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The Skin as an Immune Organ

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KEY POINTS

- The skin is an extremely active immunologic organ.
- The skin has many resident immunologically active cells.
- The skin defense system includes a physical barrier (stratum corneum and hair), a chemical barrier (fatty acids and antimicrobial peptides), an immunologic barrier (innate and adaptive immune system), and a microbiological barrier (beneficial microorganisms).
- Keratinocytes are the most immunologically active cells in the epidermis.
- The skin is commonly affected by immune system disorders.

The skin is the largest organ in the body. It has long been known as the primary physical barrier between an organism and its environment, but since the early 1980s the skin has been recognized as an active immune organ with its own skin-associated immune system. The skin’s defense system consists of physical, chemical, immunologic, and microbiologic components that protect the body against trauma, chemicals, toxins, and microorganisms.

The physical barrier represents the first line of defense against invaders. It is composed of keratinocytes tightly bonded together by a lipid-rich mortar in the stratum corneum (top layers) and keratinocytes joined together by tight cell-to-cell junctions in the lower layers. The chemical barrier consists of compounds with active antimicrobial activity, including fatty acids and antimicrobial or host defense peptides secreted by sebaceous glands and keratinocytes. If the physical and chemical defenses of the skin are overcome by invaders, components of the innate and active immune system along with beneficial microorganisms in the skin microbiome become important. Beneficial microorganisms compete for the same niche as pathogens and actively secrete antimicrobial peptides (AMPs) that inhibit the proliferation of pathogenic competitors.

When pathogenic microorganisms breach the physical and chemical defenses of the skin, they activate the skin-associated lymphoid tissue (SALT) (Table 1.1). SALT includes dendritic cells, mast cells, lymphocytes, and keratinocytes, and forms part of the innate immune system (Figure 1.1). Innate immunity, which is considered the most ancient branch of the body’s immune defenses, is characterized by a rapid onset of action (minutes to hours), a lack of specificity (it recognizes common microbial structures as opposed to specific organisms), and a lack of memory, which means the response does not improve with each exposure. Cells of the innate immune system include macrophages, dendritic cells, neutrophils, natural killer (NK) cells, mast cells, and keratinocytes. When innate immunity is overwhelmed, the adaptive branch of the immune system (Figure 1.2), primarily made of T and B lymphocytes, is activated. The adaptive immune response is characterized by a slow onset of action (days to weeks), high specificity (recognizes unique antigens), and memory, which means the speed and magnitude of the response improve with each exposure. The innate and adaptive branches of the immune system are highly interconnected. When cells of the innate immune system are activated, they secrete numerous inflammatory cytokines and chemokines that prime and direct the adaptive immune system’s response.

Table 1.1 Cells of the innate and adaptive immune system discussed in this chapter.

	Cell type	Functions	Location	Cytokines produced	Expressed molecules
Innate	Keratinocyte	Mechanical barrier, epidermal production Immune function	Epidermis	IL-1, IL-6, TNF, IL-8, IL-10, IL-12, IL-15, IL-18, IL-19, IL-20, TGF, IL-20, IL-23, GM-CSF, G-CSF	TLR, MHC-I, MHC-II, AMP
	Langerhans cell	Antigen-presenting cell	Epidermis	IL-12, IL-23, IL-6, TNF	Fc and mannose receptors, ICAM-1, IL-12, MHC-II
	Dermal dendritic cell	Antigen-presenting cell	Dermis	IL-12, IL-23, IL-6, TNF	Fc and mannose receptors, ICAM-1, IL-12, MHC-II
	Mast cell	Hypersensitivity reactions, vasodilation, chemotaxis, inflammation	Dermis	TNF, IL-1, IL-4, IL-5, IL-6, IL-13, CCL3, CCL4, IL-3, GM-CSF	TLRs, NF- κ B, NFAT, AP-1
Both innate and adaptive	Eosinophil	Hypersensitivity reactions, vasodilation, chemotaxis, inflammation	Dermis	IL-3, IL-5, IL-8, IL-10, leukotrienes, GM-CSF, hydrolases	Fc receptor
	Neutrophil	Innate immunity, phagocytosis	Dermis	ROS, proteolytic enzymes	TLRs, lectin receptor, mannose receptor
	M1 macrophage	Phagocytosis, antigen presentation, bactericidal activity	Dermis	IL-6, IL-12, TNF, iNOS	JAK1, JAK2, STAT1, STAT2
	M2 macrophage	Phagocytosis, antigen presentation, regenerative effects	Dermis	IL-10, TGF, arginase-1	JAK1, JAK2, JAK3, STAT6
	ILC (Innate lymphoid cell)	Innate immunity	Dermis	IL-1, IL-23, IL-25, IL-33, TSLP	Id2, T-bet, GATA 3, ROR
	γ/δ T cell	Elimination of intracellular microorganisms and infected cells; cell death	Dermis	IL-17, IFN	MHC- I
	Natural killer cell	Innate immunity against viruses and intracellular bacteria	Dermis	IFN, GM-CSF, IL-3	MHC-I
	Natural killer T cell	Elimination of lipid antigens	Dermis	IL-4, IL-17, IL-22, IFN	MHC-1
	B lymphocyte	Humoral response	Dermis	IL-2, IL-4, IL-6, IL-11, IL-13, TNF, BAFF	Antibodies
	T-helper lymphocyte	Coordinates immune function	Dermis	Various depending on the type of T-helper cell	Various depending on the type of T-helper cell
Adaptive	T-cytotoxic lymphocyte	Elimination of intracellular microorganisms and infected cells	Dermis	IFN	Perforin, granzyme, granulysin
	T-regulatory lymphocytes	Control of immune response	Dermis	IL-10, TGF	FoxP3, STAT5

