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Polymorphysm of tumor necrosis factor-A interleukin-10 gene with pulmonary tuberculosis susceptibility

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ABSTRACT

Pulmonary tuberculosis (TB) is an infectious disease caused by the acid-fast bacterium Mycobacterium tuberculosis (MTB). It is a progressive granulomatous infection, spreading through droplets in the air, and can be fatal. This makes a patient with pulmonary TB a primary source of transmission in the surrounding population. This case-control research was carried out at the Central Laboratory of the Lung Hospital of West Sumatra. The analysis of polymorphisms of the tumor necrosis factor-α (TNF-α) and the interleukin (IL)-10 genes was carried out at the Biomedical Laboratory of the Faculty of Medicine, Andalas University, in collaboration with 1st Base Malaysia. The results indicate that the clinical symptoms of TB can be grouped into either general or specific based on the organ involved. The clinical picture is not always typical, making clinical diagnosis difficult. TNF-α is a cytokine secreted by Th1 cells, macrophages, monocytes, neutrophils, effector T lymphocytes (T cells), and natural killer (NK) cells. It prevents pulmonary TB infection and maintains latent TB status by activating macrophages, transporting them to the site of infection, and forming granulomas that control TB infection. It also prevents the reactivation of persistent TB infection, modulates pulmonary expression of specific immunological factors, and limits the pathological response of the host.

During aerosol transmission of MTB, the first cells exposed to the pathogen are alveolar macrophages and pulmonary dendritic cells, which get activated and phagocytose MTB, producing TNF-α and IL-12 cytokines, that in turn activate host antimicrobial mechanisms, and induce IL-10 to inhibit the mechanism.

Keywords: *tumor necrosis factor-A gene; interleukin-10 gene; polymorphism; pulmonary tuberculosis*.

INTRODUCTION

Pulmonary tuberculosis (TB) is an infectious disease caused by the acid-fast bacterium Mycobacterium tuberculosis (MTB). It is a progressive granulomatous infection, spreading through droplets in the air and can be fatal. The World Health Organization (WHO) reported pulmonary TB as one of the 10 leading causes of death worldwide in 2018, with an estimated 10 (9.0–11.1) million new cases reported globally, affecting 5.7 million men, 3.2 million women, and 1.1 million children.1–3

Eight countries that accounted for 66% of new cases of pulmonary TB include India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. The number of active pulmonary TB patients in 2015 exceeded 20 million worldwide, with 9.6 million newly diagnosed pulmonary TB cases and 1.5 million death. The incidence of pulmonary TB disease is increasing, particularly in developing countries.4

Indonesia is the third country after India and China with 842,000 cases per year and an estimated 93,000 deaths per year equivalent to 11 deaths per hour.5 The prevalence of pulmonary TB in West Sumatra in 2014 was 0.11% and in 2016 it increased to 0.15% with the case detection rate (CDR) reaching 42.8% in 2018.6

The primary source of pulmonary TB transmission is the pulmonary TB patients with positive acid-resistant bacteria (BTA) which spreads in the form of droplet nuclei when the patient coughs or sneezes.

The phlegm lasts for several hours in dark and humid conditions; but direct sunlight can kill this MTB. The risk of contracting MTB is influenced by the level of exposure to sputum and the host's immune system. In Indonesia, the proportion of the population at risk of developing pulmonary TB every year is reported by the annual risk of tuberculosis infection (ARTI) index; the ARTI in Indonesia varies between 1 and 3%.3

The immunopathogenesis of pulmonary TB infection starts with the inhalation of MTB droplets which are then phagocytosed by alveolar macrophages. Some of the bacteria are immediately eliminated preventing an individual from becoming infected. However, some MTB are not immediately phagocytosed by alveolar macrophages, as the immune response to MTB is not fully effective resulting in the formation of a stable primary complex (Afzal et al., 2011; Anggraini & Oktora, 2021). This allows the individual to survive without getting sick, but the bacteria are not eliminated. Latent TB infection becomes reactive (postprimary pulmonary TB) when immunity is decreased. A small proportion (about 10%) becomes active pulmonary TB infection localizing in the lungs (primary pulmonary TB) and spreading via hematogenous to other organs.7

The macrophage response in the early stages of infection is the main nonspecific immune response. The resulting cytokines are secreted by macrophages in the innate immune system and play an important role in controlling pulmonary TB infection.

