HOW CAN WE DIAGNOSE TUBERCULOSIS MORE EFFECTIVELY?

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Tuberculosis (TB) is a contagious disease that can be transmitted from a person who has the bacteria *Mycobacterium tuberculosis* within their lungs, and who expels the bacteria by coughing, allowing TB to infect other susceptible people. TB can affect people of all ages, from kids to the elderly, and in infected people, it often spreads to other organs, in addition to the lungs and can even spread throughout the body. Today, the most common way to diagnose TB is by staining the bacteria present in sputum (coughed up mucus) samples, using a chemical that will color those bacterial cells. However, in cases where the bacteria are located outside the lungs, this strategy is not effective. Furthermore, in some cases where coughed up mucus can be obtained, it could contain too few bacteria to easily detect them. Also, there are some people in which *M. tuberculosis* remains "dormant" or hiding, without causing trouble, but upon weakening of the immune (defense) system, the bacteria "wake up" and cause disease. Because of these complications, new strategies for diagnosis of TB rely on the use of samples other than coughed up mucus, in which *M. tuberculosis* can be detected using simple tests. In this article, I discuss how the immune response varies from person to person and even within the same person,

how the immune response to *M. tuberculosis* changes with age or other circumstances, and how we could take advantage of these changes to improve diagnosis of TB.

WHO CAN GET TUBERCULOSIS (TB)?

Although anyone, from kids to the elderly, can come into contact with the bacterium *Mycobacterium tuberculosis*, the vast majority of people (about 90%) who are infected with this bacterium will eliminate it through the work of the **immune system**. However, some people (about 10%) who come into contact with *M. tuberculosis* cannot fully control the bacteria. These people can develop a disease called active tuberculosis (ATB), with fever, coughing, and weight loss. In these cases, *M. tuberculosis* makes its home within the lungs and can be transmitted to other people when the sick people expel the bacteria through coughing. In some people, another scenario occurs in which their immune system keeps the bacteria in a dormant or "sleeping" state. This is called latent TB. In these people, no fever, coughing, or weight loss will be apparent until their immune system stops working properly.

In spite of the ability of *M. tuberculosis* to infect pretty much anyone, there are only a few countries that contain the majority of people who have ATB. These countries are generally affected by either overpopulation and/or hunger, or there is a high occurrence of other diseases, such as **HIV/AIDS** or **diabetes mellitus** (DM). Overpopulation, hunger, and disease are common in many developing countries, and these conditions make it difficult to stop the disease from spreading. This means that the risk of developing ATB is higher in people who suffer from hunger, poverty, bad diet, or lack of exercise.

HOW IS ACTIVE TB USUALLY DETECTED?

When a person is infected with *M. tuberculosis* and develop ATB, bacteria often multiply without a great restriction in the body, and often can reach high numbers within the lungs. This results in a good number of bacteria being coughed up as **sputum**, so that when the secreted mucus is stained in the laboratory, it is relatively easy to find colored *M. tuberculosis* there (Figure 1). However, some people (for example, kids or the elderly) may not be able to produce the secreted mucus in an amount good enough to conduct the **staining**, or the number of bacteria being present there could be too low to find them. In some other cases, *M. tuberculosis* may even be present out of the lungs, so the process for obtaining a sample to stain it becomes more complicated and potentially results in discomfort for a patient. Other bacteria that do not produce ATB can also be detected with the staining used to find *M. tuberculosis*, therefore the risk for wrong diagnosis exists. These drawbacks call for methods that accurately diagnose ATB to allow patients the chance to be cured.

IMMUNE SYSTEM

The network of cells, tissues, and organs that work together to protect the body from infectious agents.

HIV/AIDS

Infection and disease produced by human immunodeficiency virus (HIV) that produces acquired immune deficiency syndrome (AIDS), a severe condition that reduces capacity to fight infections.

DIABETES MELLITUS

A chronic condition where abnormally high levels of sugar (glucose) are present in blood, which, among other effects, reduces the capacity of immune cells to fight infections.
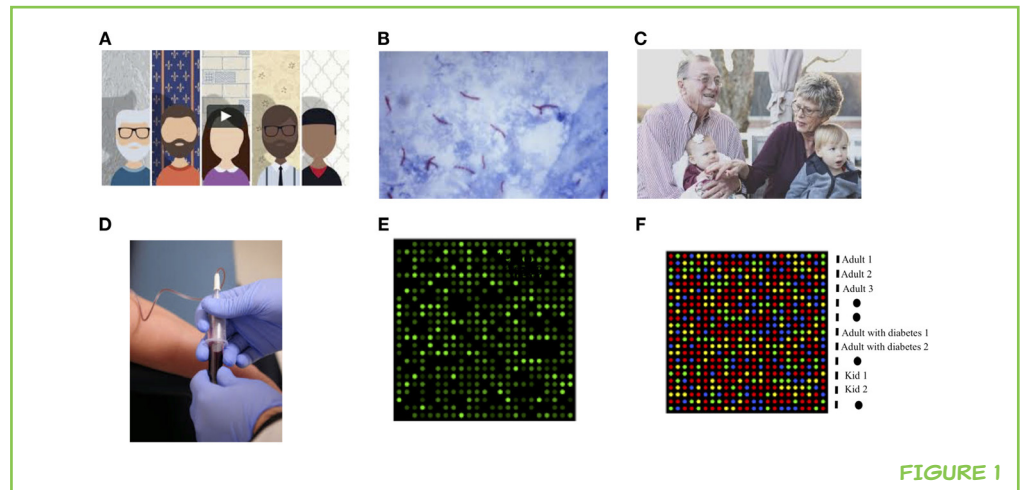
SPUTUM

A mixture of saliva and mucus coughed up from the airways.