Key: AMP, antimicrobial peptides; AP, activator protein; BAFF, B-cell activating factor; CCL, chemokine ligand; FoxP3, forkhead box P3 protein; GATA, transcription factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; Id2, DNA binding protein inhibitor 2; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T cell; NF- κ B, nuclear factor kappa B; ROR, retinoic acid-related orphan receptors; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; T-bet, T box transcription factor; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

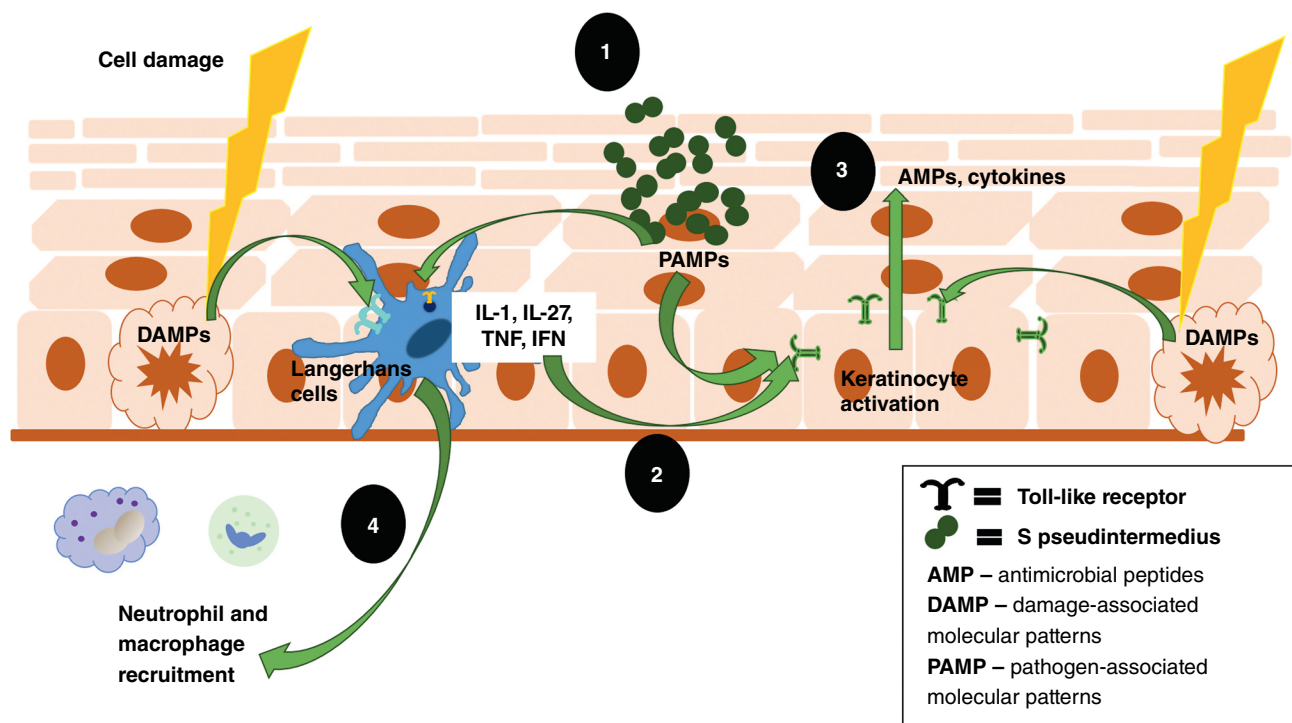


Figure 1.1 Innate skin immune system. 1. The innate immune system is activated when damage-associated molecular pattern (DAMP) molecules released by damaged cells or pathogen-associated molecular pattern (PAMP) molecules on pathogens are recognized by pattern-recognition receptors such as Toll-like receptors on both dendritic cells (Langerhans cells) and keratinocytes. 2. This leads to the activation of keratinocytes directly and the release of cytokines by the Langerhans cells that also activate the keratinocytes. 3. The activated keratinocyte releases various cytokines and AMPs to directly destroy the invading pathogen. 4. Neutrophils and macrophages are recruited to directly destroy the invaders. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Immune System of the Skin

The skin is a complex organ composed of an outermost layer, the epidermis; a middle layer, the dermis and cutaneous appendages; and an inner layer, the subcutis. Immune cells and inflammatory mediators are active in all these layers. It is important to understand that immune cells and inflammatory mediators are extremely interconnected and work in concert, as opposed to having isolated effects. If we compare the two branches of the immune system to an army, the innate immune system would be the entrenched peacekeeping force while the adaptive immune system would be the cavalry called in as reinforcements. By constantly communicating via cytokines and chemokines, they work together as one system to protect the host.

Epidermis

The major physical defense of the skin is the stratum corneum. This outermost layer continuously sheds into the environment, taking pathogens along with it. In addition to keratinocyte exfoliation, compounds present in the

intercellular lipid cement create an environment unfavorable to pathogen invasion. These compounds include sodium chloride, albumin, complement components, transferrin, interferons, lipids, and antibodies donated by the adaptive immune system.

Below the stratum corneum the living epidermis is composed mainly of keratinocytes that are bound together by various junctional structures, including desmosomes, hemidesmosomes, and tight junctions. In addition to forming the major structural component of the epidermis, keratinocytes are many times the first to detect pathogens. By initiating the immune response, they act as sentinel cells for both the innate and adaptive immune systems. Keratinocytes produce small quantities of AMPs on a regular basis. AMPs are small cationic molecules that are a first line of defense against pathogens. They block lipopolysaccharides (a major negatively charged component of the outer membrane of gram-negative bacteria), directly kill microbes, and induce histamine release from mast cells. Keratinocytes also detect highly conserved microbial surface structures (e.g. lipopolysaccharides, flagellins, teichoic acids) called pathogen-associated molecular pattern (PAMP) molecules via pattern-recognition receptors such

