Front. Biol. 2015, 10(3): 252–261
DOI 10.1007/s11515-015-1358-y

REVIEW

The bacterial and host factors associated with extrapulmonary dissemination of *Mycobacterium tuberculosis*

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Abstract **With high morbidity and mortality worldwide, tuberculosis (TB) is still an important public health threat. The majority of human TB cases are caused by *Mycobacterium tuberculosis.* Although pulmonary TB is the most common presentation, *M. tuberculosis* can disseminate into other organs and causes extrapulmonary TB (EPTB). The dissemination of bacteria from the initial site of infection to other organs can lead to fatal diseases, such as miliary and meningeal TB. Thoroughly understanding the mechanisms and pathways of dissemination would develop therapies to prevent the lethal prognosis of EPTB (miliary and meningeal TB) and vaccines to promote the development of adaptive immunity. This review focuses on risk factors of EPTB, bacterial and host genes involved in EPTB, and potential mechanisms of *M. tuberculosis* extrapulmonary dissemination.**

Keywords *Mycobacterium tuberculosis*, extrapulmonary, dissemination, risk factors, bacterial genes, host genes

Introduction

Although tuberculosis (TB) emerged about 15000 to 35000 years ago (Kapur et al., 1994), it is still an important public health threat globally, causing 8 million new cases and 1.3 million deaths each year (WHO 2014). The majority of human TB cases are caused by *Mycobacterium tuberculosis,* an aerobic bacterium that can persist in host tissues for months to decades without replication, but resumes growth when host immunity wanes. It is estimated that one-third of the worlds population are latently infected with *M. tuberculosis* (Sudre et al., 1992). Pulmonary TB is the most common presentation, but *M. tuberculosis* can disseminate into other organs and causes extrapulmonary TB (EPTB). The trafficking of bacteria from the initial site of infection to other organs can lead to fatal diseases, such as miliary and meningeal TB. Extrapulmonary involvement can occur with or without pulmonary infection sites. About 15% reactivated TB from latency occur at extrapulmonary organs without active pulmonary TB (Hopewell, 1994). It has been reported that *M. tuberculosis* DNA was isolated from extrapulmonary organs during latent infection in human samples (Barrios-Payán et al., 2012). The rate of EPTB development is between 10% and 25% among immunocompetent patients (Weir and Thornton, 1985; Pitchenik et al., 1988; Snider and Roper, 1992; American Thoracic Society, 2000). Frequent sites of extrapulmonary infection include the pleura, lymph nodes, bones and joints, CNS (meninges), larynx, skeleton (particularly the spine), genitourinary tract, eyes, gastrointestinal tract, adrenal gland, and skin. The clinical presentation of EPTB is atypical. Biopsy and/or surgery are required to procure tissue samples for confirmation of EPTB diagnosis. Thoroughly understanding the mechanisms of *M. tuberculosis* dissemination would help to prevent the lethal prognosis of EPTB and to improve diagnosis, treatment and prevention of EPTB. This review focuses on risk factors of EPTB, bacterial and host genes involved in EPTB, and potential mechanisms of *M. tuberculosis* caused extrapulmonary dissemination. Although nontuberculosis mycobacteria can cause both pulmonary and extrapulmonary TB (Alvarado-Esquivel et al., 2009; Henkle and Winthrop, 2015), it is out of the scope of this review.

M. tuberculosis infection

M. tuberculosis is a slow-growing facultative intracellular pathogen that can survive and multiply inside macrophages and other mammalian cells. It is transmitted from patients

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with active pulmonary disease by droplets, which are then inhaled. After an incubation period of 4 to 12 weeks, approximately one third of the individuals exposed become infected (Edwards and Kirkpatrick, 1986). It is the balance between bacterial virulence and the inherent microbicidal ability of the alveolar macrophages that determines whether an inhaled tubercle bacillus can successfully establish infection in the lungs (Edwards and Kirkpatrick, 1986; Dannenberg, 1989). Once inspired into the lungs, the bacilli multiply and cause inflammation, which induces neutrophils and macrophages to migrate to the area of inflammation. After phagocytizing the bacilli, alveolar macrophages are activated to release cytokines, which recruit more macrophages and activated T cells to control infection (Dannenberg, 1989). Accumulated macrophages at sites of bacterial implantation further differentiate into epithelioid cells that have tightly interdigitated cell membranes in zipper-like arrays linking adjacent cells to form tuberculous granuloma (Adams, 1976; Bouley et al., 2001). Granuloma contains the pathogen, a large population of T cells, B cells, dendritic cells, neutrophils, and fibroblasts (Flynn and Chan, 2001; Peters and Ernst, 2003). After granuloma formation, *M. tuberculosis* is maintained and persists within the center of granuloma in a low active and anaerobic state to avoid direct confrontation with the host immune defense (McKinney et al., 2000). Reactivation happens once the balance between bacillary persistence and the immune response gets disturbed due to aging, malnutrition, steroids or HIV infection (Fenton and Vermeulen, 1996; Flynn and Chan, 2001).

