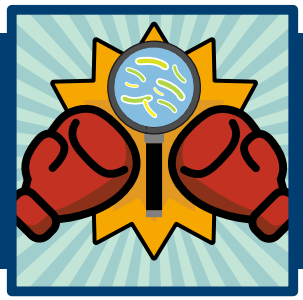
UNIT: TUBERCULOSIS

LESSON 3: ME VS. TB - BOOSTING THE IMMUNE SYSTEM TO DEFEAT AN ANCIENT ADVERSARY

Activity 3B: *Team Up to Fight TB!*



TEXAS BIOMEDICAL RESEARCH INSTITUTE
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General Information

Tuberculosis (TB), ***Mycobacterium tuberculosis***, is a bacterium that is estimated to have existed nearly as long as humans. Historically, TB infection has been known by different names: white plague, phthisis, and consumption. Most people who are exposed to TB generally recover, usually without even knowing they were infected. Tuberculosis is spread as an aerosol and generally affects the lungs. When an infected person exhales, coughs, sneezes, or even sings, the TB bacteria is carried on droplets and stays suspended in the air for hours. When someone inhales these minute droplets, the TB is carried into the lungs where it attaches to cells within the lung.

Using data from their past research, Texas Biomed scientists had evidence which showed the importance of the immune system in fighting TB. The challenge they faced was finding effective ways to fortify the immune system to fight TB without harmful side effects caused by current antibiotic therapeutics. Data from cancer research indicated the addition of Host Directed Therapies (HDTs), like Vitamin D, boosts the immune system. The HDTs increase the effectiveness of conventional cancer treatments and shorten the duration of treatments. The Texas Biomed scientists translated the result from cancer research and developed in vitro experiments to test the effectiveness of HDTs on the immune system to improve TB treatments.

Host-Directed Therapies & Cell Death Pathways

All cells have a limited life span. At the end of the cell's lifespan, it experiences a cell death pathway. Although there are several cell death pathways, the two primary pathways associated with TB research are apoptosis (A-pop-**toe**-sis) and necrosis (neh-**CROW**-sis). Apoptosis is the "normal" cell death pathway. During apoptosis, the cell membrane stays in tack, keeping all contents inside as the body eliminates the cell.

However, when a cell is infected with TB, the bacteria activate specialized receptors embedded in the cell membrane. When activated, these specialized receptors shut off apoptosis and activate the necrosis cell death pathway. With the necrosis pathway activated, the cell membrane will rupture, releasing bacteria into the body for more TB to infect other cells. As infected cells undergo necrosis chemical signals alert the immune system to send macrophages (**MAC**-row-fayj), the first line of defense. Using affixes, the word macrophage is derived from Greek meaning "big eater". The prefix "macro" meaning big and the suffix "phage" meaning to eat. The word is correctly pronounced in several ways, such as **MAC**-row-fahj or **MAC**-row-fayj.

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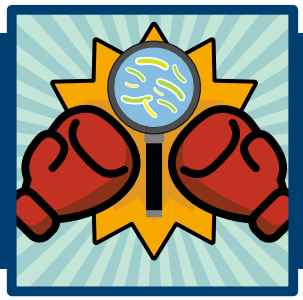

The macrophages surround cells infected with TB through phagocytosis (fay-go-sigh-**TOE**-sis). Once the cell is surrounded the macrophage destroys the cell and kills the TB bacteria. The macrophage then undergoes necrosis. As it breaks apart, the "dead" TB is released into the body which alerts other immune cells of the invader. These other immune cells migrate to the area to kill the TB. However, if there are too many TB bacteria, the other immune cells surround the infected cells. This forms a ball called a granuloma (gran-you-**LOW**-ma). Tuberculosis bacteria inside the granuloma are still alive but encapsulated and unable to infect more cells.

Antibiotics and TB

Antibiotics have been used successfully to treat TB infections, specifically rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). Of these, RIF and INH are most frequently used to treat TB. But these antibiotics have harsh side effects such as chronic fatigue, blurred vision, easy bruising or bleeding. In addition, long-term use of antibiotics can cause tingling, numbness and burning in the hands and feet. Some of these side effects may be permanent.

The formation of granulomas by macrophages and other immune cells (macrophages, T cells, neutrophils, eosinophils, fibroblasts, collogen) present another problem for treatment. Antibiotics have limited success penetrating granulomas to reach the TB bacteria inside.

TB and Apoptosis

Boosting the immune system interferes with TB's ability to shut off apoptosis, meaning cells infected with TB do not break apart preventing TB from spreading. Although dead, the cell stays intact, and the body eliminates the cell, and the TB contained inside. It had been suspected that HDTs could be a mechanism to control TB's ability to shut off apoptosis, but until this study, there was limited research to support this idea. However, the positive results shown by the introduction of HDTs to treat cancer provided the necessary evidence to investigate HDTs effect on TB treatment.

Results

In total, 10 experiments were conducted, including the control. To determine the effectiveness of various doses of HDTs on murine macrophages, the researchers counted and compared the number of Culture Forming Units (CFUs). Applying in vitro techniques, the researchers used petri dishes with an agar nutrient gel, called a substrate. When TB bacteria is placed on the nutrient substrate, it will form clusters of CFUs.

Murine Macrophages: In this stage of the experiment, scientists exposed murine macrophages to various doses of HDTs to evaluate the effectiveness of HDTs on macrophages by examining impact on cell death pathways. The number of CFUs are indicators of how different doses affect apoptosis and necrosis. If HDTs are not successful, the TB bacteria will cause necrosis. The cell membranes will rupture, releasing TB into the substrate, forming large numbers of CFUs. But if HDT treatment is successful, apoptosis will not be disrupted, meaning cell membranes will stay intact and the TB bacteria will be safely contained. This will reduce the number of CFUs.