



Organization of the Skin Immune System and Compartmentalized Immune Responses in Infectious Diseases

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SUMMARY The skin is an organ harboring several types of immune cells that participate in innate and adaptive immune responses. The immune system of the skin comprises both skin cells and professional immune cells that together constitute what is designated skin-associated lymphoid tissue (SALT). In this review, I extensively discuss the organization of SALT and the mechanisms involved in its responses to infectious diseases of the skin and mucosa. The nature of these SALT responses, and the cellular mediators involved, often determines the clinical course of such infections. I list and describe the components of innate immunity, such as the roles of the keratinocyte barrier and of inflammatory and natural killer cells. I also examine the mechanisms involved in adaptive immune responses, with emphasis on new cytokine profiles, and the role of cell death phenomena in host-pathogen interactions and control of the immune responses to infectious agents. Finally, I highlight the importance of studying SALT in order to better understand host-pathogen relationships involving the skin and detail future directions in the immunological investigation of this organ, especially in light of recent findings regarding the skin immune system.

KEYWORDS skin, cytokines, immune response, infections, innate immunity, keratinocytes, lymphocytes

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INTRODUCTION

The concept of organ-specific immunity and its implications on the evolution of diseases, especially infectious diseases, were proposed by Engwerda and Kaye in 2000 (1). In this context, it is possible to divide the pattern of tissue immune responses into three major groups: barrier epithelium immune responses, complex organ immune responses, and immunologically privileged organ immune responses (2). The skin is an archetype of organs involved in mechanical and immunological barriers to pathogens and in body homeostasis (3–7). Tissues that form host–environment interfaces, including mucosal surfaces, represent the primary stage of defense against pathogenic microorganisms (8–11). The skin has a similar organization over most of the body, but certain regions, such as the feet, scalp, and genitalia, have specific and highly specialized adaptations. The skin comprises the epidermis, dermis, cutaneous appendages, and subcutaneous tissue (12). It has a complex immune system that is histologically represented by skin-associated lymphoid tissue (SALT), which includes dendritic cells (DCs), mast cells, B and T lymphocytes, and keratinocytes (13). In certain situations, such cells may modulate the cascade of the local immune responses (14, 15). SALT acts by protecting the body against foreign microorganisms and plays a role in the pathophysiology of inflammatory diseases such as autoimmune and hypersensitivity disorders (8–13). Such diseases have pathogenetic mechanisms that are generally mediated by T lymphocytes and respond to immunosuppressive or anti-inflammatory therapy (7).

The epidermis is constituted by three major cell populations: keratinocytes, melanocytes, and Langerhans cells (LCs). It has four distinct layers: the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum (12, 13). The stratum basale (or basal stratum) is composed of a layer of undifferentiated cells in constant mitotic activity (16). From the basal stratum, cells differentiate to form the stratum spinosum (or spinous stratum), which produces keratin. The stratum granulosum is composed of keratinocytes that have blackened granules in their cytoplasm and produce keratin-forming proteins, in addition to lipids (17, 18). Finally, the stratum corneum contains keratinocytes in later stages of maturity. It eliminates most agents that are potentially toxic to the organism and helps maintain hydroelectrolytic homeostasis (18). In the basal stratum, melanocytes help protect DNA from UV radiation by producing melanin and by promoting expression of major histocompatibility complex class II (MHC-II) proteins (19–24). Merkel cells in the epidermis are responsible for skin somesthesia (sensitivity), along with LCs, whose functions are discussed below. In addition to these cells, in the basal and corneum layers are T lymphocytes, most of which are CD8⁺ lymphocytes (4, 7, 9, 14, 17, 18).

The dermis is characterized by a complex organization and a diverse immune cell population. This region contains specialized immune cells such as DCs, CD4⁺ T lymphocytes, $\gamma\delta$ T lymphocytes, natural killer (NK) cells, mast cells, macrophages, neurons, lymphatic vessels, and blood vessels, which are responsible for the efflux of cells from the blood into the skin (Fig. 1) (7, 9, 13, 15, 16).

IMMUNE SYSTEM AND THE SKIN

The skin has a complex network of cells that constitute SALT. Table 1 presents the various cellular components that make up the skin immune system (13). In addition to the immune cells themselves, certain skin cells, such as keratinocytes and melanocytes, may also affect local immune responses by releasing cytokines, which can modulate inflammatory responses (13). Therefore, the skin is an immunologically complex organ that has the ability to respond to infectious and noninfectious aggressive agents through innate and adaptive immunity mechanisms (9, 14, 15).

Keratinocytes

Keratinocytes are epithelial cells that are interconnected by intercellular bridges (tight junctions). They play important roles in maintaining the mechanical and barrier functions of the epidermis, and they contribute to the pathophysiology of infectious and inflammatory processes by producing cytokines and by expressing MHC class I and

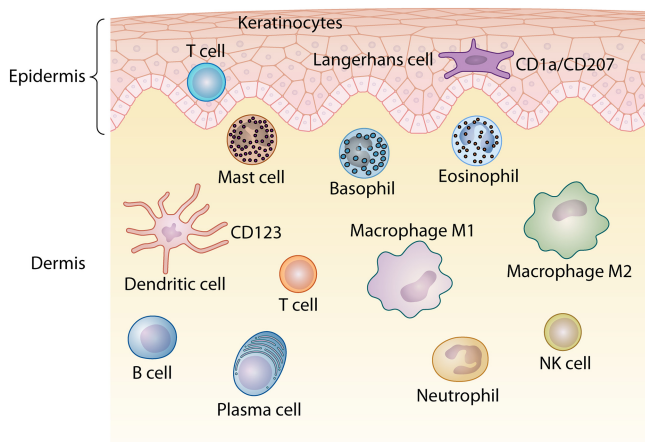


FIG 1 Schematic representation of the distribution of immune cells that form the skin-associated lymphoid tissue (SALT) in the epidermis and dermis of the skin.

II glycoproteins (13, 15, 25, 26). Similar to the epithelial cells of the gastrointestinal tract, keratinocytes can distinguish between the microbiota and potentially pathogenic agents, and they can recognize highly conserved structures known as pathogen-associated molecular patterns (PAMPs) (13, 27–29). PAMPs are often important for the survival, colonization, or invasion of microorganisms and are generally composed of lipopolysaccharides (LPSs), flagellins, nucleic acids, unmethylated CpG DNA sequences, teichoic acids, mannose-rich oligosaccharides, and other compounds (29, 30). The recognition of PAMP ensures that there is no activation of mechanisms to escape the host immune response, as is observed in the pathophysiology of some infections (31, 32). Molecules that bind to PAMPs are known as pattern recognition receptors (PPRs) and include the Toll-like receptors (TLRs) (29). The activation of TLR pathways occurs upon binding of PAMPs and induces a cascade of innate and adaptive immunity. Several TLRs are expressed in epidermal keratinocytes and are located on the cell surface (TLR1, TLR2, TLR4, TLR5, and TLR6) as well as in endosomes (TLR3 and TLR9). Moreover, TLR7 expression may be induced by the activation of TLR3 by double-stranded RNA molecules involved in immune responses to viruses (29). These factors indicate that the activation of TLRs by keratinocytes is crucial for triggering dermal immune responses, leading to a predominantly T helper cell type 1 (Th1) response accompanied by the activation of type I interferons (IFNs), including interferon alpha (IFN- α) and beta (IFN- β) (29, 30).

