Unravelling an alternative mechanism of airway mucosal immunity

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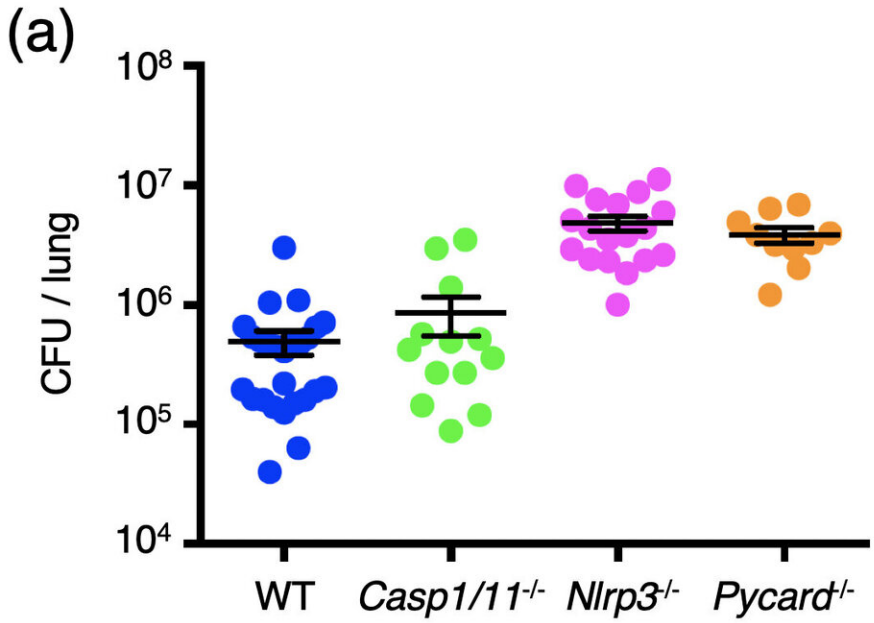
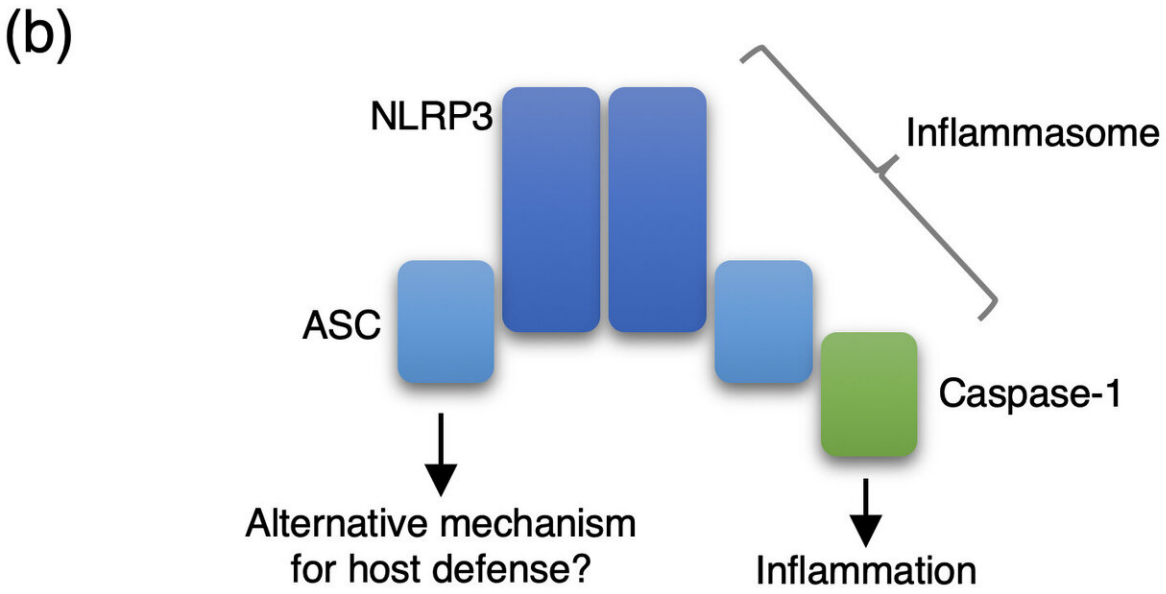




