ABSTRACTS

TRIF may be important in mechanical-ventilation-induced pulmonary inflammation

In a previous publication it was shown that mechanical-ventilation-induced pulmonary inflammation was induced by endogenous ligands signalling through the TLR-4 receptor. Downstream signalling of TLRs is extremely complex. The current paper investigates the potential role of Toll/interleukin-1 receptor domain-containing adapter-inducing interferon-b (TRIF).

The authors used their previously validated model. Wild-type and TRIF mutant mice were mechanically ventilated for 4 hours at a tidal volume of 8 ml/kg and PEEP of 4 cm H2O. After 4 hours of mechanical ventilation, TRIF mice showed significantly lower pulmonary levels of IL-1b and KC. NF-kB activity was also significantly lower in TRIF mice. There was no difference in pulmonary leukocyte influx. Plasma IL-6 levels were significantly lower in TRIF mice. Blood gas analysis and blood pressure were essentially normal after 4 hours of mechanical ventilation with no differences between TRIF and wild-type mice. There were also no differences in P/F ratio or A-a gradient.

The study confirms that mechanical ventilation in healthy mice using clinically relevant ventilator settings induces a systemic and pulmonary inflammatory response. In TRIF mutant mice this inflammatory response was significantly attenuated. TRIF is a downstream pathway for both TLR-3 and TLR-4 and results in delayed NF-kB activation. Although the results of this study have clearly advanced our understanding of the pathophysiology of mechanical-ventilation-induced inflammation, we are still a long way from translating these results into clinically applicable strategies. However, as the TRIF pathway is amenable to various inhibitors while leaving early NF-kB activation intact, further exploration is clearly indicated.


Mitigation of S. Pneumoniae pneumonia by nebulization of antithrombin

Bacterial pneumonia results in a local coagulopathy that compromises pulmonary integrity and function. Administration of systemic anticoagulants attenuates these effects but increases the risk of severe systemic bleeding. The current study investigated if local administration of anticoagulants has the same beneficial effects but without these unwanted side effects.

In a previously validated model S. pneumoniae pneumonia was induced in Sprague-Dawley rats. Rats were randomized to placebo or inhalation with rh-APC, AT III, heparin or danaparoid. The first dose was administered 30 minutes before bacterial challenge. Rats were sacrificed after 40 hours. BALF was analysed for bacterial quantification and coagulopathy. Cytokines were measured in lung homogenates. Lung inflammation and damage was analyzed by histopathology. The study was supported by several in vitro investigations on the effects of plasma-derived antithrombin.

All rats had bilateral macroscopic lung infiltrates. The pneumonia-induced increase in TATc levels was attenuated by all anticoagulants. Both rh-APC and AT III attenuated enhanced PAI-1 activity and AT-III increase plasminogen activator activity (PAA). Systemic TATc was only educed by danaparoid and none of the treatments altered plasma PAA. AT-III significantly decreased bacterial outgrowth and decreased the total numbers of neutrophils in BALF. There were no differences in cytokine levels between groups. AT-III significantly decreased lung damage analyzed by histopathology.

This elegant study from a well-known research group clearly shows that nebulized AT-III attenuates pulmonary coagulopathy and reduces bacterial outgrowth and pulmonary inflammation in a validated pneumonia model. The results are extremely promising if the safety of this treatment can be established. Although following a recent RCT in humans the systemic administration of AT-III in patients with severe sepsis has largely been abandoned, inhalation of AT-III in patients with pneumonia still seems a viable option. We eagerly await further research on this subject.