Similar to TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) can recognize PAMPs and endogenous PAMP analogs, danger-associated molecular patterns (DAMPs) (29, 33). They play important roles in the recognition of substances such as irritants and toxins. The induction of NLRs results in the activation of proinflammatory signaling pathways through inflammasomes, which are protein complexes composed of an NLR, an adapter protein termed ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain [CARD]), and pro-caspase-1 (29, 33). Activation of caspase-1 through inflammation leads to the cleavage of pro-interleukin-1 β (pro-IL-1 β) and pro-IL-18, which, in turn, leads to the expression of proinflammatory cytokines that activate immune cells and induce an elaborate immune response to harmful agents (34–36).

Keratinocytes produce antimicrobial peptides (AMPs) called defensins and cathelicidins, which are part of a highly conserved eukaryotic cell defense mechanism. AMPs are expressed on the injured epithelium to counteract the invasion of microorganisms by killing pathogens, activating immune cells, or modulating cytokine profiles (37). Keratinocytes produce cytokines such as IL-1, IL-6, IL-10, IL-17, IL-18, IL-22, and tumor necrosis factor alpha (TNF- α). In the presence of an infection, IL-17 and IL-22 can activate the production of AMPs by keratinocytes, constituting a form of innate

TABLE 1 Cells that make up the immune system of the skin, its specific markers, activation factors and factors released in the cascade of immune response^a

Cell	Function(s)	Location(s)	Marker(s)	Activation	Cytokine(s) produced	Expressed molecules/factors
Keratinocyte	Mechanical barrier, keratin production, immune function	Epidermis	CLSP, AE1, AE3	IFN- γ	IL-1, IL-6, TNF- α , IL-8, IL-10, IL-12, IL-15, IL-18, IL-19, IL-20, TGF- β , IL-20, IL-23, GM-CSF, G-CSF	TLR, MHC-I, MHC-II, defensins, cathelicidins
Langerhans cell	Antigen-presenting cell, migration and recruitment to the secondary lymphoid organs, and antigenic presentation to T lymphocytes	Epidermis	CD1a, CD207	Infectious and noninfectious antigens	IL-12, IL-23, IL-6, TNF	Fc and mannose receptors, B7, ICAM-1, IL-12, MHC-II
Dermal dendrocyte	Antigen-presenting cell, phagocytosis, regulation of collagen synthesis, and homeostasis of the dermis	Dermis	FXIIIa	Infectious and noninfectious antigens	IL-12, IL-23, IL-6, TNF	Fc and mannose receptors, B7, ICAM-1, IL-12, MHC-II
Plasmacytoid dendritic cell	Antigen-presenting cell	Dermis	CD123, BDCA-2/CD303	IL-3, CD40, virus, bacterium, CpG oligonucleotides	IL-12	TLR7, TLR9
Inflammatory dendritic cell	Antigen-presenting cell	Epidermis, dermis	CD206	Microbial and endogenous antigens	IL-12	MHC-II, CD11c, BDCA1, CD40, CD80/86
T CD4 Th1 cell	T helper lymphocyte; coordinates immune function	Mainly in the dermis and rare in the epidermis	CD3, CD4	IL-12	IFN- γ	T-Bet, STAT1, STAT4
T CD4 Th2 cell	T helper lymphocyte; coordinates immune function	Dermis; rare in epidermis	CD3, CD4	IL-4	IL-4, IL-5, IL-13	GATA 3, STAT6
T CD4 Th3 cell	T helper lymphocyte; coordinates immune function	Dermis	CD3, CD4	IL-4, IL-10, TGF- β	IL-4, IL-10, TGF- β	—
T CD4 Th17 cell	T helper lymphocyte; coordinates immune function	Dermis	CD3, CD4	IL-6, IL-1, IL-23	IL-17, IL-22	ROR γ , STAT3
T CD4 Th22 cell	T helper lymphocyte; coordinates immune function	Dermis	CD3, CD4	TNF- α , IL-6	IL-22, FGF- β , IL-13, TNF- α	—
T CD4 Th9 cell	T helper lymphocyte; coordinates immune function	Dermis	CD3, CD4	IL-4, TGF- β	IL-9, IL-10, IL-21	STAT6, IRF4, PU.1
T CD4 Th25 cell	T helper lymphocyte; coordinates immune function	Dermis	CD3, CD4	IL-25, Act1	IL-4, IL-13, IL-25, Act1	—
Treg cell	Control of the immune response	Dermis	FoxP3	IL-2, TGF- β	IL-10, TGF- β	FoxP3, STAT5
T CD8	Elimination of intracellular microorganisms and infected cells	Dermis, epidermis	CD3, CD8	IL-2, IL-12, IFN I	IFN- γ	Perforin, granzyme
T $\gamma\delta$ cell	Elimination of intracellular microorganisms and infected cells; cell death	Dermis	TCY δ	IL-2, IL-12	IL-17, IFN- γ	MHC-I
NKT cell	Elimination of lipid antigens	Dermis	CD56, CD16	IL-12, IL-18	IL-4, IL-17, IFN- γ	MHC-I
NK cell	Innate immunity against viruses and intracellular bacteria	Dermis	CD57	IL-12, IL-15	IFN- γ	MHC-I
ILC	Innate immunity	Dermis	CD127	IL-12, IL-18, IL-23, IL-25, IL-33, TGF- β	IL-1, IL-23, IL-25, IL-33, TSLP	Id2, T-bet, GATA 3, ROR γ
B cell	Humoral immune response	Dermis	CD19, CD20	IL-2, IL-4, IL-6, IL-11, IL-13, TNF- α , BAFF	Antibodies	TLR5, TLR7, TLR9, B7, MHC, CD40

(Continued on next page)

TABLE 1 (Continued)

Cell	Function(s)	Location(s)	Marker(s)	Activation	Cytokine(s) produced	Expressed molecules/factors
Plasma	Synthesis and release of antibodies	Dermis	CD138	IL-4, IL-6, IL-10, IFN- γ , BAFF	Antibodies	IRF4, AP-1, PU.1
Breg cell	Control of the immune response	Dermis	CD5, CD21, CD24	IL-2, IL-4, IL-5	IL-10, TGF- β	TLR4
M1 macrophage	Phagocytosis, antigen presentation, bactericidal action	Dermis	CD68, CD80	IFN- γ	IL-6, IL-12, TNF- α , iNOS	JAK1, JAK2, STAT1, STAT2
M2 macrophage	Phagocytosis, antigen presentation, regenerative effects	Dermis	CD163, arginase-1, CD86, MHC-II, VEGF	IL-4, IL-13	IL-10, TGF- β , arginase-1	JAK1, JAK2, JAK3, STAT6
Mast cell	Hypersensitivity reaction, vasodilation, chemotaxis, inflammation	Dermis around the vessels	CD117/C-kit	IL-3, IL-5, IL-13	TNF, IL-1, IL-4, IL-5, IL-6, IL-13, CCL3, CCL4, IL-3, GM-CSF	TLRs, NF- κ B, NFAT, AP-1
Basophil	Hypersensitivity reaction, vasodilation, chemotaxis, inflammation	Dermis	BB1, 2D7, J175-7D4	IL-3, IL-5, GM-CSF, histamine releasing factor	IL-4, IL-13	TLR2, TLR4
Eosinophil	Hypersensitivity reaction, vasodilation, chemotaxis, inflammation, IgE production	Dermis	CD9, CD23, CD32, IL-13	IL-5, IL-13, GM-CSF	IL-3, IL-5, IL-8, IL-10, leukotrienes, GM-CSF, hydrolases	Fc receptor
Neutrophil	Innate immunity, phagocytosis	Dermis, epidermis	CD11c+, CD13+, CD15+, CD16+, CD33+, CD63+, CD62L+, CD66+	C3, IFN- γ , TNF- α , GM-CSF	ROS, proteolytic enzymes	TLRs, lectin receptor, mannose receptor
Endothelial cell	Inflammation, immune response, infections	Dermis	CD31, ICAM-1/CD54, Tie-2/Tek, VCAM-1/CD106, VE cadherin	IL-1, IL-6, TNF	TNF, IL-1, IL-6, IL-8, IL-15, IL-17, IL-18, G-CSF, GM-CSF, VEGF	TLR2, TLR4, NF κ B, JAK/STAT
Fibroblast	Inflammation, immune response, infections	Dermis	TE-7, vimentin, FSP-1 (S100A4), anti-SFA	IL-1, TNF- α	PGE ₂ , GM-CSF, IL-8, MIP-2, PDGF, TGF- β , FGF- β	

