

IMMUNOLOGY

Antigens

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Keywords

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Definitions

Antigen

Antigen (Ag) can be described as a substance that reacts with the products of a specific immune response. The word originated from the notion that they can stimulate antibody generation. This phenomenon is known as antigenicity of a molecule.

Immunogen

Immunogen on the other hand is a substance that induces a specific immune response and the phenomenon is known as immunogenicity. Immunogens are usually proteins or polysaccharides. This includes parts (coats, capsules, cell walls, flagella, fimbriae, and toxins) of bacteria, viruses, and other microorganisms. Lipids and nucleic acids are antigenic only when combined with proteins and polysaccharides. Non-microbial exogenous (non-self) antigens can include pollen, egg white, and proteins from transplanted tissues and organs or on the surface of transfused blood cells.

Tolerogen

Tolerogen is an antigen that invokes a specific immune non-responsiveness due to its molecular form. If its molecular form is changed a tolerogen can become an immunogen.

Allergen

An allergen is a substance that causes the allergic reaction. The (detrimental) reaction may result after exposure via ingestion, inhalation, injection or contact with skin.

Cells present their antigens to the immune system via a histocompatibility molecule. Depending on the antigen presented and the type of the histocompatibility molecule, several types of immune cells can become activated.

Antigen Classification

Classification by origin

Exogenous antigens

Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. By endocytosis or phagocytosis, these antigens are taken into the antigen-presenting cells (APCs) and processed into fragments. APCs then present the fragments to T helper cells (CD4⁺) by the use of class II histocompatibility molecules on their surface. Some T cells are specific for the peptide:MHC complex. They become activated and start to secrete cytokines. Cytokines are substances that can activate cytotoxic T lymphocytes (CTL), antibody-secreting B cells, macrophages and other particles.

Endogenous antigens

Endogenous antigens are antigens that have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with MHC class I molecules. If activated cytotoxic

CD8⁺ T cells recognize them, the T cells begin to secrete different toxins that cause the lysis or apoptosis of the infected cell. In order to keep the cytotoxic cells from killing cells just for presenting self-proteins, self-reactive T cells are deleted from the repertoire as a result of tolerance (also known as negative selection which occurs in the thymus).

Autoantigens

An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should under normal conditions not be the target of the immune system, but due to mainly genetic and environmental factors the normal immunological tolerance for such an antigen has been lost in these patients.

Classification according to the cellular response generated

T-independent Antigens

T-independent antigens are antigens which can directly stimulate the B cells to produce antibody without the requirement for T cell help. In general, polysaccharides are T-independent antigens. The responses to these antigens differ from the responses to other antigens.

Properties of T-independent antigens

1. Polymeric structure

These antigens are characterized by the same antigenic determinant repeated many times.

2. Polyclonal activation of B cells

Many of these antigens can activate B cell clones specific for other antigens (polyclonal activation). T-independent antigens can be subdivided into Type 1 and Type 2 based on their ability to polyclonally activate B cells. Type 1 T-independent antigens are polyclonal activators while Type 2 are not.

3. Resistance to degradation

T-independent antigens are generally more resistant to degradation and thus they persist for longer periods of time and continue to stimulate the immune system.

T-dependent Antigens

T-dependent antigens are those that do not directly stimulate the production of antibody without the help of T cells. Proteins are T-dependent antigens. Structurally these antigens are characterized by a few copies of many different antigenic determinants.

Factors Influencing Immunogenicity of an Antigen

1. Foreignness

The immune system normally discriminates between self and non-self such that only foreign molecules are immunogenic.

2. Size

There is not absolute size above which a substance will be immunogenic. However, in general, the larger the molecule the more immunogenic it is likely to be.

3. Chemical Composition

In general, the more complex the substance is chemically the more immunogenic it will be. The antigenic determinants are created by the primary sequence of residues in the polymer and/or by the secondary, tertiary or quaternary structure of the molecule.

4. Physical form

In general particulate antigens are more immunogenic than soluble ones and denatured antigens more immunogenic than the native form.

