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Molecular Epidemiology and Drug Resistance of Tuberculous Meningitis

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1. Introduction

Tuberculosis (TB) continues to be one of the highest burdens and greatest challenges to public health. Annually, TB causes approximately 1.7 million deaths and 9.4 million incident cases worldwide. Although the incident rate of TB is slowly falling due to the expansion of the population, the absolute number of new TB cases is still increasing. It is estimated that two billion people (i.e., one-third of the global population) are infected with *Mycobacterium tuberculosis* (MTB), the causative agent of TB (World Health organization [WHO], 2009). MTB is one of the most successful human pathogens. Many efforts and resources have been invested to conquer this disease. Despite continuous efforts to generate effective strategies and approaches for prevention, control and treatment of TB, there has been little progress on developing vaccinations and drugs and increasing our understanding of the disease compared to the progression of the adaptability and pathogenicity of the pathogen, which is, even now, full of ambiguity regarding virulence factors and pathogenicity.

Tuberculous meningitis (TBM), or TB meningitis, is the most devastating form of TB. The disease involves the infection of the meninges of the host, which is caused by MTB and other mycobacteria. This form of TB is of greatest concern due to its fatal outcome and neurological sequelae. The challenge is concentrated around rapid reliable diagnosis, treatment and understanding of its pathogenesis. The incidences of extrapulmonary TB and TBM are increasing (Kruijshaar *et al*., 2009). Drug resistance and HIV infection are the complications that make the treatment and management of TBM patients more difficult, and there are still doubts regarding many aspects of the disease. The lack of knowledge regarding TBM is challenging for us and other researchers. This review assembles, summarizes and discusses information regarding the epidemiology and drug resistance of TBM and the associations between MTB lineages and disease drawn from previous studies, along with information from studies that have been performed in Thailand. The overview of pathogenesis and the possible mechanism of TBM development are also discussed.

1.1 Clinical features

The cardinal clinical features of TBM include fever, anorexia and headache. Confusion is a late feature, and coma is a sign of poor prognosis. However, these features are not specific for TBM. The clinical features and outcome may vary depending on the delay of treatment, underlying disease, host immunity and virulence or lineage of MTB. The duration of the symptoms may vary from 1 day to 9 months. The common symptoms of TBM in terms of proportions of patients affected are fever (60–95%), anorexia (60–80%), headache (50–80%), vomiting (30–60%) and photophobia (5–10%). The clinical signs in terms of proportions of patients affected are neck stiffness (40–80%), coma (30–60%), any cranial nerve palsy (30–50%), cranial nerve III palsy (5–15%), cranial nerve VI palsy (30–40%), cranial nerve VII palsy (10–20%), confusion (10–30%), hemiparesis (10–20%), paraparesis (5–10%) and seizures (children: 50%; adults: 5%) (Davis *et al*., 1993; Farinha *et al*., 2000; Girris *et al*., 1998; Hosoglu *et al*., 1998; Kent *et al*., 1993; Verdon *et al*, 1996; Thwaites *et al*., 2005a). The severity of TBM can be classified into three stages according to the patient's Glasgow coma score and the presence or absence of focal neurological signs by stage I: Alert and orientated without focal neurological deficit; stage II: Glasgow coma score (please see the following paragraph) 14–10 with or without focal neurological deficit or Glasgow coma score 15 with focal neurological deficit; and stage III: Glasgow coma score less than 10, with or without focal neurological deficit (British Medical Research Council, 1948; Teasdale *et al*., 1974).

Notably, the Glasgow coma score is scaled between 3 and 15, where 3 is the worst and 15 is the best. Three factors are assessed: best eye response (1=no eye opening, 2=eye opening to pain, 3=eye opening to verbal command, 4=eyes open spontaneously), best verbal response (1=no verbal response, 2=incomprehensible sounds, 3=inappropriate words, 4=confused, 5=orientated), and best motor response (1=no motor response, 2=extension to pain, 3=flexion to pain, 4=withdrawal from pain, 5=localizing pain, 6=obeys commands) (British Medical Research Council, 1948).

1.2 Diagnosis

The diagnosis of TBM is difficult because there are no specific clinical features and no rapid reliable tests. The problem of misdiagnosis and the delay of diagnosis subsequently lead to the delay of treatment and the reduction of the cure rate. The clinical criteria for differentiating TBM are essential. However, the prodrome is usually nonspecific, and the diagnosis cannot rely only on clinical signs. Due to the difficulty of diagnosis of TBM and the lack of effective diagnosis tools, there have been efforts to generate diagnosis rules for differentiating TBM from other meningitis diseases (Kumar *et al*, 1999). Confusion with other meningitis diseases (e.g., viral meningitis and other bacterial meningitis) is a problem for the diagnosis of TBM. This form of TB should be considered when a patient presents with meningoencephalitis, especially with pre-diagnosed TB or is a member of any high-risk groups (Leonard *et al.,* 1990). For the TBM diagnostic test, it is important to perform a lumbar puncture; cerebrospinal fluid (CSF) can be examined by many tests (e.g., CSF AFB staining, CSF culture, CSF analysis of protein, glucose level, white blood cell count and detection of MTB complex nucleic acids and mycobacterium). The increase of protein and decrease of glucose with mononuclear cell pleocytosis are suspected indicators for TBM (Jeren & Beus, 1982). Radiographic assessments, such as computed tomography (CT) and magnetic resonance imaging (MRI), have vastly improved the identification of

complications of TBM (Bhargava *et al*., 1982; Bullock *et al*., 1982). The ideal features of a diagnostic test for TBM would require good sensitivity, specificity and more rapidity. Acid-fast bacilli (AFB) staining from a direct specimen with careful and repeated searching for acid-fast bacilli (AFB) is still one of the most effective rapid diagnostic tests. However, AFB staining lacks sensitivity, though it is a common conventional detection method for pulmonary TB. The gold standard for definite diagnosis is based on the positive cultivation of mycobacteria from CSF. However, the culture results can be delayed and are often insufficient for aiding clinical diagnosis. There have been attempts to apply new rapid methods, such as molecular and immunological tests, to aid in the diagnosis of TBM (Kashyap *et al*., 2002; 2000; Mathai *et al*., 2001; Radhakrishnan *et al*, 1994; Robertson *et al*., 1950; Srisaimanee *et al*., 2002; Sumi *et al*., 2002). Polymerase chain reaction is helpful for bacteriological confirmation. However, these new diagnostic methods have not been completely evaluated, and many tests require specific facilities and expertise. The diagnosis of TBM is still challenging and undoubtedly requires further approaches that are practical for use in all countries with improved reliability.