Active TB occurs when the host immune response fails to contain the replication of *M. tuberculosis* associated with initial infection. It is estimated 5%–10% of those infected with *M. tuberculosis* develop active TB during the first few years following infection. The clinical manifestations of TB are quite variable and depend on host factors such as age, immune status, coexisting diseases, immunization with BCG, and microbial factors such as virulence of the organism and predilection for specific tissues (American Thoracic Society, 2000). Human immunodeficiency virus (HIV) co-infection increases the risk for active disease of TB. Among HIV-infected persons with latent TB infection, the rates of active disease are up to 100 times higher than those for individuals with latent TB infection without co-infection with HIV (Brewer and Heymann, 2005).

The immune response to *M. tuberculosis* infection is primarily a cell-mediated response with T cells as the main player (Kaufmann, 2002; Boom et al., 2003). $CD4^+$ T cells, mediated by their cytokine production (Cooper et al., 1993; Jouanguy et al., 1996; de Jong et al., 1998), are the most important aspect of the protective response in *M. tuberculosis* infection (Caruso et al., 1999; van Pinxteren et al., 2000). One of the cytokines produced by $CD4^+$ and $CD8^+$ T cells is gamma interferon (IFN-γ). It can activate antigen-presenting cells, boost expression of major histocompatibility complex (MHC) (Cooper et al., 1993; Jouanguy et al., 1996; de Jong et al., 1998), induce reactive nitrogen derivatives (especially nitric oxide) (Arias et al., 1997; Nathan and Shiloh, 2000; Shiloh and Nathan, 2000), and alternate phagocytic vesicle tracking/control (MacMicking et al., 2003). IFN-γ can also inhibit over-production of other cytokines, such as tumor necrosis factor α (TNF-α) (Rook and Hernandez-Pando, 1996; Bekker et al., 2000). Strategies employed by *M. tuberculosis* to evoke T helper-1 cell immune response include resisting intracellular killing mechanisms of microphages, and blocking apoptosis of macrophages (Sly et al., 2003) and the macrophages response to IFN-γ (Fortune et al., 2004).

Risk factors of EPTB

HIV infection

Before the HIV pandemic, about 15%–20% of TB cases developed EPTB (Weir and Thornton, 1985; Pitchenik et al., 1988; Snider and Roper, 1992; American Thoracic Society, 2000). In HIV-positive patients, however, EPTB cases increased dramatically to more than 50% of all cases of TB (Theuer et al., 1990; Shafer et al., 1991; Haas and Des Prez, 1994; Antonucci et al., 1995; Lado Lado et al., 1999; Lee et al., 2000; Yang et al., 2004). We found the risk of developing EPTB in HIV positive patients is as high as 5-fold of that in HIV negative patients, after controlling age, race, and gender (Yang et al., 2004). The close association between HIV infection and EPTB is very likely due to deficiency of $CD4^+$ T cells among HIV infected patients. It is well known that HIV targets on $CD4^+$ T cells and causes reduced $CD4^+$ T cells and less cytokine production. $CD4^+$ T-helper cells are major players for controlling *M. tuberculosis* infection. Among HIV positive patients, the risk of EPTB increases as the $CD4^+$ lymphocyte count declines (Jones et al., 1993). The most common extrapulmonary site in HIV-positive individuals is the lymph node. However, other extrapulmonary sites such as neurological, pleural, pericardial, abdominal involvement have also been described in HIV-positive patients (Raviglione et al., 1992; Barnes and Barrows, 1993; Jones et al., 1993).

