Humoral Immunity and Cell-Mediated Immunity

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Humoral immunity, or antibody-mediated beta cellular system, is a type of immunity which is mediated by macromolecules found in fluids such as the secreted antibodies, complement proteins, and bound antimicrobial peptides. In contrast to cell-mediated immunity, the term 'humoral' describes the non-cellular compositions of the blood, such as plasma and lymphatics. However, the cellular components of the blood, such as lymphocytes and antigen-presenting cells, are important for mediating antigen-specific antibody reaction.

Primary Immune Response

An antigen is any foreign substance that elicits an immune response when introduced into the tissues of a susceptible animal, and they are capable of combining with specific antibodies formed.

The primary immune response refers to the host’s first encounter with an antigen, in which naïve B cells activate and proliferate to induce an effective immune response against the antigen. The primary immune response is relatively slow in protecting against invasive pathogens, mostly because it induces the release of polyclonal, natural antibodies. These antibodies have a low affinity, but the body uses them in its initial defense against pathogens. The lag phase of this response ranges from 4-7 days to weeks or even months, depending on the type of pathogen, the amount of exposure, and...
the state of the host’s immune system.

Secondary Immune Response

In the secondary immune response, a certain type of cell called a ‘memory B cell’ becomes activated. This occurs upon the second or subsequent exposure of the host to a particular antigen. Unlike the primary response, the secondary immune response is relatively faster and more effective in suppressing infections because of its increased antibody binding affinities. This is how vaccines work. Since vaccines induce the initial primary immune response, the body responds more quickly and effectively upon re-exposure to the same antigen (secondary response) from which the vaccine was made.

The primary immune response is governed by the innate immune system. All successive responses are made by the adaptive immune system, also called acquired immunity. This system provides two types of immunity: humoral and cell-mediated. Humoral immunity is based on serum antibodies that are produced by plasma cells and bind to antigens in order to assist with their elimination. Cell-mediated immunity is based on the action of cytotoxic cells that activate other immune cells and help eliminate pathogens and infected host cells.

T cell-dependent and -independent Antigens

A B cell response is classified as T cell-dependent (TD) or T cell-independent (TI) based on whether the antigen depends on T cells to activate the B cells and elicit an immune response.

T cell-independent activation of B cells occurs when T-independent antigens interact with B cell receptors (BCRs). TI antigens, such as the polysaccharide bacteria capsules, contain repetitive epitope units within their structure, which allows for the cross-linkage of multiple BCRs at a time. This serves as the first signal for B cell activation. The second signal involves toll-like receptors with pathogen-associated molecular patterns (PAMPs) or interactions with factors from the complement system.

Once a B cell is activated, it undergoes clonal proliferation, and daughter cells differentiate into plasma cells. After differentiation, the BCRs on the surfaces of the B cells disappear, and the plasma cells secrete IgM molecules with the same antigen specificity as the BCRs. The TI response only lasts a short period of time and does not result in the production of memory B cells. Thus, it will not cause a secondary response to subsequent exposures to that particular antigen.
TD activation of B cells triggers a stronger immune response that develops memory cells with the capacity for secondary immune response. TD activation occurs in response to free protein antigens or protein antigens bonded on a pathogen’s surface. The interaction between the BCRs and free protein antigens internalizes the antigen, whereas interaction with antigens associated with a pathogen requires the extraction of the antigen from the pathogen before internalization.

The protein antigen is processed within the B cell and presented with MHC II. The presented antigen is then recognized by helper T (Th) cells specific to the same antigen. The T cell receptor (TCR) of the Th cell recognizes the antigen, and its CD4 molecule interacts with the MHC II on the B cell. This coordination between B cells and Th cells is called linked recognition.

Once activated, the Th2 cells secrete cytokines that activate the B cell, which proliferates into clonal daughter cells. Additional cytokines from the Th2 cells stimulate the differentiation of activated B cell clones into memory B cells. These memory cells can quickly respond to subsequent exposures to the same protein antigen. Differentiated plasma cells will lose their membrane BCRs and secrete IgM initially.

Later, cytokines from the Th2 cells will stimulate the plasma cells to begin secreting IgG, IgA, or IgE. This process is called class switching or isotype switching. It allows the plasma cell to switch the type of antibody it produces while the antigen-specificity remains constant.

Structure of Antibodies and Immunoglobulin Domains

Each antibody molecule consists of four polypeptides, two heavy chains, and two light chains joined to form a “Y” shaped molecule. The chains are connected by disulfide bonds. There are five types of Ig heavy chains (in mammals) denoted by the
Greek letters: $\alpha, \delta, \epsilon, \gamma,$ and $\mu.$ There are two types of Ig light chains (in mammals), which are called lambda ($\lambda$) and kappa ($\kappa$).

Antibodies consist of a variable region and a constant region. The variable region changes to various structures depending on differences in antigens. The variability is expressed in the amino acid sequence in the tips of the “Y”. The constant region determines the mechanism used to destroy the antigen.