1.3 Treatments and management of TBM

Without appropriate treatment, TBM is a fatal disease with a high mortality rate. Many drugs used for the treatment of pulmonary TB have been used for the treatment of TBM as well. Nevertheless, there is much uncertainty regarding the treatment of TBM when compared to pulmonary TB (e.g., regimens, doses and the duration of chemotherapy). Streptomycin (SM) has been used for 60 years for TB treatment (Joint Tuberculosis Committee of the British Thoracic Society, 1998). The introductions of isoniazid (INH) and para-aminosalicylic acid (PAS) have provided further improvements in prognosis. A drug that can pass the blood-brain barrier (BBB) effectively can improve the efficacy of treatment. Rifampicin is 80% protein-bound in plasma; only 20% can penetrate the CSF in those with an intact BBB (Ellard *et al*., 1993). Nevertheless, the slow penetration of rifampicin through the BBB could allow its concentration in the CSF above the minimum inhibitory concentrations for MTB (Ellard et al., 1993). In contrast, INH, which is non-protein-bound, rapidly penetrates through the BBB in both healthy and inflamed conditions, which can yield concentrations > 30 times the MIC for MTB (Fletcher, 1953). The excellent capacity of pyrazinamide (PZA) to penetrate the BBB and its sterilizing activity against MTB makes this drug as a potential treatment for TBM (Humphries, 1992). Ethionamide penetrates healthy and inflamed meninges, but it can cause severe nausea and vomiting (Donald *et al*., 1989).

Presently, treatment of TBM involves a combination of several anti-tuberculous drugs, as does treatment for pulmonary TB. The appropriate regimen of treatment recommends starting with INH, RIF and PZA. The addition of a fourth drug depends on the decision of the clinicians. The British Thoracic Society (BTS), the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) recommend a short-course of chemotherapy for the treatment of TBM, as is used for the treatment of pulmonary TB, with variations in duration: an "intensive phase" (2 months) of treatment with four drugs, followed by a "continuation phase" (6-9 months) with two drugs (BTS, 1998; Thwaites *et al*., 2009a). The 6-month duration of treatment, as is used in pulmonary TB, could be used for TBM if the likelihood of drug resistance is low (van Loenhout-Rooyackers *et al*., 2001). Ethambutol and streptomycin are less effective for TBM treatment because of their poor

penetrating capacities and the adverse effect of optic neuritis. However, the BTS still recommends the use of these drugs as a choice for the fourth drug in the intensive phase. In cases of multidrug-resistant TBM (MDR-TBM), there are still no standard guidelines for chemotherapy (BTS, 1998; Thwaites *et al*., 2009a). Resistances to INH and RIF (MDR-TBM) are strong predictors of death (Thwaites *et al*., 2005b). MDR-TB isolates in Thailand were evaluated by their *rpoB, katG* and *inhA* genes; the results revealed relatively high numbers of mutations in amino acids 531, 526 and 516 of the *rpoB* gene, amino acid 315 of the *katG* gene and the promoter region of *inhA* (Boonaiam *et al.,* 2010; Prammananan *et al.,* 2008). Ethionamide, cycloserine, ofloxacin, and PAS could be used as second-line drugs based on the susceptibility profile of the infected strain or the data available in each country. Susceptible rates for ethionamide, ofloxacin and PAS in MDR-TB isolates from Thailand were 78.8%, 90.9%, and 85.9%, respectively (Prammananan *et al.,* 2005; 2011). The molecular mechanism of ethionamide resistance in MDR-TB strains in Thailand was found to be partially related to a point mutation in the *ethA* gene in 54.1% of isolates (Boonaiam *et al*., 2010). The appropriate duration of treatment for TBM is still controversial. The conventional duration for chemotherapy for TBM is 6-9 months (BTS, 1998; CDC, 2003). In young children, the 6-month duration can be used with high doses of anti-TB agents. Children must be treated for 12 months with a combination of antibiotic therapy and adjunctive corticosteroids.

Systemic steroids may also be used, but the roles of steroids for TBM treatment are also in doubt, especially in HIV-infected patients. A finding from a drug trial study suggested that all TBM patients who are not infected with HIV should be given dexamethasone, regardless of age or disease severity (Thwaites *et al.,* 2004). Adjuvant steroids may be used in the presence of increased intracranial pressure, altered consciousness, focal neurological findings, spinal block, and tuberculous encephalopathy. The benefit for using adjuvant corticosteroids for TBM patients involves reducing inflammation (Dooley *et al.,* 1997; Humphries *et al.,* 1992; Thwaites *et al*., 2004). In patients with obstructive hydrocephalus and neurological deterioration, placement of a ventricular drain or ventriculoperitoneal or ventriculo-atrial shunt should be performed. Prompt shunting improves outcome, particularly in patients with minimal neurological deficits. Additionally, surgical therapy for TBM patients can also be used in some cases, depending on the physician's judgment.

BCG vaccination has been debated concerning its capacity to protect against TB. The severe forms of TB, such as milliary TB and TBM in children, can probably be prevented by the BCG (Bacillus Calmette-Guérin) vaccine. Several studies have indicated the protective effects of the BCG vaccine against TBM (Awasthi and Moin, 1999; Puvacic *et al*., 2004; Mittal *et al*., 1996; Trunz *et al*., 2006; Xiong *et al.,* 2009). A protective efficacy of approximately 60-70% for the BCG vaccine against TBM has been reported (Thilothammal *et al*., 1996; Chavalittamrong *et al*., 1986). The study compared clinical presentations between BCG-vaccinated and unvaccinated children and revealed that vaccinated TBM patients showed better mentation and had superior disease outcomes (Kumar *et al*., 2005). However, other studies have shown low protective effects of the BCG vaccine against TBM (Guler *et al.,* 1998; Tsenova *et al*., 2007; Wunsch Filho *et al*., 1990). More than 40% of TBM patients have been immunized with the BCG vaccine in Turkey (Hosoglu *et al.,* 2003). The protective effect of the BCG vaccine against TBM in Thailand has been shown; though Thai people who have been immunized with the BCG vaccine still develop TBM, infected individuals are in a very

small proportion. Thailand has included mass immunization with the BCG vaccine for every newborn as the national public health policy since 1970. In Thailand, 76% of the protective effect of BCG against TB has been previously demonstrated, and a significantly lower extrapulmonary TB rate compared to pulmonary TB has also been demonstrated (Chavalittamrong *et al.*, 1986). However, clear evidence of BCG vaccine efficacy against TB and extrapulmonary TB by experimental study is still required.

2. Epidemiology of TBM

Information on the epidemiology of TBM is fundamental for the prevention, treatment and control of the disease. Nevertheless, due to the difficulty of the collection of specimens from patients and its low incidence rate, TBM is a relatively rare form of TB for study. A large collection of patient samples (e.g., more than 100 samples) is even less affordable for study. Therefore, gathering study information is an easy way to obtain an overview of the available knowledge of TBM epidemiology.