Race/ethnicity

Population-based epidemiological studies reported that African Americans tend to have higher proportion of EPTB cases (Farer et al., 1979; Yang et al., 2004; Fiske et al., 2010). In the United States, data from 13 states and two cities reported the rates of EPTB in African Americans is 5 times of that in Whites (6.5 vs 1.3 per 100000 population) (Farer et al., 1979). In a case-control study with over 700 TB patients, we have found the risk of developing EPTB in African Americans is as 2-fold high as in White population, after controlling for other confounding factors, including age, gender and HIV coninfection (Yang et al., 2004). Higher risk of EPTB development in African American population may be related

to higher overall TB incidence rates (Centers for Disease Control and Prevention, 2008), higher exposure to TB, lower socioeconomic status, and lack of access to medical care (Rieder et al., 1990). Additionally higher prevalence of HIV infection might lead to higher risk of EPTB in African Americans.

People born in South Asian countries have higher incidence rates of EPTB than other foreign-born patients (Asghar et al., 2008). The mechanism is unknown. It might be due to unidentified host genetic or physiological factors that increase their risks to develop disseminated disease. One possible cause is vitamin D deficiency. Vitamin D deficiency happens more in dark-skinned people (Harris, 2006). The association between vitamin D deficiency and susceptibility to TB has been reported in epidemiologic and laboratory-based studies (Liu et al., 2006; Martineau et al., 2007; Sita-Lumsden et al., 2007). Although there was not significant independent association between the vitamin D receptor (VDR) genotype and TB susceptibility, the combination of TT/Tt genotype of VDR gene and vitamin D deficiency was significantly associated with TB susceptibility (Wilkinson et al., 2000). In clinical studies, vitamin D supplementation was observed to reduce patient pulmonary lesion (Nursyam et al., 2006). It has been reported that 25-hydroxyvitamin D can be activated by 25-hydroxyvitamin D-1α hydroxylase (CYP27B1) into 1,25-dihydroxyvitamin D3. Binding of active vitamin D to its receptor VDR on cell surface increases expressions of β-defensin 2 and cathelicidin (Wang et al., 2004; Gombart et al., 2005), which stimulate autophagy of *M. tuberculosis* infected phagocytes (Campbell and Spector, 2012), and help to inhibit bacterial replication. Vitamin D was also found to induce IL-1β expression in *M. tuberculosis* infected macrophages cocultured with human small airway epithelial cells, and to reduce bacterial burden through another antimicrobial peptide, DEFB4/HBD2, generated by the cocultured epithelial cells in response to IL-1β (Verway et al., 2013).

Gender

While men typically have higher overall rates of TB compared with women (Martinez et al., 2000), some studies have shown that among people who develop TB, women are more likely to have EPTB than men (Rieder et al., 1990; Chan-Yeung et al., 2002; Yang et al., 2004; Musellim et al., 2005; Sreeramareddy et al., 2008). A population-based case-control control study in the United States has showed that 16.9% of female patients had extrapulmonary disease compared to 9.3% of male patients (Yang et al., 2004). Similar findings have also been seen in Asian and European populations. (Chan-Yeung et al., 2002; Forssbohm et al., 2008; Zhang et al., 2011; Lin et al., 2013). It is still unclear why females tend to have more EPTB. Hormonal factors, smoking and TB exposure might be the causes of this inequality (Hudelson, 1996; Holmes et al., 1998). Older women are less able to contain bacilli in the lungs due to reduced levels of sex hormones after menopause. The prevalence of smoking is higher in males than females. Smoking is a risk factor for pulmonary TB (Bates et al., 2007; Chiang et al., 2007). Another report has suggested that smoking is associated with relapse of TB and smokers are less likely to have isolated EPTB (Chiang et al., 2007). Other possible factors accounting for the difference are stigma associated with having TB and lack of access to health care, especially for females in resource limited regions (Holmes et al., 1998).

Age

Whether age is an independent risk factor of EPTB is not certain. In the above mentioned population-based case-control study, it has been found that the risk of EPTB among younger than 25 years old is 2-fold of that among older patients (Yang et al., 2004). Other studies from the United States (Gonzalez et al., 2003) and Europe (Cailhol et al., 2005) have also reported that younger age was an independent risk factor for EPTB. However, another study from Turkey (Musellim et al., 2005) has reported that age was not associated with EPTB. These inconsistent findings could be attributed to different prevalence of host-related factors or important co-exposures among the studied populations.

Bacterial genes involved in EPTB

After infection of *M. tuberculosis* in lungs, whether EPTB occurs is likely determined by interactions between the pathogen and the host immune response. Studies on bacterial virulence genes using animal models have identified several genes that might be related to *M. tuberculosis* dissemination.

