Pathogenic Microorganisms

3rd Class Module

Lecture

Mycobacterium tuberculosis

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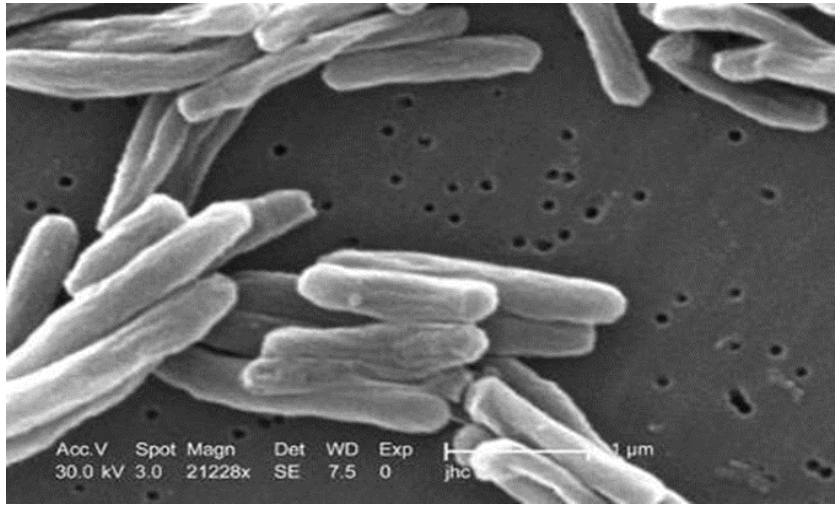
2023-2024

Mycobacterium tuberculosis



- Mycobacteria are nonmotile, nonsporulating, weakly gram-positive, acid-fast bacilli that appear microscopically as straight or slightly curved rods, 1 to 4 μm in length and 0.3 to 0.6 μm wide.

- Mycobacteria are within the order Actinomycetales, which it shares with bacteria such as *Corynebacterium*, *Nocardia*, and *Rhodococcus*.
- These bacteria also express unique mycolic acids in the cell envelope that play a critical role in the structure and function of the cell wall.

- The waxy cell wall confers many of the unique characteristics of this genus: acid-fastness, extreme hydrophobicity, resistance to drying, acidity/alkalinity, and many antibiotics, as well as distinctive immuno-stimulatory properties.

- Mtb is a member of the slow-growing pathogenic mycobacterial species, characterized by a 12- to 24-hour division rate and prolonged culture period on agar of up to 21 days.

- Why Mtb grows so slowly is not well understood.

- Proposed mechanisms include limitation of nutrient uptake through the highly impermeable cell wall and slow rates of RNA synthesis.

- During experimental infections, its metabolism can shift from an aerobic, carbohydrate-metabolizing mode to one that is microaerophilic and lipid metabolizing.

- Mycobacteria are facultative intracellular bacteria that multiply within phagocytic cells, particularly macrophages and monocytes. Although many mycobacterial species are environmental, Mtb is strictly parasitic.

- Mtb is a member of the *M. tuberculosis* complex, includes *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*, with *M. caprae* and *M. pinnipedii* considered variants of *M. bovis*. It was previously assumed that Mtb evolved from *M. bovis* during the domestication of cattle.

Mtb Virulence Factors: Who Are Involved in Disturbing Cell Death?

Virulence is the ability of a pathogen to cause disease. To define Mtb virulence, the following factors should be considered:
(1) the ability of a bacterium to avoid the host's immune response.
(2) its capacity to cause lung damage.
(3) its successful transmission to infect a new host.

Unlike other pathogens, such as Vibrio cholerae or Corynebacterium diphtheriae, Mtb does not use toxins and enzymes, which are the typical virulence factors; instead, several virulence-associated genes compensate for them.

Mycobacterial virulence factors can be divided based on their nature into (a) non-protein molecules, such as lipids, sugars, and (b) proteins. The following Mtb molecules can modify cell death pathways:

1. Non-Protein Virulence Factors
Lipids, glycolipids, glycans, nucleic acids, and metabolites are included in this group; many are vital cell surface components involved in host–pathogen interaction, recognition, intracellular survival, and virulence.

