BACTERIAL PATHOGENICITY

Pneumolysin: stimulating protection

Pneumolysin, a key *Streptococcus pneumoniae* virulence factor, is a cholesterol-dependent cytolysin that creates pores in cholesterol-containing membranes, thus causing host cell lysis. Pneumolysin has been proposed as a potential pneumococcal vaccine candidate, but although its cytolytic effects are well understood, less is known about the interactions between this potent toxin and the host immune system. Now, a new paper in *PLoS Pathogens* provides an insight into the immunomodulatory effects of this toxin.

In earlier work, conflicting results had been obtained about whether Toll-like receptor 4 (TLR4) has a role in host resistance to pneumococcal disease. Edel McNeela and colleagues found that, in their hands, endotoxin-free pneumolysin enhanced the production of interferon-γ (IFNγ), interleukin 17 (IL-17) and other pro-inflammatory cytokines by stimulated splenocytes in a TLR4-independent manner. A pneumolysin-deficient strain of *S. pneumoniae* showed reduced virulence compared with wild type in a mouse model of pneumococcal infection, and this was correlated with reduced production of IFNγ and IL-17, mainly from natural killer cells and γδ T cells. So, pneumolysin promotes the production of IFNγ and IL-17 *in vitro* and *in vivo*, and does not require TLR4 to do so.

Previous work had shown that IL-1β is also required for resistance to pneumococcal infection. As IL-1β secretion requires activation of the IL-1β zymogen by caspase 1, and this in turn requires assembly of the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome, McNeela *et al*. went on to look at the involvement of this multiprotein inflammasome complex in resistance to pneumococcal infection. They found that the ability of pneumolysin to promote IL-1β secretion from dendritic cells (DCs) was lower in *Nlrp3*$^{-/-}$ mice than in wild-type mice, indicating that pneumolysin promotes secretion of IL-1β via the NLRP3 inflammasome. Live *S. pneumoniae* also induced robust pneumolysin- and NLRP3 inflammasome-dependent IL-1β secretion by DCs. Finally, the authors found that clearance of *S. pneumoniae* infection was less efficient in *Nlrp3*$^{-/-}$ mice than in wild-type mice.

These results indicate that the NLRP3 inflammasome has a key role in protection against *S. pneumoniae* infection. This is the first demonstration of the involvement of the NLRP3 inflammasome in protection against a Gram-positive pathogen, and supports further investigation of pneumolysin as a potential pneumococcal vaccine candidate.

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ORIGINAL RESEARCH PAPER McNeela, E. A. *et al*. Pneumolysin activates the NLRP3 inflammasome and promotes proinflammatory cytokines independently of TLR4. *PLoS Pathog.* **6**, e1001191 (2010)

FURTHER READING Kadioglu, A. *et al*. The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. *Nature Rev. Microbiol.* **6**, 288–301 (2008)