Cellular immune responses include the involvement of CD4 and CD8 T cells that play a protective role in pulmonary TB infection through several mechanisms, such as producing potent antibacterial cytokines, namely tumor necrosis factor-α (TNF-α) and interferon (INF-γ), that are involved in granulomas formation, recognizing the MTB antigen presented by the major histocompatibility complex (MHC), and inducing apoptosis of infected cells. Most individuals thus survive without getting sick but the bacteria remain in the granuloma which causes latent infection of pulmonary TB.8

Macrophages initiate MTB phagocytosis and regulate immune responses mediated by proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, and IL-18. The main regulator, and an anti-inflammatory cytokine, in pulmonary TB infection is IL-10.9 The role of cytokines produced by Th1/Th2 lymphocytes is complex due to the action of proinflammatory and anti-inflammatory cytokines. Several aspects of this complex interaction have been extensively studied.9

TNF-α plays a role in granuloma formation and maintenance by limiting the growth of MTB in macrophages and preventing granuloma necrosis. TNF-α is essential for the body's defense against pulmonary TB infection; but decreased or increased TNF-α levels can cause unwanted immunopathological responses. It also has immunoregulatory properties and initiates a proinflammatory response in pulmonary TB infection.10

TNF-α also inhibits the growth of intracellular MTB bacterial infection and induces apoptosis of infected cells, facilitating the activity of the adaptive immune response. It plays a dominant role in maintaining the dormant status of MTB infection in humans.11

In the early stages of pulmonary TB infection, TNF-α levels increase resulting in infection control and MTB elimination. TNF-α prevents reactivation of TB, by modulating the pulmonary expression of specific immunological factors and limiting the pathological response of the host. During aerosol transmission of MTB, the first cells exposed to the pathogen are alveolar macrophages and pulmonary dendritic cells, which activate and phagocytose MTB, producing TNF-α and IL-12 cytokines that in turn activate host antimicrobial mechanisms and induce IL-10 to inhibit the mechanism.

The genetic variation of cytokines and their role in the pathogenesis of TB has been extensively studied, with several cytokine gene polymorphisms influencing gene transcription leading to inter-individual variation in cytokine production. These polymorphisms affect cytokine levels and Th1/Th2 balance, which in turn alter the susceptibility and severity of pulmonary TB disease. This happens in some ethnic populations but not in others.9 Environmental factors and genetic variability are also thought to be responsible for pulmonary TB infection.9

The research on the identification of host genetic factors that are susceptible to pulmonary TB contributes greatly to global TB control.12 This study thus examined the predictive ability of genetic data by identifying host genetic factors that are susceptible to pulmonary TB, by analyzing the relationship between TNF-α and IL-10 gene polymorphisms and susceptibility to pulmonary TB infection in the Minang Kabau ethnic group.

Factors Related To The Incidence Of Pulmonary Tb

Pulmonary TB, caused by MTB, is a chronic granulomatous disease transmitted by infected people through aerosols. The WHO reports pulmonary TB as one of the 10 leading causes of death globally in 2018. It is also the leading cause of death of HIV-infected people due to antibiotic resistance. In 2018, an estimated 10 (9.0–11.1) million new cases of pulmonary TB were reported globally, affecting 5.7 million men, 3.2 million women, and 1.1 million children.5

Eight countries that accounted for 66% of new cases of pulmonary TB include India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. The number of active pulmonary TB patients in 2015 exceeded 20 million worldwide, with 9.6 million newly diagnosed pulmonary TB cases and 1.5 million death. The incidence of pulmonary TB disease is increasing, particularly in developing countries.4–8, 10–15 Indonesia is ranked fifth out of 22 countries with a TB burden worldwide. The incidence rate of pulmonary TB in Indonesia in 2017 was 319 cases per 100,000 population with a death rate of 40 cases per 100,000 population.5 The prevalence of pulmonary TB in West Sumatra in 2014 was 0.11% and increased to 0.15% in 2016 with a CDR reaching 42.8% in 2018.6

MTB is an obligate aerobic intracellular bacterium, which is rod-shaped (bacilli), acid-fast, nonmotile, does not form spores and capsules, grows at 37°C with slow infecting period of 2–60 days, and infects all parts of the body, primarily the lungs. Its cell wall is composed of virulence determinants, such as lipoarabinomannan, mycolic-acid–containing glycolipids, sulfolipids, and 19-kDa lipoproteins that play a role in the immunopathogenesis of pulmonary TB infection. One of the characteristic virulent features of MTB is its high lipid content in the cell envelope, occupying 40% by weight of the total cell envelope and thereby making it highly hydrophobic.2

