──────Original Article──────

MECHANISMS INVOLVED IN THE EXTENSION OF PULMONARY *MYCOBACTERIUM AVIUM* INFECTION FROM THE PULMONARY FOCUS TO THE REGIONAL LYMPH NODES

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Abstract   [Purpose] This study was designed to evaluate the mechanism of *Mycobacterium avium* extension in lung infection. [Study design] Retrospective study. [Participants] A 42-year-old man with acquired immune deficiency syndrome and immune reconstitution inflammatory syndrome. The patient developed mediastinal lymphadenopathy and a peripheral lesion in the right upper lobe within 2 weeks of starting highly active antiretroviral therapy. [Methods] Pulmonary tissue and lymph nodes were dissected under thoracoscopy and evaluated pathologically and immunohistochemically. [Results] Pulmonary pathologic examination revealed extensive granuloma formation throughout the acini. Mycobacterial antigens were found in the macrophages in the alveoli and in the alveolar septa. Some macrophages including mycobacterial antigens were surrounded by lymphatic endothelial cells in the interstitium. In addition, a proliferative granulomatous lesion was found under the intact epithelial layer of a bronchiole. Pathological examination of the lymph nodes revealed aggregated proliferative granulomas with few mycobacteria. Genetically closely related *M. avium* strains were isolated from both tissues. [Conclusions] This study showed the mechanism involved in the progression of pulmonary *M. avium* infection from the pulmonary focus to the regional lymph nodes via the lymphatic vessels.
Key words: Extension mechanism, Immune reconstitution inflammatory syndrome, *Mycobacterium avium*

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MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS: CURRENT STATUS AND FUTURE PROSPECTS

Wing-Wai YEW

Abstract   Resistance in *Mycobacterium tuberculosis* arises from man-made selection of genetic mutants that result from spontaneous chromosomal alterations. Thus, drug-resistant tuberculosis (TB) is generally due to inappropriate treatment regimen, poor drug quality, erratic drug supply and poor patient adherence to treatment, reflecting failure in the implementation of an effective TB control programme. Multidrug-resistant TB (MDR-TB) usually denotes bacillary resistance to at least isoniazid and rifampicin. Proper implementation of the directly observed treatment, short-course (DOTS) strategy should achieve a high cure rate for disease and curtail the development of drug resistance. Innovations in reinforcement of this strategy should further facilitate its delivery and enhance its effectiveness. However, established MDR-TB is notoriously difficult to treat, and necessitates the use of alternative specific antituberculosis chemotherapy regimens. These regimens comprise combination use of second-line antituberculosis drugs, that are generally more costly and toxic, and have to be given for longer durations. The fluoroquinolones, better tolerated by patients, have a pivotal role in MDR-TB treatment. Optimal delivery of these treatment regimens mandates a programmatic basis which is now included under the Stop-TB Drug-Resistance Programme(s). The key components embrace political commitment, quality-assured drug susceptibility testing, reliable supply of quality drugs, delivery of chemotherapy under directly observed settings, and a sound recording and reporting system to monitor the individual treatment outcome of patient and overall performance of the TB control programme. Adjunctive surgery in selected MDR-TB patients help to improve their treatment success. Further exploration is required regarding the use of immunotherapy. The recent emergence of extensively drug-resistant TB (XDR-TB), representing MDR-TB with additional bacillary resistance to fluoroquinlones and one or more of the second-line injectable drugs —kanamycin, amikacin and capreomycin, threatens the global control of TB. Given the escalating size of the problem of MDR-TB and XDR-TB worldwide, gigantic instillation of resources is required for control of this formidable challenge, largely through more accurate and rapid drug susceptibility testing (especially for rifampicin and fluoroquinolone), regular drug-resistance surveillance, development of new antituberculosis drugs and other therapeutic modalities, intensive infection control, especially in HIV care settings, as well as strengthening of currently functioning DOTS and Drug-Resistance Programmes.

Key words : Multidrug-resistant tuberculosis (MDR-TB), Extensively drug-resistance tuberculosis (XDR-TB), Management

THE CONTRIBUTION OF HOST GENETICS TO TUBERCULOSIS PATHOGENESIS

Erwin SCHURR

Abstract   Assessment of the contribution of host genetics to human tuberculosis is a long-standing research challenge. Evidence of genetic factors has come primarily from twin studies and risks to first-degree relatives of cases. In addition, inferences of strong genetic influences have come from anecdotal accounts of socially prominent families, population variation in TB incidence and susceptibility to infection, and secular changes in TB severity, incidence and mortality inferred from historical information of contact between different populations, as well as accidental inoculation of vaccinees with *M. tuberculosis*.

