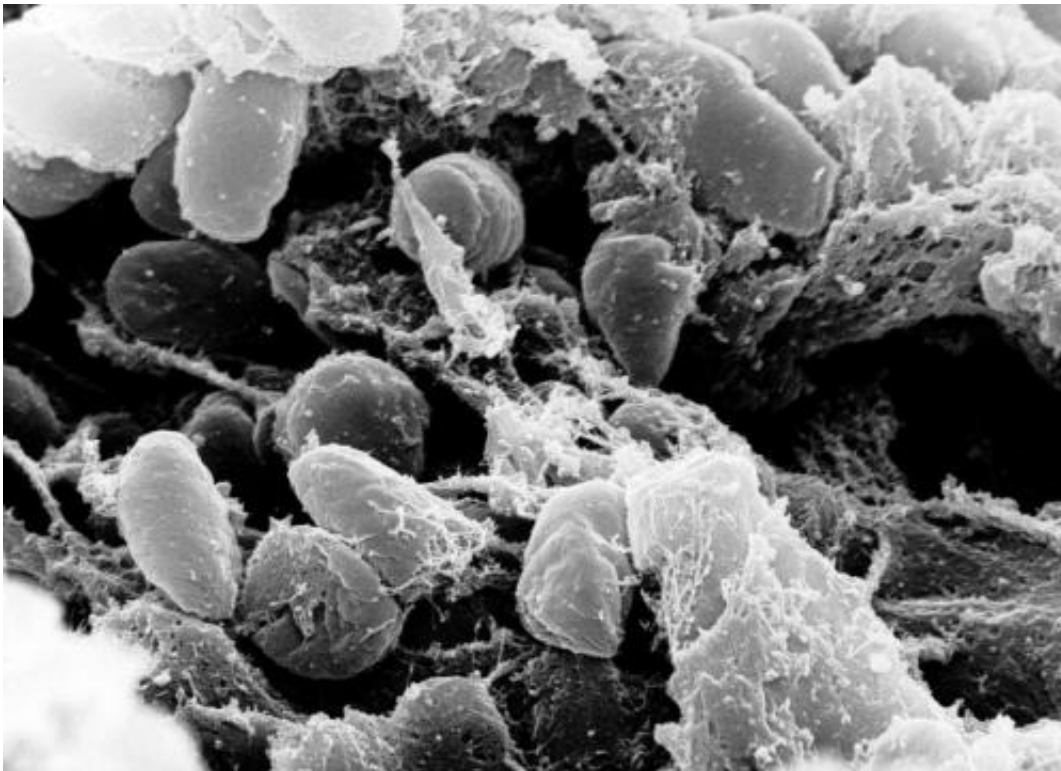


New mechanism underlying pyroptosis induced by *Yersinia* infection

June 25 2021, by Liu Jia



A scanning electron microscope micrograph depicting a mass of *Yersinia pestis* bacteria in the foregut of an infected flea. Credit: Wikipedia

Multiple strategies have been employed by pathogenic bacteria to sabotage host innate immune signaling to facilitate their infection.

Previous studies revealed that the *Yersinia* effector protein YopJ targets

and inhibits transforming growth factor- β -activated kinase 1 (TAK1) to block pro-inflammatory cytokine production. To counteract, host cells undergo pyroptosis via initiating receptor-interacting serine/threonine-protein kinase 1 (RIPK1)-dependent caspase-8-directed gasdermin D (GSDMD) cleavage. However, how RIPK1-caspase-8-GSDMD axis is instructed during *Yersinia* infection remains unknown.

In a study published online in *Science*, Prof. Liu Xing's group at the Institut Pasteur of Shanghai of the Chinese Academy of Sciences, and Prof. Judy Lieberman's group at Harvard Medical School, discovered via an unbiased CRISPR screen a critical and unexpected role of the lysosomal membrane-resident Rag-Ragulator complex in *Yersinia* infection-triggered pyroptosis.

The researchers found that loss of components of Rag-Ragulator complex resulted in the failure of pyroptotic cell death in response to *Yersinia* infection, suggesting an essential role of Rag-Ragulator complex in caspase-8-mediated pyroptosis.

Furthermore, they showed that upon infection with pathogenic *Yersinia* or its mimic (lipopolysaccharide plus TAK1 inhibitor), a FADD-RIPK1-caspase-8-containing complex was recruited via Rag-Ragulator complex to lysosomal membrane, and this process depended on Rag GTPase activity and Rag-Ragulator lysosomal binding but not Ragulator-activated mechanistic target of rapamycin complex 1 (mTORC1).

This study uncovered a critical role of Rag-Ragulator in TAK1 inhibition-induced pyroptosis during *Yersinia* [infection](#). The new role of Rag-Ragulator in caspase-8-mediated pyroptosis confirms its key function as a central hub for monitoring environmental cues to decide not only whether a cell proliferates, but also whether it survives.

Also, this study shed new light on lysosome's role in pyroptosis and in

[innate immune](#) responses. Future studies will explore mechanistic details of pyroptosis to manipulate this process for therapeutic benefits.

More information: Zengzhang Zheng et al, The lysosomal Rag-Ragulator complex licenses RIPK1– and caspase-8–mediated pyroptosis by *Yersinia*, *Science* (2021). [DOI: 10.1126/science.abg0269](https://doi.org/10.1126/science.abg0269)

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