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Combatting TB: Insights on Immunologic Mechanisms & Response

Announcer:
You're listening to *Tackling TB* on ReachMD, sponsored by Qiagen. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Tackling TB* on ReachMD. I'm Dr. Charles Turck and joining me today to share insights on the immunologic mechanisms that can alter a patient's ability to fight mycobacterium tuberculosis is Dr. Carlos Acuña-Villaorduña. He's an Adjunct Assistant Professor at Boston University School of Medicine. He's also an Infectious Disease Specialist with an interest in tuberculosis. Dr. Acuña-Villaorduña, thanks for being here today.

Dr. Acuña-Villaorduña:
Thank you for the invitation.

Dr. Turck:
Now, let's start by looking at the molecular level. Dr. Acuña-Villaorduña, when a patient is infected with mycobacterium tuberculosis, or Mtb for short, what kind of immune response do we typically see?

Dr. Acuña-Villaorduña:
Several types of immune responses. Historically it has always been considered that the adaptive immune system is more important for the control of mycobacterium tuberculosis. So, mycobacterium tuberculosis is a facultative intracellular organism. So, in this context, usually T cells and the cellular response are responsible to control tuberculosis in the lungs especially. In the last years, there has been interest by the way, the role of the innate immune system and also antibodies however, the control of tuberculosis mainly is dependent in the adaptive immune system, the T cells, specifically the Th1 cellular response.

Dr. Turck:
And if we focus on the pathogen-specific responses for a moment, how do those happen and how do they differ from our body's general global immune response?

Dr. Acuña-Villaorduña:
I mean this is an interesting question. Usually, tuberculosis is transmitted almost always by fine aerosols that are in the air and get into the lung. In this context, the first encounter of tuberculosis has with the host is with alveolar macrophage. They alveolar macrophage has a very important role in the control of tuberculosis. So, the macrophage is able to phagocyte the bacteria, however, tuberculosis is able to avoid the immune system and then the alveolar macrophage presents the antigens of tuberculosis to the T cells that are abundant in the lymph nodes in the lungs, in the mediastinum and then a cellular response is orchestrated. And the hallmark of tuberculosis control has been the production of a granuloma, this is a typical cellular response. This granulomas formation is also common with other intracellular organisms, like brucella or a histoplasma that can occur.

Now, in the last year there have been interests to see what's the role of other type of responses, like in the innate immune system or antibodies. But in general, the hallmark response of tuberculosis is a formulation of a granuloma T cell response for the control of tuberculosis.

Dr. Turck:
With that being said, Dr. Acuña-Villaorduña, are there any other immunologic mechanisms that modulate our patient's ability to fight off Mtb?

Dr. Acuña-Villaorduña:
In general for any infectious diseases it's important to try to find correlations of protection. For tuberculosis, this has been particularly challenging because there are different phenotypes of people with tuberculosis. For instance, there are people who've been exposed to tuberculosis very heavily, however, they never convert their TST or their IGRA. So, these people are considered to be resistant to infection.

There are also people that after exposure they develop, like, very large TSTs or very strong IGRAs, however, they never develop disease. These phenotypes are considered people who are resistant to disease. And there's a small percentage of people who, that is usually 5 or 10 percent, who get infected, they convert their PPD, they convert IGRA, and then they develop tuberculosis disease, usually in the first two years.

So, which are the immunologic correlates of protection in various according to each phenotype? And for each phenotype there is a different pathway. What we know based on clinical observations is that people with immunodeficiencies, especially HIV infection and also people who are using a tumor necrosis factor blockers are at very, very high risk of developing tuberculosis disease. So, in this context, this CD4 and the tumor necrosis factors play a major role in the control of tuberculosis. So, clinically this is important for our patients because people living with HIV infection and patients who have medical conditions that require the use of biologic agents are at a very high risk of developing tuberculosis and they should receive preventive therapy when needed.

Dr. Turck:
For those just tuning in, you're listening to *Tackling TB* on ReachMD. I'm Dr. Charles Turck and today I'm speaking with Dr. Carlos Acuña-Villaorduña about various aspects of our immune response to mycobacterium tuberculosis, or Mtb, for short.

So, Dr. Acuña-Villaorduña, if we zero in on our immunosuppressed patients, how can a patient's degree of immunosuppression impact the way they are able to fight an Mtb infection?

Dr. Acuña-Villaorduña:
As we mentioned before, patients who are living with HIV infection and patients with biologic agents that have increased risk of tuberculosis disease the issue seems to be a dose-response effect, meaning the larger the immunosuppression, the higher the risk of developing tuberculosis. Patients living with HIV infection when their CD4 counts are very, very low, they tend to develop disseminated disease, they express a different type of disease compared with patients with HIV who have normal CD4 counts. So, there is certainly a dose response effect in the level of immunosuppression. So, the more immunosuppression, the higher the risk of developing tuberculosis disease. And what is important is that usually people who have severe immunosuppression, they tend to develop disseminated tuberculosis that is more difficult to treat and is usually associated with higher rates of mortality.

Dr. Turck:
With that in mind, how can we better help our immunosuppressed patients combat an Mtb infection?

Dr. Acuña-Villaorduña:
So, tuberculosis is transmitted by aerosol, so this is a typical disease of the transmitted by fine aerosols, just by going to the street and breathing. It's very, very difficult to avoid being infected with mycobacterium tuberculosis, especially in high incidence settings. For this reason, the preventive strategies have been mainly a focus of people who are already infected and prevent that they develop tuberculosis disease. At the present time, we have two tests to detect tuberculosis infection; that is the tuberculin skin test, and the interferon-gamma release assays. So, the recommendation is every person who is going to start any immunosuppressive agent should be screened for latent tuberculosis with either of these tests. If either of these tests is positive, this person should receive preventive therapy. And there are courses of preventive therapy recommended by the CDC, by the European societies, by WHO. And so basically the focus is on preventing development of disease of people who are infected. Screening and treatment is very important.

Dr. Turck:
And before we close, Dr. Acuña-Villaorduña, do you have any final thoughts or take-aways you'd like to share with our audience?

Dr. Acuña-Villaorduña:
Yes. So, immunology of tuberculosis is an area that is very important and there are plenty of studies coming, there is a lot of excitement in the community to try to identify correlates of protection for the tuberculosis disease. And there is a study that was published a couple of years ago and it showed the evidence of the vaccine can prevent development of tuberculosis. This was initially studied as a vaccine named M72 that was given to people who were already infected, the studies were done in Africa and they followed this population for a total of three years, and they found that the vaccine prevented the development of disease in people who are already infected with an efficacy of 50 percent. And there are current interests in trying to identify more correlates of protection, development of vaccines that will be a huge advance in our fight to control tuberculosis.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Carlos Acuña-Villaorduña for sharing his insights on mycobacterium tuberculosis. Dr. Acuña-Villaorduña, it was great speaking with you today.

Dr. Acuña-Villaorduña:
Thank you very much for the invitation.

Announcer Close
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