

Chapter 2

Immune System of the Skin

The immune system is divided into two functional components: the innate and the adaptive. In the skin, the stratum corneum is the first line of defense (innate component). The adaptive system comes into play when there is a breach in the innate system. The skin produces specific reaction to each infectious agent and prevents it from attacking the body. These two components comprise the “skin immune system” (SIS).

Two basic types of adaptive immunity occur in the body. In one of these, the body develops circulating antibodies, which are capable of attacking the invading organism. This is called humoral immunity and is brought about by B-lymphocytes, which change to plasma cells to produce the antibodies.

The second type of adaptive immunity is achieved through the formation of large number of activated lymphocytes that are specially designed to destroy foreign agents. This immunity is called cell-mediated immunity. It is brought about by T lymphocytes.

The immune system of the skin can be studied under the following headings:

- Stratum corneum
- Cellular components of the immune system
- Molecular components of the immune system

2.1 The Stratum Corneum

This is the tough outer layer of the skin. It consists of 20–25 layers of thin, flattened cells, that overlap each other and consists of completely keratinized cells. Intercellular lipids connect the cells of the stratum corneum with each other. This dry mechanical barrier prevents the loss of fluids from the body and prevents the entry of microorganism and chemicals into the body. It also removes the contaminated organisms and chemicals from the body, through desquamation.

2.2 Cellular Components

These are the Langerhans cells, keratinocytes, T lymphocytes, mast cells, and dermal dendritic cells.

2.2.1 *Langerhans Cells*

These form the first line of cellular immune system of the skin. They are dendritic cells derived from the bone marrow; they contain cytoplasmic organelles called Birberk granules. These cells play an important role in antigen presentation. These cells can be identified by their surface markers CD1a and S-100 (present also in melanocytes).

2.2.2 *Keratinocytes*

These cells in addition to their protective role have immunological functions of their own. These cells produce large number of cytokines and produce α -melanocyte stimulating hormone, which is immunosuppressive. The keratinocytes express on their surface immune reactive molecules such as

MHC class 11 antigens, e.g., HLA-DR and intercellular adhesion molecules (ICAM-1).

2.2.3 *T Cells*

These cells circulate through the normal skin. There are different types of T cells depending upon their function. These are:

- Helper T cells (Th), these cells are CD4 positive. There are two type of T helper cells; Th 1, these promote inflammation, secrete IL-3, interferon, and tumor necrotic factor. Th 2 cells stimulate B cells to produce antibodies, and secrete IL-4, IL-6 and IL-10. B cells are not found in normal skin, only in disease states.
- Cytotoxic T cells (Tc) are CD 8 positive. These cells are recognized by MHC Class 1 molecules on their surface. These cells are capable of destroying allergenic and virally infected cells.
- Suppressor T cells (Ts), these cells regulate other lymphocytes.

2.2.4 *Mast Cells*

These cells are present in most connective tissues, predominantly around the blood vessels. They release histamine and other vasoactive molecules when stimulated. Mast cells play an important role in urticaria.

2.2.5 *Dermal Dendritic Cells*

These are poorly characterized cells, present around the small blood vessels of the papillary dermis. They bear MHC Class 11 antigen on their surface. Like Langerhans cells they probably play a role in antigen presentation.

2.3 Molecular Components

2.3.1 *Antigens and Haptens*

Antigens are molecules with large molecular weight that are recognized by the immune system, producing an immune response, usually in the form of a humoral response. Haptens are chemicals of low molecular weight that cannot provoke an immune response, unless they combine with a protein. They are important sensitizers in allergic contact dermatitis.

2.3.2 *Super-Antigens*

These molecules, often bacterial toxins, do not require to be recognized by an immune system, they directly signal to different classes of T cells, causing their proliferation and cytokine production, e.g., toxin produced by phage group 2 *Staphylococcus aureus* causes staphylococcal scalded skin syndrome.

2.3.3 *Histocompatibility Antigens*

The tissue type antigens of an individual are found in the major histocompatibility complex (MHC), located in man on the HLA gene cluster on chromosome 6. HLA-A, -B and -C are expressed on all nucleated cells and are referred to as Class 1 antigens. HLA-DR, -DP, -DQ and -DZ antigens are expressed only on some cells, e.g., Langerhans cells. They are poorly expressed on keratinocytes except during disease process. These antigens are vital for tissue recognition, but are also involved in transplant rejection.

