Mechanisms of Immunotoxicity

Subjects: Immunology

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The immune system orchestrates the body's main defense against invading biologic agents including but not limited to bacteria, viruses, chemicals, and foreign tissues. Lymphocytes, neutrophils, macrophages, eosinophils, and basophils are the main players. These cells are produced at an increased rate during childhood, where such a blood draw in a child would reveal an average number of 3000/mm3 compared to 4500–11,000/mm3 in adults, and the development of the human immune system begins in the fetal period and reaches its maximum capacity around puberty.

Keywords: immunotoxicity ; microbiota ; hypersensitivities ; allergies ; immune system ; cigarette smoke ; stressors ; chemicals

1. Overview

The immune system defends the body against certain tumor cells and against foreign agents such as fungi, parasites, bacteria, and viruses. One of its main roles is to distinguish endogenous components from non-self-components. An unproperly functioning immune system is prone to primary immune deficiencies caused by either primary immune deficiencies such as genetic defects or secondary immune deficiencies such as physical, chemical, and in some instances, psychological stressors. In the manuscript, we will provide a brief overview of the immune system and immunotoxicology. We will also describe the biochemical mechanisms of immunotoxicants and how to evaluate immunotoxicity.

2. Introduction and Overview of the Immune System

2.1. Immune Cells and Their Development

The immune system orchestrates the body's main defense against invading biologic agents including but not limited to bacteria, viruses, chemicals, and foreign tissues. Lymphocytes, neutrophils, macrophages, eosinophils, and basophils are the main players. These cells are produced at an increased rate during childhood, where such a blood draw in a child would reveal an average number of 3000/mm^3 compared to 4500–11,000/mm^3 in adults [1], and the development of the human immune system begins in the fetal period and reaches its maximum capacity around puberty [1]. A multipotent stem cell gives rise to either a myeloid stem cell or a lymphoid stem cell. Eosinophils, basophils, and neutrophils arise from myeloblasts through granulocytopoiesis. Myeloid stem cells also give rise to monoblasts, which become monocytes and later on macrophages through monocytpoiesis. Lymphoid stem cells give rise to B-cells, T-cells, and natural killer cells. Controlled by negative feedback, the immune system's headquarters is in lymphatic tissues. The primary organs are the bone marrow where immune cell production and B-cell maturation take place and the thymus where T-cell maturation takes place. The secondary organs are the spleen, lymph nodes, tonsils, and Peyer's patches. The secondary organs allow immune cells to interact with antigens. Some T-cells and B-cells undergo further differentiation and pick up various functions [1]. T-cell precursors in the bone marrow move to the cortex in the thymus to undergo positive selection and later on to the medulla where they undergo negative selection. The former is when T-cells expressing T-cell receptors capable of binding self-major histocompatibility complex (MHC) on cortical epithelial cells survive. The latter is when T-cells expressing T-cell receptors with high affinity undergo apoptosis or become regulatory T-cells. These cells later on become cytotoxic T-cells, T-helper cells, or T-suppressor cells. Cytotoxic cells destroy target cells in order to avoid the progression of a virus infection or cancerous growth. Cytokines dictate the cell-to-cell regulation of the immune system.

2.2. Innate and Adaptive Immune Cells and Their Activities

The immune system is subdivided into two complementary functions. The first is called the innate immunity, which is made up of neutrophils, macrophages, dendritic cells, natural killer cells, complement, chemokines, physical epithelial barriers, and secreted enzymes [2][3][4]. The innate immunity is germline encoded and resistance persists through generations and does not change within an organism's lifetime. The adaptive immunity's components are the T-cells, B-cells, and

antibodies, and it undergoes variation through V(D)J recombination during lymphocyte development. Microbial resistance here is not heritable. While the innate immunity's response to pathogens is nonspecific and occurs rapidly with no memory response, the adaptive immunity is highly specific, is refined over time, develops over long periods, and a memory response is formed. Once a memory response is formed, subsequent exposure to a previously encountered antigen results in a stronger and quicker immune response.

The innate immunity functions through toll-like receptors, pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to the activation of NF-κB. Some of these PAMPs are lipopolysaccharides present on Gram-negative bacteria, flagellin, and nucleic acids.

On the other hand, the adaptive immune response is much more intricate. The adaptive immune response is split into humoral and cellular immunity. T-cell activation and B-cell activation, along with class switching, occurs. Specialized antigen presenting cells called dendritic cells take up antigens and migrate to the draining lymph node. Foreign antigens are presented on MHC II in dendritic cells and are recognized by T-cell receptors on CD4+ cells. Endogenous or cross-presented antigens are presented on MHC I to CD8+ cells [1]. After T-cell activation is done, T-cell proliferation and survival is achieved through a costimulatory signal via interaction of the B7 protein (CD80/86) on dendritic cell and CD28 on naïve T-cells. Concerning B-cells, the same steps just mentioned take place as well to activate a T-helper (CD4+) cell [1]. Antigens presented on T-cell receptors of activated T-helper cells interact with MHC II on B-cells. Next, CD40 receptors on B-cells bind the CD40 ligand on T-helper cells. Finally, T-helper cells secrete cytokines that determine immunoglobulin class switching of B-cells. B-cells are activated, undergo class switching and affinity maturation, and begin producing antibodies [1]. An excessive reaction is prevented from happening due to a negative feedback caused by a decrease in T-cells.

3. Conclusions

A functioning immune system protects individuals from various stressors: chemical, physical, biological, and foreign substances along with tumor cells from within. This system requires a high level of coordination in order to interact with every antigen. Two types of immune responses exist: non-specific and acquired. The latter response could be further split into humoral and cell-mediated immunity. Since the immune system is intricate, it is vulnerable to the effects of toxic substances. An alteration in the immune response leads to either suppression, autoimmunity, or hypersensitivity. Many factors come into play when immunotoxicity is considered. Genetic factors, external risk factors, and the antigen involved are the three main pillars that dictate how the reaction proceeds. A lot of progress has been made over the past 40 years in immunotoxicology, and with the scientific advances, much more will be unraveled.

References

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