2.1.9

Type IV Hypersensitivity

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Watch the video Type IV Hypersensitivity

Type IV hypersensitivity is the only one of the four hypersensitivity reactions that is carried by the cell mediated immune system (aka cytotoxic T-cells). The other three hypersensitivities are mediated by humoral immunity and involve antibodies. Cell mediated immunity is the principal mechanism used by the body to fight several microorganisms including viruses, tuberculosis bacteria, fungi, protozoa, and parasites. It can also lead to tissue injury as it responds to some chemicals and even self-antigens (autoimmunity).

Type 4 hypersensitivity reactions can be divided into two basic responses:

1. Direct Cell-Mediated Cytotoxicity

In this response, cytotoxic T lymphocytes (CTLs) bind to antigens expressed by cells on their MHC I glycoproteins. This binding results in the release of granzymes and perforins via degranulation of the CTL. The target cell becomes punctured by the perforins. The granzymes can then enter the target cell. Granzymes are proteases that damage intracellular proteins in the target cell and activate apoptotic pathways to induce a programmed cell death. Activated CTLs also express what is known as a Fas ligand that is similar to TNF-alpha. This Fas ligand binds to Fas receptors located on the target cells to activate apoptotic pathways. An example of this direct cell-mediated cytotoxicity is type 1 diabetes where cytotoxic T-cells target insulin secreting beta cells of the pancreas. Another example is graft rejections where cytotoxic T-cells target foreign grafted tissues.

2. Delayed Hypersensitivity

Delayed hypersensitivity is a delayed immune reaction that involves immune cells but not antibodies. It is referred to as delayed because it takes 24-72 hours to have a peak in the response. This is due to the fact that the effector cells of the reaction have to be recruited and accumulate near the area that antigen is discovered and then make cytokines involved in immune signaling. This long setup is why we refer to this response as delayed type hypersensitivity or DTH. Here are some examples of this type of hypersensitivity:

- Allergic contact dermatitis due to contact with poison ivy (more specifically a hapten called urushiol oil that is found in poison ivy). Urushiol reacts with the skin and causes a rash. This occurs because urushiol binds with proteins in the skin and alters them. The immune system recognizes these changed proteins as foreign and they are processed by an APC and presented on a MHC-II to a naïve helper T-cell. After a naïve helper T-cell binds, the APC will release cytokines that cause the helper T-cell to differentiate. If the APC releases IL-12 to the helper T-cell, it will differentiate into a T_H1. The T_H1 will then release cytokines like INF-gamma to activate macrophages. Activated macrophages will then release IL-1 and TNF-alpha which will cause endothelial cells to express receptors to recruit more white blood cells to the area. Macrophages will perform phagocytosis and release reactive oxygen species and toxic enzymes that cause the tissue damage that can be observed as a skin reaction. The APC might also release IL-6 which would cause the helper T-cell to differentiate into a T_H17. T_H17 will then release IL-17 that causes the activation of neutrophils that lead to increased inflammation.
- Another example of contact dermatitis is an allergic reaction to metal that touches the skin.
- Tuberculosis skin test. This test is performed to find out if a patient has been infected with mycobacterium tuberculosis. Protein components are injected into the skin and it takes some time for them to end up on MHC-II proteins of APCs where they can activate memory T_H1 which then activates cytotoxic T-cells. A positive test shows a significantly inflamed and raised bump at the site of injection due to recruited macrophages and neutrophils and subsequent inflammation.
- Hypersensitivity pneumonitis. This reaction occurs when a susceptible individual breathes in organic dusts or occupational antigens such as moldy hay (farmer's lung), tree bark, saw dust, animal dander, bird droppings, and/or mycobacterium. The presence of these substances results in activated helper T-cells in the lungs bringing about inflammation and damage to the pulmonary system.

****Please note that "Farmer's Lung" or hypersensitivity pneumonitis is also frequently referred to as a type III hypersensitivity. It appears that individuals can form antibodies against the moldy hay allergens that are inhaled and these antibodies can sometimes precipitate and create complexes that can trigger the complement cascade and create inflammation in various tissues.*