^aGM-CSF, granulocyte colony-stimulating factor; VEGF, vascular endothelial growth factor; PGE₂, prostaglandin E₂; PDGF, platelet-derived growth factor; FSP-1, fibroblast-specific protein 1.

immune response (38–44). Particular importance has been attached to the pleotropic cytokine IL-1, which is capable of inducing a broad spectrum of biological effects, including the activation of helper T cells and DCs and the maturation and clonal expansion of B cells (43). Under physiologic conditions, keratinocytes secrete both IL-1 α and IL-1 β in biologically inactive forms. IL-1 β is released following the activation of inflammasomes in response to UV radiation. IL-1 α appears to be involved in the induction of inflammatory lesions in psoriasis, with neutrophil infiltration into the epidermis, by increasing the expression of chemokine (C-C motif) ligand 20 (CCL20) by keratinocytes. Studies have demonstrated that a reduction in the level of caspase-8 leads to active IL-1 α secretion from the pro-IL-1 α pool in mouse keratinocytes (43).

The activation of chemokine C-X-C motif ligand 9 (CXCL9), CXCL10, CXCL11, and CCL20 by keratinocytes can attract effector T cells to the skin in diseases characterized by T cell infiltration, such as psoriasis (44). The expression of CXCL1 and CXCL8 by keratinocytes may attract neutrophils to the epidermis in inflammatory diseases such as psoriasis, and furthermore, CCL20 may influence the trafficking to the epithelium of LC precursors (45, 46). Keratinocytes can express MHC-II in various skin diseases characterized by leukocyte infiltration, which implies that they function as nonspecific antigen-presenting cells (APCs). Keratinocytes can also induce CD4⁺ and CD8⁺ T lymphocyte responses by expressing Th1 or Th2 cytokines (46, 47). The activation of keratinocytes is important in inflammation and precedes the influx of lymphocytes into the epidermis following skin reactions to inflammatory mediators. The participation of keratinocytes in various skin immune response mechanisms implies their significant roles in the induction of inflammatory processes and in the control of skin conditions, such as cutaneous leishmaniasis, human papillomavirus (HPV), and staphylococcus infections (48–52).

Melanocytes

Melanocytes produce melanin, a pigment that is responsible for skin color and protection of keratinocytes against the harmful action of UV radiation, which can induce DNA damage (19–21). These cells derive from the neural crest and can control innate and adaptive local immune responses, promoting pathogen phagocytosis and the production of cytokines such as IL-1 β , IL-6, TNF- α , and chemokines. In the pathogenesis of autoimmune diseases such as vitiligo, melanocytes express MHC-II, and possibly also molecules recognized by cytotoxic T lymphocytes (19–22). A number of studies have shown that skin melanocytes can be compromised by infectious viral agents such as alphavirus, varicella-zoster virus, and parvovirus and by bacteria such as *Mycobacterium leprae* and *Leptospira*, among others (3, 23). This dual role of melanocytes, functioning both as targets and as a source of immune factors, along with their involvement in the pathophysiology of important infectious diseases, such as HIV and hepatitis C virus (HCV), makes the alteration of skin pigmentation an important symptom observed in the clinical course of these infections (24, 53). Upon contact with infectious agents of diverse nature, melanocytes can also express a variety of TLRs, including TLR1, -2, -3, -4, -6, -7, and -9 (22), with release of IL-6 and IL-8, and show increased chemokine mRNA expression involved in the recruitment of leukocytes, such as CCL2, CCL3, and CCL5 (3, 20, 22). Finally, similar to keratinocytes and other cells with immune functions in skin, melanocytes may express IFN type I and constitute the first line of defense against viruses in the skin (54, 55).

APCs and Skin Immunology

In general, skin APCs are localized in the epidermis and dermis (Table 1). Skin APCs have been classified according to their embryogenic origin. In this sense, we can classify subpopulations of APCs as classic APCs or classical DCs, which are represented by a cell population with stellate morphology, high expression of MHC-II, and the ability to migrate to the lymph nodes, activating naive T lymphocytes (56–60). A second population of APCs of the skin is represented by tissue-resident macrophages, monocytes, and other monocyte-derived cells (58, 59).

More recent ontogeny studies have shown that LCs are resident macrophages of the epidermis. However, despite this finding, LCs have functional characteristics similar to those of classic DCs, especially the ability to migrate to the lymph nodes and stimulate T lymphocyte responses (57). Studies of ontogeny, coupled with the functional characterization of LCs, have led to a great controversy in recent years concerning the identity of LCs, which were reinforced by transcriptomic analysis (56, 57). These analyses indicated that LCs are a distinct population of both DCs and macrophages, suggesting that the epidermal tissue microenvironment acts in the early stages of development of LCs, modulating their biological characteristics, despite their ontogeny (57). In this way, we can functionally consider LCs a subtype of DCs for the purpose of our discussion (59, 60).

LCs are the major DCs dispersed in the epidermis, whereas dermal DCs are located in the skin, immediately below the dermal-epidermal junction (13, 61–65).

DCs consist of several subpopulations of APCs that play important roles in the activation of immune responses (Table 1). They are produced continuously from hematopoietic precursors in the bone marrow and are distributed as immature cells in both lymphoid and nonlymphoid tissues (65, 66). The term dendritic cells was first used in 1973 by Steinman and Cohn based on their studies of the morphology of cells found in the lymph nodes of mice (66).

Four distinct human DC subtypes have been delineated based on biological studies of these cells in human skin: LCs, dermal dendrocytes (DDs), plasmacytoid dendritic cells (pDCs), and inflammatory dendritic cells (iDCs) (Table 1). LCs and DDs express myeloid markers, including CD13 and CD33 (13, 61–72). However, LCs exclusively express CD1a, Birbeck granules, langerin, and E-cadherin adhesion molecule (73). In contrast, DDs exclusively express the blood coagulation factor XIIIa. LCs and DDs may activate naive CD4⁺ and CD8⁺ T cells, with subsequent secretion of IL-12 (74–76). However, DDs can induce the differentiation of naive B cells into immunoglobulin-secreting plasma cells, whereas LCs cannot (Table 1) (77, 78).

pDCs resemble immunoglobulin-secreting plasma cells when visualized by ultrastructural microscopy. They are found in the thymus, blood tissues, and the lymph node T cell zone. pDCs secrete large quantities of interferon alpha following viral stimulation (13, 71, 79). In this context, precursor pDCs in blood correspond to natural IFN- α -producing cells, suggesting that they play an important role during viral infections. Unlike LCs and DDs, IL-3 induces pDC differentiation and promotes the expression of the myeloid markers CD14, CD13, and CD33. pDCs are devoid of mannose receptors and express high levels of CD123. However, like LCs and DDs, pDCs also activate CD4⁺ and CD8⁺ antigen-specific T lymphocytes and secrete IL-12 during viral infections (Table 1) (13, 71, 79, 80).

iDCs are characterized by the expression of CD206 (macrophage mannose receptor) and are observed in inflamed epidermal tissues of patients with various inflammatory skin diseases. These cells express an Fc-like receptor that has a high affinity for immunoglobulin E (IgE) and is involved in allergen-specific inflammatory processes. Although these cellular activities have been described to occur in the epidermis, they are involved in inflammatory processes in both the epidermis and dermis (Table 1) (67, 80).