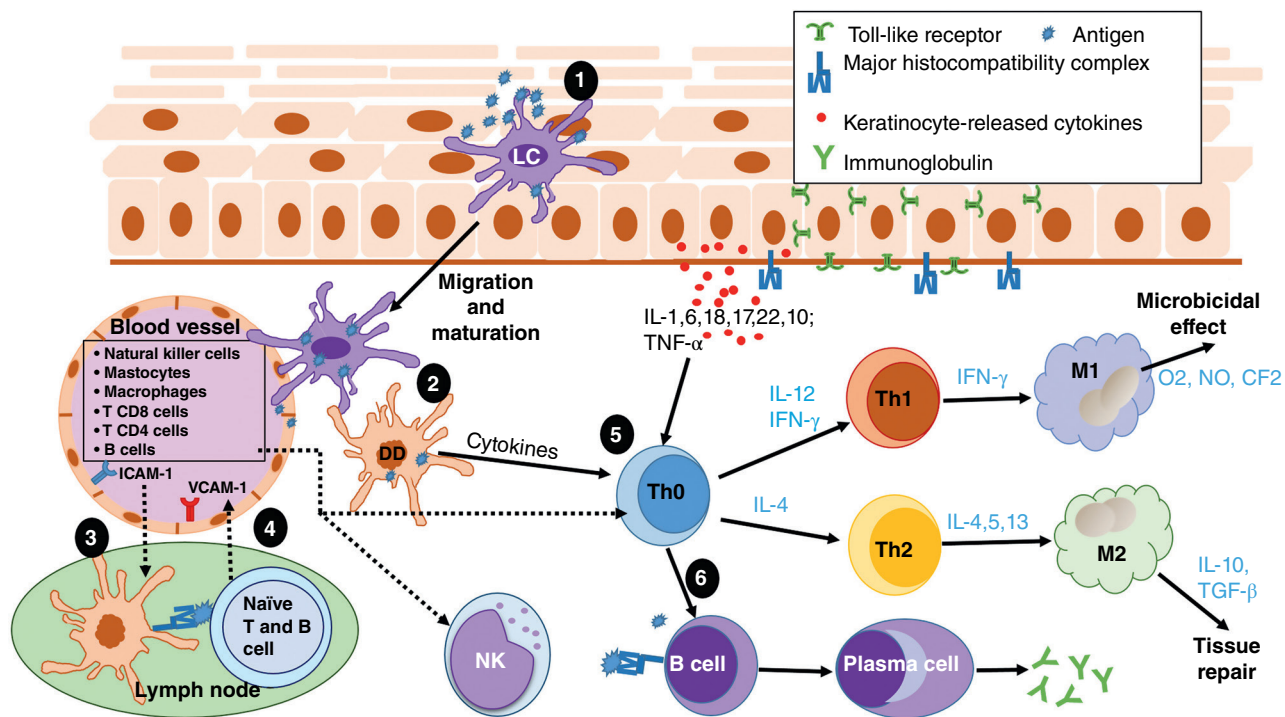


Figure 1.2 Adaptive skin immune system. 1. Langerhans cells (LCs) are activated once they uptake and process the antigen. 2. Some will mature and migrate along with some activated dermal dendritic (DD) cells to the local lymph node. 3. The antigen in association with major histocompatibility complex (MHC) I or II will prime naïve T and B cells. 4. The primed T-helper (CD4+) and cytotoxic cells (CD8+) enter the blood system and return to the area of inflammation along with other inflammatory cells via adhesion molecules like intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. 5. The primed T lymphocytes mature into various types of T-helper (Th) cells, depending on which cytokines are produced by keratinocytes and dendritic cells. These mature T-helper cells are responsible for amplifying the inflammatory response. 6. Primed T-helper cells are also able to prime B cells in the skin that are displaying the same antigen in association with MHC on the B cell's surface. The B cell will then mature into plasma cell and produce immunoglobulins against that antigen. CF, chorion factor; IFN, interferon; IL, interleukin; M, macrophage; NK, natural killer cell; NO, nitric oxide; TGF, transforming growth factor; TNF, tumor necrosis factor.

as Toll-like receptors. Other pattern-recognition receptors on the keratinocyte surface detect damage-associated molecular pattern molecules (DAMP) that are endogenous ligands/markers produced by injured or dying host tissue. These are important in the detection of irritants and toxins. Once pattern-recognition receptors are triggered, the keratinocyte is activated. Depending on the type of assault and which pattern-recognition receptors are triggered, the activated keratinocyte then produces more AMPs, and various pro-inflammatory cytokines (a large group of