بسم الله الرحمن الرحيم

Case study : Chronic granulomatous disease (CGD)

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ILOS : to understand the immunologic bases of CGD

:to understand phagocytosis as part of the innate immune system.

Background: the components of the innate immune system include phagocytic cells which are macrophages and neutrophils. These two cells phagocytose pathogens and products of cell injury through a three step process:

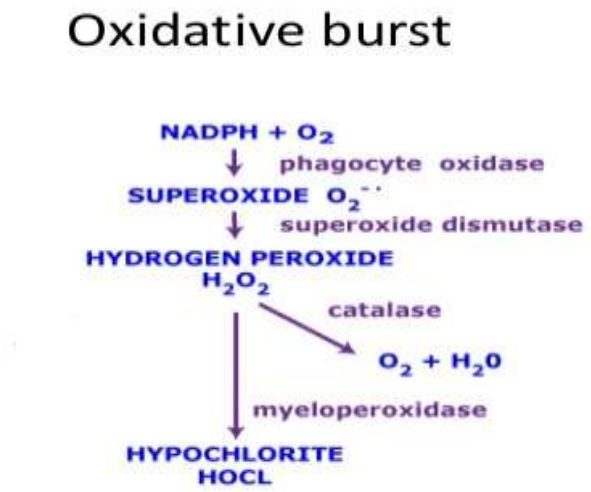
A. Recognition, by **pattern recognition receptors** (toll-like and inflammasomes)
B. Engulfment to form a phagosome
C. Killing by fusion of the phagosome to a lysosome, forming a phagolysosome. Pathogens are killed inside the phagolysosome to decrease the collateral damage of cells.
   Pathogens are killed by: lysosomal enzymes, reactive oxygen species (ROS) and reactive nitrogen species (RNS)

CGD is an **inherited** disease where there is a defect in phagocytosis involving the killing process. So recognition and engulfment are normal but killing is affected.

The precise problem in CGD is in killing by ROS as there is a defect in the enzyme used within the phagolysosome to create ROS. This enzyme is called phagosome oxidase or **NADPH oxidase**.

NADPH oxidases: this is the main enzyme that generates free radicals within the phagolysosome. It generates superoxide radical which undergoes dismutation to produce Hydrogen peroxide, which reacts with chlorine ions to form HOCL radical (hydrochlorite) which is highly lethal to pathogens.

Note that H2O2 can be neutralized by catalase.. see diagram below.



The presence of this multistep fashion is very important to protect our cells from the damaging effects of these highly reactive ROS.

Another mechanism important for protection of our cells is that the phagosome oxidase is inactive in phagocytes if they do not recognize a threat. It is normally inactive because it is actually composed of **six subunits**, some of them are in the cytosol, and others are attached to the phagosome membrane. As long as these subunits are not attached to each other the enzyme is inactive. Once the phagocyte is stimulated the cytosolic subunits translocate to the membrane and the enzyme is assembled and can now function.

One of the most important subunits is cytochrome b subunit in the membrane complex which has the catalytic site of the enzyme

If there is a genetic defect in *any* of the six subunits the enzyme cannot be assembled and no efficient bacterial killing will occur.

CGD: this is an inherited disease where there is genetic defect in any of the subunits. Some defects are inherited in an autosomal fashion whereas others are X linked (which is the commonest variant)

Because in these patients the phagosome oxidase cannot be assembled the above cascade of ROS production doesn't happen or is defective, so pathogens cannot be killed efficiently.

Note that the recognition and engulfment are not affected, so *there phagocytosis not leading to killing, this is called frustrated phagocytosis.* The macrophages accumulate and form a granuloma, hence the name chronic granulomatous disease.

Clinical features: patients with CGD have **recurrent infections** and unusual (**opportunistic infections**) that start at a **young age**.

Common pathogens affecting these patients include Staph. Aureus, aspergillus, pseudomonas and others.

Note that the problem is worse if the bacteria is catalase positive, because bacterial catalase will neutralize the hydrogen peroxide which is already deficient.

Catalase negative bacteria cannot neutralize the H2O2 produced and although the amount of this H2O2 is low it might be enough to kill that bacteria (like Strept pneumonia).

Diagnosis: nitro blue tetrazolium dye (NBT)is a pale yellow dye used to detect if there is H2O2. The dye is mixed with blood from the patient and if H2O2 is present it will be reduced and its color becomes purple. (don't worry about these details)

Immunoglobulin in these patients are usually high.

Treatment: (don't worry about these details)

Antibiotics

Bone marrow transplantation.. to provide normal precursors that give normal phagocytes

Gene therapy