STAINING

Use of dyes that binds to components present in cells, which facilitate their visualization under a microscope.

FIGURE 1

Improved diagnosis of tuberculosis for everyone. In the near future, it may be possible to detect *Mycobacterium tuberculosis* no matter where the bacteria responsible for producing it is hidden in the body. As we reach this goal, we will be able to: (**A**) Better understand why different people respond differently to *M tuberculosis*, with each one of us producing a unique response to infection. (**B**) In some cases, when *M. tuberculosis* is present in large amounts in the lungs, the bacteria can be detected in the sputum (coughed up mucus) using dyes (staining/coloring them). The bacteria in this image are the purple rod-like structures. (**C**) Not all people are able to produce sputum, and the bacteria are not always present in the lungs. Moreover, as we grow up and depending on other conditions (for example, pollution or food intake), our capacity to produce an antibodies varies. (**D**) To improve our chances of finding *M. tuberculosis*, we hope to use other body fluids in addition to sputum (blood, urine, saliva, etc.). If we can detect antibodies to *M. tuberculosis* in these fluids, the antibodies might indicate that the person is infected with this organism. (**E**) Antibodies present in body fluids can be used to detect specific structures on *M. tuberculosis*, and these antibodies can be used to produce a visual signal that can be easily detected. In the example shown, every bright, green dot represents one single

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HOW DOES THE BODY REACT TO *M. TUBERCULOSIS*?

The body's first line of defense against *M. tuberculosis* is something called **innate immunity**, which will fight the attempt of *M. tuberculosis* to establish and maintain an infection. The innate immune response starts with cells and proteins of the immune system that recognize structures present on the bacterial surface. This recognition results in the production, by white blood cells (leukocytes), of a number of compounds that are toxic to bacteria. Moreover, white blood cells also produce additional substances that attract other defense cells, so that the immune cells join forces in an attempt to avoid spread of the invading bacteria to other places in the body.

In most people, innate immunity will lead to the elimination of *M. tuberculosis*. Conversely, in susceptible people, another kind of immunity called the **adaptive immune response** will take place, in an effort to contain the infection and optimally, eradicate it at this stage.

In contrast to the innate immune response, the adaptive immune response is based on recognition of unique structures on an invading bacteria, which are not shared by other bacteria in the body. The adaptive immune response stores cells called B lymphocytes that produce substances called **antibodies**. If the same *M. tuberculosis* bacteria are encountered again, anywhere in the body, the B lymphocytes will rapidly produce the antibodies needed to fight the battle against those bacteria.

CAN WE DETECT TB BY LOOKING FOR ANTIBODIES?

As we have already stated, antibodies are substances produced by B lymphocytes. Antibodies are large, Y-shaped proteins that are used by the immune system to bind to specific structures on bacteria like *M. tuberculosis*, or other infectious organisms, and effectively neutralize their dangerous properties.

INNATE IMMUNITY

The first line of defense against invading pathogens, also known as non-specific immune system or in-born immunity system.

ADAPTIVE IMMUNE RESPONSE

Also known as the acquired immune system, composed of highly specialized, systemic cells and processes that eliminate pathogens or prevent their growth.

Antibodies can be found in different body fluids (saliva, blood, tears, and urine) so that in cases where mucus secretion cannot be obtained from a patient, it is still possible to look for an infection. No matter where the *M. tuberculosis* infection occurs (lungs, liver, stomach, bones, etc.), the immune response produces antibodies that circulate throughout the entire body. This makes antibodies a more effective way to detect *M. tuberculosis*—especially when it is present in organs other than the lungs. A limitation to the use of technologies based on these compounds is that antibodies can be found even in cases where the harmful bacteria have already been eliminated from our body thanks to our defense system.

We need to be aware that every one of us will react slightly differently to the presence of *M. tuberculosis* in our bodies, because of inherent differences in our genes. These differences can result in variations in antibody responses [1]. Some people may produce more antibodies than others. Also, as people grow up and age, additional differences in the amount and also the kinds of antibodies produced may occur, due to natural changes in the immune system. Last, malnutrition or diseases like DM may also affect a person's capacity to produce antibodies to *M. tuberculosis*.

Because of all these differences, scientists are working to produce different methods to diagnose ATB for different people, for example, to detect antibodies produced by children, patients with diabetes, or the elderly (Figure 1). It could be that we need to look for antibodies that are useful at early, medium, and late stages of TB disease.

In my research group, we are trying to use the presence of antibodies to detect *M. tuberculosis* in patients who have DM. DM is a disease where blood sugar is higher than in normal people, and that among other characteristics, reduces the capacity of the immune system of these patients to fight infections, including ATB. At this point, we do not know whether people with DM will produce antibodies against *M. tuberculosis*, so we are studying this question and hope to discover an effective method to detect *M. tuberculosis* in patients with DM before ATB has developed in them.

ACKNOWLEDGMENTS

REFERENCE

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FUJIA, AGE: 15
He is a high school student who promises several things. He promises that he is never going to give you up, never going to let you down, never going to run around and desert you, never going to make you cry, never going to say goodbye, and never going to tell a lie and hurt you. Some of Fujia's favorite activities include tennis, the sport where you hit a ball with a racquet over a net; unnecessary explaining things; and speaking in the third-person.

AUTHOR

MARIO ALBERTO FLORES-VALDEZ
I am a Microbiologist and Molecular Biologist, and I am profoundly interested in understanding how a tiny cell (*Mycobacterium tuberculosis*) is able to interact with our defense system and remain viable for long time without causing evident signs of disease, and I try to generate means (vaccines and methods of diagnosis) to stop it from further causing trouble to human beings. *floresv@ciatej.mx, floresvz91@gmail.com