small molecules important in cell signaling). Some of these cytokines have immediate effects on the invaders (innate response) that directly neutralize the pathogen, while others are important in recruiting and activating B and T lymphocytes (adaptive response). Once activated, keratinocytes express a wider variety of pattern-recognition receptors. Keratinocytes can also act as antigen-presenting cells for the adaptive immune response. They can express both major histocompatibility complex molecules (MHC) I and II on their surface. They are not able to prime naïve T cells,

but can present antigen to both T-helper (CD4+) and cytotoxic (CD8+) T lymphocytes.

Melanocytes and Langerhans cells are the other major immunologically active cell types in the epidermis. Melanocytes' major function is the production of melanin to protect keratinocytes from the harmful effects of ultra-violet radiation (UVR). However, they also play an important regulatory role in both the innate and adaptive immune systems by promoting phagocytosis and producing a series of pro-inflammatory cytokines. Like keratinocytes, they can also express various pattern-recognition receptors such as Toll-like receptors.

Langerhans cells and dermal dendritic cells are the most important antigen-presenting cells in the skin, as they are the only cells able to activate naïve T lymphocytes. Depending on the microenvironment and the immunologic triggers present, Langerhans cells can mediate a tolerogenic response through the production of interleukin 10 (IL-10), or they can promote an inflammatory response. Once in contact with an invader, Langerhans

cells phagocytose the antigen, process it, and represent it on their surface in association with MHC-II. This causes the maturation of the Langerhans cells, which then migrate to the regional lymph node to prime naïve T lymphocytes.

