Growth regulating systems may be the cause of the evasive nature of tuberculosis

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Tuberculosis is a disease caused by bacteria which can give rise to an infection that may remain undetectable for years without causing symptoms and then suddenly kick-start a fully active and deadly infection. The rude awakening might be controlled by so called toxin-antitoxin systems. Tuberculosis kills more than a million people yearly and an estimated 9 million get infected. The infection can be highly evasive due to this phenomenon known as latency. Mycobacterium tuberculosis, the bacterial species that's causing the air-borne disease, is able to control its growth through two types of proteins called toxins and antitoxins. These proteins, also known as toxin-antitoxin systems (TA-systems) are prime candidates for researchers trying to understand how latent infections are formed.

Proteins known as toxins and antitoxins controls growth in tuberculosis bacteria

As humans are infected with *M. tuberculosis*, the cause of tuberculosis, the infection might go unnoticed for years. In a random event, or when the immune system is somehow defected, the infection might suddenly burst into full force. The bacteria invade immune cells known as macrophages that normally tries to engulf and degrade the invaders. When inside the macrophage the bacteria can either make progeny thus causing an active infection, or it can turn into a kind of non-growing state. This state causes a latent infection, which show none or very minor symptoms. At any point in the infected person's future the latent infection might turn into a deadly active tuberculosis. Without treatment one in two dies as a result of the active infection.

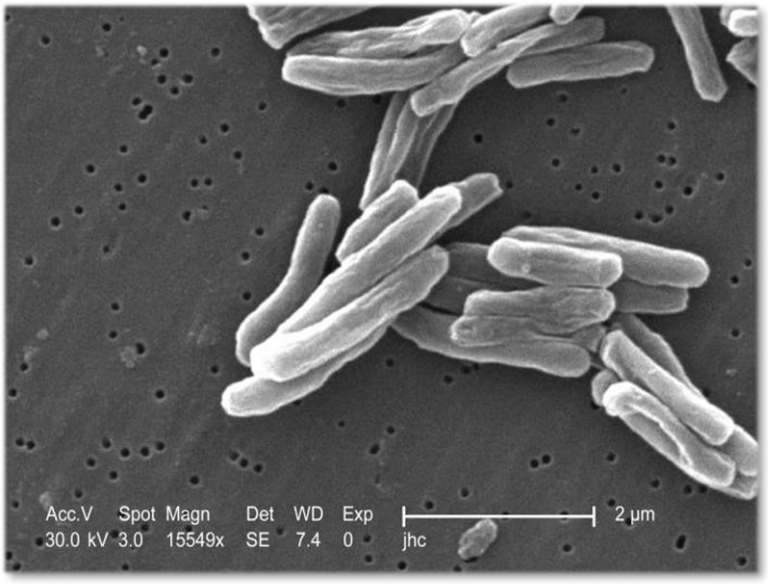

Figure 1. An electron microscope photograph of *M. tuberculosis* cells. Scale of 2 micro meters (one millionth of a meter) shown in the bottom part (WikiMedia Commons, https://upload.wikimedia.org/wikipedia/commons/c/cb/Mycobacterium_tuberculosis.jpg)

The decision between latency and active infection is believed by researchers to be executed by toxin-antitoxin systems. These are made up by two kinds of proteins. A toxin which can halt some cellular process, like DNA replication, to stop the bacteria from creating daughter cells but not killing it. The antitoxin can, as the name implies, neutralize the toxin. In the ordinary growth state of the bacteria the toxin is deactivated by the antitoxin, but at some kind of queue, the antitoxin is degraded by enzymes known as

proteases. Proteases generally degrade proteins and can be turned on or off to regulate when and which protein they are to degrade. As the antitoxin is no longer able to counter the toxin, cell growth is restricted. This restriction may exist for some time and then be relieved, by some signal from the environment, for example a weaker immune system. Then, a raging infection is able to form. Also, during latency, the bacteria show an increased resistance to antibiotics. This poses a second problem in addition to the difficult identification of latent tuberculosis.

M. tuberculosis causes 1.4 million deaths per year

Among infective agents *M. tuberculosis* could be seen as one of the most successful ones. According to WHO (World Health Organization) it killed 1.4 million people 2014 and 9.6 million were infected. It is estimated that in total a third of the world population are infected. The wide occurrence of the pathogen (term describing infective organisms) is believed to be attributed to the ability to form latent infection. Above that, drug resistant subtypes of the species have been widely found and described. Antibiotic drug resistance is a major problem in health care today, some bacterial species even show total resistance to all known antibiotic classes. Recently, an effort was made by WHO to increase the awareness of the resistance and governments and organizations around the world are starting to take action. As *M. tuberculosis* might be getting even more difficult to get rid of, when treated with antibiotics, it is very important to understand its basic infective abilities, such as latency. If latency could be somehow drugged and prevented, the treatment of the disease might prove to be much quicker and easier. Most importantly, the amount of people surviving the infection may increase.

In the *M. tuberculosis* genome there are 79 different TA-systems encoded on genes. The bacteria contain about 4000 genes in total. Compared to other pathogens the number of TA-systems is strikingly high and has been suggested to be the reason for the infective successfulness of the bacteria. Other similar pathogens such as the salmonella bacteria contains 9 TA-systems and *Mycobacterium leprae*, the cause of the dreaded disease leprosy have only four TA-systems.

Read more about TA-systems in *M. tuberculosis*:

Gudmunds E. 2016. Förekomst och funktion av TA-system i Mycobacterium tuberculosis. Litteraturstudie, Uppsala universitet.