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Mycobacterium Tuberculosis

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Abstract

Tuberculosis (TB) is a potentially fatal contagious disease that can affect almost any part of the body but is mainly an infection of the lungs. It is caused by a bacterial microorganism, the *tubercle bacillus* or *Mycobacterium tuberculosis*. Although TB can be treated, cured, and can be prevented if persons at risk take certain drugs, scientists have never come close to wiping it out. Diagnosis still depends largely on sputum microscopy, which is unsuitable for a large number of patients. The efficacy of the BCG vaccine is limited. Major obstacle in the cure and prevention of tuberculosis is posed by the latent or persistent *M. tuberculosis* infection. This is due to the fact that most of the currently available drugs are ineffective against latent infection. Scientist are searching for new targets for mycobacterium tuberculosis disease through biological studies (Proteonomics, Bioinformatics) then Synthetic modification in existing drug & study of some naturally existing drug. This review is useful to study the disease tuberculosis, Bacillus Characteristics, Clinical aspect, drug resistance study, treatment and study of new drug target for mycobacterium tuberculosis.

Keywords: Tuberculosis, Mycobacterium.

1. Introduction

Worldwide, tuberculosis (TB) remains the most frequent and important infectious disease causing morbidity and death. One-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB), the etiologic agent of TB. Each year, according to the WHO, eight to ten million new tuberculosis cases are reported worldwide, and two million people die of the disease. Tuberculosis is second only to AIDS as a cause of death from infectious disease in adults. The vast majority of cases (95%) and deaths (98%) occur in poor countries. The AIDS epidemic (twelve million people with TB are co-infected with HIV) and the growing problem of resistance to tuberculosis drugs (half a million new cases of multi-drug resistant TB annually) have further complicated tuberculosis management.[1]

1.1 The disease

Tuberculosis (TB) is a potentially fatal contagious disease that can affect almost any part of the body but is mainly an infection of the lungs. It is caused by a bacterial microorganism, the tubercle bacillus or Mycobacterium tuberculosis. Although TB can be treated, cured, and can be prevented if persons at risk take certain drugs, scientists have never come close to wiping it out. Few diseases have caused so much distressing illness for centuries and claimed so many lives.[2]

Each year, according to the WHO, eight to ten million new tuberculosis cases are reported worldwide, and two million people die of the disease. Tuberculosis is second only to AIDS as a cause of death from infectious disease in adults. The vast majority of cases (95%) and deaths (98%) occur in poor countries. The AIDS epidemic (twelve million people with TB are co-infected with HIV) and the growing problem of resistance to tuberculosis drugs (half a million new cases of multi-drug resistant TB annually) have further complicated tuberculosis management.

1.2 Epidemiology [10-11]

a) Bacillus characteristics

TB is caused by bacilli belonging to the *Mycobacterium tuberculosis*. In the majority of cases, TB is due to Mycobacterium tuberculosis (Koch's bacillus). *M. africanum* may be observed in western Africa (it is often naturally resistant to thioacetazone). In both of these cases, humans are the only reservoir of bacilli.

2. Clinical Aspect [3-4]

2.1 Pulmonary TB

Certain signs of PTB are quite specific: prolonged cough (> 2 weeks), sputum production and chest pain, while others are less so: weight loss, anorexia, fatigue, moderate fever, and night sweats. The most characteristic sign is

haemoptysis (presence of blood in sputum). All these signs are variable, and they evolve in a chronic, insidious manner.

2.2 Differential diagnosis for PTB

Bronchial carcinoma.

Chronic obstructive bronchitis: in tropical zones, this is a frequent complication of successive and poorly treated bronchopulmonary infections.

Pulmonary abscesses from common germs (often oropharyngeal flora [staphylococcus] or a mixed bacterial infection).

Paragonimiasis (pulmonary distomatosis) in certain areas of South-Eastern Asia, western. (The treatment is praziquantel).

Other infectious pneumopathies: chlamydia, mycoplasma, Pneumocystis pneumonia (mainly in immunodeficient patients).

Silicosis, sarcoidosis, berryliosis, melioidosis.

Profound mycosis (cryptococcosis, aspergillosis).

Pulmonary echinococcosis.

2.3 Extrapulmonary (EP)

Starting from an initial pulmonary localisation (primary infection), *M. tuberculosis* can spread to the entire organism during a silent phase, generally at the beginning of the infection. Active TB can therefore develop in many other organs, in particular lymph nodes, meninges, vertebrae, joints, genital organs, and kidneys.

3. TB and HIV [13]

TB is a leading cause of HIV-related morbidity and mortality and is one of the main opportunistic diseases.

4. Resistance to TB

Resistance to anti-TB drugs emerged at almost the time as the discovery of streptomycin. The prevalence of drug resistant (DR) strains has increased since the early 1990s. It has become a major problem in some countries.