The epidermis also hosts resident memory T lymphocytes, part of the adaptive immune system. These cutaneous memory T lymphocytes may possess either α/β or γ/δ T-cell receptors. Those with γ/δ receptors are considered a hybrid between an innate and an adaptive immune cell. They bind to common PAMP molecules or respond to the class Ib MHC molecules produced by stressed, cancer-, or virus-infected cells.

Dermis

The dermis is mainly composed of extracellular matrix proteins that provide structure and elasticity to the skin. It is separated from the epidermis by the basal membrane, a thin layer of extracellular matrix proteins. This membrane regulates the movement of cells and substances from the dermis to the epidermis and anchors the basal epidermal keratinocytes to the dermis via hemidesmosomes. The dermis contains hair follicles, glandular structures, specialized neural receptors, as well as blood and lymphatic vessels essential for the support and maintenance of dermal and epidermal cells.

Fibroblasts are the most abundant immunologically active cells in the dermis. Their primary function is production of the extracellular matrix that provides structural support for the dermis and a scaffolding that allows cells of the immune system to move easily through the dermis. Fibroblasts secrete a variety of cytokines, including chemoattractants for T lymphocytes, and direct the inflammatory response that is part of wound healing. Fibroblasts produce matrix metalloproteinases, a group of enzymes responsible for the degradation of the extracellular matrix, but they also produce tissue inhibitors of matrix metalloproteinases. Therefore, fibroblasts facilitate both activation and termination of inflammation.

Endothelial cells and neurons are also essential for the dermal immune response. Endothelial cells regulate the influx of inflammatory cells from the blood into the dermis through the activation of adhesion molecules and cytokines. During the initial phase of inflammation, endothelial cells activate multiple Toll-like receptors and various adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins E and P. As the inflammatory response progresses, endothelial cells secrete more pro-inflammatory cytokines such as IL-1, tumor necrosis factor alpha (TNF- α),

and interferon gamma (IFN- γ), which in turn increase the expression of adhesion molecules to further facilitate leukocyte migration and extravasation.

Nerves are important for sensation and they also have an intimate connection with memory T cells. Neurons modulate signals between the innate and adaptive branches of the immune system by producing substance-P, calcitonin gene-related peptide, and alpha melanocyte-stimulating hormone. These substances support a healthy level of inflammation and help to resolve the inflammatory response when needed.

The dermis is home to other cells of the innate immune system (granulocytes, NK cells, dendritic cells, macrophages) and lymphocytes (adaptive immune system cells). Neutrophils and macrophages are part of the first line of defense against microorganisms. As soon as an invader is detected, these cells are called to the site of infection by potent chemoattractants. Once there, they express receptors that recognize, bind, capture, and phagocytose microorganisms. Neutrophils are also able to externally project their DNA and DNA-associated proteins to form “sticky” neutrophil extracellular traps (NETs) that trap pathogens like flies on a spider’s web.

Macrophages are a bridge between the innate and adaptive arms of the immune system. In addition to phagocytosing microorganisms, macrophages remove debris, dead cells, and exogenous or endogenous inflammatory stimuli (e.g. free melanin or keratin). They also act as antigen-presenting cells. Macrophages can recognize, bind, capture, and destroy microorganisms directly or via their recognition of antibody molecules, complement proteins, or lectins. Macrophages secrete various cytokines that direct the immune response. Different types of macrophages have recently been identified: M0, M1, M2, M4, M17, and Mreg. M1 macrophages secrete TNF- α , IL-6, and IL-12, cytokines that promote a T-helper type 1 pro-inflammatory immune response. M2 macrophages promote an anti-inflammatory immune response through the secretion of IL-10 and IL-4. M4 macrophages secrete TNF- α , IL-6, matrix metalloproteinases 7 and 12, and macrosialin, all of which reduce phagocytosis and induce a pro-inflammatory immune response. Finally, M17 and Mreg cells have been proposed, but their characterization and involvement in the inflammatory process need further clarification.