Three main characteristics are attributed to DCs: capture, processing, and antigen presentation to T cells (67).

Endocytic activity is high in immature DCs, whereas this characteristic is less apparent in mature cells. DCs degrade antigens within the MHC class II endosomal compartment and subsequently display them on their surface bound to MHC-II (81, 82). Such antigens are captured by phagocytosis involving membrane receptors, and DCs can capture whole cells, including those undergoing necrosis and apoptosis (67). In contact with foreign particles of microbial or endogenous origin, the process of maturation of DCs begins with the expression of MHC class II glycoproteins, with increased ability of DCs to capture antigens. Following antigen incorporation, molecules that facilitate migration to the lymph nodes adhere to DCs (68–72). The DCs then

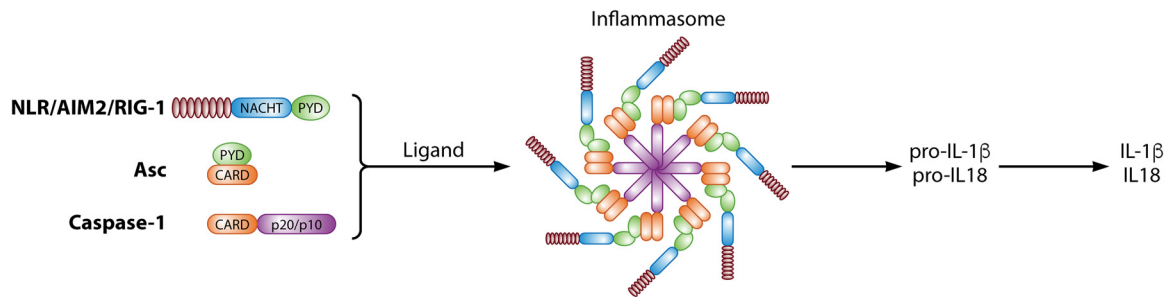


FIG 2 Schematic representation of the components of the inflammasome and its role in the production of proinflammatory cytokines. NLRP inflammasome activation can be induced by cytosolic PAMPs and DAMPs, leading to IL-1 β and IL-18 activation. Activation of caspase-1 by the inflammasome may also induce pyroptosis.

interact with lymphocytes, and there is an increase in the expression of cytokines and costimulatory molecules. The activation of costimulatory molecules in DCs induces signals that cooperate with T cell receptors (TCRs) to promote T cell activation. Among these costimulatory molecules, B7-1 (CD80) and B7-2 (CD86) molecules are expressed by DCs, macrophages, and lymphocytes. B7 stimulates molecules present on T lymphocytes, known as CD28, which are responsible for the secondary signs of T lymphocyte activation (83). Programmed cell death-1 (PD-1), encoded by the *PDCD1* gene, is a 288-amino-acid receptor that belongs to the B7/CD28 superfamily and is involved in the regulation of T cell activity. It is expressed on the surface of T, B, and NK cells and some subclasses of DCs and monocytes, as well as in the cytoplasm of T CD4⁺ and Treg lymphocytes (84–87). There is also an increase in the level of MHC-II expression in DCs. DC maturation is complete when they receive a stimulus to migrate to lymphatic tissues. DCs provide three signals that allow antigen-specific CD4⁺ T cells to initiate proliferation and differentiation (68–72). They capture antigens and readily degrade them to produce antigenic linear peptides of at least 13 amino acids in length that are capable of binding to MHC class II molecules and are trimmed by peptidases to no more than 17 amino acids in length (88). Subsequently, DCs express on their surface a high density of MHC class II/peptide complexes for TCR recognition expressed by T CD4⁺ cells (signal 1) and costimulation receptors CD40 and B7 to induce the proliferation of CD4⁺ T lymphocytes (signal 2) (89). IL-12 secretion by DCs (signal 3) induces CD4⁺ lymphocyte maturation in cell types 1 and 2. Dendritic cells are quite heterogeneous in the skin, but individual subsets can be identified by the careful use of markers. However, a successful functional analysis of these subsets of dendritic cells requires systems that allow the analysis of individual subsets, with the use of techniques involving separation of cell populations, culture *in vitro*, and antigenic challenge of these cells with specific antigens (Table 1) (57, 90).

Inflammasomes and Infectious Skin Diseases

The inflammasomes are constituted by a group of complex proteins of innate immunity (Fig. 2). They act as mediators of inflammatory responses to PAMPs and DAMPs. Inflammasomes induce the activation of caspase-1, the secretion of IL-1 β and IL-18, and pyroptotic cell death (91, 92). Depending on the type of caspase involved, they can be classified into one of two types of signaling pathways: classical/canonical, which requires the activation of caspase-1, and noncanonical, which uses other caspases to cause inflammation (91–93).

The PRRs involved in the formation of inflammasomes include the NLRs. Their basic structure consists of a variable N-terminal effector domain, a central NACHT (central nucleotide binding domain/NOD) domain, and a leucine-rich repeat (LRR) C-terminal region (92). There are 22 types and four subfamilies of NLRs in humans, classified according to their N-terminal acid activation domain (NLRA), BIR (baculovirus-inhibitor-repeat)-type domain (NLRB), activation and recruitment of caspase domain (NLRC), and pyrin domain (NLRP) (91). The accessory molecule ASC is an adapter protein common

to several inflammasomes. Two protein domains constitute this molecule: an N-terminal PYD (pyrin domain) and a C-terminal CARD. These molecules actively participate during the development of the inflammasome, establishing the connection between the NLR and pro-caspase (Fig. 2). Twelve caspases are known in humans and are classified into inflammatory caspases (caspase-1, -4, and -5), and apoptotic caspases (which are further divided into initiator caspase-2, -8, -9, and -10 and executioner caspase-3, -6, and -7). Caspase-1 is the key inflammatory caspase that activates IL-1 β and IL-18 cytokines and the pyroptotic mediator gasdermin D (91, 93). Other caspases may also be involved in the release of cytokines and pyroptosis. Caspase-4 and -5 are activated by Gram-negative bacteria, which may cleave gasdermin D, contributing to pyroptosis. Caspase-8 can induce inflammatory responses and apoptotic cell death; it forms the inflammasome and leads to the activation of IL-1 β , IL-18, and gasdermin D. Caspase-8 participates in the induction of a noncanonical pathway that activates IL-1 β independently of caspase-1, through the dectin-1 receptor (also known as a lectin C receptor family member) (91, 93).