(a) Mice of the indicated genotypes were infected with *Streptococcus pneumonia* intranasally, and CFU counts in the lung were determined 48 h after infection. *Casp1/11*$^{-/-}$, *Nlrp3*$^{-/-}$, and *Pycard*$^{-/-}$ mice are deficient in caspase-1, NLRP3, and ASC, respectively. The result suggests that NLRP3 and ASC, but not caspase-1,

are required for host resistance to pneumococcal pneumonia.(b) NLRP3 and ASC form the NLRP3 inflammasome in response to distinct stimuli, including S. pneumoniae. The inflammasome recruits and activates caspase-1, thereby promoting inflammation. However, NLRP3 and ASC seem to protect against pneumococcal pneumonia in a caspase-1-independent manner, suggesting an alternative mechanism for host defense that involves NLRP3 and ASC. Credit: Kanazawa University

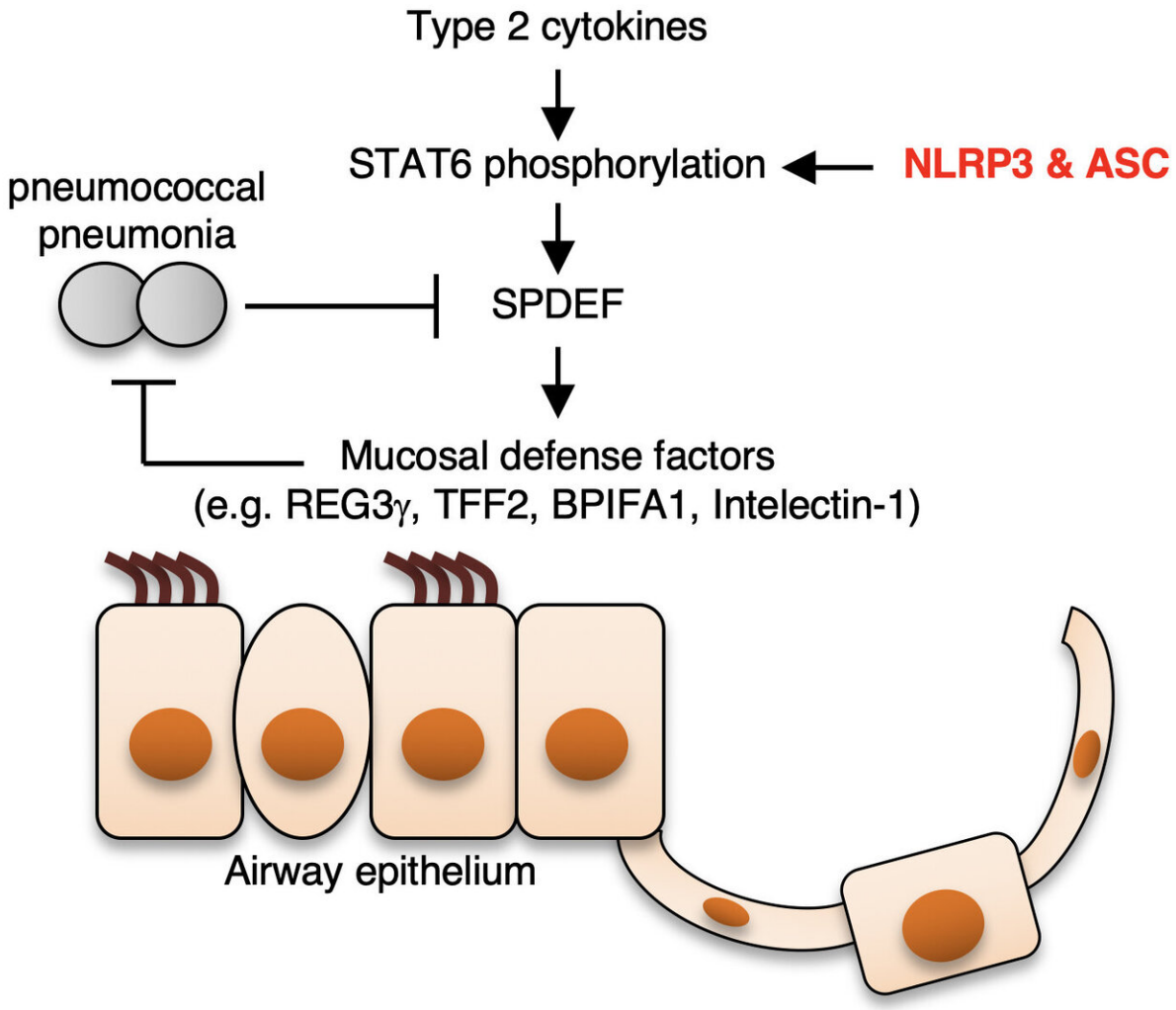
Contrary to popular belief, there may be more than one mechanism involved in microbial airway protection. Researchers from Japan and China have found an alternative mechanism that may be involved in fighting microbial infections.