Eosinophils are more abundant in the later stages of inflammation. They are important in the pathogenesis of allergic and parasitic diseases, both driven by T-helper type 2 cytokines. Once eosinophils reach the site of inflammation, they release granular proteins highly toxic to parasites. Eosinophils are also essential in secreting cytokines characteristic of an allergic response. Finally, eosinophils

release prostaglandins and leukotrienes that cause vasodilation and chemotaxis of neutrophils and prolong an allergic response. Eosinophils have a very strong connection with mast cells, mononuclear granulocytes essential for the allergic response and wound healing.

Mast cells in the skin are highly associated with blood vessels and have both immunoglobulin (Ig) E and complement receptors on their surface. Upon activation, mast cells release a variety of vasoactive and pro-inflammatory substances, including histamine, serotonin, proteases, leukotrienes, prostaglandins, and cytokines. Along with pro-inflammatory mediators, mast cells also secrete large quantities of transforming growth factor beta (TGF- β), platelet-derived growth factor (PDGF), and fibroblast growth factors (FGFs), all of which are essential mediators of tissue repair.

NK cells and dendritic cells represent the other innate immune cells present in the dermis. NK cells are lymphocytes that express neither T- nor B-cell receptors. Until recently, they were thought to belong exclusively to the innate immune system because of their ability to recognize patterns more than specific antigens. However, more recent studies have shown that NK cells have memory, making them part of the adaptive immune system. Another peculiarity of NK cells is their ability to recognize MHC-I on cell surfaces. This ability makes NK cells the major sentinel cells in the recognition of virally infected or cancerous cells. Finally, NK cells can bind IgG-coated pathogens and cells (antibody-dependent cellular cytotoxicity), leading to the release of cytotoxins (granzyme, granulysin, and perforin), which kill the infected cell. Another cell that has characteristics of both innate and adaptive immunity is the NK T cell, which is a hybrid between T cells and NK cells.

Dendritic cells are found in the dermis as well as the epidermis. They reside in the upper dermis just below the basal membrane. Dermal dendritic cells along with Langerhans cells in the epidermis are the major antigen-presenting cells of the skin. They deliver processed antigen to lymph nodes to prime naïve T lymphocytes of the adaptive immune system. Once dermal dendritic cells are stimulated by antigen, they begin the maturation process, which involves a decrease in their phagocytic ability and an increase in expression of MHC-II glycoproteins, increasing their antigen-presenting function. Mature dermal dendritic cells are also able to redirect the local immune response through the secretion of inflammatory cytokines. In addition, they can express epithelial cell adhesion molecules and stimulate the transformation of B lymphocytes into plasma cells.

The dermis is also home to B and T lymphocytes, the major cells of the adaptive immune system. It has been

estimated that the healthy dermis contains twice as many lymphocytes (~20 billion T cells) as there are in the blood. Most of these dermal lymphocytes are a heterogeneous population of T memory lymphocytes, including T-helper (Th) type 1, 2, and 17, and T-regulatory cells (Treg). More recently, Th3, 9, 22, and 25 lymphocytes have also been identified. These cells form an intricate network of resident adaptive immune cells ready to act in case of exposure to previously encountered antigens. They are mainly localized around capillaries, the dermoepidermal junction, and hair follicles and glands. Each one of these T-cell subsets produces a specific pattern of cytokines. Th1 cells are mainly involved in fighting infection with intracellular microorganisms and secrete IFN- γ , which activates macrophages. Th2 cells are mainly involved in fighting infections with extracellular microorganisms and allergies and secrete IL-4 and IL-13. Th17 cells are mainly involved in the inflammatory response against bacteria and fungi, and their role in atopic dermatitis and other cutaneous inflammatory diseases is being investigated. Th17 cells secrete IL-17 and IL-22. Th22 cells secrete only IL-22, so are considered by some to be a subset of Th17 cells. Th22 cells are essential for keratinocyte proliferation and, like Th17 cells, are involved in atopic dermatitis and other inflammatory skin diseases. Treg cells secrete IL-10 and TGF- β . This subset of T lymphocytes is mainly involved in the suppression of the inflammatory response and plays a fundamental role in decreasing the immune response once the trigger has been eliminated. Alterations in the number of Treg cells and their characteristics have been associated with allergic and inflammatory skin diseases.

B lymphocytes are also found in the dermis, but in much lower numbers than T cells. B lymphocytes have multiple roles in the immune response besides producing antibodies once they have transformed into plasma cells. They express MHC-II glycoproteins so they can present antigens, and they produce a variety of cytokines affecting both local and systemic immune responses. Recent evidence suggests that skin-associated B cells may play a significant role in host defenses, regulation of microbes, and wound healing.

