

Critical involvement of pneumolysin in production of interleukin-1 α and caspase-1-dependent cytokines in infection with streptococcus pneumoniae in vitro: a novel function of pneumolysin in caspase-1 activation

ABSTRACT

Pneumolysin is a pore-forming cytotoxin known as a major virulence determinant of *Streptococcus pneumoniae*. This protein toxin has also been shown to activate the Toll-like receptor 4 (TLR4) signaling pathway. In this study, a mutant *S. pneumoniae* strain deficient in pneumolysin (Δply) and a recombinant pneumolysin protein (rPLY) were constructed. Upon infection of macrophages in vitro, the ability to induce the production of interleukin-1 α (IL-1 α), IL-1 β , and IL-18 was severely impaired in the Δply mutant, whereas there was no marked difference in the induction of tumor necrosis factor alpha (TNF- α) and IL-12p40 between the wild type and the Δply mutant of *S. pneumoniae*. When macrophages were stimulated with rPLY, the production of IL-1 α , IL-1 β , and IL-18 was strongly induced in a TLR4-dependent manner, whereas lipopolysaccharide, a canonical TLR4 agonist, hardly induced these cytokines. In contrast, lipopolysaccharide was more potent than rPLY in inducing the production of TNF- α , IL-6, and IL-12p40, the cytokines requiring no caspase activation. Activation of caspase-1 was observed in macrophages stimulated with rPLY but not in those stimulated with lipopolysaccharide, and the level of activation was higher in macrophages infected with wild-type *S. pneumoniae* than in those infected with the Δply mutant. These results clearly indicate that pneumolysin plays a key role in the host response to *S. pneumoniae*, particularly in the induction of caspase-1-dependent cytokines.