Mtb has a lipid-rich envelope essential for its survival and virulence. The mycobacterial cell wall contains up to 60% lipids, and many cell wall components that are secreted, shed, or localized on the bacterial surface, interact with the host cells

a. Phosphatidyl-myo-inositol mannosides (PIMs) are the most abundant glycolipids in the mycobacterial cell envelope and are precursors of lipomannan (LM) and lipoarabinomannan (LAM). The PIMs comprise variable numbers of mannose units and levels of acylation. Virulent species possess PIMs with five or six mannoses that bind to the mannose receptor (MR), contributing to macrophage uptake.

b. LM is a multi-glycosylated lipid or polymannosylated PIMs, which is the basic structure of LAM (glycolipoconjugate). LM efficiently activates the innate immune response via a tetra-acylated form that activates macrophages through toll-like receptor-2 and 4 (TLR2 and TLR4, respectively).

c. LAM is a glycolipoconjugate composed of LM bound to multiple arabinose residues. When LAM acquires extra and random formation of mannose-capped LM, it is called ManLAM.

PIMs, LM, LAM, and ManLAM, are recognized by specific receptors, expressed on the cell surface of antigen-presenting cells, and dendritic cell activating receptor, facilitating Mtb uptake into host cells

2. Protein Virulence Factors

Along with abundant lipids, the Mtb cell wall also contains proteins that directly affect the host's immune response. Various reports have shown that protein families, and lipoproteins, alter the host immune response. The effects include modulating cytokine production and arresting phagosome maturation, phagosome escape, autophagy, and cell death.

2.1. Major Proteins Virulence Factors from Mtb

Mtb possesses an early secretory antigenic target (ESAT-6) secretion (ESX) system, also known as the type VII secretion system. Mtb has five secretion systems, or ESX, ranging from ESX-1 to ESX-5. The ESX-1, -3, and -5 are essential for mycobacterial virulence and regulate protein secretion and transport across the cytoplasmic membrane and complex mycobacterial cell wall.

2.2. Major Lipoproteins Virulence Factors from Mtb

Lipoarabinomannan carrier protein (LprG) is a 27 kDa triacylated lipoprotein of the Mtb cell wall, which is involved in cell wall biosynthesis, and is essential for the expression of surface LAM.

2.3. Major Phosphatases and Kinases Virulence Factors from Mtb

SapM and PtpA are phosphatases that participate in phagosomal arrest.

Cell Death Mechanisms Activated by Mtb Virulence Factors:

Cell death was initially classified into three main types based on morphological, biochemical, and immunological criteria: type I (apoptosis); type II (autophagy); and type III (necrosis).

Apoptosis

Apoptosis is a highly regulated cell death process, wherein a broad definition of molecular mechanisms allows it to be classified as type I cell death. It is characterized by cytoplasmic contraction, confinement of cytoplasmic contents, chromatin condensation, nuclear fragmentation, and blebs in the plasma membrane, forming tiny, apparently intact vesicles (known as apoptotic bodies) that can be removed by phagocytosis.

Necrosis

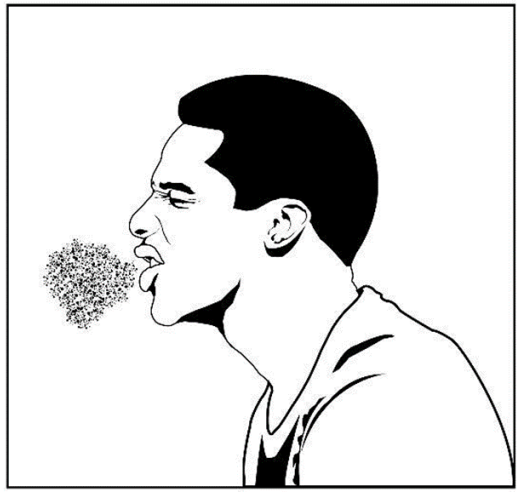
Necrosis is considered to be a form of accidental cell death induced by pathological or physiological conditions, such as heat shock, mechanical stress, oxidative stress, inhibition of caspase activity, reduced levels of ATP, and radiation. This process encompasses several cell death modalities, commonly including the loss of plasma membrane integrity and the release of intracellular components that favour the inflammatory response, unlike that in apoptosis.

