Cytokine Expression in Heart Tissue of Caspase 1 Knock Out, Community-Acquired MRSA Sepsis Infected Mice

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**ABSTRACT**

Introduction: Community-acquired MRSA sepsis is an important clinical problem leading to multiple organ failures, including cardiac dysfunction. Studies show caspase 1 inhibition reduced myocardial dysfunction in other cases such as heart failure and ischemia-reperfusion injury. In this study, we seek to identify the role of caspase 1 in sepsis-associated myocardial cytokine expression.

Materials and Methods: Caspase 1 KO mice and control NOD1 mice were infected intravenously with CA-MRSA strain TCH1516. RNA from heart tissue and quantitative PCR was performed to measure cytokine expression levels.

Results: Caspase 1 KO mice showed no significant change in mortality. However, TNF-α, IL-1β, and IL-6 expression in the heart were reduced significantly, especially in later stages of infection.

Discussion: Caspase 1 did not lead to reduced mortality, but it reduced expression of inflammation markers. This suggests other cytokines not affected by caspase 1 or alternative mechanisms may contribute to cardiac dysfunction. Reduced inflammation due to lack of caspase 1 may be contributing to mortality as well.

**References**

- More cytokines are contributing to myocardial dysfunction and death than those associates with caspase 1 in this study.

**Materials and Methods**

- **Infection:** CA-MRSA strain TCH1516, a clinical isolate from a lethal case of sepsis, was obtained from ATCC. Caspase 1 KO mice and control NOD1 mice were infected intravenously via tail vein.
- **Echocardiography:** The fractional shortening of the mice hearts was calculated following echocardiography data obtained using an Acuson Sequoia 512 echocardiogram machine with a 15L8 8-14 mHz probe.
- **Heart Tissue:** At indicated time points after infection, CO2 inhalation was used to kill the mice, and the hearts were removed and flash frozen in liquid nitrogen.

**Results**

- Caspase 1 KO mice displayed a trend towards greater mortality at higher inocula, but this was not statistically significant.
- IL-1β and IL-6 showed greatest up-regulation at 12 and 24 hour marks of disease. These up regulation were reduced substantially in caspase 1 KO mice however (p<0.05).
- TNF-α also showed a substantial down regulation at the 12 hour mark of infection in caspase 1 KO mice compared to WT mice (p<0.05).

**Discussion**

- The mechanism of septic cardiac dysfunction is still not fully understood, and most previous studies investigated gram-negative bacterial sepsis models only.
- Previous studies linked caspase 1 to myocardial dysfunction in heart failure and ischemia-reperfusion injury. Inhibition of all caspases has been shown to reduce cardiac dysfunction in gram negative septic models.6,9
- Our results showed mortality rates were equivalent or greater in CA-MRSA infected Caspase 1 KO mice than in WT mice, despite lower myocardial expression of the major inflammatory mediators TNF-α, IL-1β, and IL-6, previously associated with myocardial dysfunction .
- Possible mechanisms that may contribute to these results:
  - More cytokines are contributing to myocardial dysfunction and death than those associates with caspase 1 in this study.
  - Eliminating caspase 1 activity is detrimental resulting in insufficient inflammation needed to fight infection.
  - Absence of caspase 1 may trigger an alternative, acute apoptotic pathway.
- Future Directions:
  - Perform RNA microarray assay on heart tissue to identify other cytokines/inflammation mediators up regulated in septic shock.
  - Use caspase 1 inhibitors instead of Knocking out gene.

**References**

- Macias, E. S., Pereira, F. A., Rietkerk, W., & Safai, B. (2010). Absence of caspase 1 may trigger an alternative, acute apoptotic death than those associates with caspase 1 in this study.