**The War Within: Immune Disorders and Autoimmunity**[Exploring the Cellular and Molecular Pathology of Human Diseases: A Case-Based Approach]

*Transcript updated on March 6, 2024*

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| **Slide 1** | *Title slide* |
| **Slide 2** | In this module, we will begin by introducing the immune system and the two branches of immunity: innate and adaptive immunity. We will then look into immune disorders and the four types of hypersensitivity disorders. Finally, we will apply these concepts to a case study. |
| **Slide 3** | The immune system is composed of various mechanisms that protect the human body against disease. It recognizes and eliminates pathogens, tumour cells, and microbial toxins. Pathogens are organisms that cause disease to their host and include viruses, bacteria, mycobacteria, parasites, and fungi. |
| **Slide 4** | The immune system can be divided into two major components: innate and adaptive immunity.  Innate immunity does not require previous exposure to an offending agent to activate and always leads to an immediate maximal response. Innate immunity offers limited protection as it can only recognize pathogens, which are predetermined by the genome.  On the other hand, adaptive immunity requires previous exposure and protects against pathogens that evade innate immunity. There is a delay between exposure and maximal response, but adaptive immunity offers broader and more robust protection as it can adapt and recognize any pathogen. As adaptive immunity requires previous exposure, it is pathogen- and antigen-specific and has immunological memory. Immunological memory allows for adaptive immunity to create an accelerated response upon re-exposure to previous pathogens. |
| **Slide 5** | Three components of the innate immune system include surface barriers, cells, and humoral and chemical barriers. Surface barriers are physical barriers that prevent entry of pathogens. The skin is an example of a surface barrier.  There are many cell types involved in innate immunity. These include phagocytes, granulocytes, natural killer cells and dendritic cells. Phagocytes are cells that engulf and digest microbes and cell debris through recognizing pattern-recognition receptors. Neutrophils, macrophages, and dendritic cells all act as phagocytes. Granulocytes include cells like eosinophils, basophils, and mast cells. These cells secrete chemical mediators to regulate the inflammatory response. Natural killer cells simply kill damaged or abnormal cells, and dendritic cells present antigens to initiate T cell responses.  The humoral response includes cytokines from injured cells being released into the extracellular fluid which stimulates inflammation. |
| **Slide 6** | The components of the adaptive immune system include cell-mediated and humoral responses.  Cells involved in adaptive immunity include lymphocytes and antigen-presenting cells. Lymphocytes include T cells, B cells, and Natural Killer cells. B-cells produce immunoglobulins, also known as antibodies. Antibodies bind to specific antigens to neutralize microbes and injured cells or target them for attack by other immune cells. Antigen-presenting cells include dendritic cells and macrophages.  Circulating antibodies, made by B cells, is part of the humoral response of the adaptive immune system.  Antibodies allow for the recognition of specific non-self antigens and lead to the development of immunological memory. These features allow for a faster response upon reinfection of the same pathogen. |
| **Slide 7** | Immune disorders can be broadly classified as either diseases of hypofunction or hyperfunction.  Hypofunction indicates a decrease in function and can lead to increased susceptibility to infections and cancer.  Hyperfunction, also known as hypersensitivity, indicates an increase in function and could lead to damage to normal tissue. Diseases resulting from hypersensitivity are often chronic due to persistence of these antigens amplifying the immune response. |
| **Slide 8** | There are four types of hypersensitivity reactions.  Type I hypersensitivity reaction, also known as an anaphylactic, allergic, or atopic reaction, is caused by an exaggerated IgE-mediated immune response against normal non-pathogenic antigens. IgE molecules are attached to mast cells and upon binding an antigen, IgE antibodies activate the mast cells causing them to degranulate. Degranulation of mast cells leads to the release of histamine, which increases vascular permeability and mediates an inflammatory response. Type I hypersensitivity reactions can be fatal.  A severe allergic reaction to a bee sting can cause rapid swelling and breathing difficulties. This is an example of a Type I reaction. |
| **Slide 9** | Type II hypersensitivity reactions are antibody-mediated. Antibodies bind to antigens on the surface of cells or tissues and target them for destruction. This reaction is mediated by IgM and IgG antibodies.  Autoimmune hemolytic anemia is a type II reaction. It is a rare red blood cell disorder where antibodies attack a person’s own red blood cells leading to anemia. |
| **Slide 10** | Type III hypersensitivity reactions are caused by excessive amounts of circulating immune complexes. Immune complexes are formed when antibodies bind to antigens. These complexes become trapped in various tissues causing injury by activating innate immune mechanisms and neutrophilic-mediated inflammation.  Glomerulonephritis is a type III reaction. It is a disorder caused by the lodging of immune complexes in the filtering vessels of the kidney, leading to inflammation and damage. |
| **Slide 11** | Type IV hypersensitivity is cell-mediated and includes two types: delayed type hypersensitivity, and T cell-mediated cytotoxicity.  Delayed type hypersensitivity is mediated by CD4+ T cells, which differentiate into helper T cells upon antigen exposure. Upon subsequent antigen exposure, differentiated helper T cells migrate to the site of exposure, activating macrophages and neutrophils. Thee activated macrophages lead to phagocytosis and the neutrophils cause acute inflammation, overall resulting in tissue damage. Poison ivy exposure can cause this type of hypersensitivity reaction and lead to inflammation of the skin.  On the other hand, T cell-mediated cytotoxicity is mediated by CD8+ T cells. These CD8+ T cells destroy cells expressing a particular antigen. Type I diabetes is an example of T cell-mediated cytotoxicity. |
| **Slide 12** | Let’s take a look at a case study. Maria Albu is a 22-year-old college student. She has a persistent rash on her skin and complains of recurrent respiratory infections. She reports a family history of autoimmune disorders. Maria is otherwise healthy and has no significant medical history. |
| **Slide 13** | Upon initial examination, Maria’s vital signs are within normal physiological range. She does, however, have decreased levels of IgA and a high number of eosinophils. Eosinophils are identifiable by bi-lobed nuclei and large red granules, similar in colour to red blood cells. |
| **Slide 14** | Maria undergoes a skin biopsy to examine the histological changes in the persistent rash. Three features are revealed:   * First, her skin is undergoing subepidermal blistering. This is caused by the formation of fluid-filled spaces below the top layer of the skin. * Second, there is infiltration of neutrophils causing acute inflammation. * Third, linear deposits of IgA are found along the basement membrane. This is consistent with dermatitis herpetiformis, which is a skin manifestation associated with celiac disease. |
| **Slide 15** | *Histological analysis* |
| **Slide 16** | Maria’s blood test indicates a deficiency in IgA, a crucial component of humoral immunity. This could explain her recurrent respiratory infections as IgA plays a significant role in protecting mucosal epithelia, such as that of the lungs. Furthermore, histopathological examination of the skin biopsy revealed a T cell infiltration in the dermal-epidermal junction, suggesting immune dysregulation. |
| **Slide 17** | *Hypersensitivities* |
| **Slide 18** | *Knowledge check* |
| **Slide 19** | *Knowledge check* |
| **Slide 20** | *Knowledge check* |
| **Slide 21** | *Knowledge check* |