Pyroptosis

Pyroptosis is a type that depends on the formation of pores in the plasma membrane, and is often induced by the inflammatory activation of caspases.

TB Transmission

Transmission is defined as the spread of an organism, such as *M. tuberculosis*, from one person to another.



TB is spread person to person through the air via droplet nuclei

M. tuberculosis may be expelled when an infectious person:

- Coughs
- Sneezes
- Speaks
- Sings

Transmission occurs when another person inhales droplet nuclei

Probability that TB will be transmitted depends on:

-Infectiousness of person with TB disease

-Environment in which exposure occurred

-Length of exposure

-Virulence (strength) of the tubercle bacilli

The best way to stop transmission is to:

-Isolate infectious persons

-Provide effective treatment to infectious persons as soon as possible

Latent TB Infection (LTBI)
Occurs when tubercle bacilli are in the body, but the immune system is keeping them under control

Detected by the Mantoux tuberculin skin test (TST) or by blood tests such as interferon-gamma release assays (IGRAs).
People with LTBI are NOT infectious.

TB Disease

- Develops when immune system cannot keep tubercle bacilli under control.
- May develop very soon after infection or many years after infection.
- About 10% of all people with normal immune systems who have LTBI will develop TB disease at some point in their lives.
- People with TB disease are often infectious

TB Pathogenesis

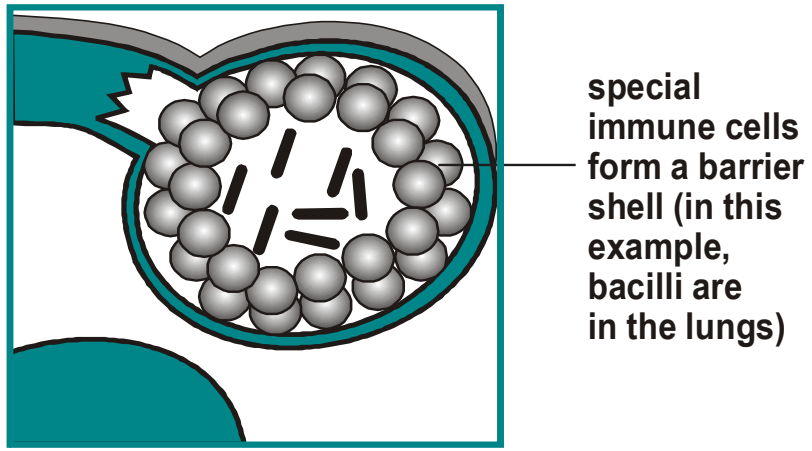
1- Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli).

