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Immune responses in *Burkholderiapseudomallei* infection

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Melioidosis is a life-threatening infectious disease caused by the Gram-negative bacillus,*Burkholderiapseudomallei*, predominantly found in southeast Asia and northern Australia. Our group has setup an extensive surveillance system in Sri Lanka over the last few years and identified increasing numbers of cases. Overall, we have screened ~3156 patient samples using in-house IHA testing for high levels of antibodies since mid-2014. A total of 171 positive cases were detected up to date (~5.4 % of all suspected cases). Multiple projects were carried out with these samples and a portion was used for the following studies.

The aim of this study was to establish useful correlation with disease biomarkers, comparing healthy individuals, patients with melioidosis and patients with sepsis caused by other pathogens, by analyzing gene expression levels of important cytokines. The study population consisted of 55 melioidosis cases, 20 healthy controls and 20 sepsis cases caused by other pathogens. A Qiagen common human cytokines array profiling the gene expression of 84 important cytokines were analyzed by real time quantitative PCR (RT-qPCR). Further, gene expression profiles of 25 gene targets including 19 immune response genes and 6 epigenetic factors using total RNA extracted from peripheral blood mononuclear cells (PBMC's) of study subjects were also analyzed.

Results of the first part showed consistently upregulated expression of interleukin (IL)-4, IL-17A, IL-23A, IL-24, IFNA1 and IFNB1, TNF superfamily 4 (TNFSF4), transforming growth factor (TGF), TGF beta 1, superfamily, bone morphogenetic proteins 3 and 6 (BMP3 and BMP6), and other growth factors such as macrophage colony-stimulating factor (M-CSF), C-fos induced growth factor (FIGF), and platelet-derived growth factor alpha (PDGFA) polypeptide, in melioidosis patients compared to their expression in other sepsis cases regardless of comorbidities, duration of fever/clinical symptoms, and antibiotic treatment. This suggests a dominant Th2- and Th17-type-cytokine response indicating their important role in disease pathogenesis though they were found to be dysregulated at initial stages of infection. IL-1A, IL-1B, and IL-8 were significantly downregulated in septicemic melioidosis patients compared to other sepsis cases. Thus, these differentially expressed genes may serve as biomarkers for melioidosis diagnosis and to understand immune response mechanisms.

The second set of experiments show Inflammatory response genes; TLR4, late onset inflammatory mediator HMGB1, genes associated with antigen presentation; MICB, PSMB2, PSMB8, PSME2, epigenetic regulators; DNMT3B, HDAC1, HDAC2 were significantly down regulated, whereas the anti-inflammatory gene; IL4 was up regulated in melioidosis patients compared to sepsis cases caused by other pathogens. Septicaemic melioidosis cases showed significant down regulation of IL8 compared to sepsis cases caused by other pathogens. HMGB1, MICB, PSMB8, PSMB2, PSME2, HDAC1, HDAC2 and DNMT3B showed consistent down regulation of gene expression in melioidosis patients compared to other sepsis infection,

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irrespective of comorbidities such as diabetes, duration of clinical symptoms and antibiotic treatment.

This work is currently being expanded to decipher the specific pathways to understand how *B. pseudomallei* affects these human gene expression patterns