The inflammasome canonical pathway activation begins when NLRs recognize an intracellular PAMP or DAMP, which leads to the recruitment of the adapter ASC in a PYD-PYD binding step. Subsequently, via a CARD-CARD linkage, pro-caspase-1 binds to the ASC (Fig. 2). This complex leads to the canonical activation of the inflammasome, resulting in the production of IL-1 β and IL-18 and induction of pyroptosis (93).

The inflammasome noncanonical pathway can follow two routes. In the first, caspases-4 and -5 are activated by LPS from Gram-negative bacteria, activating gasdermin D, causing pyroptosis, which triggers the activation of the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome. This attracts caspase-1, resulting in production of IL-1 β . The second noncanonical pathway involves the activation of caspase-8 following the recognition of PAMPs by C-type lectin receptors, which leads to the production of IL-1 β independently of caspase-1 (Fig. 2) (91, 93).

Inflammasomes have an important role in the host immune response to certain skin infectious diseases, such as cutaneous leishmaniasis and leprosy (93–95). In cutaneous leishmaniasis, the response of macrophages begins when the parasite invades and multiplies within the macrophage, which can kill the parasite through the production of free radicals (94). Macrophages may also act as APCs for T lymphocytes. The role of the inflammasome in macrophages infected with species of the genus *Leishmania* was evaluated by Lima-Junior and colleagues (95). These authors demonstrated that, in macrophages infected by *Leishmania amazonensis*, caspase-1 and IL-1 β are activated (95). IL-1 β production is caspase-1 dependent, because *casp1*^{-/-} animals do not produce caspase-1 or IL-1 β upon infection with *L. amazonensis*. IL-1 β expression and caspase-1 activation were lower in cells treated with *L. amazonensis* than in cells treated with LPS and nigericin (NLRP3 activators), indicating that the parasite inhibits inflammasome activation in some cases (95, 96). The functions of NLRP3 in parasite elimination were demonstrated in an assay in which macrophages of *Nos2*^{-/-}, *Asc*^{-/-}, *casp1*^{-/-}, or *NLRP3*^{-/-} mice, when infected with *Leishmania*, had a higher number of infected cells and more amastigotes (the tissue stage of the parasite) than macrophages from normal animals. Furthermore, potassium, cathepsins, and K⁺ channels are required for *L. amazonensis* to activate NLRP3 (97, 98). Inflammasome-deficient cells did not show increased leishmanicidal activity or nitric oxide (NO) production when treated with exogenous IL-1 β . That is, inflammasomes seem to be involved in the process of macrophage resistance (99–101). *L. amazonensis*-infected macrophages show decreased expression of nitric oxide synthase 2 (NOS2) and IFN- γ , but not of TNF- α , indicating that inflammasomes may contribute to the efficient production of IFN- γ and IL-1 β . NO production by inflammasomes may also restrict the multiplication of the parasite via a mechanism involving IL-1 β and IFN- γ (96–98).

In leprosy infections, dectin-1 acts as a C-type lectin PRR. It is present primarily in DCs and is targeted with the induction of the Th1 and Th17 protective response. According to a study by Gringhuis and coworkers (102), dectin-1 acts as an extracellular sensor for mycobacterial PAMPs and directly activates caspase-8 for pro-IL-1 β process-

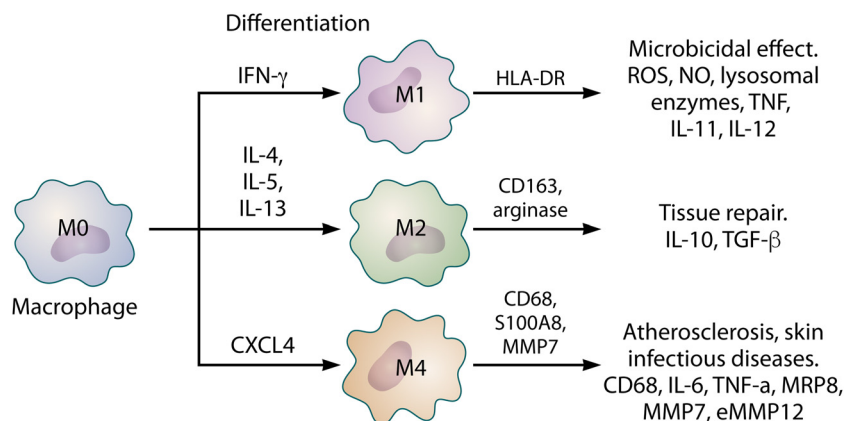


FIG 3 Phenotypic subpopulations of macrophages and their differentiation based on the specific profile of cytokines and chemokines. Each subpopulation is involved in specific physiological and pathological processes and the expression of a particular profile of cytokines, enzymes, and metalloproteinases, which may contribute to microbicidal, regenerative, and atherosclerotic plaques.

ing. IL-1 β expression in response to the stimulation of DCs with *Mycobacterium leprae* is induced primarily via dectin-1 and is completely dependent on caspase-8. Thus, recognition of *M. leprae* by dectin-1 results in the noncanonical activation of caspase-8-dependent inflammasomes and pro-IL-1 β processing (103, 104). The pathogen-dectin-1 bond acts as a trigger for the formation and activation of a noncanonical inflammasome complex—consisting of CARD9, Bcl-10, MALT1, caspase-8, and ASC—which converts pro-IL-1 β to its biologically active form. While PRRs such as NLRs recognize pathogens intracellularly, dectin-1 detects *M. leprae* PAMPs extracellularly, enabling a rapid response to the pathogen without the need for internalization. The existence of a caspase-8-dependent noncanonical inflammasome emphasizes the diversity and versatility of immune responses to infection (103–106).

Neutrophils and Macrophages

Blood neutrophils are recruited to the sites of tissue infection or injury by multiple-step processes that are dependent on selectins, integrins, and chemokines (107, 108). When these cells are recruited to a site of infection they express receptors that recognize and bind to microorganisms, ingesting and destroying them by phagocytosis and microbicidal molecules present in phagolysosomes (109, 110). These microbicidal molecules can be grouped into three main classes: reactive oxygen species (ROS), NO, and proteolytic enzymes (111).

The mononuclear phagocytic system includes monocytes (circulating in blood) and macrophages (resident in tissues) (112, 113). Macrophages play important roles in innate and adaptive immunity and are located in organs and connective tissue. Skin macrophages can migrate to the lymph nodes under immunologic conditions (112, 113). Macrophages are part of a group of cells that undergo phenotypic modification and express receptors, costimulatory molecules such as CD163, CD68, CD80, CD86, and CD206, and cytokines that induce the development of suppressive or proinflammatory responses (Fig. 3) (112–114).

More recent studies have shown that like for DCs, different phenotypes of macrophages can be identified by the expression of HLA-DR, CD163, arginase, and MRP8 (115–118). These studies identified three different macrophage populations: (i) M1 macrophages, which characteristically express HLA-DR, (ii) M2 macrophages, identified by the presence of CD163 and arginase, and (iii) M4 macrophages, characterized by the expression of MRP8 (Fig. 3) (115–118). Macrophages ingest microorganisms by phagocytosis, which is the energy-dependent envelopment of large particles. Microbial destruction in macrophages occurs in phagolysosomes, vesicles formed from the fusion of phagosomes with lysosomes during phagocytosis, necessarily involving enzymes

and ROS (112, 119–123). Macrophages have high-affinity receptors that bind to antibody molecules, complement proteins, and lectin, which are essential receptors for the phagocytosis of many different microbes. Increasing evidence suggests a new subpopulation of macrophages known as M4. M0 macrophage differentiation gives rise to M4 macrophages in the presence of CXCL4; M4 macrophages produce IL-6, TNF- α , MRP8, MMP7, MMP12, and CD68 (118, 124, 125). The first reports of M4 macrophages showed that these cells are abundant in atherosclerotic lesions, where the expression of low-density lipoprotein receptor (LDL-R) by macrophages is increased. This provokes the accumulation of fat in phagocytes, causing the development of atheroma plaques and consequent oxidative lesions. However, recent data have pointed to the expression of LDL-R in infectious skin lesions such as leishmaniasis and leprosy, which demonstrates a possible association and role of M4 macrophages in immune responses to these diseases in the skin (Fig. 3) (118, 124–130).

