Special Article

Immune Response to *Burkholderia pseudomallei*

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Burkholderia pseudomallei are the causative agents of melioidosis, a disease found mostly in people with underlying risk factors. Fifty percent of cases are community-acquired septicemias and manifestation can vary from acute septicemia (with or without shock), to chronic, to subclinical infections. There is no vaccine to prevent the condition. It is difficult to eradicate the bacteria. Prolonged antibiotic therapy is required. Finally, there is a high rate of relapse when therapy is not completed. The bacteria can activate both innate and adaptive immune responses but B. pseudomallei employ numerous tactics to evade these immune responses. The pathogenesis of melioidosis is poorly understood, especially the interaction between the host and the pathogen that results in acute and chronic infections. The objective of this review was to summarize the current understanding of the immunology of melioidosis.

This review presents an overview of host immune response to B. pseudomallei and benefits the development of research into immunology and promotes an understanding of the mechanism and pathology of B. pseudomallei infection.

Keywords: *Burkholderia pseudomallei, Melioidosis, Immune response*

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Burkholderia pseudomallei are gram-negative bacilli environmental saprophytes that cause melioidosis. The disease is transmitted by air or transcutaneous infection and is most common in South-East Asia and Northern Australia[1,2]. The clinical manifestation can vary from acute infection to chronic localized pathogenic symptoms to latent infection that may reactivate decades later. Immunosuppressive persons are most at risk to melioidosis, especially those suffering from diabetes type II (50% of cases) and thalassemia[3-5]. In Thailand, 50% of melioidosis cases are community-acquired septicemias resulting in death for 80-95% of treated patients. The most common cause of mortality is septic shock[1,6,46].

B. pseudomallei invade hosts in different ways. The main virulent factors are essential for the intracellular life cycle such as quorum sensing, type III secretion system, lipopolysaccharide (LPS) capsular polysaccharide and flagella. These virulent factors can support *B. pseudomallei* in the invasion of host cells and escape from endocytic vesicles, and can multiply intracellularly and induce actin-tail formation and membrane protrusions, leading to direct cell-to-cell spreading[7-11]. A host's immunity to *B. pseudomallei* causes the disease to have both innate and adaptive immune responses. Severe melioidsepsis is a condition of bacterial infection that may stimulate a high level of pro-inflammatory cytokines, interleukin-1 (IL-1), IL-6, IL-15, gamma interferon (IFN-γ), tumor necrosis factor –alpha (TNF-α), TNF-β, chemokines, and macrophage inflammatory protein 1 (MIP-1) and MIP-1 β are found to increase[12,13].

The conventional management of patients with septic shock is the eradication of microorganisms by appropriate antibiotic therapy, surgical drainage, support of hemodynamic, respiratory functions and prevention of complications of critical illness. Furthermore, infection relapse is common despite adequate antimicrobial therapy[1,3,14]. *B. pseudomallei* are intrinsically resistant to many antibiotics, including first-second generation cephalosporins, macrolides, and aminoglycoside[1,2].

There are two phases for treatment of severe melioidosis, the eradication phase and the maintenance phase. Ceftazidime is the choice of antibiotic for eradication therapy [15,16]. However, imipenem is a safe and effective treatment for acute severe melioidosis[17]. It may be considered an alternative to ceftazidime in the cases of patients who are ceftazidime-resistant. The maintenance phase selects antibiotics that fight against *B. pseudomallei* by surviving and hiding in important organs and preventing relapse. Doxyclycline, trimethroprim-sulfamethoxazole and

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amoxicillin-clavulanic acid are oral regimens for at least 12 to 20 weeks in the maintenance phase[5,15].

