Review

Advances in Studies on Prevalence and Interaction Mechanism of Acquired Immunodeficiency Syndrome and Tuberculosis Coinfection

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Abstract

Human immunodeficiency virus (HIV) and tuberculosis (TB) coinfection is a serious public health problem. HIV and TB promote each other, accelerating development of HIV to acquired immunodeficiency syndrome (AIDS) and heightening TB mortality. Determining interaction mechanism between HIV and *Mycobacterium tuberculosis* can lead to development of effective treatments. This study summarizes prevalence status of AIDS and TB coinfection and research advances concerning their interaction mechanism.

Acquired immunodeficiency syndrome (AIDS) is a disease characterized by retrovirus injury of CD4+ cells and causes incompetent cellular immune function. Tuberculosis (TB) is chronic infectious disease caused by *Mycobacterium tuberculosis* (Mtb) infection. Mtb invades various organs of the body and mainly infects lungs. TB is also called phthisis and white plague, which was an ancient infectious disease. TB is the common and early occurring opportunistic infection (occupies 20% to 50%) of AIDS. Morbidity of AIDS-infected patient with TB is 30 to 50 times that of normal individuals. Patient conditions may rapidly deteriorate because of coinfection of AIDS and TB and mutual promotion of these diseases.

Epidemic Status of Coinfection of AIDS and TB

Epidemic Status of TB

In 1990, the number of newly infected TB patients reached 6.6 million globally. In 2000, the number increased to 8.3 million rose to 9.27 million in 2007. TB patients mainly came from Asia (55%) and Africa (31%), followed by the Middle East (6%), Europe (5%), and America (3%). The top five countries affected by TB include India (2 million cases), China (1.3 million cases), Indonesia (530,000 cases),

Nigeria (460,000 cases), and South Africa (460,000 cases)^[1]. According to statistics of the World Health Organization (WHO), existing TB patients approximately reach 20 million. Approximately 3.8 million TB patients die, and 8 million individuals are infected per year^[2].

China is one of the 22 countries that are severely infected by TB and features the second highest number of patients in the world after India^[2]. From 2001 to 2010, notification cases of TB were constantly the highest among infectious diseases in China. In reference to fifth epidemiological investigation in 2010, morbidity of active TB totals 392/100,000 population, whereas morbidity of infectious TB reaches 100/100,000 population. These findings indicate that an average of 400 active TB patients exist out of 100,000 people in China. A quarter of these patients are infectious. Accordingly, in 2010, the estimated total number of active TB in China totaled 5.23 million, and infectious TB accounted for 1.34 million cases^[3].

Epidemic Status of AIDS

In 1982, the American Centers for Disease Control and Prevention (CDC) officially named the disease as "Acquired Immune Deficiency Syndrome". In 1983, the first human immunodeficiency virus (HIV) was successfully isolated and identified as pathogen of AIDS.

The WHO statistics indicated that in 2009, the total number of HIV/AIDS infections in the world reached 39.5 million, almost reaching the growth of 15,000 cases per day^[4]. Up to 95% of these cases came from developing countries. SubSaharan Africa, South Asia, and Southeast Asia will become the main endemic areas. Thailand, India, and Myanmar showed the highest prevalence of HIV infection in South Asia, whereas Cambodia and Vietnam featured the fastest growing rate in recent years^[5]. Some reports showed that HIV spreads at a rapid rate in certain areas; when effective treatment measures are undertaken, accumulative number of cases reach four times that of today^[6]. Among HIV(+) patients, less than 5% become AIDS-infected patients within two years. Up to 20% to 25% become AIDS-infected patients within six years, and 50% turn into AIDS-infected patients within 10 years.

Epidemic Status of HIV/Mtb Coinfection

When HIV(+) individuals are infected by Mtb, then morbidity of TB is 30 times higher compared with the rate of HIV(-) individuals. This condition mainly affects people aged 25 to 44; this age group is also a high-risk group of HIV infection. In 2007, 9.27 million cases of TB infection were reported, and 1.37 million (15%) cases were HIV-positive. Up to 79% of cases were in obtained from Africa, and another 11% were discovered in Southeast Asia^[1].

In developing countries, 25% to 65% of HIV/AIDS cases present TB. In China, current situations of AIDS and TB are severe. In reference to document^[7], among 482 AIDS-infected patients in six regions of this country, TB accounts for 15.9%, whereas the rate for Shanghai reaches 45.4%, Xinjiang 28.3%, and that of Yunnan is 16.7%. TB patients also feature high HIV infection rate. Statistical results of 15 developing countries displayed 17%–49% and 44%–77% HIV infection rates of patients with TB and those with extra pulmonary TB, respectively^[8]. HIV/Mtb coinfection promotes both diseases. This condition causes difficulties in controlling TB and AIDS infection. Globally, 9% of new TB-infected cases are caused by HIV infection^[9]. In sub-Saharan areas, 31% of new TB-infected cases are caused by HIV^[10].

HIV/Mtb coinfection drew extensive attention among various countries in the world. Global HIV/Mtb coinfection cases increased at a rate of 10% per year since 1990. Up to 70% of patients originate from sub-Saharan Africa and Western Pacific areas, whereas the rate of coinfection in Africa areas exceeds 80%^{[11][12]}. Multidrug resistance was also

observed with HIV/Mtb coinfection^[13].

Prevalence of HIV causes high TB mortality. In accordance to WHO statistics in 2009, the number of AIDS-related deaths reached 1.8 million, a quarter of which was caused by TB. In 2000, 11% of AIDS-infected patients died of TB. To date, at least 14 million patients present HIV/Mtb co-infection. As the most common opportunistic infectious disease, TB is the most common cause of death in AIDS patients^{[14][15]}.