Seven genes *whiB1* through *whiB7* at separate loci are in the *M. tuberculosis* genome (Cole et al., 1998; Camus et al., 2002) as orthologs of the *whiB* gene of *Streptomyces coelicolor* A3(2), which was annotated as a putative transcription factor, and has been shown to be involved in sporulation (Davis and Chater, 1992). Among them, WhiB4 has been postulated to act as a sensor of oxidative stress. *M. tbΔwhiB4* showed a defect in dissemination to guinea-pig spleen, suggesting that *whiB4* is essential for successful dissemination. It is likely WhiB4 regulates oxidative stress response to modulate survival in macrophages, and thus helps bacterial dissemination (Chawla et al., 2012).

A locus in *M. tuberculosis* genome, designated as *mel2*, plays an important role during persistence in mice (Cirillo et al., 2009). Like the *whiB4*, the *mel2* mutant displays increased susceptibility to reactive oxygen species (ROS) (Cirillo et al., 2009). In aerosol infected mice, the mutant grew normally until the persistent stage, where it did not persist as well as the wild type, resulted in reduced pathology and CFU in spleen at 4 weeks post infection (Cirillo et al., 2009).

The most severe type of EPTB is meningitis, which happens when *M. tuberculosis* infects the central nervous system (CNS). Bacterial genes required for invasion or survival in mouse CNS were identified by using a pooled defined *M. tuberculosis* mutants library to intravenously infect mice (Be et al., 2008), including *Rv0311*, *Rv0805*, *Rv0931c*, and *Rv0986*. *Rv0805* and *Rv0986* mutants were significantly attenuated on day 1 in brain tissue, in comparison with them in blood, suggesting that they have roles in invasion of the CNS. In addition, *Rv0311*, *Rv0805*, and *Rv0931c* might also play roles in survival in the CNS, because mutants of *Rv0311*, *Rv0805*, and *Rv0931c* were found to be significantly attenuated in brain on day 49, in comparison with them in brain on day 1(Be et al., 2008). Using rabbits infected intrathecally with different *M. tuberculosis* clinical isolates, the group of rabbits infected with HN878, a *M. tuberculosis* strain caused 60 cases of TB in Texas from 1995 to1998 (Manca et al., 2001), was found having the highest bacillary load in the brain and the most severe leukocytosisin cerebrospinal fluid (Tsenova et al., 2005). The higher bacterial load and leukocytosis in CNS caused by HN878 was ascribed to a polyketide synthase (PKS)–derived phenolic glycolipid (PGL), because the PKS genes deleted strain *HN878pks1-15::hyg* infected animals showed reduced bacterial load, less severe pathologic changes and attenuated clinical manifestations (Tsenova et al., 2005), and the PGL-deficient mutant of HN878 was found to be more immunogenic and less lethal in infected mice (Reed et al., 2004).

Another region named "*igr*" for the defect in intracellular growth might play roles in dissemination, intracellular survival, and lipid catabolism (Sassetti and Rubin, 2003; Schnappinger et al., 2003; Rengarajan et al., 2005; Chang et al., 2007). The *igr* region is composed of 6 genes (*Rv3540c–Rv3545c*) (Chang et al., 2007). Three of these six open reading frames are lying in the same orientation and annotated as a cytochrome P450 (*cyp125*), and two acyl-coenzyme A (CoA) dehydrogenases (*fadE28* and *fadE29*); the other three genes are two conserved hypotheticals (*Rv3541c* and *Rv3542c*), and one lipid transfer protein (*ltp2*) (Chang et al., 2007). Aerosol infection of mice showed the strain having a deletion of this region had delayed dissemination to the spleen, and reduced lung pathology (Chang et al., 2007). However, the deletion mutant of this region showed no difference in persistence in comparison with the wild type strain (Chang et al., 2007).

Host genes involved in disseminated TB

After *M. tuberculosis* infection, bacterial replication and dissemination are first controlled by the host innate immune response, and then by a T cell mediated adaptive immune response. The innate immune response to *M. tuberculosis* is primarily through macrophages and intracellular signaling pathways. Bacterial antigen pattern recognition receptors, such as Toll-like receptors, are involved in bacterial recognition and macrophage activation. Toll-like receptor 2 (TLR2) has been found to recognize *M. tuberculosis* and initiate the innate immune response to infection. TLR2 genotype T597C was found associated with TB meningitis in a case-control study (Thuong et al., 2007). The association increased with the severity of neurologic symptoms (Thuong et al., 2007). TNF-α is an important cytokine for controlling *M. tuberculosis* infection. Individuals treated with the anti-TNF-α agent infliximab were found associated with disseminated TB (Keane et al., 2001). Another anti-TNF-α agent, adalimumab, caused disseminated TB in non-human primate model (Lin et al., 2010).