Research has shown that immunization with heat-inactivated *B. pseudomallei* cells can protect murine melioidosis[18]. However, there is no licensed vaccine used currently that provides protection for humans against *B. pseudomallei*. Diagnosis is difficult because *B. pseudomallei* is a great mimicker of other bacteria but past history, especially of underlying diseases such as diabetes and thalassemia, occupations such as a farmer and native habitat such as Khon Kaen or Ubon Ratchathani provinces, is beneficial. Sometimes it is difficult to differentiate melioidosis from tuberculosis. The most important factor in diagnosis is the bacterial culture but this takes a long time to grow and identify. An immune assay, indirect hemmaglutination (IHA), was developed in non-endemic areas to diagnose melioidosis, but it gives false positives in endemic areas, maybe due to the presence of antibodies in the people being tested. Latex agglutination by the use of a monoclonal antibody was developed for detection in endemic areas. This method was highly sensitive and specific to *B. pseudomallei*.

Future study of melioidosis involves immuno-pathology, such as TLR2, CpG and biochemical and chemical substances' ability to suppress or block the molecular cascade in melioidosis pathology and role of biofilms formation to infection relapse, as *B. pseudomallei* has been reported to be resistant to antibiotics.

Content

Host-pathogen interactions during B. pseudomallei infection

Innate immune response

The modes of transmission of melioidosis are inhalation, ingestion, and/or inoculation through the skin lesion from contaminated soil. Innate immune response occurs when cells of the innate immune system recognize the conserved surface motifs of bacterial cells. The pattern recognition receptors on host cells interacted with the pathogen-associated molecular patterns (PAMPs) on the *B. pseudomallei* surface. *B. pseudomallei* have many PAMPs that can interact with toll-like receptors (TLRs) such as CD14 (a ligand-binding molecule) with TLR4, peptidoglycans with TLR2, flagellin with TLR5 and bacterial DNA or CpG with TLR9[19]. The first lines of a host's defense against *B. pseudomallei* are natural peptides (defensins), complement system, and phagocyte cells.

Defensins:

Normally, the epithelial barrier can produce natural antibiotic peptides. These peptides are defensins that are present in the host's skin. The activity of defensins can be to kill bacteria. However, defensins do not kill *B. pseudomallei*, as seen in the experiment by Jones et al that exposed defensins and *B. pseudomallei in vivo*[20,21]. This increased the viable cell count, indicating that *B. pseudomallei* are resistant to defensins, an antimicrobial activity in natural immunity.

Complement system:

The major role of complement is as an opsonin. After opsonization, the phagocyte cells can direct the cell damage of invading organisms via phagocytosis. *B. pseudomallei* produce an extracellular polysaccharide capsule. This capsular polysaccharide is often shed during bacterial growth. The role of shedding the capsule is the prevention of complement attack. These capsules can interfere with the association of C3b on the bacterial surface. Capsules of *B. pseudomallei* seem to form a barrier by the blocking of the CR1 receptor on phagocytes cells[22]. Then C3b reduces the amount of deposit on the bacterial surface. It can be concluded that capsules of *B. pseudomallei* act as anti-phagocytosis by the inhibition of opsonization and the complement cascade.

Phagocyte cells:

The most common phagocyte cells are neutrophils and macrophages. The primary functions of these cells are to ingest and destroy microbes. *B. pseudomallei* are known to intracellular pathogen, survive inside phagocytic cells, and may be able to spread directly from cell to cell.

The role of macrophages to B. pseudomallei

Macrophages' responses to *B. pseudomallei* differ from those of other bacteria. High levels of TNF-α, IFN-γ and IFN-β have been found when macrophages and *B. pseudomallei* interact *in vivo*. However, these cytokines are at higher levels when induced with other bacteria. Moreover, the inducible nitric oxide synthase (iNOS) are suppressed when compared to the cells are exposed to *Escherichia coli* or *Salmonella typhi*[23,24]. Although the rate of infection is high, MOI (10:1) does not express a detectable level of iNOS. The main mechanism of iNOS is an enzyme found in macrophages for clearance of