2.1 Incidence

Human migration and the availability of air travel are the major factors that have distorted the human population structure, geographic distribution and spread of MTB. Nevertheless, associations between the human race in certain regions and specific lineages of MTB have still been observed (Gagneux *et al.*, 2006). In 1997, TBM was the fifth most common form of extrapulmonary TB (WHO, 1997). From all TB cases, 90-95% of infected cases only have asymptomatic latent TB, whereas 5-10% of individuals (8-9 million people) have developed active disease, accounting for approximately 2 million deaths annually. The most common form of the disease is pulmonary TB, which has been estimated to represent 80% of all TB cases. Apart from the 20% of extrapulmonary TB cases, TBM has been calculated to represent 5.2% of extrapulmonary TB (WHO, 2009). The incidence of TBM from all reported TB cases is 0.7%. The incidence of central nervous system (CNS) TB is related to the prevalence of TB in the community. In countries with a high burden of pulmonary TB, the incidence of extrapulmonary TB and TBM are expected to be proportionately high. The incidence of TBM in the United States has been calculated to represent approximately 4.5% and 4.7% of total extrapulmonary TB cases in 1969-1973 and 1975-1990, respectively. From all samples that were sent to Siriraj Hospital in Bangkok, Thailand, for TB identification during 2000-2007, approximately 15% were CSF samples, 10% of which contained MTB and were identified as TBM.

2.2 Mortality rate

TBM is the most severe form of TB that involves the central nervous system. The mortality rate ranges from 20-60%, with an average of approximately 35% (table 1). Neurological sequelae can be found in approximately 25% of surviving patients (Hosoglu *et al*., 2002). It is not clear whether HIV infection is associated with TBM outcome. The summarized data indicate that the high mortality rate of TBM in South Africa from both studies is associated with a high proportion of HIV-infected cases, whereas no such associations were found in Thailand or France (table 1). Conflicts of such associations have been found in previous studies (Katrak *et al.*, 2000; Thwaites *et al*., 2005a). However, HIV infection seems to be the

strongest factor that predisposes an individual to development of TBM. The mortality rate of TBM is different among countries, which may involve differences in medical personnel, management and facilities.

Authors	Countries of study	Year	Mean (range) age (yrs)	Gender (% M/F)	HIV-infected (number/%)	Mortality rate (%)
1. Faksri *et al.*, 2011a and Yorsangsukkamol *et al.*, 2009	Thailand (n=184)	1996-2007	33.6 (0.25-83)	64/36	48/72 (66.7%)	25
2. Roca *et al*., 2008	Spain (n=29)	1991-2005	34 (17-78)	59/41	15/29 (52%)	41
3. Nagarathna *et al*., 2007	Egypt (n=336)	2001-2005	NA (13-50)	68/32	48/107 (44.9%)	NA
4. Thwaites *et al*. 2005a	Vietnam (n=545)	2001-2003	33 (15-88)	72/28	96/528 (18.2%)	30
5. Patel *et al.*, 2004	South Africa (n=30)	1999-2002	25.7 (0.4-45)	30/70	18/30 (60%)	56
6. Sutlas *et al.*, 2003	Turkey (n=61)	1988-2000	34.5 (16-74)	64/36	NA	27.8
7. Kalita and Misra, 1999	India (n=58)	1992-1996	25.6 (1-64)	69/31	NA	20.6
8. Hosuglo *et al*., 1998	Turkey (n=101)	1985-1996	30.6 (14-67)	60/40	NA	43.5
9. Karstaedt *et al*., 1998	South Africa (n=56)	1994-1997	33.5 (18-59)	53/47	39/56 (69.6%)	69.6
10. Verdon *et al.*, 1996	France (n=48)	1982-1993	46 (18-83)	67/33	10/32 (31.25%)	64.5
11. Davis *et. al*., 1993	United States (n=54)	1970-1990	NA (4-86)	NA	NA	23

Note: NA= data not available, M=male, F= Female, HIV=human immunodeficiency virus

Table 1. Epidemiological information of TBM patients from previous studies

2.3 Predisposing risk factors

The strongest risk factors for developing TBM are immunological status (e.g., HIV infection) and pre-diagnosed TB. Ages and genders of TBM patients also affect predisposition for TBM development. Prior to the predomination of HIV, the age of the patient was the most important factor leading to the development of TBM. The ages of TBM patients are different from pulmonary and other extrapulmonary TB diseases; TBM is commonly found in children ages 0-5 years (Farer and Meador, 1979). In populations with a low prevalence of TB, most cases of TBM occur in adults. In general, TBM is more common in children than in adults. Notably, the young ages of children are not always the most prevalent risk factors for TBM in all populations with high TB burdens, which might result from worldwide BCG

vaccination. For instance, in the Thai population, the most predominant ages of TBM patients are 31-45 years (35.3%), and only 12% of TBM patients are less than 15 years old (Yorsangsukkamol *et al.,* 2009). With BCG vaccination, a significantly lower incidence of disseminated TB, such as TBM, was found in patients less than 12 years old compared to pulmonary TB (Chavalittamrong *et al*., 1986). The average ages of TBM patients in particular regions, even on different continents, are around 30 years higher (table 1). This evidence supports the idea that the HIV epidemic has increased the risk for adult TBM in the last three decades. In general, young children are more likely to develop meningeal or disseminated TB, whereas adolescents more frequently present with pleural or peritoneal TB compared to adults.

Patient gender is also a predisposing factor for TBM development. Incidence is consistently higher for men than for women, with a ratio around 2:1. The proportion of affected females is slightly lower than that of males in the overall world population. However, the 2:1 ratio between male and female TBM patients has been found consistently in many countries. In children with TBM, the ratios between males and females are less affected. In Thailand, a male/female TBM patient ratio of 3:2 has been conserved over three periods of four-year intervals (Faksri *et al*., 2011a). The effect of gender on TBM development may be explained by socio-economic or anatomical-physiological factors.

Co-infection with HIV and MTB, especially in AIDS patients, is also the strongest risk factor for progression to active TB. Compared to non-HIV-infected individuals, who have a 5-10% risk of developing active TB, HIV increases the risk of developing clinical TB post-infection to 1 in 3 individuals (Selwyn and Lewis, 1989). Furthermore, HIV also increases the possibility of developing extrapulmonary TB, especially TBM (Bishburg *et al.,* 1986). The increase in TBM incidence is most likely due to an increased incidence of CNS-TB among patients with HIV/AIDS and to the increasing incidence of TB among infants, children and young adults. Cell-mediated immunity is the most important defense against TB infection, and a decline of CD4 T cells is associated with the development of TBM (De Cock *et al*., 1992). Although patients who have HIV infection and TB are at increased risk for TBM, the effects of HIV infection on the clinical features and outcomes of TB are still disputed (Berenguer *et al*., 1992). Several studies that have assessed the effects of HIV infection on the clinical presentation of TBM have identified conflicting findings. HIV-infected patients may have altered clinical presentations, such as in pathological features, CSF parameters, frequency of infection with MDR-TB and mortality. Hospital-associated mortality was significantly higher in HIV-infected patients (Cecchini *et al.,* 2009; van der Weert *et al*., 2006; Katrak *et al.,* 2000; Bandyopadhyay *et al*., 2009). Other studies have found that HIV infection was not associated with mortality rate or altered neurological presentation in TBM, though additional extrapulmonary TB was more likely to occur in HIV-infected patients and may have also affected the survival rate (Faksri *et al*., 2011a; Thwaites *et al*., 2005a).

