Tuberculosis: a tough adversary

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Populärvetenskaplig sammanfattning av Självständigt arbete i biologi VT 2010
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Consumption. Tuberculosis. Wasting disease. Names that many of us have heard but few of us understand. Instead, romanticized images of the 19th century come to mind where promising artists' lives are prematurely snuffed out from a vague wasting condition. Keats, the Brontë sisters and Chopin all died in this manner. Sadly, tuberculosis (tb) is not the stuff of romance novels. 4,900 people die from TB every day making it the world's leading infectious killer. The disease, caused by the bacteria Mycobacterium tuberculosis *(M.t), is found across the globe but has hit hardest in developing countries where risk factors such as poverty, malnutrition and HIV/AIDS are much more prevalent. Anti-tuberculosis drugs have existed since the 1940's and are indeed effective against the disease if used correctly. Unfortunately, improper use of these drugs has led to the development of drug resistant TB, which along with the HIV/AIDS pandemic has greatly complicated efforts to control the disease.*

The CV of TB

Man and tb have coexisted for thousands of years. Evidence of TB has been found in mummified bones from 5000 B.C., in Chinese texts from 4000 B.C., Indian religious texts from 2000 B.C., and both Aristotle and Hippocrates mention a chronic lung disease which is most likely to have been TB. The cause of this mysterious and fatal disease was unknown until 1882 when Robert Koch identified the troublemaking bacterium *Mycobacterium tuberculosis* (*M.t*).

What is *Mycobacterium tuberculosis?*
M.t is the bacterium responsible for causing TB. What makes *M.t* unique is its thick and fatty outer covering, a feature which lends the bacterium the characteristics of a ball of wax. This attribute makes the bacterium particularly hardy to unfriendly environments and is also the basis of its disease-causing capabilities.

What is tuberculosis?
TB is an airborne infectious disease which primarily spreads when an infected individual coughs, sneezes or spits. Only a minute amount of these droplets teeming with bacteria need to be inhaled in order for the infection to spread. Although TB most often affects the lungs, so called pulmonary tb, it is important to note that it is not exclusive to the lungs. TB can spread throughout an individual's body and infect a variety of organs such as the heart, liver and kidneys.

TB symptoms vary from person to person. Some individuals are completely asymptomatic. Classic symptoms of pulmonary TB include a chronic bloody cough, fever, weight loss and night sweats. Non-pulmonary TB often has similar symptoms with the addition of pain and decreased function in the infected organ(s).

What happens during the infection process?
An *M.t* infection can fall into one of two groups. The infection can either be primary, where the individual comes into contact with the bacteria for the first time, or secondary, where the individual develops active tb.

Primary infection
When airborne droplets from an infected individual are inhaled by an uninfected individual, the released bacteria lodge deeply within the lungs. Cells of the immune system recognize the bacteria as foreign and promptly ingest them. Once inside these cells, the bacteria should be broken down and killed. This process, however, is not as straightforward when it comes to *M.t*. While the above can and does happen with *M.t*, more often than not *M.t*s unique outer covering serves as a shield and prevents the bacteria from being broken down. Instead of being killed off, the bacteria survive and replicate within the cell. Eventually the cell becomes so full that it bursts, releasing more bacteria out into the body.

When bacteria are ingested and broken down, the immune system cell presents a fragment of the bacteria on its surface. One can liken it to raising a flag. This signals to other cells of the immune system that there is a foreign invader present and that an infection is in the making. As a result of this signal, a large number of immune system cells rush to the site of infection and, through a complex series of events, completely surround the bacteria-containing cells forming a ball-like capsule within which the infection is restricted and controlled. The environment within the capsule of cells is extremely inhospitable to *M.t*. The bacteria are doused in toxic chemical cocktails in order to stave off the infection and as a result, the center of the cell mass becomes filled with a cheese-like substance consisting of live bacteria, dead bacteria, dead immune cells and dead tissue.

The aforementioned immune response is very effective at controlling the primary infection. Rarely though are the bacteria completely eliminated; instead, the infection is simply kept in check within the cell capsule. Kept within the capsule, the infection is essentially inactive or "sleeping". This is known as a latent TB infection and it is completely asymptomatic. Often times this is where the disease process ends. It is extremely rare for someone to develop TB during the primary infection.