Subcutis

The subcutaneous tissue is mainly composed of fat and the primary cell type is the adipocyte. This tissue is highly innervated and vascularized. Historically, adipocytes' only functions were thought to be energy storage, protection, and thermogenesis; however, new evidence suggests that

adipocytes can play an important role in local and systemic immunity. Adipocytes express various innate immune receptors such as Toll-like receptors and Nod-like receptors. They can secrete inflammatory cytokines and can serve as antigen-presenting cells for lymphocytes.

Defense from Harmful Substances

Acids, bases, free radicals, UVR, and natural or synthetic poisons are not always avoidable, thus the immune system is essential for protecting the host from these harmful substances. While it is intuitive that the innate immune system would protect against toxins and chemicals, both adaptive and immune responses are involved. Solar UVR causes formation of damaging free radicals. Natural moisturizing factors in the stratum corneum (specifically urocanic acid), keratinocyte DNA, and Langerhans cells all function as chromophores that absorb the UVR. When the UVR is absorbed, these cells produce TNF- α , IL-10, and IL-4 that encourage an adaptive immune response. TNF- α and IL-10 limit the recruitment of inflammatory cells to ensure an environment with just enough neutrophils and NK cells to eliminate any pathogens breaking through the temporarily damaged skin barrier.

Dysfunction of the Immune System

The immune system is a marvelous and extremely complex machine able to recognize and respond to an innumerable number of stimuli. Occasionally the system produces an excessive or inappropriate response to a stimulus, and this is the basis of hypersensitivity reactions.

Type I (Immediate) Hypersensitivity Reaction

Type I hypersensitivity is an acute inflammatory response to antigens (allergens) recognized by IgE receptors on tissue mast cells. Once the allergen cross-links several IgE molecules, the mast cell degranulates, releasing inflammatory mediators into the surrounding tissue and causing acute inflammation. This type of hypersensitivity is typical of allergic reactions such as anaphylaxis.

Type II (Cytotoxic) Hypersensitivity Reaction

Type II hypersensitivity reactions are characterized by the presence of antibodies (mainly IgG) and complement proteins attached to host cells, which leads to the destruction of these cells. This type of hypersensitivity

reaction is characteristic of autoimmune diseases. Medications, vaccinations, pathogens, toxins, and neoplasia can alter host cell morphology, thereby signaling that the cell is foreign rather than self; however, many autoimmune diseases occur without any known trigger. Pemphigus foliaceus is a common cutaneous autoimmune disease in which IgG antibodies are formed against desmosomal proteins, the attachment structures of keratinocytes.

Type III (Antigen–Antibody Complex) Hypersensitivity Reaction

Immune complexes are antigens bound to their antibodies. When excessive amounts of antigen are present in the body, more complexes than can be cleared efficiently by the body are formed. These complexes precipitate in tissue in large amounts and cause severe inflammation. The antigen–antibody complexes may remain at the initial site of attack or move through the bloodstream and lodge in distant locations such as capillaries or renal glomeruli. Once in the tissue, they trigger the accumulation of neutrophils, which release oxidants, inflammatory mediators, and enzymes that trigger additional inflammation and tissue damage. This type of hypersensitivity reaction is seen in many tick-borne diseases and leishmaniasis, as well as autoimmune diseases such as systemic lupus erythematosus and vasculitis.

Type IV (Delayed or Cell-Mediated) Hypersensitivity Reaction

Delayed hypersensitivity reactions involve Th lymphocytes, macrophages, and cytotoxic T lymphocytes. Delayed-type hypersensitivities are induced by chronic intracellular infectious disease agents such as *Mycobacteria* spp. or *Leishmania* spp., as well as contact allergens. For dermatology, contact allergy is the perfect example of a type IV reaction. In contact allergic dermatitis, small molecules from plants or chemicals are absorbed into the skin. These molecules by themselves do not elicit a response from the immune system and are called haptens. Once these haptens attach to a host protein, this larger complex can then be recognized, processed, and presented as a complete antigen by Langerhans cells. During presentation to naïve T cells in the lymph node, the Langerhans cell releases cytokines that induce the formation of Th1 and Th17 cells. These cells then return to the skin and upon reexposure release Th1 cytokines and activate macrophages, causing the clinical signs associated with delayed hypersensitivity.

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