Immune Responses to Bacteria

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Via complement-mediated lysis

When bacteria, such as ***Neisseria meningitidis,*** invade the body, they are attacked by immune proteins called **complement proteins**. Complement proteins assist in bacterial killing via three pathways, the classical complement pathway, the alternative complement pathway or the lectin pathway.

The first steps of the **classical complement pathway** require the binding of antibodies to the surface of the target bacterium. The antibodies then become targets for one particular complement protein complex, known as **C1** – C1 binds to the tail (known as **Fc region**) of the antibody. Once bound, C1 initiates a cascade of cleavage and reforming of complement complexes that ends in the binding of several complement proteins to the surface of the bacterium in the form of a **membrane attack complex** (**MAC**) (**Figure 1**), or can generate **opsonins** that label a bacterium for destruction. MAC can insert into the cell membrane of Gram-negative, but not Gram-positive, bacteria. There, it produces pores that allow the entry of membrane damaging molecules, such as **lysozyme**, and makes the bacterium susceptible to osmotic **lysis**.

The **alternative complement pathway** does not require antibody to initiate the lysis of bacteria. In this pathway, complement proteins from a complex known as **C3** directly bind to bacteria and activate downstream components in the complement cascade, once again ending in formation of MAC that causes lysis of the bacterium.

During the **lectin pathway**, **mannan-binding lectin** (**MBL**) binds to proteins containing mannose residues that are found in some types of bacteria (such as ***Salmonella spp.***). Once bound, MBL forms a complex with an enzyme called **MBL-activated serine protease** (**MASP**). In this form, this enzyme activates **C3 convertase** (by cleaving C2 and C4 complement components) that participates in forming MAC.

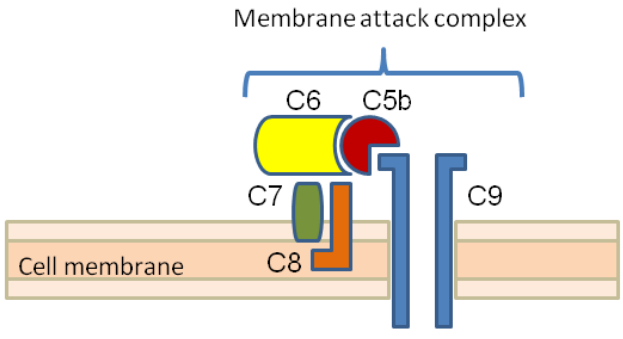

Figure 1. Complement proteins form a membrane attack complex in the membrane of bacterial cells that allows lysis of the bacterium

Via phagocytosis

Bacteria may also be killed by **phagocytes**. Immune proteins like **acute phase proteins** (like complement) and **antibodies** bind to the surface of bacteria by a process called **opsonisation**. Opsonised bacteria are, therefore, coated with molecules that phagocytic cells recognise and respond to. Activated phagocytes engulf and destroy opsonised bacteria by a process called **phagocytosis**. Complement C3b is a particularly important opsonisation protein for controlling bacterial infections by this mechanism. Opsonisation allows killing of Gram-positive bacteria (e.g. ***Staphylococcus spp***.) that are resistant to killing by MAC.

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Immune Responses to Bacteria *cont.*

Via phagocytosis *cont.*

After bacteria are ingested by phagocytosis (**Figure 2**), they are killed by various processes that occur inside the cell, and broken into small fragments by enzymes. Phagocytes present the fragments on their surface via **class II major histocompatibility** (**MHC class II**) **molecules**.

Circulating **helper T cells** recognise these bacterial fragments and begin to produce proteins called **cytokines**. Two major groups of helper T cells are known as **Th1** and **Th2** cells. These cell types differ in the types of cytokine they secrete. Th1 cells predominantly produce **interferon-g** (**IFN-g**), which promotes **cell-mediated immune mechanisms** (see below). Th2 cells produce mostly **interleukin-4** (**IL-4**), which promotes **humoral immunity** by activating **B cells**. B cells make antibodies that stick to extracellular bacteria and prevent their growth and survival.

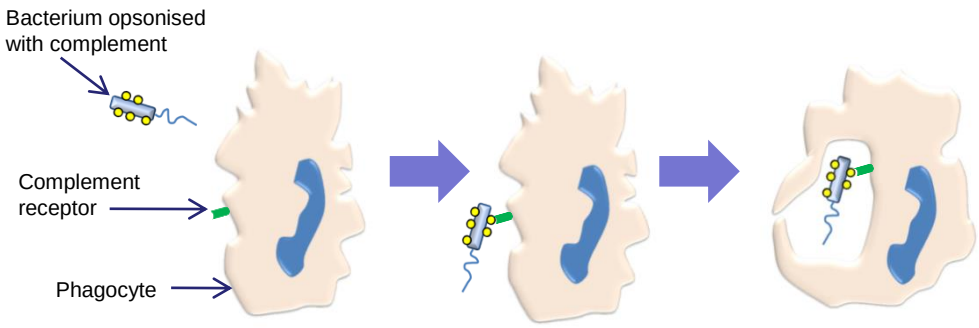

Figure 2. Opsonised bacteria are engulfed and destroyed by phagocytes

Via cell-mediated immunity

Some bacteria engulfed during phagocytosis avoid the killing mechanisms of the phagocyte to survive inside cells. **Macrophages** are a common targets for **intracellular bacteria** (e.g. ***Salmonella spp.)*** that live inside cell compartments. These bacteria cannot be detected by complement or antibody but, instead, are eliminated using a **cell-mediated response**. Infected macrophages present bacterial peptides on their cell surface using MHC class II molecules. This mechanism is called **antigen presentation**.

A helper T cell surveys MHC class II molecules with its **T-cell receptor** (**TCR**) to observe the peptides they hold. If a bacterial peptide is presented, the Th1 cell releases IFN-g. This cytokine stimulates killing mechanisms, (such as production of **lysozyme**) inside the infected macrophage to digest and destroy the invading bacterium. IFN-g also increases antigen presentation by cells, making the bacterium more visible to the immune system and more prone to attack (**Figure 3**).