M17 and Mreg (regulatory) macrophages have also been proposed, in addition to the subpopulations described above. However, their characterization and involvement in the physiological and pathological processes of the skin and other organs require further investigation (115, 117).

Finally, it is important to emphasize that both macrophages and DCs of the skin are characterized by a marked phenotypic heterogeneity that reflects their diversity and involvement in the various types and stages of cutaneous immune responses.

Basophils and Mast Cells

The morphology and physiology of basophils and mast cells are similar; however, basophils are found predominantly in blood, while mast cells are mainly found in tissue (131, 132). According to their tissue distribution and enzymatic composition of their granules, it is possible to distinguish at least two subpopulations of mast cells: mucosal mast cells, which contain trypsin, and connective tissue mast cells, which contain chymotrypsin. A high-affinity receptor for IgE is expressed by basophils and mast cells, which is strongly bound to their surfaces, leading to degranulation and the release of various substances, including serotonin, histamine, platelet-activating factor, and leukotrienes (Table 1) (133, 134).

Mast cells constitute one of the most abundant cell populations of the skin and express complement C5a (CD88) receptors (132). Their location in the dermis, their ability to release vasoactive and proinflammatory substances, and the expression of IgE receptors on their surfaces imply that they have important roles in the immunity of the skin to infectious or harmful agents (132–134). Mast cells are probably involved in the mechanisms of fibroblast proliferation, blood flow control, and angiogenesis (135–139). These functions are implicated in extracellular matrix remodeling and in the cicatricial (scarring) and fibrotic processes associated with skin lesions (Table 1) (139).

Eosinophils

Eosinophils are abundant cells in the inflammatory infiltrates of late-phase reactions. These cells are granulocytes derived from bone marrow and are involved in the pathogenesis of allergic diseases and infections (140, 141). Th2 profile cytokines promote eosinophil activation and recruitment at sites of inflammation, stimulating the release of granular proteins that are toxic to parasitic helminths, particularly nematodes, and actively participate in the inflammatory cascade underlying allergic processes (141–146). The presence of such parasites is linked to the production of IgEs, which bind to parasites and trigger the release of various eosinophil-derived microbicidal substances, such as cationic proteins, peroxidase, and neurotoxins (147, 148). Eosinophils can also release prostaglandins that may induce vasodilation and chemotaxis by neutrophils, leukotrienes involved in allergic skin diseases, and cytokines (Table 1) (148).

NK and Natural Killer T (NKT) Cells

NK cells are lymphocytes that do not express T or B cell receptors (149). They can participate in both innate immunity and adaptive immunity via antibody-dependent

cytotoxicity, the downregulation of MHC class I expression, or IL-12 stimulation with IFN- γ release (Table 1) (150–152). They can also produce granzyme, perforin, and granulysin and thereby participate in the direct destruction of microorganisms and neoplastic cells. Furthermore, they play key roles in the pathogenesis of inflammatory and infectious skin diseases (153). They are detected primarily by the expression of CD16 (phagocytosis and antibody-dependent cellular cytotoxicity), CD56 (an NCAM-neural cell adhesion molecule), and CD57 (HNK-1 sulfated carbohydrate chain). NK cells also release TNF- α , GM-CSF (a growth-stimulating factor for granulocyte and monocyte colonies), and IL-3. These cells also promote macrophage activation, leading to phagocytosis and the destruction of microorganisms (150, 151).

Another type of NK cell is the NKT cell. NKT cells have both NK and T cell characteristics and are also capable of releasing cytokines such as IFN- γ , IL-22, and IL-17; these cytokines are involved in the activation of macrophages and in the maintenance of epithelial barrier integrity, which stimulates the generation of antimicrobial peptides and production of chemokines in the skin (Table 1) (154). Moreover, they can express chemokine receptors such as CXCR3, CCR5, and CCR6, which facilitate the recruitment of lymphocytes. Despite their role in inducing skin inflammation in experimental mouse models of psoriasis, further studies are needed to elucidate the role of NKT cells in this process (155–157).

ILCs

During hematopoiesis, lymphoid precursors give rise to T and B cells, which have specific antigen receptors that are characteristic of each of these subpopulations (158). Until recently, it was thought that there were only two subpopulations that had no characteristic antigen receptors. The first subpopulation has already been described as NK cells. The second subtype comprises lymphoid tissue-inducing (LTI) cells, which are important for lymphoid tissue development, including Peyer's patches, lymph nodes, and other lymphoid cells (159). However, more recently, cells resembling LTI cells have been identified and termed NK22 cells. These cells concomitantly present markers of NK cells and express the cytokine IL-22 (160, 161). Both LTI and NK22 cells are now considered a subtype of innate lymphoid cells (ILCs), referred to as ILC3 cells (Table 1).

Studies have indicated the importance of ILCs in responses to infections, especially with helminths. These cells are observed in tissues such as the gut and appear to play key roles in the immunopathogenesis of psoriasis and skin infections. Recently, they were named innate lymphoid cells (108) and were divided into three categories according to the adaptive response phenotype mediated by T CD4⁺ helper lymphocytes—namely, ILC1 (Th1), ILC3 (Th17), and ILC2 (Th2)—which are, respectively, directed against intracellular agents, extracellular microbes, and large parasites. Furthermore, they appear to play a central role in the control of adaptive immune responses (108, 161).

B Lymphocytes

B lymphocytes typically play a central role in the humoral immune response because they synthesize antibodies (162). In addition to their central role in antibody production, B lymphocytes can function as APCs and produce cytokines that affect tissue and systemic immunity (163) (Table 1). Moreover, recent evidence suggests a role for B lymphocytes in both homeostasis and pathological processes involving the skin associated with local immune responses in neoplastic and infectious processes. B lymphocytes are rarely observed in normal skin, and although several techniques have been used to characterize this population, the specific roles of B cells in dermal homeostasis and immunological surveillance have not been fully clarified (164).

Nevertheless, B lymphocytes are known to migrate to the skin through the endothelium and interact with receptors of selectins, chemokines, and integrins (165). B lymphocytes migrate toward the antigenic focus, where APCs activate naive lymphocytes present in the tissue microenvironment (166).

