CATIONIC ANTIMICROBIAL PEPTIDE, E35, REDUCES LPS-INDUCED INFLAMMATION IN MICE

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Background: Cationic antimicrobial peptides (AMPs) are a promising approach against multidrug-resistant bacteria due to their membrane-disruption mechanisms, the lower propensity to invoke selection of resistance compared to conventional antibiotics, and bacterial killing properties that are typically not affected by the metabolic state of the bacterial cells. An engineered cationic AMP, E35, has been shown to be highly effective against multi-drug-resistant bacteria, and also can bind LPS in vitro. We tested whether E35 would reduce LPS-mediated inflammation in a mouse model in vivo.

Methods: Male C57BL/6 (WT) mice were given no treatment, intravenous (IV via tail vein) E35 peptide alone (5mg/kg and 10mg/kg), intraperitoneal (IP) LPS (5mg/kg), LPS followed 30min later by E35 or E35 followed by LPS immediately. N=3-6/expm.gp. Blood was collected after 4h and TNFα, IL1β and IL-6 were measured by ELISA. Liver was also collected and MAPK activation (JNK, p38MAPK, ERK) measured by Western blot (WB) of whole liver lysates.

Results: E35 peptide alone showed little or no effect on circulating inflammatory cytokines (Figure 1), but increased JNK activation in the liver at both 5mg/kg and 10mg/kg (Figure 2). LPS, as expected, significantly increased inflammatory cytokines and liver MAPK activation at 4h. Importantly, E35 given after LPS immediately significantly reduced TNFα ($p=0.03$), and trended towards reduced IL1β ($p=0.36$) compared to LPS alone. Activation of p38MAPK in liver was also reduced in LPS+E35 mice compared with LPS alone.

Conclusions: E35 peptide can reduce LPS-mediated inflammation when given after LPS. These data suggest that cationic AMPs may be beneficial to kill bacteria and reduce bacterial-mediated inflammation in sepsis.

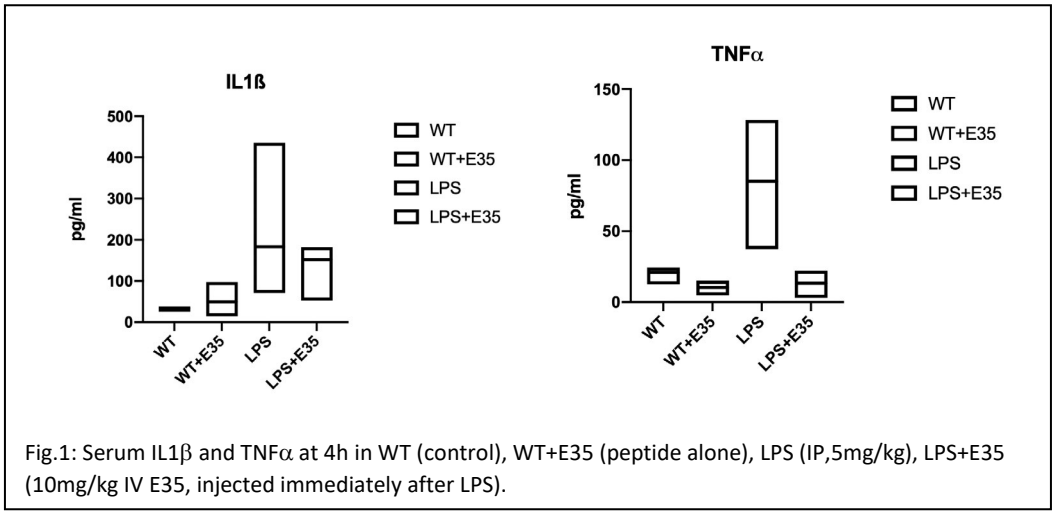

Fig.1: Serum IL1β and TNFα at 4h in WT (control), WT+E35 (peptide alone), LPS (IP,5mg/kg), LPS+E35 (10mg/kg IV E35, injected immediately after LPS).

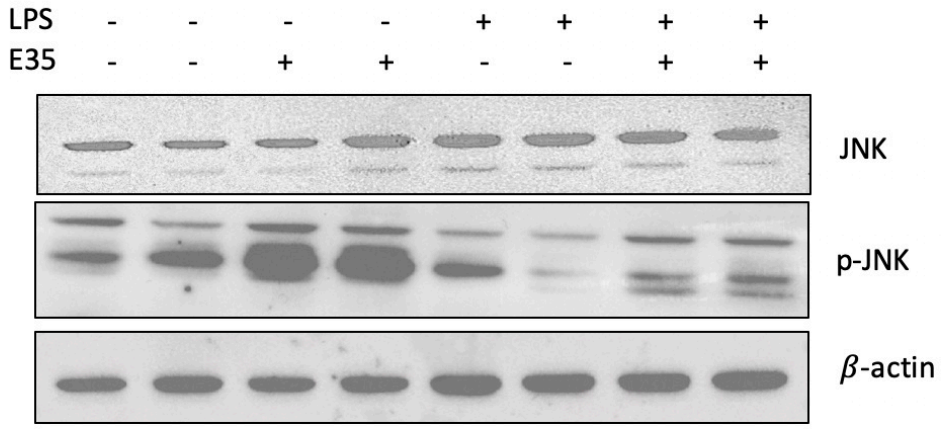

Fig 2: Western blot of whole liver lysates. 5mg/kg IV E35, injected 30 minutes after LPS IP, 5mg/kg. β-actin as control.