The inflammation pathway in response to microbial infections involves multiprotein complexes known as inflammasomes. It is known that inflammasomes induce inflammation by activating caspase-1, an enzyme that cleaves other proteins. In turn, caspase-1 converts the precursors of interleukin-1β and interleukin-18 known as pro-inflammatory cytokines to their active forms. In addition, caspase-1 processes gasdermin D, leading to pyroptosis, a necrotic form of inflammatory cell death.

In a study published in July of this year in Mucosal Immunology, the researchers found that caspase-1 is unnecessary in maintaining innate immune homeostasis in the airway. Instead, two protein components of the inflammasome, ASC and NLRP3, have found to be key players in this process.

"Based on previous reports, we understood that the protein NLRP3, plays a protective role against *Streptococus pneumonia*," says study author Kohsuke Tsuchiya. "Hence, we decided to further investigate the role of NLRP3 in microbial protection. Using mice models, we found that NLRP3, along with ASC, may play a protective role against *S.*

pneumoniae."



ASC and NLRP3 are components of the NLRP3 inflammasome that promotes inflammation by activating caspase-1. However, ASC and NLRP3, but not caspase-1, are required for resistance to pneumococcal pneumonia, suggesting a protective role of ASC and NLRP3 independent of the inflammasome. This study aimed to elucidate the mechanism by which ASC and NLRP3 protect the host from pneumococcal pneumonia in an inflammasome-independent manner. Gene expression profiling revealed that the expression of mucosal defense factors, including TFF2 and intelectin-1, is maintained by ASC and NLRP3, but not caspase-1, in the airway during pneumococcal pneumonia. Mechanistically,

ASC and NLRP3 maintain the expression of SPDEF, a transcription factor that positively regulates the expression of the mucosal defense factors, by enhancing STAT6 activation. Hence, ASC and NLRP3 are suggested to promote airway mucosal innate immunity by an inflammasome-independent mechanism involving the STAT6-SPDEF pathway. Credit: Kanazawa University

The research team also found that ASC and NLRP3 protect the mice from *S. pneumonia* through a mechanism that is independent of caspase-1. Therefore, the researchers set out to elucidate this caspase-1-independent mechanism.

The results revealed that ASC and NLRP3 positively controlled the expression of the protein SPDEF during infection with *S. pneumonia*. SPDEF is a transcription factor involved with the expression of the mucosal defense factor genes. The study also showed that ASC and NLRP3 was key in activating STAT6, a regulator of the *Spdef* gene.

"Our results suggest that ASC and NLRP3 protect against microbial infections possibly through the STAT6-SPDEF pathway, which is independent of the caspase-1-dependent mechanism. This also means that both ASC and NLRP3 are acting independent of the inflammasome mechanism," says author Rendong Fang.

The group's findings may allow for new understanding of different possible mechanisms involved in maintaining innate immunity in the airway. However, further experiments are required, such as investigation into the mechanism linking *S. pneumonia* infection to STAT6 activation and whether both ASC and NLRP3 will maintain the expression of mucosal defense genes when infected by other microbial agents.

More information: Rendong Fang et al, ASC and NLRP3 maintain

innate immune homeostasis in the airway through an inflammasome-independent mechanism, *Mucosal Immunology* (2019). DOI: 10.1038/s41385-019-0181-1