bacterial pathogen. When a macrophage infected with *B. pseudomallei* does not express iNOS, the pathogen survives and multiplies inside the host macrophage. In addition, IFN-γ has a major role in activating the macrophage that can kill the pathogen. Therefore, the lower level of IFN-γ production by macrophage may mediate the poor intracellular control, resulting in higher intracellular bacterial load in patients with melioidosis[25]. The important cytokine in early immune response is TNF-α. The functions of TNF-α is to activate pro-inflammatory cytokines and induce multiple organ failure from its cascade. High systemic TNF-α levels are associated with bacterial septic shock. LPS from gram-negative bacilli is activated by high levels of TNF-α. When compared to other gram-negative bacteria, *B. pseudomallei* show lower levels of TNF-α[26]. However, high TNF-α levels are associated with mortality in melioidosis patients[27]. High levels of IFN-γ, TNF-α and IL-12 are observed in serum from patients with melioidosis. The ultra-structural interaction between macrophages and *B. pseudomallei* was studied in patients with melioidosis and a healthy control group[25]. The present study found less phagolysosome fusion in macrophages from patients with melioidosis, and this may have resulted in higher intracellular bacterial loads in these patients.

The role of neutrophils to B. pseudomallei

Neutrophil plays an important role in the host's inflammatory response against infection. The main mechanism is to kill bacteria by migration to the site of infection, phagocytosis, and to kill bacteria via both oxygen-dependent and oxygen-independent pathways. In addition, activated neutrophil produces a lot of chemokines and cytokines that can recruit and activate other immune cells. Neutrophil function was compared between *B. pseudomallei* and other gram-negative bacilli, *Salmonella enteric* serovar Typhimurium and *Escherichia coli*[28]. Results showed that *B. pseudomallei* displayed reduced uptake by neutrophil when compared to *Salmonella enteric serovar Typhimurium* and *E. coli*. Moreover, 24 hours after incubation, intracellular survival of *B. pseudomallei* can be detected, indicating the intrinsic resistance of *B. pseudomallei* to killing by neutrophil. Moreover, the present study observed the impaired phagocytosis and inability to delay apoptosis of neutrophil of patients with diabetes[28]. These experiments may explain diabetic hosts' susceptibility to melioidosis.

The role of epithelial cells to B. pseudomallei

The interaction between *B. pseudomallei* and epithelial cells were studied *in vivo*. *B. pseudomallei* can adhere to human epithelial cell lines derived from alveolar, bronchial, laryngeal oral, conjunctival and cervical tissue[29]. The present study made comparisons between *B. pseudomallei* and *B. thailandensis* (no virulence) and results showed that *B. pseudomallei* was more efficient in invasion, adherence and induction of cellular damage of respiratory epithelial cells than *B. thailandensis*. Another study confirmed the adherence activity by using *B. pseudomallei* defective in *pilA* (mutant a putative type IV pilus gene). Mutant *pilA B. pseudomallei* had reduced adherence to human epithelial cells[30]. The high adherence activity supports the entry of *B. pseudomallei* into the host cells.

Early proinflammatory cytokines

IFN-γ is the pro-inflammatory cytokine and essential for initial bacterial control in infected mice. IFN-γ has an important role in the host's resistance against *B. pseudomallei* infection. Mice with suppressed IFN-γ expression showed lower LD50 from >5 x 10^5 to 2 colony-forming units (CFUs)[31]. Inhibition of IFN-γ was associated with increased bacterial loads of more than 8,500-fold and 4,400-fold in liver and spleen respectively[31]. When the endogenous inducer (IL-12, IL-18) expression of mice was suppressed, the mortality rate of the mice increased[32]. Thus, IFN-γ, IL-12, IL-18 may be related to Th1 cell mediated immune response. Moreover, mouse macrophages were infected with *B. pseudomallei* induced suppressor of cytokines signaling 3 (SOCS3) and cytokine-inducible Src homology 2-containing protein (CIS) leading to the suppression of the response to IFN-γ stimulation[33].

