible for carrying oxygen. Infections or disease can cause red blood cells to rupture in a process called hemolysis. This releases hemoglobin into the bloodstream. When hemoglobin breaks down into its components, it releases free heme, which is known to cause significant inflammation and organ damage. The researchers tested many different combinations of pathogens, PAMPs and DAMPs to see if NLRC5 was required for a response.

"Among all the combinations we tested, we identified that the combination of heme plus PAMPs or cytokines specifically induces NLRC5-dependent inflammatory cell death, PANoptosis," said co-first author Balamurugan Sundaram, Ph.D., St. Jude Department of Immunology. "Our results showed for the first time that NLRC5 is central to responses to hemolysis, which can occur during infections, inflammatory diseases and cancers."

Energy depletion triggers NLRC5 function

Upon identifying the heme-containing PAMP, DAMP and cytokine combinations that trigger NLRC5-dependent inflammatory cell death, the researchers further investigated how NLRC5 is regulated. They found that NAD levels drive NLRC5 protein expression. If NAD is depleted, that sounds an alarm that there is a threat the immune system should recognize. The researchers found that depletion of NAD is sensed by NLRC5, triggering PANoptosis.

"By supplementing with the NAD precursor, nicotinamide, we reduced NLRC5 protein expression and PANoptosis," said co-first author Nagakannan Pandian, Ph.D., St. Jude Department of Immunology. "Therapeutically, nicotinamide has been widely studied as a nutrient supplement, and our findings suggest it could be helpful in treating inflammatory diseases."

The researchers also discovered that NLRC5 is in an NLR network with NLRP12, which come together with other cell death molecules and form an NLRC5-PANoptosome complex that triggers inflammatory cell death. The finding builds on previous research by the Kanneganti lab showcasing the role of NLRP12 in PANoptosis.

A promising target for therapeutic development

NLRs are associated with diseases related to infection, inflammation, cancers and aging. This makes them intriguing targets for the development of novel therapeutics. The work of the Kanneganti lab shows that deleting Nlrc5 can provide protection against inflammatory cell death through PANoptosis and prevent disease pathology in hemolytic and inflammatory disease models, making NLRC5 an exciting therapeutic prospect.

"The fundamental knowledge that we have gained into how innate immune sensing works can be translated to numerous diseases and conditions," Kanneganti said. "Aging, infectious disease, inflammatory disorders—things for which there are no targeted therapies, this could be an option."

The study's other authors are Emily Alonzo, Department of Research and Development at Cell Signaling Technology; and Hee Jin Kim, Hadia Abdelaal, Omkar Indari, Roman Sarkar, Rebecca Tweedell, Jonathan Klein, Shondra Pruett-Miller and Peter Vogel, all of St. Jude, and Raghvendra Mall, formerly of St. Jude now of the Technology Innovation Institute, Abu Dhabi.

More information: Balamurugan Sundaram et al, NLRC5 senses NAD+ depletion, forming a PANoptosome and driving PANoptosis and inflammation, *Cell* (2024). DOI: 10.1016/j.cell.2024.05.034

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