2.3.4 *Antibodies*

A number of antibodies are produced in response to antigens. Antibodies (IgA, IgD, IgE, IgG, and IgM) are produced by

the differentiation of B-lymphocytes to plasma cells. The antibodies neutralize or opsonize antigens and activate the complement system. The highly specific mechanism of the immune system serves to recognize the particular antigen whose elimination is then accomplished in a relatively nonspecific way. In addition, the antigen (with T and B memory cells) is held in memory.

- IgG is responsible for the secondary response to most antigens. It can cross the placenta, activate complement (classical pathway), coat the neutrophils and macrophages, and act as an opsonin by cross-bridging the antigen.
- IgM is the largest antibody; it does not cross the placenta, and it is responsible for most of the primary response to antigens.
- IgA is the most common antibody in secretions; it does not bind complement but can activate it by the alternate pathway.
- IgE is bound to the receptors in the mast cells and basophils. Its release causes Type I immediate hypersensitivity reactions such as hay fever and asthma. It is present in very small quantities in the blood.
- IgD has some properties of IgG, and is found exclusively on the surface of the B-lymphocytes.

2.3.5 *Cytokines*

Some cells such as T lymphocytes, macrophages, Langerhans cells, fibroblasts, endothelial cells, and keratinocytes secrete cytokines, these are small proteins. They regulate the amplitude and duration of an inflammation by acting locally on nearby cells (paracrine), on the cells which produce them (autocrine); seldom do they act away from the site of production.

The term cytokine includes a number of substances such as interleukins, interferons, colony stimulating factor, cytotoxins, and growth factors. Cytokines frequently have overlapping actions, some may act synergistically and some may antagonize each other.

2.3.6 *Eicosanoids*

These are nonspecific inflammatory mediators, e.g., prostaglandins, leukotrienes, thromboxanes. These are products of arachidonic acid, present on cell membrane lipid, and they play an important part during inflammation, they serve as both intracellular messengers and extracellular mediators.

2.3.7 *Cellular Adhesion Molecules (CAMs)*

These are surface glycoproteins that are present on different type of cells; they are involved in cell-cell adhesion and cell-matrix adhesions. CAMs are classified in to four families – selectin, integrin, immunoglobulins superfamily (molecules similar in structure to immunoglobulin), and cadherins.

2.3.8 *Complement*

The complement is a group of about 20 proteins in the blood, which interact with one another and with the other components of innate and adaptive immune system. Microorganisms activate the complement system. Complement stimulates the antigen antibody complexes via the alternative or classical pathway. The principal activities of the complement system are directed at protection against infection. It has a wide range of biological effects. One of its components, C_3 , seems to play a role in immunological memory.

The complement helps in the following biological effects: histamine release, neutralization of viruses, release of kinins, increased vascular permeability, leukocyte immobilization, promotion of phagocytosis, promotion of fibrinolysis, and promotion of coagulation.

2.4 Hypersensitivity Reactions

2.4.1 *Type I (Immediate)*

IgE is bound to the surface of the mast cells. On encountering an antigen, the mast cells degranulate, with the release of inflammatory mediators such as histamine, e.g., urticaria and in severe cases anaphylaxis.

2.4.2 *Type II (Cytotoxic Reaction)*

Antibodies are directed against an antigen present on target cells; they produce cytotoxicity, e.g., IgG antibodies in pemphigus act on the desmoglein on the keratinocyte. This results in separation of the keratinocytes, with the production of intraepithelial blister formation.

2.4.3 *Type III (Immune Complex Disease)*

Immune complexes are formed by the combination of antigen and antibodies in the blood; these are deposited in the walls of small blood vessels, often to those of the skin, e.g., leukocytoclastic vasculitis.

2.4.4 *Type IV (Cell-Mediated or Delayed Hypersensitivity Reaction)*

Lymphocytes rather than antibodies mediate this reaction. Specially sensitized T cells have secondary contact with the antigen when it is presented on the surface of antigen presenting cells as the Langerhans cells, e.g., allergic contact dermatitis.

Langerhans cells form the first line of defense of cellular immune system.

Skin contains all the elements of the cellular immune system, with the exception of B cells.

All four types of hypersensitivity reactions occur in the skin.

Keratinocytes are immunologically active cells.

The skin, its afferent blood supply, lymphatic drainage, regional lymph nodes, circulating lymphocytes, and resident immune cells form a regulatory immune unit.



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