Besides main factors in innate immunity, cytokines and chemokines playing roles in T cell mediated immunity are also involved in dissemination of *M. tuberculosis*, including genes encoding IFN-γ receptor, IL-12 receptor, and the signal transducer and activator of transcription-1 (STAT-1). A mutation in the IFN-γR1 chain was identified from six children with disseminated environmental mycobacterial infection, suggesting that the IFN-γR gene mutation is associated with mycobacterial dissemination (Levin et al., 1995). Mutations in IL-12 receptor β 1 chain were found from three patients having severe, recurrent, and systemic Mycobacterial and Salmonella infections (de Jong et al., 1998). These patients also had reduced IFN-γ production from NK cells and T cells (de Jong et al., 1998). A genetic polymorphism in the Manose Binding Protein (MBP) encoding gene was associated with TB meningitis in a South African population (Hoal-Van Helden et al., 1999). The MBP B allele (G54D) led to low MBP levels, which provided protection against tuberculous meningitis (Hoal-Van Helden et al., 1999). Genetic polymorphisms in interleukin (IL)-1β/IL-1R (Wilkinson et al., 1999), IL-10, IFN-γ (Henao et al., 2006), and NRAMP1 (Kim et al., 2003) were associated with pleural TB. In addition, a polymorphism in the P2X7 gene, which encodes a receptor expressed on macrophages, was associated with EPTB (Fernando et al., 2007).

Mechanisms of dissemination

It is well accepted that *M. tuberculosis* can migrate from the primary infection site, lungs, to the lymphatic system and bloodstream. However, the detailed mechanisms of bacterial dissemination remain unclear. To migrate from lungs to the draining lymph nodes and blood stream, the bacilli must break through alveolar epithelium. So far, some evidences have shown that bacteria inside alveolar macrophages or dendritic cells can be relocated by these professional phagocytes into lymph nodes and blood. Bacteria could also invade and lyse epithelial cells after infecting epithelial cells.

Bacteria relocated by professional phagocytes

One of the ways for *M. tuberculosis* to infect other organs is to use professional phagocytes as vehicles to approach organs far away from lungs by following blood stream. After phagocytized by professional phagocytes, mycobacteria can survive within phagosomes, the hostile acidic niche, and prevent fusion of phagosome to lysosome (McDonough et al., 1993) by using sulfatides (Goren et al., 1976), by producing ammonia or ammonium chlorides (Gordon et al., 1980; Hart et al., 1983), and by deactivating calmodulin and calmodulin dependent protein kinase 2 (Malik et al., 2001). Once infection is established, the infected macrophages and dendritic cells are surrounded by T cells and B cells to form granulomas. It was a dogma that granuloma helps confine bacterial dissemination. However, studies using zebra fish embryo infected with *M. marinum* demonstrated that macrophages within granulomas helped mycobacteria disseminate from initial infection sites to distant sites (Clay et al., 2007; Davis and Ramakrishnan, 2009). Early secretory antigenic target 6 kDa (ESAT6) and culture filtrate protein 10 kDa (CFP10) are two proteins encoded by *Rv3874* and *Rv3875* within the RD1 gene cluster, which is present in *M. tuberculosis* genome but not in the *M. bovis* bacillus Calmette-Guérin (BCG) genome (Cole, 2002). In the *M. marinum* infected zebra fish embryo, RD1 deleted mutant could not disseminate to distant sites (Clay et al., 2007). It suggested that genes in the RD1 region are important for bacterial dissemination by migrating within granulomas. These studies were conducted with *M. marinum* in immune immature zebra fish model. It remains to test whether these observations hold true in *M. tuberculosis* infected mature mammal model.

Another professional phagocyte, dendritic cell, also plays important roles in controlling *M. tuberculosis* infection. Using aerosol infected mouse model and flow cytometry, it has been found that the majority of infected cells in the lungs and mediastinl lymph node were $CD11c^{high}CD11b^{high}$ myeloid DCs and recruited macrophages (Wolf et al., 2007). After phagocytizing mycobacteria, dendritic cells present bacterial antigens to T cells to prime IFN-γ producing T cells and to induce cell-mediated response to infection (Tascon et al., 2000). Mannosylated lipoarabinomannan (ManLAM) on mycobacteria cell wall can interact with a c-type lectin receptor on dendritic cells to modify host response to inhibit dendritic cell maturation (Fortune et al., 2004). These investigations suggest *M. tuberculosis* may utilize macrophages and dendritic cells to traffic to the lymph nodes and blood (Menozzi et al., 1996).

