NLRP12 as a new drug target for infection, inflammation and hemolytic diseases

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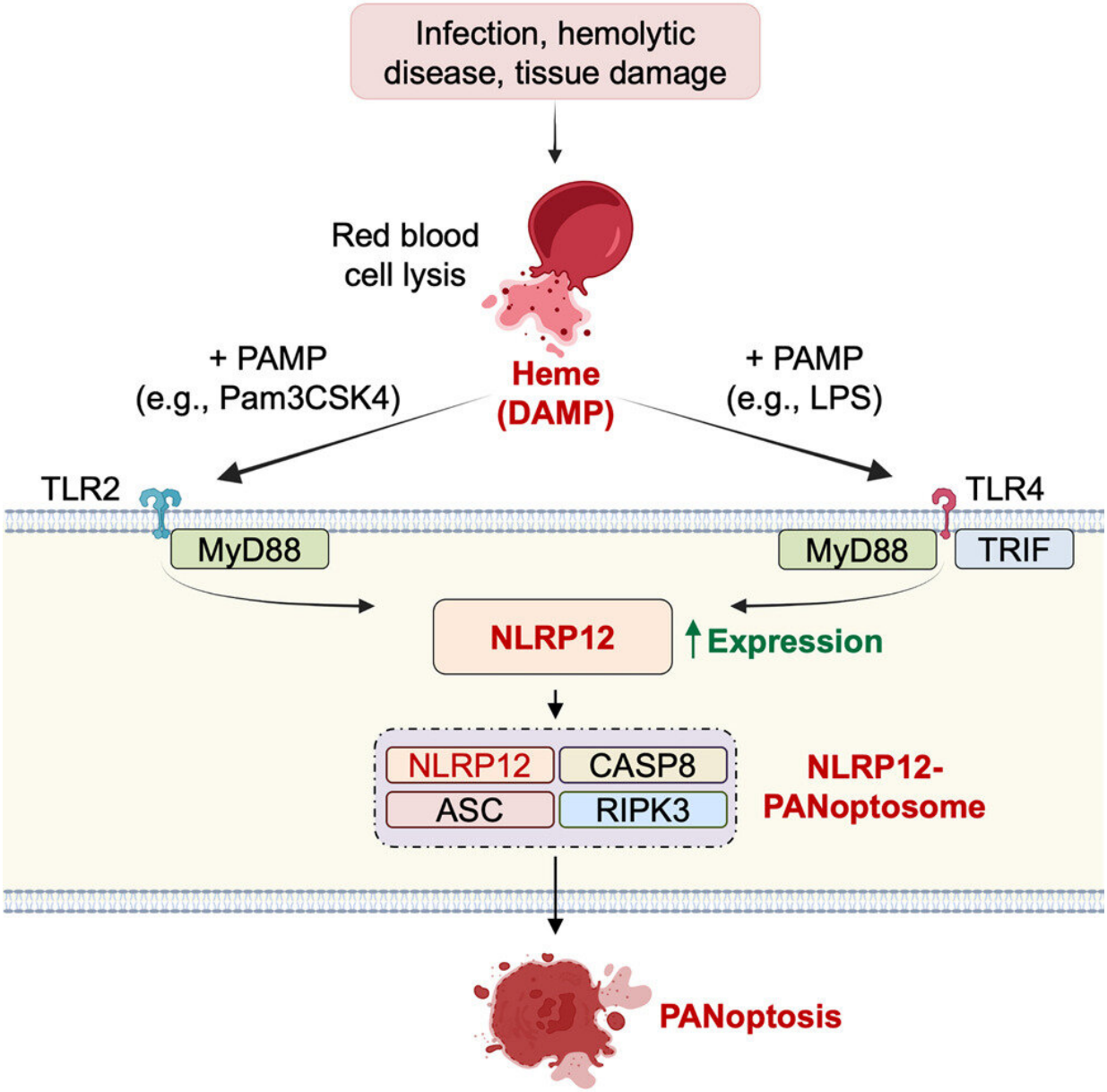

Graphical Abstract. Credit: *Cell* (2023). DOI: 10.1016/j.cell.2023.05.005

Infections and other diseases can cause red blood cells to rupture, releasing the oxygen-binding molecule hemoglobin, which breaks down into heme. Free heme can cause significant inflammation and organ damage, leading to morbidity and mortality.

