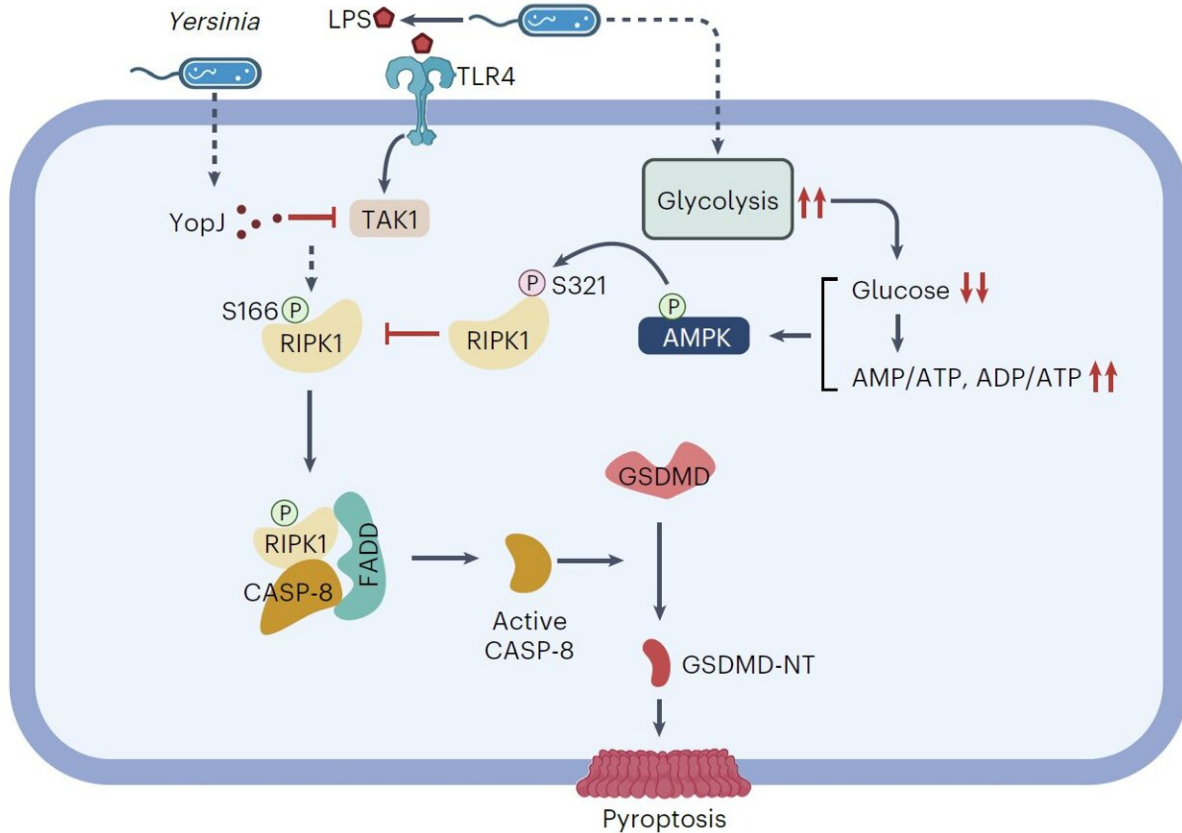


# Scientists reveal molecular link between glucose sensing and pyroptosis cell death

June 12 2024, by Zhang Nannan



Molecular mechanism by which *Yersinia* escapes RIPK1-mediated pyroptosis by interfering with host cell glucose homeostasis to activate AMPK. Credit: Xu Daichao

According to a study published in [Nature Microbiology](#) on June 6, researchers led by Prof. Xu Daichao from the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences have uncovered the molecular link between glucose sensing and non-classical pyroptosis.

Nutritional status and pyroptosis play a critical role in host defense against pathogens. Accumulating evidence suggests that changes in the nutritional status of host cells, particularly glucose levels, are critical for their response to pathogen infection.

Host cell glucose levels may fluctuate during [bacterial infection](#). This fluctuation may be part of the host's immune defense and therefore beneficial, or it may also be an inevitable adverse consequence of infection.

Pyroptosis is a regulated form of cell death that induces an inflammatory response in host cells and contributes to the [host cell](#)'s immune defense. However, the molecular link between host cell nutritional status and pyroptosis during microbial infection remains unclear.

AMPK is an intracellular serine/threonine kinase and a central energy sensor that responds to metabolic stress. It can be activated not only by sensing a decrease in intracellular energy status, but also by sensing glucose levels.

During microbial infection, host cells require large amounts of energy to drive the immune response. Therefore, most intracellular pathogen infections are associated with the activation of host AMPK.

In this study, the researchers found that in the early stages of Yersinia infection, Yersinia can induce a sharp increase in glycolysis levels in host

immune cells, leading to a rapid and significant decrease in glucose levels within immune cells and blood glucose levels in mice, and ultimately overactivation of host AMPK.

Under normal conditions, host cells activate the RIPK1-caspase-8-GSDMD-mediated non-classical pyroptosis pathway upon *Yersinia* infection to restrict their proliferation. However, AMPK activated in host cells can directly inhibit RIPK1 through an inhibitory phosphorylation at the highly conserved S321 site, thereby limiting its kinase activity and subsequent caspase-8 activation, thus preventing pyroptosis, and promoting unfavorable responses to infection.

The researchers found that overactivating AMPK in mice, either by using AMPK agonists or methods such as glucose depletion during *Yersinia* infection, can worsen the severity of the infection. Conversely, knocking out AMPK in macrophages or supplementing glucose to inhibit AMPK activity during *Yersinia* infection in mice can significantly improve the resistance of mice to *Yersinia* infection.

In conclusion, this study investigated the impact of alterations in [glucose homeostasis](#) on the regulation of AMPK activation and RIPK1-dependent pyroptosis during *Yersinia* infection.

Additionally, the regulatory effect of pathogen infection on alterations in host cell nutritional status and its impact on host cell immune defense was elucidated. The results of this study suggest that maintaining patients' [nutritional status](#) and blood [glucose levels](#) may be crucial in the treatment of *Yersinia* infection.

**More information:** Yuanxin Yang et al, *Yersinia* infection induces glucose depletion and AMPK-dependent inhibition of pyroptosis in mice, *Nature Microbiology* (2024). [DOI: 10.1038/s41564-024-01734-6](https://doi.org/10.1038/s41564-024-01734-6)

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