Bacteria invade and lyse epithelial cells

Epithelial cells are the first lining of the alveolus that inhaled *M. tuberculosis* interacts with. After infecting epithelial cells, *M. tuberculosis* can replicate and undergo cell-to-cell spreading (Castro-Garza et al., 2002). Some studies suggest that *M. tuberculosis* can lyse epithelial cells and cause necrosis of epithelial cells (Dobos et al., 2000). Cytotoxicity for epithelial cells is associated with bacterial virulence (McDonough and Kress, 1995). The heparin binding hemagglutinin (HbhA) of *M. tuberculosis* was found to play important roles in infecting epithelial cells. HbhA was initially identified in *M. tuberculosis* and *M. bovis* (BCG) (Menozzi et al., 1996; Menozzi et al., 1998). It is located on the surface of the mycobacterium and mediates binding of the bacillus to epithelial cells and fibroblasts (Menozzi et al., 1996). Mutation of *hbhA* leaded to reduced adherence of bacteria to epithelial cells but no effect on adherence to macrophages (Pethe et al., 2001). In intranasal infected mice, mutation of *hbhA* did not affect colonization in lungs, but severely reduced colonization in spleen. However, this discrepancy was not observed when infection is through i.v., suggesting that HbhA is critical for escaping from lung, but not for colonization in extrapulmonary organs (Pethe et al., 2001; Sohn et al., 2011; Lebrun et al., 2012). Overall, these studies advocate that HbhA is important for *M. tuberculosis* to infect and transcytose epithelial cell layer and to escape from lungs.

Mammalian cell entry (mce) genes were identified when a DNA fragment of *M. tuberculosis* H37Ra was transformed into *E. coli*, which enabled this non-pathogenic bacterium to invade a nonphagocytic HeLa cell line. Initially, this gene was named *mce* (Arruda et al., 1993) . Subsequently, other paralogous genes were found in *M. tuberculosis* H37Rv and these genes are now named *mce1A*, *2A*, *3A*, and *4A* (Casali and Riley, 2007). These four gene are located in four separated *mce* operons, *mce1* to *mce4*, with similar organization and a 450 bp core sequence (Kumar et al., 2003). In mice intratracheally infected with mutants of mce 2 or 3, bacterial loads in both lung and spleen are significantly lower than the bacterial loads in the wild type strain; whereas in intraperitonealy infected mice, there were not significantly different bacterial loads in lung and spleen among the mutant and wild type strains infected groups (Gioffré et al., 2005). These results indicate genes in *mce 2* and *mce 3* operons might be involved in extrapulmonary dissemination. It remains to further characterize the detailed mechanisms and functions of each genes of *mce* operons.

Although ESAT6 and CFP10 were shown to be important for dissemination through the mechanism of being relocated by professional phagocytes as above discussed, there are evidences showing that they could help bacterial dissemination by lysing epithelial cells. Transposon disruption of the *esat6* and *cfp10* operon of RD1 showed defect of cytolysis in pneumocytes and macrophages (Hsu et al., 2003). ESAT6 can bind to laminin on the basolateral surface of alveolar epithelial cells and lyse pneumocytes (Kinhikar et al., 2010). In this way, ESAT6 helps bacteria directly disseminate through the alveolar wall.

Summary

Among TB patients, 10%–20% can develop EPTB, which complicates diagnosis and treatments, and thus increases morbidity and mortality of the disease. Although many factors have been reported involved or associated with EPTB development, the detailed mechanisms remain unclear. The phenotype of *M. tuberculosis* dissemination from initial infection site in the infected host is a sign of failure of containing bacteria by the granuloma. However, since lymph nodes are the critical place for professional phagocytes to present antigens to T cells, and thus to prime T cells, bacterial dissemination into regional lymph nodes also helps to develop protective T cell mediated immune response. There have been many evidences showing both bacterial and host factors play important roles in *M. tuberculosis* dissemination. As studies on bacterial and host genes related to dissemination move forward, more and more new factors and pathways will be identified and characterized. These results will, without a doubt, broaden and deepen our knowledge of TB pathogenesis, and thus improve our methods of diagnosis, treatment and prevention of TB.

Acknowledgements

Work in the authors' laboratory was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R21HL115463. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethics guidelines

Dong Yang and Ying Kong declare that they have no conflict of interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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