Interaction of AIDS and TB

HIV/AIDS and Mtb spread rapidly in the world, especially in developing countries. HIV invades and destroys the human immune system, increasing susceptibility of the body to opportunistic infections. Mtb is the most common opportunistic infectious pathogen. HIV and TB interact with each other. Globally, 30% of HIV deaths results from Mtb infection^[2]. Some studies reported that high mortality after HIV and Mtb coinfection possibly results from activation of innate and adaptive immunity of organisms by Mtb, generation of cytokines, and intracellular signal transduction that induces HIV replication. HIV replication leads to increased viral load, large destruction of CD⁺ T lymphocytes, and high mortality rate of coinfection^[16].

Effects of HIV to Mtb Infection

Risk of HIV TB infection increases by 20 times from unapparent infection to active TB^[17]. HIV(-) TB patients feature 10% chance of developing active TB in their lifetime, whereas HIV(+) patients possess 10% chance of developing active TB in just one year and 60% chance in their lifetime. HIV infection is the most important risk factor of Mtb infection; it can lead to TB endogenous recrudescence, exogenous reinfection, and primary infection. HIV is a retrovirus characterized by reverse transcription replication in T4 cells, damaging CD4⁺ cells. Damage mechanism is as follows: (1) when HIV enters the human body, it selectively infects T4 lymphocytes, ruptures cell, and causes progressive decrease in T4 lymphocytes. Human anti-TB is mainly mediated by T lymphocytes and macrophages (cytoimmunologic monitoring plays a leading role). Therefore, ability of macrophages to inhibit Mtb and form granuloma decreases. 2) With progression of AIDS, antibody-dependent cytotoxicity, which is mediated by gp120+ antigen complex for HIV outer membrane, can also

impair CD4+ cells and decrease its functions and number. 3) Studies showed that HIV affects generation of interleukin (IL)-2 and reduces interferon gamma (IFN- γ). Thus, cell resistance to Mtb decreases, considering the ruptured balance between the body and Mtb. 4) HIV damages bone marrow stem cells, inhibits formation of CD4 cells, and thus weakens the immune system^[18]; 5) Secretion of Th2 cytokines increases in plasma of HIV-infected patients. Th2 cytokines can inhibit immune function, inducing susceptibility of the body to Mtb. 6) Finally, deletion of Mtb-specific CD4+ cells is a key factor for susceptibility to Mtb after HIV infection^[19].

Effect of Mtb to HIV Infection

In 1996, the WHO CDC in the United States considered TB and extra pulmonary TB as “directional disease” for HIV(+) to become AIDS^[20]. Mtb is first engulfed by macrophages during Mtb invasion in the human body. Macrophages act as antigens that regulate and activate T cells (mainly including CD4+ T and CD8+ T cells, of which CD4+ T cells are the most important immune cells), secreting a series of cytokines to activate macrophages. Thus, specific immune responses to Mtb are generated. Any abnormality occurring at any step during this process causes abnormal immune responses.

Host immune response to Mtb can exacerbate HIV replication and infection of the body. Related mechanisms are as follows: (1) Mtb mainly attacks CD4+ T cells, improving expression of chemokine receptor CXCR4 on peripheral blood CD4+ T lymphocytes. At the same time, Mtb infection activates T lymphocytes in the body. Cytokines released by lymphocytes significantly increase transcriptional quantity of HIV provirus. Mtb infection increase by 2.7 times monocyte chemoattractant protein-1 (MCP-1), which is secreted by monocytes and macrophages. MCP-1 activates HIV transcription, whereas Tat protein, a HIV transcript, enables MCP-1 expression. In this manner, MCP-1 and HIV promote each other, increasing HIV transcription quantity in TB infection areas and deteriorating diseases; (2) IFN- γ , IL-2, IL-2, and tumor necrosis factor (TNF)- α is released after Mtb infection. Level of TNF- α in blood of HIV/TB patients is 31 times than those of simple HIV infectors^[21]. These factors can stimulate repeat sequence of 5' long terminal of HIV genome to speed up HIV replication^[3], accelerate course of AIDS, and reduce survival rate of HIV-infected patients^[22]; (3) The main component of Mtb cell wall, lipoarabinomannan, induces HIV replication.

Mtb infection promotes HIV penetration and accelerates replication^[23]; (4) Mtb itself and pure protein derivatives induce HIV expression in monocytes and rapidly increase P24 content in the body^[23]; (5) Mtb enhances susceptibility of HIV to CD4+ T cells through Toll-like receptor-2-mediated pathway^[24]; (6) Lastly, Mtb infection and bacillus Calmette–Guérin vaccination may also be an important factor during HIV infection^[24].

Perspective

Emergence and prevalence of AIDS enable resurgence of TB. AIDS and TB promote each other, accelerate development of HIV into AIDS, and increase mortality rate of TB. To date, no effective prevention and treatment measures address HIV/Mtb coinfection. The interaction between HIV and MTB should first be clarified to determine effective therapeutic measures. To improve survival rate and quality of life of patients, we should strengthen collaboration, timely identify HIV and Mtb patients using existing technology, and actively prevent and treat these diseases.

Declarations

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No.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

C Meng and N Li made the literature analysis and wrote, discussed and revised the manuscript of this review. ZX Tong, HX Yan and SX Min critically analyzed and corrected the manuscript. All authors read and approved the final manuscript.

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