**Antibody Polymers and Antibody Binding to Antigens**

The antigen-antibody reaction is widely used in laboratory diagnostics, including immunohematology. It is a reversible chemical reaction:

\[ \text{Antigen} + \text{antibody} \rightleftharpoons \text{antigen-antibody complex} \]

The forces connecting the antigen-antibody are not sturdy valence bonds, but weaker bonds that are fittingly named “weak interactions.”

The part of the antibody that interacts with the antigen is in the Fab portion of the antibody molecule and is assembled from the hypervariable regions of the heavy and light chains located at the tips of the “Y.” The binding between this site and the antigen takes place with the following characteristics and processes:

- The bonds holding the antigen to the antibody are non-covalent/reversible in nature. They may be hydrogen bonds, electrostatic bonds, or Van der Waals forces.
- Usually, there are multiple bond formations observed to ensure relatively tight binding between antibody and antigen.
- The specific binding between the antigenic determinant on the cell (known as epitope) and the antigen combining site (paratope) on the antibody involves very small portions of the molecules, usually comprising only a few amino acids.
- These sites are critical in antigen-antibody reactions as specific binding has to overcome the natural repulsion between the two molecules.
- When the two sites come together they are first attracted to each other by ionic and hydrophobic forces.
- These forces help them overcome their hydration energies and allow for the expulsion of water molecules as the two parts approach each other.
- This attraction becomes even stronger when Van der Waals forces are employed later on to bring the epitope and paratope even closer.
The Function of Antibodies

- **IgG:**
  - Provides long term protection because it persists for months or years after initial exposure to the antigen
  - Protects against bacteria and viruses
  - Neutralizes bacterial toxins
  - Triggers complement protein systems and bind antigens to enhance the effectiveness of phagocytosis

- **IgA:**
  - Binds antigens on microbes before they invade tissues
  - Aggregates antigens and keeps them within mucosal secretions, so that the antigen will be expelled with the secretion (e.g. coughing, sneezing)
  - Defends mucosal surfaces such as the intestines, nose, and lungs

- **IgM:**
  - Involved in the antigens on the surface of red blood cells that determine the ABO blood group
  - Enhances the ingestion of cells via phagocytosis

- **IgE:**
  - Binds to mast cells and basophils which participate in the immune response
  - Protects against parasites

- **IgD:**
  - Present on the surface of B cells
  - Plays a role in the induction of antibody production
Classes of Antibodies (Immunoglobulin)

<table>
<thead>
<tr>
<th>IgM pentamer</th>
<th>IgG monomer</th>
<th>Secretory IgA dimer</th>
<th>IgE monomer</th>
<th>IgD monomer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heavy chains</strong></td>
<td><strong>μ</strong></td>
<td><strong>γ</strong></td>
<td><strong>α</strong></td>
<td><strong>ε</strong></td>
</tr>
<tr>
<td>Number of antigen binding sites</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Molecular weight (Daltons)</td>
<td>900,000</td>
<td>150,000</td>
<td>385,000</td>
<td>200,000</td>
</tr>
<tr>
<td>Percentage of total antibody in serum</td>
<td>8%</td>
<td>80%</td>
<td>13%</td>
<td>0.062%</td>
</tr>
<tr>
<td>Crosses placenta</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fixes complement</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fc binds to</td>
<td>phagocytes</td>
<td>mast cells and basophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor</td>
<td>Main blood antibody of secondary responses, neutralizes toxins, opsonization</td>
<td>Secreted into mucus, tears, saliva, colostrum</td>
<td>Antibody of allergy and antiparasitic activity</td>
</tr>
</tbody>
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Autoimmune Disease

Autoimmune diseases can affect the human immune system, so the primary goal is to create self-immunity. However, if a person’s body hasn’t developed an adequate immune system, some autoimmune diseases can appear, such as rheumatic fever, rheumatoid arthritis, ulcerative colitis, myasthenia gravis, Guillain-Barré syndrome, Reiter’s syndrome, reactive arthritis, or type 1 diabetes mellitus.

Conclusion of Humoral Immunity and Cell-Mediated Immunity

Antigens are generally of high molecular weight and consist of proteins or polysaccharides. One of the most familiar antigenic pathogens is microbes, which contain and produce many antigens. Antigens consist of many specific sites called epitopes that connect and bind to antibodies. There are two kinds of immune responses and resulting immunity: humoral or circulating antibody system (mainly dependent on B cells) and cell-mediated immunity (mainly dependent on T cells).
The human immune system begins at birth, as it develops from the embryonic stage, beginning with hematopoietic stem cells. Those stem cells develop and differentiate into bigger cells in the immune system (granulocytes, monocytes, and lymphocytes).

Stem cells differentiate throughout human life into cells that may or may not be involved in immune system function (erythrocytes and megakaryocytes).

**Humoral immune responses to antigens** begin by exposing the host to an antigen for the first time. Here, the immune system begins to make low levels of antibodies, approximately within a week. During the second exposure to the same antigen, the human immune system produces a much faster response and the ability of these antibodies to bind.

Whilst injecting a new antigen can only elicit a primary response, it shows that memory or prior exposure is required for a fast response.

**References**


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