TNF-α is an elemental pro-inflammatory cytokine in early immune response primarily produced by macrophages after infection. High systemic TNF-α levels are associated with septic shock. Neutralization of TNF-α in a mouse model causes increased susceptibility to melioidosis[31,34]. TNF-α was further studied regarding its involvement in human disease. The mutation of TNF-α promoter is associated with increased production of TNF-α. These mutations occur at base -308 by G substituted A called TNF2 allele[35]. The polymorphism of 308 TNF-α promoter (TNF2 allele) is associated with increased severe septicemia and is related to the severity of disease for several other infectious diseases and with both the occurrence

and severity of melioidosis[35,36]. Nine percent of Thai patients with melioidosis were found to have TNF2 allele[35]. The presence of TNF2 was associated with an increased risk of death, septicemia and multiple organ involvement[2]. Patients with melioidosis were found to have elevated levels of IFN-γ, IL-12, TNF-α, pro-inflammatory mediators such as IL-6, IL-15, IFN-γ-inducible protein (IP)-10, monokine induced by IFN-γ (Mig) and anti-inflammatory cytokines (IL-10)[27]. The high levels of these elements indicated that melioidosis might be related to multiple inflammatory pathways and cellular activation. IP-10 and Mig are chemokines induced by IFN-γ that share a common receptor (CXC chemokines receptor 3, CXCR3). This pathway was stimulated by T cells and natural killer (NK) cells. Granzymes A and B were detected at high levels in melioidosis serum. Thus, cytotoxic T cells and NK cells may be related to the immune response to *B. pseudomallei*[37].

High levels of IFN-γ and TNF-α were detected in severe *B. pseudomallei* infection[27]. However, the use of low doses of steroid as an adjunct in the treatment did not provide benefit in the treatment of murine melioidosis and may have had negative effects on humans who had diabetic mellitus as diabetic mice infected with *B. pseudomallei* and given hydrocortisone-ceftazidime showed increases in their blood glucose and reductions in survival[38].

Intracellular signaling pathway

The interaction of pathogen associated molecular patterns (PAMPs) through host cell pattern recognition receptors, such as Toll like receptors (TLRs), induces intracellular signaling pathways. Two well-characterized signaling pathways associated with TLR stimulation are the MyD88- dependent pathway, resulting in NF-κB activation and the TANK-binding-kinase-1 (TBK1) dependent pathway that induces transcription of type I interferon genes. These have been demonstrated to play an important role in controlled intracellular bacterial infections[39,40]. The present study developed tbk1-deficient cell lines by the use of shRNA for transient knockdown of the tbk1 gene in Hela and RAW 264.7 cells. These results suggested that the tbk1 gene and its activation may be able to control invasive *Escherichia coli*, non-invasive *E. coli* and *Brucella melitensis* growth, but may not be able to control *B. pseudomallei* infection[41].

Adaptive immune response

B. pseudomallei infection requires both humoral- and cell-mediated adaptive immunity. High levels of immunoglobulin (Ig)G, IgA and IgM are found in serum from patients with melioidosis. These antibodies are related to the severity of the diseases. It was found that invasive diseases had more elevated levels than localized diseases. Moreover, Thai patients were found to have specific human leukocyte antigen class II (HLA class II). DRB1*1602 allele was positively associated with septicemic melioidosis, whereas, DQA1*03 allele was negative[42]. Ketheesan et al (2002) found evidence of antigen-specific cell-mediated immune response from patients who had recovered from melioidosis[43]. This response increased enhanced lymphocyte proliferation and IFN-γ production in response to *B. pseudomallei* antigen. The significantly higher proliferation of lymphocyte and high levels of IFN-γ in culture supernatants from these patients were indicative of the recognition of *B. pseudomallei* antigens by memory T cell. In addition, CD69 is a protein expressed early on the surface of stimulated T cells. CD69 was used as a marker for antigen-specific proliferative response of lymphocyte, which expressed on days 2 to 6 after stimulation. The increased CD69 expression in CD4+ and CD8+ were found to be higher in patients with melioidosis than in controls. Asymptomatic seropositive individuals showed a stronger cell-mediated adaptive immune

Table 1. Summary of *B. pseudomallei*'s ability to survive, proliferate and escape from immunity

