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Genome Wide Expression Profiling of A Murine Acute Melioidosis Model Reveals New Insights Into How *Burkholderia pseudomallei* Circumvents Innate Immunity

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How infected organisms respond appropriately to *Burkholderia pseudomallei*, the causative agent of melioidosis, remains a central question within the Burkholderia research community. Melioidosis is a potentially acute and fulminating disease in humans and animals in endemic areas of Southeast Asia and northern Australia. Through this study, we sought to develop a comprehensive picture of the host transcriptional response during the acute stage of melioidosis to understand how the host responses towards this pathogen. We established a murine acute-phase melioidosis model where viable *B. pseudomallei* cells were consistently detected in the blood, liver and spleen during the 42 hr course of infection. Whilst no significant levels of *B. pseudomallei* specific antibodies were detectable, an increase in granulocyte counts was observed. Microarray technology was then used to compare the transcriptome of infected versus uninfected liver and spleen. Genes involved in immune response, stress response, cell cycle regulation, proteasomal degradation, cellular metabolism and signal transduction pathways were differentially regulated during the acute phase of infection. The transcriptional profile demonstrated that a TLR2-mediated signalling pathway is responsible for early recognition and initiation of an inflammatory response. Most of the “core host immune response” genes were initially expressed in response to the pathogen but were eventually repressed towards the latter stages of the acute infection period. In addition, activation of the complement system responsible for restoring host cellular homeostasis and eliminating intracellular bacteria was delayed. This study demonstrates that in the face of a *B. pseudomallei* acute infection, a broad range of innate immune mechanisms are initially highly activated in the host. Nevertheless, expression is then down regulated and in tandem with delayed activation of the complement system, uncontrolled spread of the bacteria is promoted leading to the eventual death of the host.

Keywords: Melioidosis, Acute Infection, Inflammatory response, Expression profiling