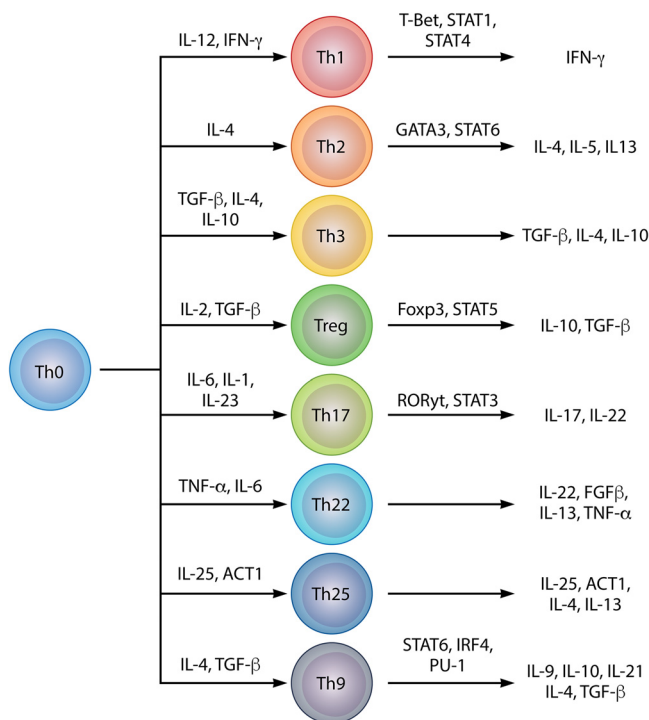


FIG 4 Diversity in helper T lymphocyte profiles, their differentiation factors, and characteristic cytokine profiles.

In the pathophysiology of infectious and inflammatory skin processes, B cells can exhibit both proinflammatory and suppressive effects. Infiltration by B lymphocytes has been observed in cutaneous lesions in leishmaniasis, as well as in inflammatory diseases such as atopic dermatitis (166–168). The mechanisms by which B cells contribute to inflammatory skin pathogenesis occur through their interaction with components of innate immunity and with T lymphocytes (166). In *Staphylococcus aureus* skin infections, B lymphocytes play an important role in the synthesis of specific antibodies, as well as in bacterial opsonization and in the induction of phagocytosis by macrophages and neutrophils (169, 170). More recently, regulatory B lymphocytes (Breg) have been identified and appear to play an important role in attenuating inflammation and inducing the maintenance of immune tolerance mechanisms through the release of IL-10 (171, 172) (Table 1).

T Lymphocytes

There are approximately twice as many local lymphocytes in normal skin as there are in the blood. Although the presence of T cells in the skin was first described some 70 years ago, this population of lymphocytes has attracted scientific attention only within the last 25 years (173, 174). The skin has a phenotypically heterogeneous population of lymphocytes, mainly comprised of memory T cells (Fig. 4 and Table 1) (175, 176). In the epidermis, T cells are located in the suprabasal and basal strata, close to LCs (Fig. 1) (176). In the dermis, T cells are distributed in clusters around the capillaries; they are also frequently found at the dermo-epidermal junction and around cutaneous appendages. CD4⁺ and CD8⁺ T lymphocytes are present in the skin in similar proportions, and most of these are memory T cells (177). The skin has a heterogeneous population of T lymphocytes that participate in classical immune responses, including Th1, Th2, Th3, Th17, and regulatory T (Treg) cells, which have been found in the skin in various infectious and inflammatory diseases (13). More recently, differentiated subpopulations involved in specific physiological and pathological processes have been identified, including Th9, Th22, and Th25 lymphocytes (Fig. 4 and

Table 1) (178–180). In the case of infections by intracellular microorganisms, Th1 cells predominantly release IFN- γ and lymphotoxins, leading to the activation of macrophages with microbicidal activity (181). Classically, Th1 lymphocytes in the skin are associated with the resolution of infections and the pathogenesis of autoimmune or immunomediated diseases such as psoriasis (181, 182). In immunocompromised patients, Th2 cells participate in the inflammatory response to infectious agents and are referred to in the context of allergic diseases such as atopic dermatitis and psoriasis (181, 183). Th3 lymphocytes were primarily identified in oral tolerance models (184–186). They are characterized predominantly by the production of transforming growth factor β (TGF- β) and secondarily by the production of IL-4 and IL-10, which are involved in the class switching of B cells to produce IgA, with inhibitory effects on Th1 and Th2 lymphocytes (185–195). In view of the ability of Th3 profile lymphocytes to stimulate the production of antigen-specific lymphocytes, and to inhibit the production of non-antigen-specific lymphocytes, these cells can be considered a subtype of Treg lymphocytes (Fig. 4 and Table 1) (181–195).

The Treg cell population consists of Th3 T CD4⁺ cells and regulatory T cells (Tr1). Th3 CD4⁺ cells are characterized by their ability to express primarily TGF- β , whereas Tr1 lymphocytes are characterized by high expression of IL-10 (188–193).

Tr1 lymphocytes are a subset of CD4⁺ T lymphocytes, whose function is to suppress immune responses and maintain self-tolerance (7, 189). Although other types of T cells with suppressor activities have been described, Tr1 lymphocytes are characterized by CD4⁺, FoxP3⁺, and CD25⁺ markers (189). These cells are produced primarily through the recognition of autoantigens in the thymus or of external antigens in peripheral lymphoid organs, in which these cells do not express FoxP3 constitutively but acquire the function of Tr1 cells by increasing FoxP3 expression in response to the presence of IL-2 and TGF- β , or stimulated by the presence of small molecules such as retinoic acid (188, 189). The production of some Tr1 cells requires the cytokine TGF- β , and the maintenance and effectiveness of this profile is dependent on IL-2 (190). Tr1 cells suppress immune responses at multiple stages of their life cycle, and appear to be capable of inhibiting B cell activation, as well as differentiation and proliferation of NK cells (191). Several mechanisms of action have been proposed for Tr1 cells, including the production of immunosuppressive cytokines such as TGF- β and IL-10 (191). Another mechanism involves the inhibition of T cell stimulation by APCs via the binding of CTLA-4 (CD152)—a Tr1 cell surface molecule—to B7 (CD80/CD86), which is expressed on the surface of APCs. This ultimately increases IL-2 cytokine consumption through an increase in IL-2 receptor expression on Tr1 cells (7).

In normal, noninflamed skin, Treg lymphocytes are preferentially distributed close to and in close association with hair follicles, with fewer cells located in the dermis between these structures (196, 197). In general, because of the role of Treg cells in the control of skin immune responses, the biological and functional characterization of these cells in the cutaneous tissue environment is of vital importance for the understanding of inflammatory diseases of the skin (198–200). Because of their close relationship with hair follicles, these structures play a key role in the control of skin homeostasis and in the activation of Treg cells (197, 201–203). Dysregulation of follicle stem cell function has been shown to be linked to Treg cell function, and studies of polymorphisms have linked this to high-affinity IL-2 α receptor genes (*IL-2RA* and *CD25*), *FOXP3*, and cytotoxic-T-lymphocyte-associated antigen (*CTLA*), among others (197, 202, 203). These aspects are confirmed by the observation of the presence of Treg lymphocytes in lesions of alopecia areata undergoing regeneration after institution of specific therapeutic treatments. In addition to the cellular components of the hair follicles, other cell types, including fibroblasts, DCs and LCs, also play important roles in controlling the Treg lymphocyte population of the skin (196, 197).

Th17 cells are implicated in the pathogenesis of both psoriasis and atopic dermatitis and are a key cell type in the body's first line of defense against infection by certain fungi and bacteria (40, 183, 204, 205). Studies have pointed to important roles of IL-17 and IL-22, including increasing the expression of keratinocyte antimicrobial peptides

(38). Therefore, Th17 lymphocytes may form a bridge between immune cells and epithelial cells, thus improving the efficiency of the skin's immune responses to pathogens (Fig. 4 and Table 1) (199, 200).