Immunity	Mechanism
Defensins	Do not kill *B. pseudomallei*
Complement system	Polysaccharide capsule can interfere with the association of C3b on the bacterial surface
Epithelia cells	*B. pseudomallei* can adhere to epithelia cell and are more efficient in invasion and induction of cellular damage
Phagocyte cells	
Neutrophil	Reduced uptake *B. pseudomallei* and impaired phagocytosis
Macrophage	Does not express iNOS for clearance of *B. pseudomallei*

response than clinical patients with melioidosis[44]. This evidence suggested a strong cell-mediated immune response might provide protection against disease progression. T cell response to *B. pseudomallei* infection was biphasic as described by Haque et al (2006). In the early cytokine-induced phase, T cells functioned by initial bacterial clearance[32]. The later stage antigen-induced phase was *B. pseudomallei*-specific CD4+ T cells. This stage was important for late host resistance against *B. pseudomallei* because CD4+ T cells produced IFN-γ activated macrophages to become more bactericidal. However, the importance of CD4+ T cells in the control of infection was unclear.

Recently, the complete genome sequence of *B. pseudomallei* K9243 has been revealed[45]. This sequence of *B. pseudomallei* was studied by microarrays to determine patterns of gene presence and absence across 94 Asian strains derived from clinical, environmental and animal sources. Eighty six percent of *B. pseudomallei* K9243 genome was common to all strains and represented the core genome. The different part was the accessory genome and encompassed multiple genomic islands. Genomic islands contained regions of DNA directly acquired by horizontal transfer from other microbes and were associated with bacterial virulence[45].

However, the characterized sequence of *B. pseudomallei* needs further study for described pathogenesis of melioidosis. Although patients with melioidosis were treated with appropriate antibiotics, the mortality rate was more than 80%. Therefore, prevention is critical and vaccine research is needed for human protection.

Conclusion

The host immune response to *B. pseudomallei* infection showed both innate and adaptive immunity. However, *B. pseudomallei* were able to escape from phagocytic cells and invade many cell types and were able to survive and proliferate for prolonged periods. Although IFN-γ was significant in the protection against *B. pseudomallei* infection in mice, high levels of IFN-γ activated immune response and triggered a molecular cascade of proinflammatory cytokines leading to severe sepsis. However, low doses of hydrocortisone did not benefit the suppression of IFN-γ in mice with severe sepsis and may have had negative effects in cases with diabetic mellitus.

Potential conflicts of interest

None.

References

1. White NJ. Melioidosis. Lancet 2003; 361: 1715-22.
2. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. Clin Microbiol Rev 2005; 18: 383-416.
3. Chaowagul W, Suputtamongkol Y, Dance DA, Rajchanuvong A, Pattara-arechachai J, White NJ. Relapse in melioidosis: incidence and risk factors. J Infect Dis 1993; 168: 1181-5.
4. Suputtamongkol Y, Chaowagul W, Chetchotisakd P, Lertpatanasuwun N, Intaranongpai S, Ruchutrakool T, et al. Risk factors for melioidosis and bacteremic melioidosis. Clin Infect Dis 1999; 29: 408-13.
5. Leelarasamee A. Recent development in melioidosis. Curr Opin Infect Dis 2004; 17: 131-6.
6. Chaowagul W, White NJ, Dance DA, Wattanagoon Y, Naigowit P, Davis TM, et al. Melioidosis: a major cause of community-acquired septicemia in northeastern Thailand. J Infect Dis 1989; 159: 890-9.
7. Ulrich RL, Deshazer D, Brueggemann EE, Hines HB, Oyston PC, Jeddeloh JA. Role of quorum sensing in the pathogenicity of *Burkholderia pseudomallei*. J Med Microbiol 2004; 53: 1053-64.
8. Warawa J, Woods DE. Type III secretion system cluster 3 is required for maximal virulence of *Burkholderia pseudomallei* in a hamster infection model. FEMS Microbiol Lett 2005; 242: 101-8.
9. Steinmetz I, Rohde M, Brenneke B. Purification and characterization of an exopolysaccharide of *Burkholderia (Pseudomonas) pseudomallei*. Infect Immun 1995; 63: 3959-65.
10. Reckseidler SL, DeShazer D, Sokol PA, Woods DE. Detection of bacterial virulence genes by subtractive hybridization: identification of capsular polysaccharide of *Burkholderia pseudomallei* as a major virulence determinant. Infect Immun 2001; 69: 34-44.
11. Stevens MP, Wood MW, Taylor LA, Monaghan P, Hawes P, Jones PW, et al. An Inv/Mxi-Spa-like type III protein secretion system in *Burkholderia pseudomallei* modulates intracellular behaviour of the pathogen. Mol Microbiol 2002; 46: 649-59.
12. Lauw FN, Simpson AJ, Prins JM, Smith MD, Kurimoto M, van Deventer SJ, et al. Elevated plasma concentrations of interferon (IFN)-gamma and the IFN-gamma-inducing cytokines interleukin (IL)-18, IL-12, and IL-15 in severe melioidosis. J Infect Dis 1999; 180: 1878-85.