Another important risk factor is pre-diagnosed TB. The most often associated form is milliary TB on chest x-rays, which presents as a disseminated form of TB with small 1- to 2-mm lesions spreading in a large area of the lung and/or other organs. The development of TBM can consist of either the primary infection with a short incubation or a secondary reactivation of pulmonary TB with a long latent period.

Previous studies using the tuberculin conversion rate have shown that black-skinned people are more susceptible to TB infection than are white-skinned people (Stead *et al*., 1990).

Consequently, the development of TBM may associate with certain host groups. The most striking study of host variation and TB is from Gagneux *et al*., which showed that the lineages of MTB are associated with certain geographical regions and ethnic groups from the patients' countries of origin: the East Asian (Beijing) lineage predominates in patients from East Asia, whereas the Euro-American lineage mostly infects European people (Gagneux *et al*., 2006). Certain lineages of MTB are predominant in certain geographical regions and ethnic groups that are associated with TBM. Therefore, environmental factors (i.e., geographical region and race) also predispose individuals to develop TBM. More discussion on host variation and predisposing factors follows in sub-topic 5.2: "Host variation and development of TBM".

Other risk factors that may be involved in TBM development include: diabetes mellitus (Bernard-Griffiths *et al*., 1959; Pablos-Mendez and Knirsch, 1997), malignancy, malnutrition, alcoholism, head trauma (Davis and Lambert, 1993) and recent corticosteroid use (Mori and Welty, 1992).

3. Overview of the pathogenesis of TBM

A pathological view of TBM was first described in 1836 (Green, 1836). Then, in 1882, Robert Koch demonstrated that TB was caused by MTB (Koch, 1882). In 1912, a pathological experimental infection of TBM in an animal model was demonstrated (Manwaring, 1912). Subsequently, there have been several studies focused on the pathogenesis of TBM using animal experiments, in which a rabbit model is commonly used, as mice do not provide similar pathological characteristics to human TBM (Behar *et al*., 1963; Matsubara, 1956; Sidel'Nikova and Rozina, 1956; Tsenova *et al*. 2005; 2007; van Well *et al*., 2007).

For an overview of pathogenesis (Figure 1), MTB infection occurs through the inhalation of aerosol droplets containing the bacilli. Only small droplets (1-5 μm in diameter) can reach and eventually deposit in the alveoli of the lungs. Inside the alveoli, the bacilli are engulfed by alveolar macrophages. Because MTB can survive in this hostile environment, the bacteria can infect and grow inside the macrophages *ex vivo*. Once these immune cells are triggered, numerous cytokines and chemokines are released. The activation of a Th1 cell-mediated immune response, the critical defense mechanism that plays a major role against MTB infection, occurs; ultimately, a granuloma, mainly composed of macrophage-derived giant cells and lymphocytes, is formed. In latent tuberculosis cases, the granuloma functions to contain the bacilli and is maintained depending on the strength of the host cellular immune response. Furthermore, the interaction between immune factors in the host and virulence factors in the pathogen may determine whether the infection will be restricted or disseminated and progressed into the next stage of the disease. Before the bacilli can gain access to the brain, spreading outside of the lung into the blood circulation is the critical step for extrapulmonary TB, a step that is poorly understood. The transportation of infected alveolar macrophages into the blood circulation is a current hypothesis for extrapulmonary spread. However, the discovery that MTB hematogenous dissemination is dependent on heparin-binding hemagglutinin adhesin, a bacterial virulence factor that interacts with epithelial cells, has suggested that other trafficking pathways may be important (Pethe *et al*., 2001). The failure of immune responses from the host, along with virulence factors from the pathogen that promote a high capacity for evading immune responses (which may determine by lineages), are the factors that promote extrapulmonary spreading.