The clinical symptoms of TB can be grouped into either general or specific based on the organ involved. The clinical picture is not always typical, making clinical diagnosis difficult. The common symptoms include a persistent cough for more than 3 weeks (possibly accompanied by blood), a fever that is not too high, lasts for a long time, comes and goes, usually felt at night with night sweats, decreased appetite and weight, malaise, and weakness.4 The specific symptoms of TB depend on the infected organ. For instance, if there is a blockage of a part of the bronchus due to enlarged lymph glands, it can cause weak breath sounds, shortness of breath, and pleural effusion accompanied by complaints of chest pain; if it hits the bones, symptoms of bone infection occur; and if it affects the brain, it can cause meningitis with symptoms of high fever, decreased consciousness and seizures.6

The diagnosis of a person suspected of being infected with TB is established based on clinical symptoms, chest x-ray, and the discovery of TB germs (BTA) through microscopic sputum examination with Ziehl Neelsen staining by collecting three sputum specimens in two consecutive visits in the form of sputum at any time in the morning (SPS). The gold standard for the diagnosis is the MTB culture on the Lowenstein–Jensen medium. However, the diagnosis of pulmonary TB should not be based solely on a chest x-ray examination as it may not always give a characteristic picture and can lead to overdiagnosis.

The examination method widely used in TB-endemic countries is microscopic examination. But it has low sensitivity and cannot determine drug sensitivity, and the quality may vary based on the technician's skill. This can lead to patients receiving inappropriate treatment, increasing the possibility of developing drug-resistant TB strains and resistance.6

The WHO has recommended the use of Xpert MTB/RIF as an initial examination for the diagnosis of MDR TB and TB in HIV patients since 2010. Xpert MTB/RIF is a molecular examination with nucleic acid amplification technology (NAAT) that can diagnose TB and resistance to rifampicin in time of 2 h, reducing the overall incidence of TB.14

Role of tumor necrosis factor-α in pulmonary TB infection

TNF-α is a cytokine that plays an important role in preventing pulmonary TB infection and maintaining latent TB status. It is secreted by Th1 cells and other cells including macrophages, monocytes, neutrophils, effector T lymphocytes (T cells), and natural killer (NK) cells. Studies have shown that TNF-α is crucial in macrophage activation, recruitment to the site of infection, and granuloma formation which helps control TB disease.15 Further, TNF-α limits the growth of intracellular MTB infection by inducing apoptosis in infected cells, which is an important event in TB immunopathogenesis, as it not only contributes to the direct bactericidal repertoire of the innate immune system but also facilitates the adaptive immune system.16

TNF-α's function is balanced by IL-10, which is also induced by MTB components. The balance between TNF-α and IL-10 greatly determines the level of resistance and infection outcome.5 The importance of TNF-α in the control of TB in humans was realized when rheumatoid arthritis patients infected with latent TB received anti-TNF therapy, which caused reactivation of TB. Several studies and observations in human and mouse models prove the importance of TNF-α in preventing reactivation of latent TB.

Role of interleukin-10 in pulmonary TB infection

Cytokine IL-10 is produced by macrophages, T cells, and B cells. It is a major regulator of the innate immune response and adaptive immune response. It directly affects the (CD)4+ T cells by inhibiting the expression of IL-2, TNF-α, IL-5, and chemokine receptor (CXCR)4. T-cell activation due to IL-10 triggers nonresponsiveness or anergy that cannot be countered by IL-2 stimulation. The IL-10 cytokine also stimulates B cells by increasing the expression of MHC class II molecules and increasing their ability to survive. IL-10 inhibits phagocytosis, as an innate immune response to MTB, and microbial killing by limiting the production of ROS and RNS. Inhibition of phagosome maturation increases MTB survival and growth. Several studies have shown that Th1 inhibitory effects reduce INF-α secretion and support the growth of MTB bacteria, which further prevents macrophage activation and dendritic cell function.7

IL-10 inhibits macrophage killing, dendritic cell uptake, processing, and presentation, and DC migration from the site of infection to the lymph nodes to promote Th0 to Th1 cell polarization. It also plays a role in the suppression of chemokines involved in Th1 migration from lymph nodes to the lungs. IL-10 has been reported to modulate both innate and adaptive immune responses, potentially creating a favorable environment for microbial persistence, intracellular pathogens, and chronic infection. It has been demonstrated in vivo that the production of IL-10 can reactivate chronic pulmonary TB, as the cytokine has been shown to reduce immunity.16