13. Wiersinga WJ, Dessing MC, Kager PA, Cheng AC, Limmathurotsakul D, Day NP, et al. High-throughput mRNA profiling characterizes the expression of inflammatory molecules in sepsis caused by *Burkholderia pseudomallei*. Infect Immun 2007; 75: 3074-9.
14. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327.
15. Chaowagul W. Recent advances in the treatment of severe melioidosis. Acta Trop 2000; 74: 133-7.
16. Dance DA. Melioidosis. Curr Opin Infect Dis 2002; 15: 127-32.
17. Simpson AJ, Suputtamongkol Y, Smith MD, Angus BJ, Rajanuwong A, Wuthiekanun V, et al. Comparison of imipenem and ceftazidime as therapy for severe melioidosis. Clin Infect Dis 1999; 29: 381-7.
18. Sarkar-Tyson M, Smither SJ, Harding SV, Atkins TP, Titball RW. Protective efficacy of heat-inactivated *B. thailandensis*, *B. mallei* or *B. pseudomallei* against experimental melioidosis and glanders. Vaccine 2009; 27: 4447-51.
19. Wiersinga WJ, van der Poll T, White NJ, Day NP, Peacock SJ. Melioidosis: insights into the pathogenicity of *Burkholderia pseudomallei*. Nat Rev Microbiol 2006; 4: 272-82.
20. Jones AL, Beveridge TJ, Woods DE. Intracellular survival of *Burkholderia pseudomallei*. Infect Immun 1996; 64: 782-90.
21. Jones AL, DeShazer D, Woods DE. Identification and characterization of a two-component regulatory system involved in invasion of eukaryotic cells and heavy-metal resistance in *Burkholderia pseudomallei*. Infect Immun 1997; 65: 4972-7.
22. Reckseidler-Zenteno SL, DeVinney R, Woods DE. The capsular polysaccharide of *Burkholderia pseudomallei* contributes to survival in serum by reducing complement factor C3b deposition. Infect Immun 2005; 73: 1106-15.
23. Utaisincharoen P, Anuntagool N, Arjcharoen S, Limposuwan K, Chaisuriya P, Sirisinha S. Induction of iNOS expression and antimicrobial activity by interferon (IFN)-beta is distinct from IFN-gamma in *Burkholderia pseudomallei*-infected mouse macrophages. Clin Exp Immunol 2004; 136: 277-83.
24. Utaisincharoen P, Anuntagool N, Limposuwan K, Chaisuriya P, Sirisinha S. Involvement of beta interferon in enhancing inducible nitric oxide synthase production and antimicrobial activity of Burkholderiapseudomallei-infected macrophages. Infect Immun 2003; 71: 3053-7.
25. Puthucheary SD, Nathan SA. Comparison by electron microscopy of intracellular events and survival of *Burkholderia pseudomallei* in monocytes from normal subjects and patients with melioidosis. Singapore Med J 2006; 47: 697-703.
26. Utaisincharoen P, Tangthawornchaikul N, Kespichayawattana W, Anuntagool N, Chaisuriya P, Sirisinha S. Kinetic studies of the production of nitric oxide (NO) and tumour necrosis factor-alpha (TNF-alpha) in macrophages stimulated with *Burkholderia pseudomallei* endotoxin. Clin Exp Immunol 2000; 122: 324-9.
27. Simpson AJ, Smith MD, Weverling GJ, Suputtamongkol Y, Angus BJ, Chaowagul W, et al. Prognostic value of cytokine concentrations (tumor necrosis factor-alpha, interleukin-6, and interleukin-10) and clinical parameters in severe melioidosis. J Infect Dis 2000; 181: 621-5.
28. Chanchamroen S, Kewcharoenwong C, Susaengrat W, Ato M, Lertmemongkolchai G. Human polymorphonuclear neutrophil responses to *Burkholderia pseudomallei* in healthy and diabetic subjects. Infect Immun 2009; 77: 456-63.
29. Brown NF, Boddey JA, Flegg CP, Beacham IR. Adherence of *Burkholderia pseudomallei* cells to cultured human epithelial cell lines is regulated by growth temperature. Infect Immun 2002; 70: 974-80.
30. Essex-Lopresti AE, Boddey JA, Thomas R, Smith MP, Hartley MG, Atkins T, et al. A type IV pilin, PilA, Contributes To Adherence of *Burkholderia pseudomallei* and virulence in vivo. Infect Immun 2005; 73: 1260-4.
31. Santanirand P, Harley VS, Dance DA, Drasar BS, Bancroft GJ. Obligatory role of gamma interferon for host survival in a murine model of infection with *Burkholderia pseudomallei*. Infect Immun 1999; 67: 3593-600.
32. Haque A, Easton A, Smith D, O'Garra A, Van Rooijen N, Lertmemongkolchai G, et al. Role of T cells in innate and adaptive immunity against murine *Burkholderia pseudomallei* infection. J Infect Dis 2006; 193: 370-9.
33. Ekchariyawat P, Pudla S, Limposuwan K, Arjcharoen S, Sirisinha S, Utaisincharoen P. *Burkholderia pseudomallei*-induced expression of suppressor of cytokine signaling 3 and