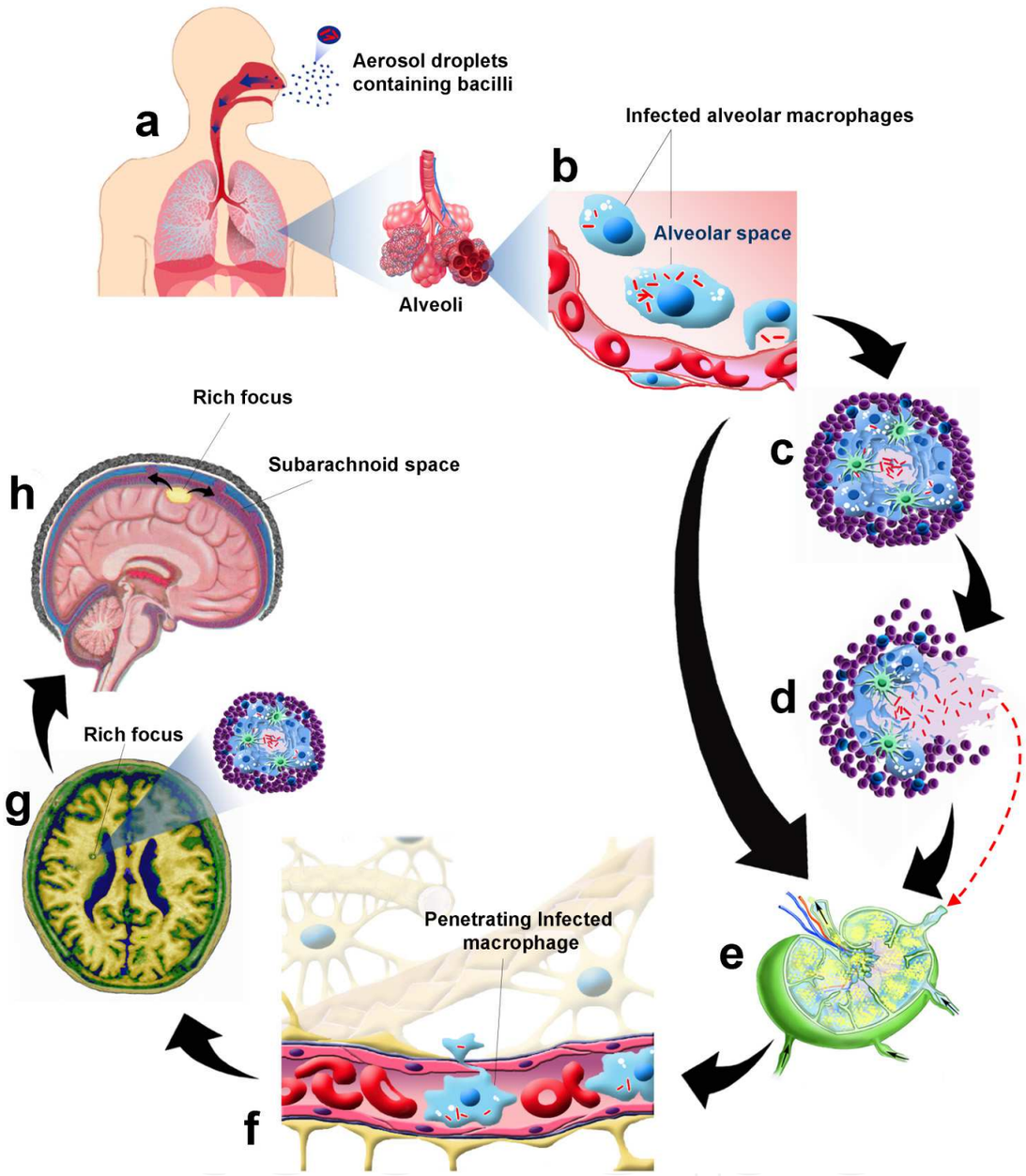


Fig. 1. Pathogenesis of TBM and postulation of the formation of Rich foci. (a) Aerosol transmission of MTB, (http://www.graphicshunt.com/health/ images/alveoli-268.htm) (b) Phagocytosis of MTB by alveolar macrophages inside alveoli. (c) Granuloma formation in the lung, which subsequently occurs due to cellular and cytokine network responses; 90% of hosts with granulomas maintain them stably over the course of their lives. (d) MTB escapes from the granuloma, which occurs in 10% of latent TB patients. (e) MTB can cause TBM by escalating from the lung or by secondary reactivation from a "leaked granuloma", which is then filtered into a regional lymph node. (http://www.graphicshunt.com/health/ images/alveoli-268.htm) (f) After spreading through the blood circulation, MTB can enter the CNS through the BBB, likely by a Trojan horse mechanism. (g) Bacilli seed to the meninges or the brain parenchyma, forming subpial or sub-ependymal primary complexes,

termed "Rich foci". (h) Rich foci increase in size, rupture and discharge into the subarachnoid space, which indicates the onset of TBM. (http://digitalunion.osu.edu/r2/summer08/dzeleznikar/anatomy.html). Some part of figures (a, e, h) were modified from online sources as described.

For TBM, the process of pathogenesis can be divided into two steps (Rich, 1993). First, the bacilli are filtered and disseminated into the draining lymph nodes. During this stage, there is a short but significant bacteremia that can seed the bacilli into other organs. Hematogenous spreading occurs most frequently in regions of the body that are highly oxygenated, including the brain. The pathogenesis of TBM might occur from a primary infection of MTB and develop into TBM directly or might be derived from the reactivation of pulmonary TB that subsequently develops into TBM (figure 1). Like other bacterial meningitis diseases, a prerequisite step of the pathological mechanism of TBM is the movement of the bacilli through the BBB (Kim *et al.*, 2008). The factors that contribute to this movement remain unknown. The process may be a multifactorial process involving host–pathogen interactions. The bacilli can cross the BBB using both transcellular and paracellular mechanisms; alternatively, infected phagocytes may transmigrate via a so-called Trojan horse mechanism (Kim *et al.*, 2008). Consequently, the pathogen can cause BBB dysfunction by inducing injury to the endothelium, resulting in an increase in permeability, pleocytosis and encephalopathy. For TBM, the Trojan horse mechanism seems to be the most possible strategy for traversal, as MTB is an intracellular pathogen and primarily infects macrophages; including a mechanism in which the bacilli, by themselves, evade the host immune responses and reach the brain would be difficult. However, transcellular penetration of the BBB has also been demonstrated for this pathogen (Jain *et al.*, 2007). In addition, the factors that determine the fate of bacilli for hematogenous dissemination and development of TBM include the capacity to survive and replicate inside macrophages. Furthermore, the capacity of bacilli to reduce the occurrence of programmed cell death, which would reduce the viability of bacilli, may also be involved in the process of TBM pathogenesis. In those who develop TBM, bacilli seed to the meninges or the brain parenchyma, forming subpial or sub-ependymal primary complexes, termed "Rich foci" (Rich, 1993). This step, which has not yet been defined, may also determine the progress of the disease by both pathogen and host factors. In the second step, in approximately 10% of the cases that develop such complexes, particularly in children and immunocompromised hosts, the primary complex does not heal but progresses. This event can occur months or years after the formation of Rich foci (Rich, 1993; Thwaites and Schoeman, 2008). The location of the Rich foci determines the type of CNS involvement. In TBM, the Rich foci increase in size until they rupture and discharge into the subarachnoid space, which indicates the onset of TBM. The following processes can also take place: adhesions around the interpeduncular fossa can lead to CN palsies; adhesive exudates can obstruct CSF, leading to hydrocephalus; and obliterative vasculitis can lead to infarction. Encephalitis and tuberculomas can also occur. Rich foci located deeper in the brain or the spinal cord parenchyma can cause tuberculomas or abscesses. Notably, abscesses or hematomas can rupture into the ventricle, but not in the case of Rich foci (Rich, 1993). After the rupture of Rich foci, the bacilli and numerous leukocytes are released into the subarachnoid space. Then, the local T-cell-dependent response is activated. The subsequent necrotizing granulomatous and inflammatory responses are the result of the pathological events of TBM.

On the cellular scale of TBM pathogenesis, the cytokines and chemokines that are consequently released from the host cellular response are thought to be important factors of

pathogenesis. Most of the symptoms, signs, and sequelae of TBM are the result of an immunological inflammatory reaction to the infection. Tumor necrosis factor-alpha TNF-α) is the key cytokine in the inflammatory response and is the critical cytokine in the neuropathogenesis of MTB (Mastroianni *et al.*, 1997; Tsenova *et al.*, 1999). Evidence has indicated a direct correlation between the level of this cytokine in the CSF and the progression of the pathogenesis of TBM (Tsenova *et al.*, 1999). Also, TNF-α is a major determinant of disease in a rabbit model of meningitis (Tsenova *et al.*, 2005). TNF-α also benefits the host by playing an important role in granuloma formation (Kaneko *et al.*, 1999). These conflicting roles of TNF-α might depend on which polarity of cytokine responses (i.e., Th1 or Th2) dominate. Metalloproteinase-9 (MMP-9) is another cytokine that may play an important role in TBM pathogenesis by increasing the degradation of the BBB, which results in an increase in its permeability. Evidence has demonstrated that different genotypes of MTB can induce different host immune responses (Chaves *et al.*, 1997, Yorsangsukkamol *et al.*, 2011).

Alternatively, host genetic polymorphisms can also affect their susceptibility for developing disease. Some cytokines and proteins that are released from host cells, such as TNF-α, are related to the development and pathogenesis of TBM. In TB, a strong Th1-like immunity is considered important for containment of mycobacteria. The major immune effector mechanism involved in the activation of infected macrophages is stimulated by Th1-type cytokines (Seth and Sharma, 2002). The protective effects of Th1-type cytokines can be antagonized by Th2-type cytokines (Manca *et al.*, 2001), and increased production of Th2-type cytokines may be responsible for the characteristic immunopathology of the disease. A balance between the Th1- and Th2-type cytokine responses in TB may influence mycobacterial growth, immunopathology and the fate of the disease (Seth and Sharma, 2002). In addition, regarding the cytokine response, inflammatory cytokines are also determinants of immunopathology. The pathogenesis and virulence of the pathogen can also be determined by the balance between pro-inflammatory and anti-inflammatory cytokines.