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The low level of IL-10 produced by activated macrophages is an antimicrobial response in controlling MTB growth and preventing lung damage. Thus, modulation of IL-10 levels during TB therapy is thought to shorten the duration of treatment and accelerate bacterial clearance. The absence of IL-10 enhances the immune response and clearance of MTB in the early stages of infection.2 The occurrence of TB in certain races, ethnicities, and families indicates a genetic predisposition to TB susceptibility. This is associated with the complex interaction of MTB with environmental and host genetic factors, which explains why some people are more or less susceptible to TB infection.13

Host genetics strongly influences TB susceptibility, as shown by several whole-genome linkage and genome-wide association studies (GWAS), which identified several genes with TB infection. However, assessing the contribution and functional consequences of certain genetic variations (polymorphisms) in the human genome to become susceptible or resistant hosts to TB is still a challenge in population genetics research and further research is needed to answer many unanswered questions.17

TNF-gene polymorphism in TB infection

Polymorphisms in the promoter region of the TNF gene are thought to affect transcriptional activity related to TB susceptibility. The polymorphisms of the TNF-238 G/A rs361525 gene have been shown to increase the risk of active TB as it substantially affects the levels of TNF-α production. TNF-α levels were increased in patients with active pulmonary TB compared to controls.17

The study by Deveci et al. (2005) proved that the incidence of TNF-238A allele was significantly higher in the TB group than in the non-TB group ($P < 0.01$), based on the allele frequency analysis.

The presence of the -238A allele was associated with susceptibility to TB disease incidence and severity ($P = 0.000002$; OR = 0.15; IC = 0.06–0.36).13

IL-10 gene polymorphism in TB infection

A previous study on the IL-10-1082 G/A polymorphism compared TB patients with healthy controls. A meta-analysis of the Caucasian, African, and Asian populations showed that the IL-10-1082 G/A (rs 1800896) polymorphism was not associated with TB susceptibility in the Asian and African populations, but there was a significant relationship in the Caucasian population. Another study1 conducted in Pakistan showed that the frequency of occurrence of the genotypes of IL-10-1082 G/A (rs 1800896) and IL-10-1082 A/A did not differ between TB patients and healthy groups.1

However, a study in Italian and Cambodian populations found a significant association between IL-10-1082 G/A polymorphism (rs 1800896) and pulmonary TB susceptibility. These observations may reflect the presence of ethnically specific genetic variation and suggest that a distant promoter element is involved. Single nucleotide polymorphisms (SNPs) in cytokine genes can alter the levels and functions of secreted cytokines, which may influence the immune response to TB infection.14 Research by GWAS showed an association between the IL-10-1082 G/A gene SNP (rs 1800896) and susceptibility to TB infection. Another study showed that IL-10 levels are increased in patients with active pulmonary TB compared to controls.17

Three types of IL-10 gene polymorphisms namely IL-10-1082G/A, -592A/C, and -819C/T play a role in TB susceptibility. Research reported that the IL-10-1082 allele A causes increased resistance to TB,2 while the IL-10-1082 allele G increases the risk of TB by 2.1 times.

These gene polymorphisms affect the Th1/Th2 balance thereby increasing the risk of TB. A meta-analysis study reported that the IL-10-1082G/A gene polymorphism increased the risk of TB in European and American populations, but this was not proven in Asian and African populations. The prevalence of IL-10-1082G/A gene polymorphisms was greater in TB patients while IL-10-819 C/T and -592C/A were greater in asthmatic patients.10

Polymorphisms Of Tnf-A And Il-10 Gene With Pulmonary Tb Susceptibility

Figure 1 shows how the polymorphisms of TNF-α and IL-10 genes affect pulmonary TB susceptibility. The immunopathogenesis of pulmonary TB infection begins with the MTB antigen (Ag) inhaled through droplets. The activated macrophages—the main cells involved in the nonspecific immune response to MTB that plays an important role in initiating specific immunity—will recognize Ag MTB through their surface receptors and the binding between Ag MTB and receptors will stimulate immune and inflammatory responses. The activated antigen-presenting cells (APC) will process Ag MTB into peptides, which will be bound by MHC class II to the cell surface to activate nave T-helper cells.

The conversion of Ag MTB by phagocytic cells triggers the activation and production of cytokines and chemokines causing an increase in the production of IL-12, which stimulates the differentiation from T0 (nave T) cells to Th1 cells.