Recently, a major tuberculosis susceptibility locus has been mapped to the long arm of human chromosome. A number of host genetic factors have been directly implicated in tuberculosis susceptibility but strong genetic effects on tuberculosis risk have been difficult to detect both by candidate gene and genome-wide association studies. The reason for our current inability to trace strong genetic effects is unknown. However, a number of possible explanations are supported by direct experimental data. For example, it has been shown that host genetic control of susceptibility is limited to specific host *M. tuberculosis* strain combinations. In addition, it is known that proper inclusion of gene environment interactions is of critical importance for the detection of strong host genetic effects on tuberculosis susceptibility.

By contrast, few genetic studies stratify on *M. tuberculosis* or try to model gene-environment interactions. Until now, most of the human genetics studies in tuberculosis have focused on the identification of genetic variants that impact on progression from infection to disease. There are few studies that aim at the identification of genes that impact on resistance to infection with *M. tuberculosis* or genes that control the extent of anti-mycobacterial immunity. Yet, estimates of heritability for these quantitative traits provide clear evidence for an important role of host genetics in anti-mycobacterial immunity.

Recent work involving scientists from South Africa, France and Canada has focused on the study of innate resistance to infection with *M. tuberculosis*. Employing the tuberculin skin test as a tool to evaluate resistance to infection, a major locus (*TST1*) on chromosomal region 11p14 was identified that T-cell independent resistance to *M. tuberculosis*. In addition, a second major locus (*TST2*), on chromosomal region 5p15 was identified that controls the intensity of T-cell mediated delayed type hypersensitivity (DTH) to tuberculin.

These results pave the way for the understanding of the molecular mechanisms involved in resistance to *M. tuberculosis* infection in endemic areas (*TST1*), and for the identification of critical regulators of T-cell dependent DTH to tuberculin (*TST2*). The finding of a strong host genetic control of anti-mycobacterial immunity raises the questions to what extent host genetics will be a barrier to the development of a universally efficacious tuberculosis vaccine. In fact, epidemiological studies in highly endemic areas and experiments in animal models suggest a strong contribution of host genetic factors to vaccine efficacy making the identification of the corresponding genes one of the new frontiers of mycobacterial research.

CLINICAL USE OF RIFABUTIN, A RIFAMYCIN-CLASS ANTIBIOTIC, FOR THE TREATMENT OF TUBERCULOSIS

(A supplement to the 2008 revision of "Standards for tuberculosis care")

August, 2008

The Treatment Committee of the Japanese Society for Tuberculosis

The Treatment Committee of the Japanese Society for Tuberculosis published statements on the "Standards for tuberculosis care" in April 2008. Therein we referred to rifampicin as follows; "Use of rifampicin requires attention because of the interactions with a number of other drugs. Particularly for HIV-infected patients who need antiviral drugs, the replacement of rifampicin by rifabutin should be considered". Rifabutin, belonging to rifamycin-class antibiotics like rifampicin, causes less significant drug-drug interactions than rifampicin, and can be used in combination with antiviral drugs mentioned above. In July 2008, rifabutin was approved as antituberculous drug, and is expected to be added to the drug price listing in the near future*. Therefore, to the published opinions, we add new statements concerning the use of rifabutin for the treatment of tuberculosis.

*Added to the list in September 2008.

[Recommended cases for use of rifabutin]

For the treatment of tuberculosis, rifampicin is used in patients who are infected with rifampicin-sensitive strains and have no trouble in using rifampicin; however, the substitution of rifabutin for rifampicin is recommended in the following cases;

(1) In cases where the use of rifampicin is limited due to drug-drug interactions, especially when anti-HIV drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors are administered.

(2) In cases where rifampicin cannot be used because of adverse effects.

[Dosage and administration of rifabutin]

Rifabutin, 5 mg/kg in body weight/day, maximum 300 mg/day, once daily.

The dosage of rifabutin can be increased up to the maximum daily dose of 450 mg in cases where decreased rifabutin serum levels are expected due to anti-HIV drugs such as efavirenz, and in other cases if necessary.

In non-HIV-infected patients, rifabutin can be used for intermittent treatment with a regimen of twice or three times a week, with the same dosage as daily administration.

[Important points for use of rifabutin]

(1) Rifabutin causes drug interactions due to induction of hepatic enzyme though less significantly than rifampicin.

(2) Rifabutin and rifampicin have the common adverse effects such as hepatic dysfunction, and discolored body fluid; therefore, close observation is necessary when rifabutin substitutes for rifampicin because of adverse effects.

(3) Rifampicin-resistant strains of *Mycobacterium tuberculosis* are also resistant to rifabutin in most cases. Concerning the use of rifabutin in multidrug-resistant strains, we need more cases to assess involving drug sensitivity assay methods.

[References]

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