TB or Not TB: That is Our Question

The role of Interleukin-12 Receptor in The Immune System and Preventing Tuberculosis

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Abstract

According to the National Network for Immunization, the first tuberculosis(TB) vaccine was given in 1921 and has been administered to over 4 billion people. Unfortunately, the vaccine is not as effective as it once was because tuberculosis is becoming increasingly resistant to antibiotic treatments. As a result, new methods of treating and/or preventing this disease are underway. One method that could be used to prevent tuberculosis is to study the Interleukin-12 Receptor (IL-12R) and its essential protein in initiating the immune response. When a pathogen invades the host, T-helper cells send signals to initiate an attack against the pathogen. IL-12, a cytokine, binds to IL-12R, which can signal macrophage activation to mount an attack against the invading pathogen. Some people have a mutated IL-12R which causes the patient to be infected by a similar disease to TB upon vaccination with BCG which contains live bacteria. IL-12 is a heterodimer with two glycoprotein subunits, p40 and p35, that are bound to the IL-12R via two disulfide bonds. If the IL-12R is mutated, the IL-12 will not bind properly to IL-12R, and the helper T cell's immune response to destroy the TB cell will not commence. Although IL-12R has not yet been crystalized, the Grafton SMART Team (Students Modeling A Research Topic) modeled gp130, a homolog of IL12R, using 3D printing technology. Ser 122 and Trp142 are highlighted on our model because this is where gp130 binds to IL-6, the homolog of IL-12.

Statistics on Tuberculosis

• 2nd to HIV/AIDS as the greatest worldwide killer due to a single infectious agent.
• Having AIDS will make a host more susceptible to TB.
• There is a multi-drug resistant form of TB, called MDR-TB.
• According to 2011 data:
  - 1.4 million people died from this disease in 2011.
  - There are 8.7 million people infected with TB.
• Below is a world map that includes the general number of tuberculosis infections in each country.

Tuberculosis

Tuberculosis (TB) is a bacterial disease caused by Mycobacterium tuberculosis (picture to the right), which is primarily located inside the lungs. The lungs are responsible for the intake and outtake of molecules in the air that are vital for human survival. It is because of this fact that the bacteria can easily escape and be readily available for the next unsuspecting host. Symptoms include: body weakness, loss of weight, chest pains, fever, or night sweats.

Introduction to Interleukin-12

To prevent people from getting tuberculosis, a vaccine is administered. In theory, since the vaccination has a small portion of tubercle bacillus, a person should replicate T cells into memory T cells so they can fight off TB; however, if there is a mutation on IL-12R, then the person is infected with this disease. This occurs when there is a mutation in the IL-12 receptor site, which is a protein found in the membrane of a T cell. The mutation hinders the ability of the IL-12 cytokine to bind to the receptor site. The IL-12 cytokine is secreted by a macrophage when the bacteria invades the lung tissue of a human. Then IL-12 will attach to gp130 which will cause the production of antibodies in order to help fight this bacteria.

Cell Response Without IL-12 Receptor

When the signal is made, the normal reaction is the release of IL-12, a cytokine. IL-12 is then supposed to attach to IL12RB1 receptor. When this does not happen, the bacterium does not get neutralized, and can multiply exponentially. (pictured below)

The Importance of the IL12RB1 Receptor

• The first lung (lung A) is from a genetically normal mouse.
• The second lung (lung B) is from a mouse that lacks IL12RB1.
• It can be derived that the IL12RB1 receptor is vital to the prevention of TB, as it gives a three dimensional reference for researchers. A physical model of Interleukin-6 and gp 130 may prove helpful in the study of TB as it gives a three dimensional reference for researchers. A model designed by the Grafton SMART Team includes interleukin-6 and glycoprotein 130. Highlighting the amino acids Ser122 and Thr142 gives an insight into how binding may occur and possibly where the problem lies.

Model of Interleukin-6 and gp 130

Amino acid Tryptophan-142 is colored lime.
Amino acid Serine-122 is colored yellow.

Model specifications:
• Serine are colored yellow.
• Hydroxy bonds are colored orange.
• Glycine-190 is colored mid-blue.
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