Researchers from St. Jude Children's Research Hospital discovered NLRP12, an innate immune pattern recognition receptor, to be the key molecule responsible for inducing inflammatory cell death and pathology in response to heme combined with other cellular damage or infection. The finding provides a new potential drug target to prevent morbidity in certain illnesses. The research was published today in *Cell*.

Many infectious and inflammatory diseases, including malaria or SARS-CoV-2 virus infections and sickle cell disease, cause red blood cells to break apart and spill their contents. The process, hemolysis, releases the hemoglobin. In the bloodstream, hemoglobin then breaks down into a substance called heme.

"Scientists have known for decades that hemolysis leads to organ damage , but the underlying mechanism driving disease pathology was unclear," said co-first author Balamurugan Sundaram, Ph.D., St. Jude Department of Immunology. St. Jude researchers found the answer in the innate immune sensor, NLRP12 protein.

"The NLR family contains proteins that have been known to be important in disease for years, but what many of these proteins respond to for activation and how this affects pathology has remained a mystery," said corresponding author Thirumala-Devi Kanneganti, Ph.D., St. Jude Department of Immunology vice chair and Center of Excellence for

Innate Immunity and Inflammation director.

"After a two-decades-long search for the trigger of NLRP12 and the specific signaling pathway it activated, we found that heme, combined with specific components of infection or cellular damage, can activate NLRP12 to drive inflammatory cell death and pathology in disease."

NLRP12 is the bridge between hemolysis and inflammatory cell death

The St. Jude group showed that NLRP12 was the crucial innate immune molecule that drives the heme-induced inflammatory cell death response. But heme alone was insufficient to induce NLRP12 expression and start the subsequent cell death process. Another simultaneous component, such as from an infection—a pathogen-associated molecular pattern (PAMP)—or cellular damage—such as cytokine release—was also necessary to trigger NLRP12 production and cell death. These combinations are common during infections and disease.

"We showed when heme joins forces with some other PAMPs or cytokines, such as TNF, it is very lethal," said co-first author Nagakannan Pandian, Ph.D., St. Jude Department of Immunology. "Two kinds of signals come into the cell and then NLRP12 engages many other proteins as an organizer to drive cell death."

Researchers showed that NLRP12 recruits these other molecules to create a PANoptosome, a cell death complex which induces a form of innate immune inflammatory cell death called PANoptosis.

The PANoptosome contains several cell death-inducing molecules, including the inflammasome, and the PANoptosome components caspase-8 and RIPK3 are central in driving PANoptosis downstream of

NLRP12 activation. Overactivation of PANoptosis is known to lead to inflammatory disease. Therefore, NLRP12 is a direct bridge from hemolysis to inflammatory disease.

Connecting inflammatory cell death and pathology

The researchers also found that NLRP12 was highly expressed in patients with various diseases, including traditionally hemolytic diseases, such as sickle cell disease and malaria, and infections, such as SARS-CoV-2, influenza and bacterial pneumonia. When the researchers knocked out the Nlrp12 gene in mice, they no longer succumbed to organ damage in a model of hemolytic disease. Together, the results showed that NLRP12-mediated PANoptosis is a key driver of morbidity and mortality.

"In this study, we identified that NLRP12 could potentially serve as a drug target to decrease disease pathology during hemolysis, whether from hemolytic or other diseases, because its absence reduced mortality and reduced tissue damage," said Sundaram.

"Beyond the fundamental contribution to the innate immunity and cell death fields, this study identifies a druggable target to directly reduce the organ-damaging inflammation caused by infection and hemolytic diseases," added Kanneganti.

These results have important implications not only in hemolytic disease but also in infections and other conditions where hemolysis occurs. Research has linked genetic mutations in NLRP12 to several diseases. Now that NLRP12's regulation and function in inflammatory cell death have been identified in this study, potential therapies can be developed to prevent cell death and inflammation in diseases.

More information: Balamurugan Sundaram et al,

NLRP12-PANoptosome activates PANoptosis and pathology in response to heme and PAMPs, *Cell* (2023). DOI: 10.1016/j.cell.2023.05.005