It remains unclear why only some individuals develop disseminated TB that spreads to the meninges and then the central nervous system, while most people suffer only localized disease in the lung. Important factors include HIV infection and younger patient age. This may indicate that the host immune response is a major factor that plays a role in the development of TBM. Apart from socio-economic and environmental factors, pathogen and host factors are considered to be more important in the development of TBM. However, it is not yet known which factors are the most important. Although it seems to be a multifactorial process, a number of studies have recently demonstrated that not only pathogen factors but also host factors could influence the development of TBM (Takahashi *et al.*, 2005; Thuong *et al.*, 2007; 2008). Studies have demonstrated that genetic polymorphism of Toll-interleukin 1 receptor domain-containing adaptive protein (TRAP-MAL) and Toll-like receptor 2 (TLR2) are associated with the susceptibility for developing TBM (Hawn *et al.*, 2006; Thuong *et al.*, 2007). Gene expression profiles of human monocyte-derived macrophages (MDMs) have demonstrated that certain genetic variations, especially chemokine (C-C motif) ligand 1 (CCL1), could predispose an individual to develop a particular disease phenotype (i.e., pulmonary or latent TB, or TBM) (Thuong *et al.*, 2008). Furthermore, Caws *et al.* demonstrated that particular mycobacterial genotypes (East Asian and Euro-American lineage) identified by large sequence polymorphisms (LSPs) and host genetic polymorphisms in TLR2 influence the development of TBM (Caws *et al.*, 2008). A

study of the capacity of the HN878 Beijing strain to cause TB meningitis in a rabbit model revealed that a disruption of the *pks15/1* gene that encodes a polyketide synthase-derived phenolic glycolipid (PGL) reduced virulence (Tsenova *et al*., 2005). However, *pks15/1* is not a unique property of the Beijing lineage of MTB (Chaiprasert *et al*., 2006). Despite these findings, however, the pathogen virulence and host genetic polymorphism factors governing the development of TBM are still unclear.

4. Anti-tuberculous drug resistance in TBM

Many decades ago, TB was considered an incurable, deadly disease. With the availability of effective treatments, TB can now be cured. However, the complete treatment requires several months to stabilize the patient's condition and to prevent the reoccurrence of disease. Pan-drug-resistant (PDR) TB strains are now a new emerging and serious public health problem. Although the incidence of PDR-TB is not yet high, we cannot underestimate the adaptability of MTB, a highly successful human pathogen. In addition, the TB burden dominates in low- and middle-income countries (LMIC) where the drug susceptibility test is not fully available. The real prevalence of drug-resistant TB may therefore be markedly higher than the estimation. Furthermore, extensively drug-resistant (XDR) TB, which is more expensive and more difficult to treat than multidrug-resistant (MDR) TB, has more serious adverse effects, and the outcomes for patients are much worse. Despite the fact that there are several novel anti-tuberculous drugs that have been developed and discovered recently, the levels of drug-resistant TB, especially MDR- and XDR-TB (and PDR-TB), are still increasing. It is very threatening to consider the imbalance between the effective anti-tuberculous drugs and drug-resistant TB, especially with the outbreak of MDR-TB in large areas. The most effective way to eradicate TB is with effective vaccination and control of latent TB. However, we are still struggling to find ways to beat this pathogen. For now, treatments for drug-resistant TB are still where we must focus. Yet, PDR-TB and TB with resistance to new drugs should be surveyed and monitored worldwide (Prammananan et al., 2006). The real hope lies with continuing to develop novel, effective anti-tuberculous drugs and vaccines.

In TBM, drug resistance and HIV infection constitute additional conditions that make the treatment of patients become more complex and difficult. The diagnosis, treatment and management of these patients are major challenges. The delay of diagnosis and treatment of TBM can cause the subsequent deaths of patients. Therefore, drug-resistant TBM is a major issue of concern for the treatment and management of TBM.

From data collected on TB cases from 81 countries between 2002 and 2006, the WHO reported that the incidence of pulmonary MDR-TB was approximately 4.8%. The highest numbers of MDR-TB were found in China, India, and the Russian Federation (WHO, 2008). In 2009, 3.3% of all new TB cases had MDR-TB (WHO, 2009). Unfortunately, information on the drug resistance of TBM from these countries was not available for this review. Studies on the drug resistance of TBM are relatively rare. From the data available, the drug-resistance patterns for TBM were obtained from four countries: Thailand, Egypt, Vietnam and South Africa. Information gathered from previous studies found that the average incidence of TBM that was resistant to any drug was approximately 21.5% (with a range of 12-31%). MDR-TBM was found in 2.2 to 8.6% of cases, with an average of approximately 3.3% (table 2). The incidence of MDR-TBM was up to 18% in pediatric cases, with a mortality rate of 100%. Nevertheless, the sample size from this study was only 20 cases

(Chander, 2008). Resistance to particular anti-tuberculous drugs, such as isoniazid, represented the most resistant MTB strains in four out of five studies in the available data (table 2). Isoniazid resistance in TBM has been suggested to correlate with HIV co-infection (Thwaites *et al*., 2002). The second most-resistant drug is streptomycin. TBM showed minimal resistance to rifampicin (which can partially penetrate an intact BBB) and ethambutol. There was no evidence to support an increase in penetration capacity through the BBB for rifampicin after inflammation (Nau *et al.,* 1992). The information in this review may support the idea that rifampicin is a good drug for effective treatment of TBM, with a lower chance of development of drug-resistant TBM, compared to isoniazid and streptomycin. Ethambutol has been called a poor choice for a first-line treatment for TBM due to its poor penetration capacity and the adverse effect of optic neuritis (Donald *et al.,* 1998). The summarized information shows that ethambutol resistance is less likely to occur when it is used as a first-line agent for TBM treatment. However, the low resistance level may be a result of poor exposure between the drug and the pathogen.

Compared to other countries, Thailand has the second-highest drug-resistance rate for TBM (table 2). The trend for drug-resistant TBM in Thailand has been previously analyzed; it was found that a 3% incidence of MDR-TBM in the first period increased into a 12% incidence in the third period (Faksri *et al*., 2011a). Information regarding the trends of drug resistance in other regions is unknown. Nevertheless, it is more likely that drug resistance is underestimated, which indicates that the incidence of drug-resistant TBM may be increasing. Patel *et al.* reviewed the medical records of TBM patients from South Africa and found that MDR–TBM is a serious problem that has increased the mortality rate up to 57%, with the majority of the patients having been treated with anti-tuberculous drugs (Patel *et al*., 2004). Whether or not HIV co-infection and AIDS are involved in the development of MDR-TBM, these combined factors result in a marked increase in the difficulty of treatment and the mortality rate (Daikos *et al*., 2003; Patel *et al.,* 2004). This information has raised our concerns regarding proper treatment and drug-resistance surveillance for TB and TBM.