4.1 Natural resistance

Natural resistance concerns bacilli that are naturally resistant to an individual TB drug due to spontaneous genetic mutation. Certain mycobacterial species are consistently resistant to individual drugs: *M. africanum* is naturally resistant to thioacetazone, and *M. bovis* is naturally resistant to pyrazinamide.

4.2 Primary resistance

When resistance is found in a patient who has never before received anti-TB treatment, the patient is said to have primary resistance, having been infected by someone harbouring a strain of TB already resistant to TB medication (i.e. from a patient who has secondary resistance.

The most frequent primary resistances affect the most widely distributed drugs, i.e. isoniazid and streptomycin. Increased rates of primary resistance typically occur when secondary drug resistance is already significant and conditions favour TB transmission (overcrowding, poor case-finding or improper patient isolation).

4.3 Secondary resistance

Secondary resistance develops in patients during the course of TB treatment and is entirely manmade. High rates of secondary resistance are often found in countries where treatment regimens are inadequate or suffered economic and social disruption leading to interrupted drug supplies.

Resistance to anti-TB drugs

a) *Initial resistance*

Resistance to one or more anti-TB drugs in a new case. This might be a primary resistance or an undiagnosed secondary resistance.

a) *Multi-drug resistance (MDR)*

A multi-drug-resistant strain is defined as a strain resistant (at least) to isoniazid and rifampicin.

b) *Mono or poly-drug resistance (PDR)*

Resistance to at least isoniazid or rifampicin but not both simultaneously. These patterns of resistance require adapted regimen in order to prevent possible evolution to MDR-TB under standard regimen.

c) *Ultra-resistance (XDR = extensive drug resistance)*

A strain is considered extremely resistant if it is multi-drug resistant and also resistant to at least fluoroquinolones and one second-line injectable drug (kanamycin, amikacin or capreomycin).

d) *Main causes leading to development of resistance*

Use of monotherapy, for whatever reason: inadequate prescriptions, shortages of drugs, self-medication. Resistant bacteria will continue to grow, soon replacing the sensitive bacterial population. From this springs the first absolute rule: never administer monotherapy.

Use of ineffective antibiotic combinations during initial phase: e.g., isoniazid and ethambutol, isoniazid and thioacetazone, or only isoniazid and rifampicin in areas with high primary resistance to isoniazid.

5. Treatment

First-line anti-TB drugs Rifampicin, Rifabutin, Pyrazinamide (Z), Ethambutol (E). Newer drugs like bedaquililine used in treatment of TB.

6. New drug targets for *Mycobacterium tuberculosis* [9]

In spite of the availability of effective chemotherapy and Bacille-Calmette-Guerin (BCG) vaccine, tuberculosis remains a leading infectious killer world-wide. Many factors such as, human immunodeficiency virus (HIV) co-infection, drug resistance, lack of patient compliance with chemotherapy, delay in diagnosis, variable efficacy of BCG vaccine and various other factors contribute to the mortality due to tuberculosis. In spite of the new advances in understanding the biology of *Mycobacterium tuberculosis*, and availability of functional genomics tools, such as microarray and proteomics, in combination with modern

approaches, no new drug has been developed in the past 30 yr.

Therefore, there is an urgent need to identify new drug targets in mycobacteria and eventually, develop new drugs. The release of the complete genome sequence of *M. tuberculosis* has facilitated a more rational, and directional approach to search for new drug targets. In general, gene products involved in mycobacterial metabolism, persistence, transcription, cell wall synthesis and virulence would be possible targets for the development of new drugs. The exploitation of host cell signaling pathways for the benefit of the pathogen is a phenomenon that deserves to be looked into with a new perspective in the current scenario to combat *M. tuberculosis*.

7. Status of current tuberculosis drug therapy [12]

Drugs available for the treatment of tuberculosis can be classified into two categories; first line drugs such as, isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB) *etc*., and second line drugs like para amino salicylate (PAS), kanamycin, cycloserine (CS), ethionamide (ETA), amikacin, capreomycin, thiacetazone, fluoroquinolones *etc*. Current TB therapy, also known as DOTS (directly observed treatment, short-course) consists of an initial phase of treatment with 4 drugs, INH, RIF, PZA and EMB, for 2 months daily, followed by treatment with INH and RIF for another 4 months, three times a week. The targets of these drugs are varied. INH inhibits synthesis of mycolic acid, a cell wall component; PZA targets cell membrane whereas rifampin and streptomycin interferes with the initiation and streptomycin interferes with the initiation of RNA and protein synthesis respectively. EMB blocks biosynthesis of arabinogalactan, a major polysaccharide present in the mycobacterial cell wall and kanamycin and capreomycin, like streptomycin, inhibit protein synthesis through modification of ribosomal structures at the 16S rRNA. Cycloserine prevents the synthesis of peptidoglycan, a constituent of cell wall.