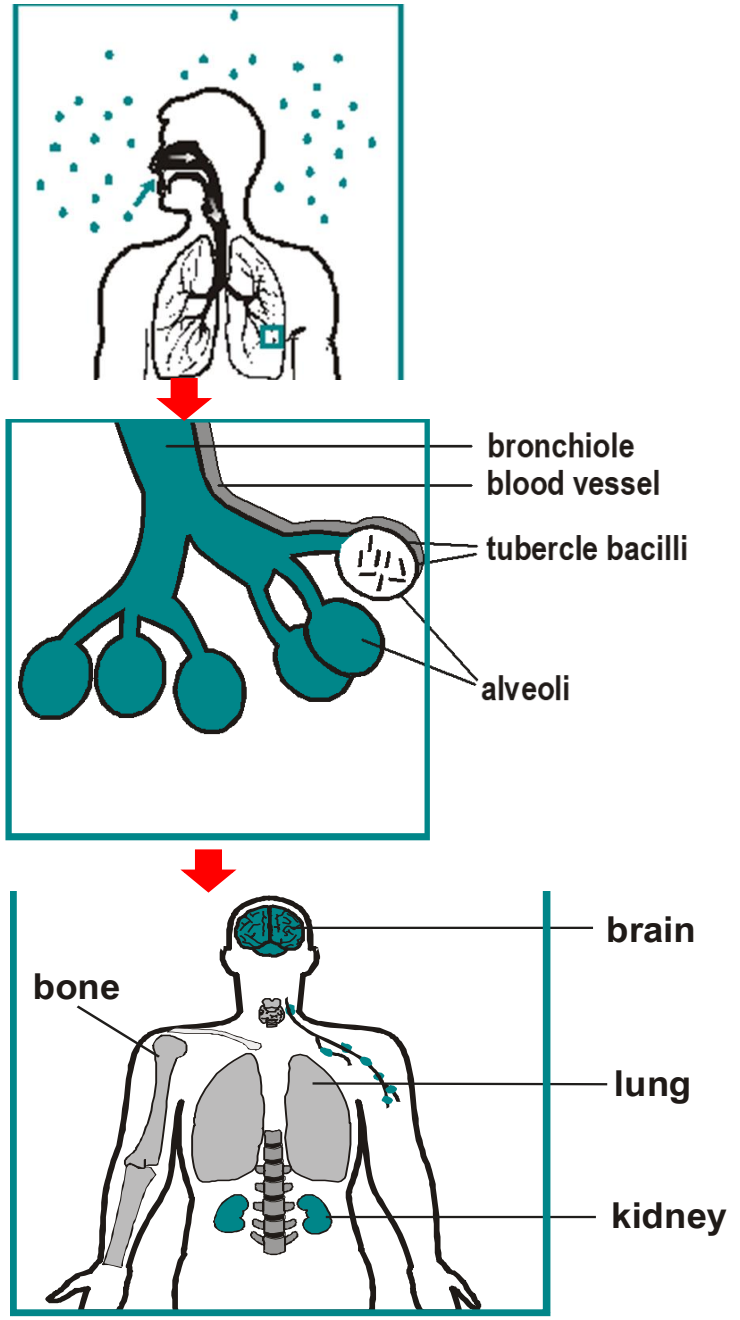
2- Tubercle bacilli multiply in alveoli, where infection begins.

3- A small number of tubercle bacilli enter bloodstream and spread throughout body.

4- Within 2 to 8 weeks the immune system produces special immune cells called macrophages that surround the tubercle bacilli.

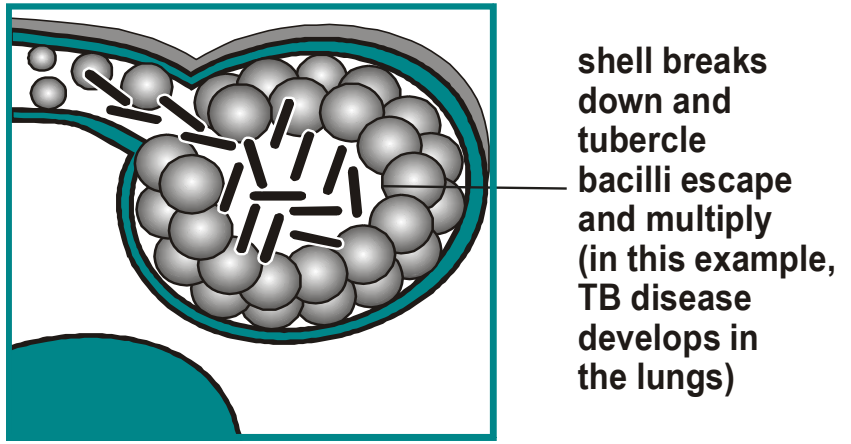
These cells form a barrier shell that keeps the bacilli contained and under control (LTBI).





5- If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease.

This process can occur in different places in the body.



When a person inhales air that contains droplet nuclei containing *M. tuberculosis*, where do the droplet nuclei go?

- Most of the larger droplet nuclei become lodged in the upper respiratory tract, where infection is unlikely to develop

- However, droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection begins

After the tubercle bacilli reach the small air sacs of the lung (the alveoli), what happens to them?

- Tubercle bacilli multiply in alveoli and some enter the bloodstream and spread throughout the body.
- Bacilli may reach any part of the body.
- Within 2 to 8 weeks, the immune system usually intervenes, halting multiplication and preventing further spread.

In people with LTBI (but not TB disease), how does the immune system keep the tubercle bacilli under control?

- The immune system produces special immune cells that surround the tubercle bacilli. These cells form a shell that keeps the bacilli contained and under control.

What happens if the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly?

- When this happens, TB disease develops. The risk that TB disease will develop is higher for some people than for others.