cytokine-inducible src homology 2-containing protein in mouse macrophages: a possible mechanism for suppression of the response to gamma interferon stimulation. Infect Immun 2005; 73: 7332-9.
34. Santanirand P, Harley VS, Dance DA, Raynes JG, Drasar BS, Bancroft GJ. Interferon-gamma mediates host resistance in a murine model of melioidosis. Biochem Soc Trans 1997; 25: 287S.
35. Nuntayanuwat S, Dharakul T, Chaowagul W, Songsivilai S. Polymorphism in the promoter region of tumor necrosis factor-alpha gene is associated with severe meliodosis. Hum Immunol 1999; 60: 979-83.
36. Kumar A, Short J, Parrillo JE. Genetic factors in septic shock. JAMA 1999; 282: 579-81.
37. Lauw FN, Simpson AJ, Hack CE, Prins JM, Wolbink AM, van Deventer SJ, et al. Soluble granzymes are released during human endotoxemia and in patients with severe infection due to gram-negative bacteria. J Infect Dis 2000; 182: 206-13.
38. Panomket P, Chetchotisakd P, Sermswan RW, Pannengpetch P, Wongratanacheewin S. Use of a low-dose steroid as an adjunct in the treatment, in mice, of severe sepsis caused by *Burkholderia pseudomallei*. Ann Trop Med Parasitol 2009; 103: 635-46.
39. Moynagh PN. TLR signalling and activation of IRFs: revisiting old friends from the NF-kappaB pathway. Trends Immunol 2005; 26: 469-76.
40. McWhirter SM, Fitzgerald KA, Rosains J, Rowe DC, Golenbock DT, Maniatis T. IFN-regulatory factor 3-dependent gene expression is defective in Tbk1-deficient mouse embryonic fibroblasts. Proc Natl Acad Sci U S A 2004; 101: 233-8.
41. Panomket P, Splitter G, Harms J, Sermswan RW, Chedchotisakd P, Wongratanacheewin S. TBK1 does not play a role in the control of in vitro *Burkholderia pseudomallei* growth. Trans R Soc Trop Med Hyg 2008; 102 Suppl 1: S95-100.
42. Dharakul T, Vejbaesya S, Chaowagul W, Luangtrakool P, Stephens HA, Songsivilai S. HLA-DR and -DQ associations with melioidosis. Hum Immunol 1998; 59: 580-6.
43. Ketheesan N, Barnes JL, Ulett GC, VanGessel HJ, Norton RE, Hirst RG, et al. Demonstration of a cell-mediated immune response in melioidosis. J Infect Dis 2002; 186: 286-9.
44. Barnes JL, Warner J, Melrose W, Durrheim D, Speare R, Reeder JC, et al. Adaptive immunity in melioidosis: a possible role for T cells in determining outcome of infection with *Burkholderia pseudomallei*. Clin Immunol 2004; 113: 22-8.
45. Holden MT, Titball RW, Peacock SJ, Cerdeno-Tarraga AM, Atkins T, Crossman LC, et al. Genomic plasticity of the causative agent of melioidosis, *Burkholderia pseudomallei*. Proc Natl Acad Sci U S A 2004; 101: 14240-5.
46. Waiwarawooth J, Jutiworakul K, Joraka W. Epidemiology and clinical outcome of melioidosis at Chonburi hospital, Thailand. Infect Dis Antimicrob Agents 2008; 25: 1-11.