Authors	**Geographical regions**	**Year of collection**	**Drug resistant profiles (%)**					
			H	R	S	E	MDR	Suscep
1. Yorsangsukkamol *et al*., 2009 and Faksri *et al.,* 2011a	Thailand (n=184)	1996-2007	20.4	6.1	17.0	5.4	6.1	75.5
2. Nagarathna *et al*., 2008	Egypt (n=336)	2001-2005	13	0	0.3	0.2	2.4	82.2
3. Caws *et. al*., 2006	Vietnam (n=198)	2000-2003	18.7	3	24.2	0.5	2.5	68.7
4. Patel *et al.,* 2004	South Africa (n=350)	1999-2002	NA	NA	NA	NA	8.6	NA
5. Cooksey *et al*., 2002	Egypt (n=67)	1998-2000	10.4	1.5	7.5	1.5	0	76.1
6. Padayatchi *et al*., 2006	South Africa (n=362)	1992-2003	NA	NA	NA	NA	2.2	88.4
7. Girgis *et al*., 1998	Egypt (n=857)	1976-1996	10	3	0	7	0	80
8. Karstaedt *et al*., 1998	South Africa (n=56)	1994-1997	NA	NA	NA	NA	4.3	NA

Note: H: isoniazid, R; rifampicin, S: streptomycin, E; ethambutol, MDR: multidrug-resistant, Suscep; susceptible to all drugs

Table 2. Summary of drug-resistant profiles in TBM patients from previous studies

5. MTB lineages, TBM and evolution

The most common pathogen of TB and TBM is MTB. There are a few reports of TBM caused by *M. bovis (*Cooksey *et al*., 2002; Tardieu *et al*., 1988*)*. Meningitis can also be caused by nontuberculous mycobacteria (NTM) (Huempener *et al.,* 1966). Interestingly, several studies have shown different pathogenicities, determined by clinical analysis among MTB lineages (Ganiem *et al*., 2009; Lan *et al.,* 2003; Kong *et al.,* 2007). Studies in animal models (Manca *et al.,* 2001; Reed *at el*., 2004) and macrophage cell lines (Li *et al*., 2002; Lopez *et al*., 2003) have also indicated that the Beijing genotype of MTB is the most virulent genotype. Furthermore, this genotype is also associated with drug resistance, especially MDR (Drobniewski *et al.,* 2005). It has been hypothesized that this genotype is an escape mutant of the BCG vaccine (van Soolingen *et al.,* 1995). Six lineages of MTB have defined names according to specific markers based on large sequence polymorphisms (i.e., regions of difference) and geographical regions: East Asian (Beijing), Euro American (EuA), East African Indian (EAI), Indo-Oceanic (IO), West African I (WA I) and West African II (WA II).

5.1 TBM and the variation of MTB lineages

For TBM, the Beijing lineage is also suggested to be the most neurovirulent genotype. The most predominant genotype of TBM in Thailand is the Beijing (East Asian) genotype, with an incidence of 58%. The Indo-Oceanic (34%) and Euro-American lineages (10%) are the second most and least predominant genotypes (Faksri *et al*., 2011a). MTB lineages found in TBM may associate with the lineages that are found in pulmonary TB. However, the proportions of lineages may not be the same. More than half of MTB from TBM patients were the Beijing genotype (Yorsangsukkamol *et al*., 2009), whereas only approximately 20% of MTB from pulmonary TB were the Beijing genotype (Rienthong *et al*., 2005). The proportion of MTB lineages in TBM patients in Thailand is roughly concordant with TBM strains from Vietnam, in which the Beijing (42%) and Indo-Oceanic lineages (44%) are in higher proportions; the Euro-American lineage (14%) is the least prevalent. Studies conducted in Vietnam suggest that Beijing MTB is the most virulent genotype that causes TBM, based on correlation analysis with clinical features. They found that the Beijing lineage showed associations with a shorter duration of illness before presentation and drug resistance (i.e., the influence of disease progression, intracerebral alteration of inflammatory responses and difficulty of treatment) (Thwaites *et al.,* 2008). In Thailand, the predominance of the Beijing lineage revealed associations with MDR-TB, a trend that is increasing in proportion; additionally, it had the highest clustered rate, supporting its virulence for causing TBM. Inversely, the Euro-American lineage has been thought to be the attenuated lineage, causing the lowest proportions of TBM, with a decreasing trend of proportion and lacking cluster formation (Faksri *et al.,* 2011a). RFLP pattern analysis of CNS–MTB strains also suggested that the occurrence of CNS TB might be strain-dependent (Cooksey *et al*., 2002; Arvanitakis *et al.,* 1998). Nevertheless, the absence of an association between MTB genotypes and the clinical presentation and outcome of TBM has also been described. The most predominant strain in this study was not the Beijing genotype (principal genetic group 1, or PGG 1) of MTB. They found that all 3 PGGs were represented (group 1, 27.1%; group 2, 59.3%; group 3, 13.6%) (Maree *et al*., 2007). This information may indicate the variations in capacities for causing neurovirulence and TBM among MTB lineages.

In addition, variations in virulence within the Beijing family of MTB have been proposed (Alonso *et al.,* 2010; Faksri *et al.,* 2011b; Hanekom *et al.,* 2007; Iwamoto *et al.,* 2009; Kong et al., 2007; Theus *et al*., 2007). Particular sublineages of the Beijing family of MTB seem to be more virulent based on associations with drug resistance and MDR (Twamoto *et al.,* 2008; Mokrousov *et al.,* 2006) and exhibit greater transmissibility (Wada *et al.,* 2009). The genetic analysis of the Beijing family of MTB isolates based on SNPs, LSPs, IS*6110* and VNTR profiles from Thailand revealed interesting genetic polymorphisms among Beijing strains. While the SNPs showed good correlations with other genetic markers, such as LSPs and IS*6110*, some SNPs may not be irreversible genetic events (i.e., they may occur repeatedly in phylogeny). A determination of the variation of virulence of the Beijing sublineages based on a combination of genetic markers has been conducted. The results demonstrated associations between Beijing sublineages based on phylogeny and virulence, with the modern Beijing lineage being more virulent than the ancestral strain (Kaksri *et al.* unpublished). The modern Beijing strain has an increasing trend toward causing TBM in Thailand than the ancestral Beijing strain in Thailand (Faksri *et al.,* 2011b). The differences in transmissibility based on cluster analysis and the increasing trend of proportion in TBM patients compared to the ancestral Beijing sublineage support this hypothesis.

5.2 Host variation and development of TBM

Certain host groups seem to be susceptible to TB infection. There are several studies that indicate the association of host genetic vitiation and pulmonary TB. For instance, the polymorphisms of genes that are involved with cytokines and chemokines showed associations with the susceptibility of TB, such as IFN-gamma (Hashemi *et al.,* 2011), TNF-alpha (Fan *et al*., 2010), CXCL-10 (Tang *et al*., 2009), CCL5 (Sanchez-Castanon *et al.,* 2009) and SLC11A1 or NRAMP1 (Bellamy *et al*., 1998). Genome-wide SNP-based linkage analysis in TB cases in Thailand showed particular regions, such as 5q, 17p and 20p, on chromosomes associated with TB susceptibility (Mahasirimongkol *et al*., 2009). Other examples of genetic polymorphisms and susceptibility to TB are the MC3R promoter, the CTSZ 3'UTR (Adams *et al*., 2011), P2X7 (Xiao *et al*., 2010) and MMP-9 (Lee *et al*., 2009). Notably, MMP-9 is the enzyme that may be involved in BBB permeability. The variation in MMP-9 encoding gene may also be associated with the development of TBM. The origin countries of patients are associated with the development of TBM (Bidstrup *et al,* 2002). The association between host genetic variations and susceptibility to the development of TBM has been proposed. SNPs at genes encoding Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) (Dissanayeke *et al.,* 2009) and Toll-like receptor-2 (TLR-2) have been shown to be associated with TB caused by the East Asian (Beijing) lineage of MTB (Thuong *et al.,* 2007), which indicates an association between host variation, the preference of certain strains of MTB and the development of certain disease types.