Secondary infection/active disease
In order for the infection to remain latent, the infected individual's immune system must actively retain the bacteria within the encapsulation. As we will soon see, the bacteria that survive the hostile environment within the encapsulation are the seeds of a secondary infection. If an individual's immune response declines, the integrity of the cell capsule declines as well. If and when the capsule bursts, the infection "re-awakens" and the bacteria spread within the individual who quickly develops active tuberculosis. This process is known as a secondary infection. If the capsule bursts within the individual's lungs, the cheese-like substance inside the encapsulation can be coughed up and the infection can spread to others. It is only during a secondary infection that an individual is contagious. If left untreated, a person with active TB will pass the infection on to circa 15 others every year. However, unless coinfected with HIV/AIDS, only five to ten percent of infected individuals actually develop TB.

How do we treat tuberculosis?

M.t's fatty outer layer renders TB very difficult to treat, as an effective drug must be able to bypass the bacteria's shield. There are several anti-TB drugs available on the market and these can be divided into two different categories, namely first-line drugs and second-line drugs. The most effective anti-TB drugs to date are the first-line drugs isoniazid and rifampicin which are often given in combination with other drugs. A treatment regime with first-line drugs takes approximately 6 months. Second-line drugs are used if first-line treatment is unsuccessful or the patient is unable to tolerate one of the given first-line drugs. Treatment with second-line drugs takes between 12 and 24 months. Fluoroquinolones are some of the most effective second-line anti-TB drugs avaliable.

Antibiotic resistance
If the process of treatment and recovery was likened to a road, then antibiotic resistance would be a pot hole on said road. Drug-resistant TB has been found in all countries where TB is prevalent. Drug-resistant TB can be divided into two groups, multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB involves resistance to at least both isoniazid and rifampicin. MDR-TB is treated with second-line drugs which are more expensive, less effective and more toxic than first-line drugs. XDR-TB is defined as MDR-TB with resistant to fluoroquinolones and one other second-line drug. Treatment options for XDR-TB are severely limited. To reduce the likelihood of antibiotic resistance, treatment of TB always involves a combination of drugs. Drug-resistant TB is largely due to human error and the resulting misuse or mismanagement of anti-TB drugs. Examples of this include patients feeling well and not completing their full course of treatment, incorrectly prescribed dosage or lack of availability of the drugs.

HIV/AIDS
The growing HIV/AIDS pandemic has, just like drug resistance, thrown a spanner in the works for TB treatment. An estimated one third of all HIV-infected individuals are coinfected with *M.t*. Over the past decade *M.t.* infection rates have increased fourfold in countries heavily affected by HIV and approximately 50 % of HIV infected individuals die from TB. In light of these statistics it is obvious that in order to successfully eliminate or at the least control the TB pandemic one must simultaneously attempt to control the HIV/AIDS pandemic. The problem arises when trying to treat these two conditions simultaneously as the anti-TB drugs interact with anti-HIV agents, reducing the latter's efficacy.

The arms race continues...

Research for new anti-TB drugs has fallen on the wayside for the past several decades. Lack of potential profit has been cited as the main reason for the disinterest in TB research. However, with the increasing global threat of TB, specifically its spread to industrialized nations, the hunt for new anti-tb drugs in on and several have reached clinical testing stages. And so the arms race between us and bacteria ensues. We develop antibiotics to control infectious diseases and bacteria counter these attempts by developing defense mechanisms enabling their survival.

More information

Interested in learning more about tuberculosis? Then check out the following articles and links:

Ducati, R.G., Ruffino-Netto, A., Santos, D.S. 2006. The resumption of consumption–a review on tuberculosis. Mem Inst Oswaldo Cruz. **101**: 697-714.

Huebner, R., Castro, K. 1995. The changing face of tuberculosis. Annu Rev Med. **46**: 47-55.

Ma, Z., Lienhardt, C., McIlleron, H., Nunn, A.J., Wang, X. 2010. Global tuberculosis drug development pipeline: the need and the reality. Lancet. **375**: 2100-2109

WHO. 2010. Tuberculosis. http://www.who.int/topics/tuberculosis/en/. Accessed:2010-07-07.