5. Degradability

Antigens that are easily phagocytosed are generally more immunogenic. This is because for most antigens (T-dependant antigens, see below) the development of an immune response requires that the antigen be phagocytosed, processed and presented to helper T cells by an antigen presenting cell (APC).

Antigenic Determinants

Determinants recognized by B cells

1. Composition

Antigenic determinants recognized by B cells and the antibodies secreted by B cells are created by the primary sequence of residues in the polymer (linear or sequence determinants) and/or by the secondary, tertiary or quaternary structure of the molecule (conformational determinants).

2. Size

In general antigenic determinants are small and are limited to approximately 4-8 residues. (amino acids and or sugars). The combining site of an antibody will accommodate an antigenic determinant of approximately 4-8 residues.

3. Number

Although, in theory, each 4-8 residues can constitute a separate antigenic determinant, in practice, the number of antigenic determinants per antigen is much lower than what would theoretically be possible. Usually the antigenic determinants are limited to those portions of the antigen that are accessible to antibodies.

Determinants recognized by T cells

1. Composition

Antigenic determinants recognized by T cells are created by the primary sequence of amino acids in proteins. T cells do not recognize polysaccharide or nucleic acid antigens. This is why polysaccharides are generally T-independent antigens and proteins are generally T-dependent antigens. The determinants need not be located on the exposed surface of the antigen since recognition of the determinant by T cells requires that the antigen be proteolytically degraded into smaller peptides. Free peptides are not recognized by T cells, rather the peptides associate with molecules coded for by the major histocompatibility complex (MHC) and it is the complex of MHC molecules + peptide that is recognized by T cells.

2. Size

In general antigenic determinants are small and are limited to approximately 8-15 amino acids.

3. Number

Although, in theory, each 8-15 residues can constitute a separate antigenic determinant, in practice, the number of antigenic determinants per antigen is much less than what would theoretically be possible. The antigenic determinants are limited to those portions of the antigen that can bind to MHC molecules. This is why there can be differences in the responses of different individuals.

Haptens

A Hapten is a substance that is non-immunogenic but which can react with the products of a specific immune response. It is a small molecule which can elicit an immune response only when attached to a large carrier such as a protein, the carrier may be one which also does not elicit an immune response by itself (Generally, only large molecules, infectious agents, or insoluble foreign matter can elicit an immune response in the body.). On their own they can never induce an immune response. Free haptens, however, can react with products of the immune response after such products have been elicited. Haptens have the property of antigenicity but not immunogenicity.

Once the body has generated antibodies to a hapten-carrier adduct, the small-molecule hapten may also be able to bind to the antibody, but it will usually not initiate an immune response; usually only the hapten-carrier adduct can do this. Sometimes the small-molecule hapten can even block immune response to the hapten-carrier adduct by preventing the adduct from binding to the antibody. A well known example of a hapten is urushiol, which is the toxin found in poison ivy. When absorbed through the skin from a poison ivy plant, urushiol undergoes oxidation in the skin cells to generate the actual hapten, a reactive molecule called a quinone which then reacts with skin proteins to form hapten adducts. Typically the first exposure only causes *sensitization*, in which there is a proliferation of B cells able to make antibody to the hapten adduct. After a second exposure later, the proliferated B cells can become activated, generating an immune reaction producing the typical blisters of poison ivy exposure.

Some haptens can induce autoimmune disease. An example is hydralazine, a blood pressure lowering drug which occasionally can produce drug-induced lupus erythematosus in certain individuals. This also appears to be the mechanism by which the anaesthetic gas halothane can cause a life-threatening hepatitis, as well as the mechanism by which penicillin-class drugs causes autoimmune hemolytic anemia.

Suggested Reading

1. Alberts, Bruce; Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walters (2002). *Molecular Biology of the Cell*; Fourth Edition. New York and London: Garland Science.
2. Janeway CA, Jr. *et al* (2005). *Immunobiology*, 6th ed., Garland Science.
3. Microbiology and Immunology On-Line Textbook: USC School of Medicine