Th1 cells produce proinflammatory cytokines IFN-γ (interferon-γ), TNF, and IL-2 and activate macrophage antimicrobial function by recruiting monocytes and granulocytes to limit MTB growth.

The MTB antigen activates Treg cells to produce large amounts of IL-10 cytokines and transforms growth factor-β (TGF-β). Unlike Th1 and Th2 cells, the induced Treg cells show immunosuppressive activity.

The activation of these Treg cells further stimulates differentiation from T0 cells (T nave) to Th2 cells. These Th2 cells will bind MTB Ag peptides with MHC class II resulting in the production of IL-4, IL-13, and IL-10 cytokines which in turn induce an anti-inflammatory immune response when the infection is progressing. MTB bacteria induce the expansion of Treg cells thus allowing the bacteria to replicate continuously in the lungs. The increased levels of IL-10 and TGF-β cytokines inhibit the activity of proinflammatory cytokines thereby causing downregulation of the adaptive immune response that aids the bacterial infection to avoid the immune system.

The presence of TNF gene polymorphism at the promoter region is thought to affect transcriptional activity related to TB susceptibility. TNF-238 G/A gene polymorphism (rs 361525) has been shown to increase the risk of active TB because it substantially affects levels of TNF-α production. The presence of SNPs in the IL-10-1082 G/A cytokine gene (rs 1800896) can alter the levels and functions of the secreted IL-10 cytokines, thereby influencing the immune response to susceptibility of the TB infection.

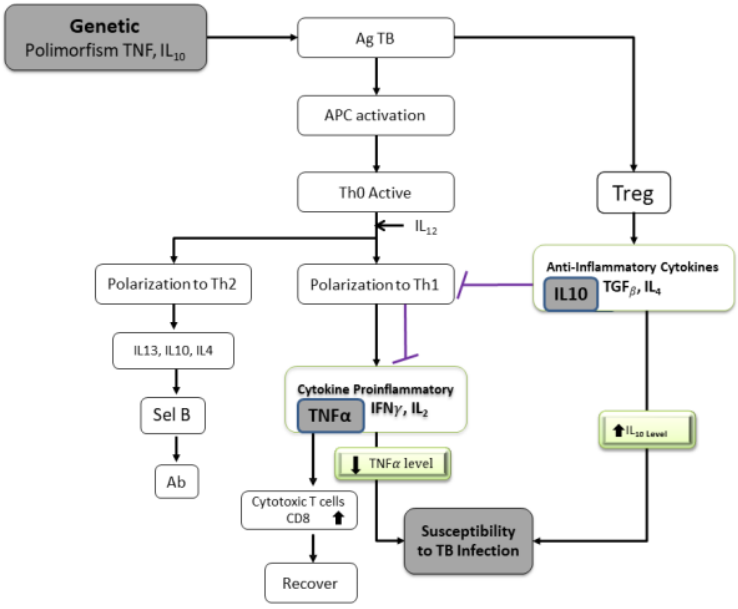

FIG 1. Polymorphism of tumor necrosis factor-α and IL-10 gene with pulmonary TB susceptibility. APC, antigen-presenting cells; IL, interleukin; TB, tuberculosis; TGF, transforming growth factor; TNF, tumor necrosis factor.

The acid-fast bacillus MTB has special properties with resistance to acid in staining (acid-fast bacilli) as the bacilli have lipoid cells. The primary source of pulmonary TB transmission is pulmonary TB patients with positive acid-resistant bacteria (BTA) which spreads in the form of droplet nuclei when the patient coughs or sneezes. The phlegm lasts for several hours in dark and humid conditions; but direct sunlight can kill this MTB. The risk of contracting MTB is influenced by the level of exposure to sputum and the host's immune system. In Indonesia, the proportion of the population at risk of developing pulmonary TB every year is reported by the ARTI index. The immunopathogenesis of pulmonary TB infection starts with the inhalation of MTB droplets which are then phagocytosed by alveolar macrophages. Some of the bacteria are immediately eliminated preventing an individual from becoming infected.

However, some MTB are not immediately phagocytosed by alveolar macrophages, as the immune response to MTB is not fully effective resulting in the formation of a stable primary complex.

CONCLUSION

Polymorphisms of cytokine genes have been investigated and have been shown to affect gene transcription, which causes inter-individual variations that affect levels of cytokine production. These polymorphisms are involved in the susceptibility, severity, and clinical outcome of several diseases, particularly for pulmonary TB disease in some ethnic populations, but not in others.

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