The NLRP3 inflammasome contributes to brain injury in pneumococcal meningitis and is activated through ATP-dependent lysosomal cathepsin B release.

Abstract:
Streptococcus pneumoniae meningitis causes brain damage through inflammation-related pathways whose identity and mechanisms of action are yet unclear. We previously identified caspase-1, which activates precursor IL-1 type cytokines, as a central mediator of inflammation in pneumococcal meningitis. In this study, we demonstrate that lack of the inflammasome components ASC or NLRP3 that are centrally involved in caspase-1 activation decreases scores of clinical and histological disease severity as well as brain inflammation in murine pneumococcal meningitis. Using specific inhibitors (anakinra and rIL-18-binding protein), we further show that ASC- and NLRP3-dependent pathologic alterations are solely related to secretion of both IL-1β and IL-18. Moreover, using differentiated human THP-1 cells, we demonstrate that the pneumococcal pore-forming toxin pneumolysin is a key inducer of IL-1β expression and inflammasome activation upon pneumococcal challenge. The latter depends on the release of ATP, lysosomal destabilization (but not disruption), and cathepsin B activation. The in vivo importance of this pathway is supported by our observation that the lack of pneumolysin and cathepsin B inhibition is associated with a better clinical course and less brain
inflammation in murine pneumococcal meningitis. Collectively, our study indicates a central role of the NLRP3 inflammasome in the pathology of pneumococcal meningitis. Thus, interference with inflammasome activation might be a promising target for adjunctive therapy of this disease.