5.3 Co-evolution between MTB and the host in TBM

In terms of evolution, MTB is regarded as a young pathogen, which means that its evolutionary process has occurred relatively recently. MTB underwent an evolutionary bottleneck and was derived from the most recent common ancestor (MRCA) approximately 15,000-30,000 years ago (Gibbons, 2008; Kapur, 1994; Hughes *et al*., 2002; Wirth *et al*., 2008). Inversely, MTB may have infected humans for hundreds of thousands of years, or longer,

before the MRCA appeared (Smith *et al*., 2009). The nature of this pathogen includes an intracellular lifestyle. Humans are always a definite host of MTB. Nevertheless, infection caused by MTB can also be found in some animals, such as non-human primates (Corcoran and Thoen, 1991) and elephants (Angkawanish *et al*., 2010; Murphree *et al*., 2009). Although the natural defense mechanism of the host is the elimination of pathogens and foreign agents mediated by immune responses, co-adaptation between host and pathogen also occurs in nature. A good classical model of co-evolution between humans and bacteria involves the hypothesis that mitochondria used to be bacteria that co-adapted to live within eukaryotic cells as organelles (Henze and Martin, 2003). A similar model has been posited involving chloroplasts or plastids of plant cells (Patrick, 2004). A more obvious co-adaptation of bacteria to human hosts is the *Escherichia coli* found in the human gastrointestinal tract. The co-evolution between MTB and human hosts may have occurred several hundreds of thousands of years ago. However, the pathogens try to survive within the host by avoiding or suppressing the host immune response. Latent TB may be the result of a co-adaptation between MTB and host immune responses.

Regarding TBM, MTB is an obligate aerobe and prefers oxygen for growth. The underlying reason for this may reflect a preference of MTB to spread to other tissues that contain a high oxygen content, including the brain. As evidence of this, lung lesions usually occur in the right upper lobe. The altered capacity to pass the BBB may an evolutionary response for better growing conditions. Unlike other body tissues, the CNS and the CSF are parts of the body in which the immune system is less strict. The adaptation of the pathogen by escaping from the host immune system and passing the BBB for more oxygen may explain the variation of virulence and the evolution of MTB-associated TBM. However, TBM is a severe from of TB, and the evolution of MTB toward a better capacity to enter the CNS, eventually causing the death of the host, in turn causing its own death, seems to conflict with an adaptive evolutionary response. Further studies are certainly needed to explore this possibility.

6. Future research topics for TBM

The neurovirulence of MTB is still unknown. The virulence determinants of the causative agent of TBM can contribute to clinical intervention. The lineage-dependent virulence of MTB is also interesting to study, especially when applied to the consequences of treatment and vaccination. It is worthwhile to note that certain MTB strains may have specific properties that facilitate meningeal involvement and result in neurotropism, as found in *M. leprae,* which predispose it to infect peripheral nerves. Information in our unpublished study shows that certain MTB strains that vary in the copy numbers of variable number tandem repeats (VNTR2163A and 2163B) are associated with TBM rather than pulmonary TB. Further studies are needed to confirm this finding.

The pathogenesis of TBM is mainly based on studies that were performed many decades ago. The use of animal models, which are mostly based on rabbits and mice, limit the validity of the results. There is a need for appropriate animal models, such as non-human primates, for experiments that better reflect human TBM and that may reveal novel knowledge regarding pathogenesis and treatment for TBM and TB. Cynomolgus monkeys (Walsh *et al*., 1996) and pigs (Bolin *et al*., 1997) developed TBM with similar pathologic characteristics to human TBM following intratracheal or intravenous inoculation of mycobacteria. The mouse model is not a good animal model for TBM study due to its

immunological response against infection and granuloma formation. However, because of its ease of use and the availability of facilities, mouse models are still practical to use as animal models for studying TBM. An attempt to modify the mouse model to provide the immunological inflammatory response of TBM is an applicable approach (van Well *et al.*, 2007). Other aspects of the pathogenesis of TBM can help identify novel interventions. The mechanism by which the pathogen spreads hematogenously from the lung or other infected organs into the CNS is unknown. The roles of some cytokines, such as MMP-9, vascular endothelial growth factor (VEGF) and TNF-α, for controlling the breakdown and permeability of the BBB and the role of cell death mechanisms in the pathogenesis of TBM, such as apoptosis and autophagy, are included in the list of unanswered questions. The implications of the findings from these studies will help to improve the treatment and intervention of not only TBM but also other extrapulmonary TB diseases.

The improvement of molecular methods and strategies to gain more sensitivity and specificity can largely aid the diagnosis of TBM. The development of a rapid diagnostic method with high sensitivity and specificity that is appropriate for LMIC is also a challenge. Furthermore, the rapid diagnosis of drug-resistant TB and TBM will facilitate the treatment and management of TBM patients and drug resistance surveillance.

The development of new effective treatments and novel drugs, especially drugs that can effectively penetrate the BBB, is challenging. The role of adjunctive corticosteroids in TBM patients co-infected with HIV and the effects or relationships involved in HIV-MTB co-infection, particularly the aspects of promoting effects of HIV infection and the development of MDR-TBM, are also important to study. Developing a rapid method for detection of drug-resistant strains (especially for MDR- and XDR-TB) in TBM can promote good prognoses and positive outcomes. A few studies have shown that bacteriophages can increase the sensitivity of detecting MTB in the CSF by using a fluorescent signal that can be detected within a few days rather than weeks, as in conventional culture techniques (Jacobs 1993; Drobniewski 1997). The improvement of the reliability and the standardization of these diagnosis methods may improve the phenotypic-based drug susceptibility testing of MTB. Whether there is a protective effect against the severe form of TB (i.e., TBM) and determining the immunological role of BCG vaccination against TBM are also important topics to address.

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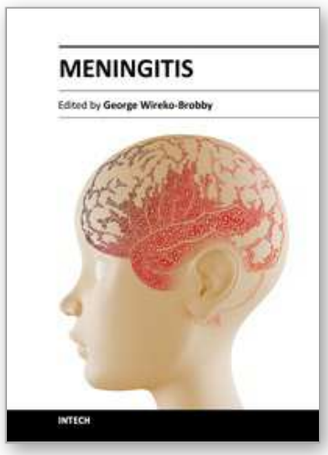
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Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

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