การตอบสนองของระบบภูมิคุ้มกันต่อเชื้อ *Burkholderia pseudomallei*

ภาวนา พนมเขต

Burkholderia pseudomallei เป็นเชื้อสาเหตุที่ก่อให้เกิดโรคเมลิออยโดสีส พบมากในผู้ป่วยที่มีประวัติมีโรคประจำตัวบางอย่าง ร้อยละ 50 เป็นโรคติดเชื้อที่มาจากชุมชน อาการแสดงของโรคมีหลายแบบตั้งแต่การติดเชื้อแบบเฉียบพลัน อาจร่วมกับภาวะช็อกหรือไม่ก็ตาม ไปจนถึงการติดเชื้อแบบเรื้อรังตลอดจนการติดเชื้อแบบไม่แสดงอาการทางคลินิก ยังไม่มีวัคซีนป้องกันสำหรับโรคนี้ การกำจัดเชื้อออกจากร่างกายทำได้ยาก ต้องการให้ยาปฏิชีวนะเป็นเวลานาน และพบการกลับเป็นซ้ำในอัตราที่สูงเมื่อการรักษาไม่ครบสมบูรณ์ แบคทีเรียสามารถกระตุ้นระบบภูมิคุ้มกันทั้งภูมิคุ้มกันที่มีมาแต่กำเนิดและภูมิคุ้มกันที่เกิดขึ้นภายหลัง แต่เชื้อก็สามารถหลุดหนีออกจากการกำจัดของระบบภูมิคุ้มกันได้ด้วยหลายกลไก การเกิดพยาธิสภาพของโรคเมลลิออยโดสีสก็ยังมีความเข้าใจไม่ชัดเจน โดยเฉพาะบทบาทของการเกิดปฏิกิริยากันระหว่างเชื้อ B. pseudomallei กับเซลล์ในระบบภูมิคุ้มกันทำให้เกิดการติดเชื้อเฉียบพลันและเรื้อรัง วัตถุประสงค์ของการทบทวนครั้งนี้เป็นการสรุปความเข้าใจในปัจจุบันเกี่ยวกับระบบภูมิคุ้มกันกับโรคเมลิออยโดสีส เนื้อหาจะแสดงภาพรวมของการตอบสนองของเซลล์ host ต่อตัวเชื้อและประโยชน์ของการพัฒนางานวิจัยเกี่ยวกับภูมิคุ้มกันเพื่อส่งเสริมความเข้าใจในแง่มุมของกลไก และการก่อพยาธิสภาพของการติดเชื้อ B. pseudomallei