8. Limitations of current drug therapy and need for new drug targets [10]

In the present scenario, due to the emergence of multi drug resistant tuberculosis (MDR-TB) and association between HIV and TB, DOTS is becoming rapidly ineffective in controlling tuberculosis. Recent reports indicate that, areas where there is a high incidence of MDR-TB, DOTS is failing to control the disease. In such circumstances, the second line drugs are prescribed in combination with DOTS. However, this combination of drugs is very expensive, has to be administered for a longer duration and has significant side effects. One major drawback of current TB therapy is that the drugs are administered for at least 6 months.

The length of therapy makes patient compliance difficult, and such patients become potent source of drug-resistant strains. The second major and serious problem of current therapy is that most of the TB drugs available today are ineffective against persistent bacilli, except for RIF and PZA. RIF is active against both actively growing and slow metabolizing non-growing bacilli, whereas PZA is active against semi-dormant non-growing bacilli. However, there are still persistent bacterial populations that are not killed by any of the available TB drugs. Therefore, there is a need to design new drugs that are more active against slowly growing or non-growing persistent bacilli to treat the population at risk of developing active disease through reactivation. Secondly, it is important to achieve a shortened therapy schedule to encourage patient's compliance and to slow down the development of drug resistance in mycobacteria.

Thiolactomycin (TLM) targets two ketoacyl-acyl-carrier protein synthases, KasA and KasB enzymes that belong to the fatty acid synthase type II system involved in the fatty acid and mycolic acid biosynthesis. TLM has also been shown to be active against MDR-TB clinical isolate. Several TLM derivatives have been found to be more potent *in vitro* against fatty acid and mycolic acid biosynthesis. Cerulenin, an inhibitor of fatty acid synthesis, has also been shown to inhibit mycobacterial lipid synthesis and is active against *M. tuberculosis in vitro* with an MIC of 1.5-12.5 mg/ml. Octanesulphonyl acetamide (OSA) has recently been identified as an inhibitor of fatty acid and mycolic acid biosynthesis in mycobacteria. The inhibitor was found to be active against both slow growers such as *M. tuberculosis* and also MDR-TB strains with a MIC of about 6.25-12.5 mg/ml. Interestingly, OSA was found to be less active against fast growers such as *M. smegmatis* and *M. fortuitum*. These reports clearly suggest that several genes of the cell wall synthesis pathway and enzymes involved in fatty acid and mycolic acid synthesis could be good candidates for further drug development.

9. Common anti-tubercular plants from Ayurveda [5-7]

Table 1: A brief description of common anti-tubercular plants from Ayurveda

Sr. No	Botanical/family Name	Ayurvedic name	Part used	Chemical constituents	Other biological activities
1	*Acalypha indica*, Euphorbiaceae	Kuppi	Leaves	Kaempferol, acalyphamide and other amides, quinone, sterols, cyanogenic glycoside	Antibacterial, used in bronchitis, asthma
2	*Adhatoda vasica.* Acanthaceae	Vaasaa	Leaves	Quinazoline alkaloid	Expectorant (used in bronchial asthma)
3	*Allium cepa*, Liliaceae	Palaandu	Bulbs	Volatile oil with sulphurous constituents, including allylpropyldisulphide, sulphur containing compounds, including allicin, alliin, flavonoids; phenolic acids and sterols	Antibiotic, antibacterial, antisclerotic, anticoagulant
4	*Allium sativum*, Liliaceae	Lashuna	Bulbs	Sulphur containing amino acids known as alliin	Antibiotic, bacteriostatic, fungicide, anthelmintic, antithrombic, hypotensive, hypoglycaemic,
5	*Aloe vera*, Liliaceae	Ghritkumaarika	Leaves, gel from leaves	Anthraquinone glycosides, known as aloin	Purgative
6	*Vitex negundo*, Verbenaceae	Nirgundi	Leaves, seeds	Iridoid glycosides, isomeric flavanones and flavonoids	Anti-inflammatory, Analgesic
7	*Trichosanthes dioica*, Cucurbitaceae	Patola	Roots, fruits	Free amino acids, nicotinic acid, riboflavin, vitamin C, thiamine, 5-hydroxytryptamine	Cathartic, febrifuge
8	*Tinospora cordifolia*, Menispermaceae	Guduuchi	Stem, leaves	Alkaloidal constituents, including berberine; bitter principles, including columbin, chasmanthin, palmarin and tinosporon, tinosporic acid and tinosporol	Antipyretic, antiperiodic, anti-inflammatory

9. Conclusion

Major obstacle in the cure and prevention of tuberculosis is posed by the latent or persistent *M. tuberculosis* infection. This is due to the fact that most of the currently available drugs are ineffective against latent infection. This study also useful to face different problems related to tuberculosis such as drug resistance and TB along with other disease (e.g. AIDS).

Scientist are searching for new targets for mycobacterium tuberculosis through biological studies (Proteonomics, Bioinformatics) and Synthetic modification in existing drug & Naturally existing drug i.e. Plant drug extract. [8]

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