Th22 cells constitute another recently identified subgroup of T cells that express IL-22 but not IL-17 or IFN- γ (180). pDCs are able to induce the Th22 profile by releasing TNF- α and IL-6. These cells were identified in cultures from patients with atopic dermatitis, and the authors of several other studies have investigated the role of this profile in the skin under normal and pathological conditions, including psoriasis, lupus erythematosus, lymphoma, allergic and infectious diseases, epidermal skin immunity, and tissue remodeling (Fig. 4 and Table 1) (180, 206–212).

Th9 and Th25 lymphocytes have also been described recently. Th9 lymphocytes are distinguished by the expression of IL-4, IL-9, IL-10, IL-21, and TGF- β and differentiate from Th0 lymphocytes in the presence of IL-4 and TGF- β (213–215). In the skin, Th9 cells appear to be involved in autocrine and paracrine control of local inflammatory responses and in *Candida albicans* infections. In addition to stimulating IL-9 expression, these cells also induce the release of TNF- α and granzyme B (216, 217). Th25 lymphocytes are characterized by the expression of Act1, IL-4, IL-13, and IL-25 (IL-17E) and are involved in IgE release and mast cell degranulation. Recent data have implicated Th25 in the immunopathogenesis of skin diseases, namely, coccidioidomycosis, chronic mucocutaneous candidiasis, and lepromatous leprosy (Fig. 4 and Table 1) (178, 218–222).

$\gamma\delta$ T lymphocytes are so-called nonconventional immune cells (223, 224). These cells have receptors composed of γ and δ heterodimers that are homologous to the α and β chains of TCRs found in CD4⁺ and CD8⁺ T lymphocytes, and they are identified through the CD3 and TC $\gamma\delta$ markers (Table 1). $\gamma\delta$ T lymphocytes do not recognize peptide antigens associated with MHC-II and are not restricted to the MHC. $\gamma\delta$ T lymphocytes recognize alkyl amines, small phosphorylated molecules, lipids not commonly found in mycobacteria and other microorganisms (presented by nonclassical molecules such as MHC class I glycoproteins), and protein and nonprotein antigens that do not require any kind of processing by APCs (223–227). In human skin, $\gamma\delta$ T lymphocytes constitute a small percentage of T cells in the dermis and epidermis (2 to 9% and 1 to 10%, respectively) (170, 171, 228). Little is known about their roles in human skin, but an increase in the population of $\gamma\delta$ T lymphocytes has been observed in patients with melanoma, LC histiocytosis, leishmaniasis, and leprosy, among other disorders, suggesting their involvement in the pathogenesis of these skin diseases (Table 1) (229–234).

Endothelial Cells

Endothelial cells play key roles in controlling the flow of immune cells from blood to tissue through the expression of various adhesion molecules, cytokines, and chemokines, which serve as chemoattractants for leukocyte migration (Table 1) (235, 236). The endothelium is one of the first lines of defense against harmful and infectious agents in blood, and it directly affects innate and adaptive immune responses (236). During the initial phase of inflammation, when the innate response is more apparent, endothelial cells activate TLR proteins (mainly TLR2 and TLR4), which mediate immune responses (236). TLR2 is a crucial agent in the inflammatory response against bacteria and other pathogens, whereas TLR4 is a strong regulator of the innate and adaptive immune responses (Table 1) (236–239). However, these molecules are present at low levels before the activation of endothelial cells, and activation of the endothelial system leads to elevated expression of TLRs. In addition to providing standard receptors for TLR2 and TLR4, the endothelium is responsible for interacting with mediators from the immunoglobulin family such as ICAM-1 and VCAM-1 (240–242). Other adhesins, such as E- and P-selectins, are also present in greater quantities during the inflammatory response and are mainly mediated by cytokine stimuli (243). Such adhesin molecules are constitutively expressed in the membranes of endothelial cells, but when the levels of proinflammatory agents increase, they induce elevated expression of adhesins (240–

242). This leads to greater interaction between blood leukocytes and their endothelial ligands, which involves these cells in the cascade that leads to rolling, firm adhesion, and diapedesis (Table 1) (236, 243).

In inflammation, endothelial cells are directly influenced by several factors that facilitate the formation of inflammatory infiltrate (243, 244). The mechanisms responsible for this alteration include oxidative stress, which results from immune responses and increases the expression of adhesion molecules such as VCAM-1, ICAM-2, and selectins CD62E and CD62P. However, the cytokines of the immune system act as direct agents in mediating oxidative stress and influence leukocyte adhesion (243).

The endothelial immune response is associated with increased expression of cytokines such as IFN- γ , TNF- α , IL-1 α , and IL-1 β , which increase the expression of adhesion molecules (243, 244). IFN- γ appears to be one of the most important factors inducing MHC class II expression and is an important agent in the formation of costimulatory molecules, including adhesion molecules such as ICAM-1 and E-selectin (245). TNF- α leads to the increased expression of molecules such as VCAM-1 and ICAM-1. Depending on the phenotype and the intensity of the inflammatory stimuli, it is possible to detect various adhesion molecules in the membranes of endothelial cells (Table 1) (246). Such molecules modify the processes of cell rolling and tissue transmigration in leukocytes. Cell transmigration through the endothelium is possible only following rupture of the endothelial wall, which is mainly mediated by cell changes induced by proinflammatory cytokines (246–248). A cascade of intracellular events leads to changes in the cytoskeleton which allow the extravasation of fluid, chemical mediators, and cells toward the cytokine source. This process results in the formation of perivascular edema and directly combats microbial agents at the site of infection (Fig. 5) (215).

Other Cellular Components of the Skin

Other cells are also part of this complex organization of the skin, and although they may not act as the first line of host defense, they cooperate with the immune system during immune responses (249–253). The key function of fibroblasts is the production of structural proteins that constitute cutaneous tissue. They also coordinate with immune responses, allowing the migration of blood cells to sites of injury, and interact with other local cells, thereby potentiating the signaling cascade of host responses to infectious agents (254–257). Fibroblasts are relatively abundant cells in skin, and more recent work has shown that these cells release a chemoattractant that is sensed by dermal lymphocytes. In addition, fibroblasts possibly play an important role in attracting and maintaining Treg cells in this environment (258–260). The authors of several studies have discussed the importance of the extracellular matrix of the skin in the pathogenesis of infectious diseases and have characterized the importance of these tissue components in the evolution of infections (261). Moreover, similar to keratinocytes, fibroblasts can produce cytokines such as TGF- β and FGF- β , among others, and thus may influence the local immune response pattern (261–264).

Cutaneous appendages are of fundamental importance in maintaining the physiological homeostasis of the skin. Hairs are keratinized structures formed by invagination of the epidermis in the dermis (265). A terminal dilatation is observed in the process of hair follicle growth—the hair bulb—and, in its central portion, a dermal papilla that induces hair growth (249–253). The cells that cover the papilla and form the root of the hair include keratinocytes and melanocytes. During the differentiation process of keratinocytes, which occurs in the hair root, they undergo keratinization and incorporate melanin. Hair follicles of human skin are specialized structures that may also be involved in the control of local immune responses in the skin. Activation of stem cells from hair follicles may be involved in the hair growth process and in the control of immune responses, through interaction with Treg lymphocytes, as described previously (197, 201–203).

Sebaceous glands, as with hair follicles, originate from the same epithelial sheath and secrete cholesterol and triglycerides (252, 253, 266, 267). These glands can express TLR2 and TLR4 and secrete immune factors such as defensins, cytokines, chemokines,

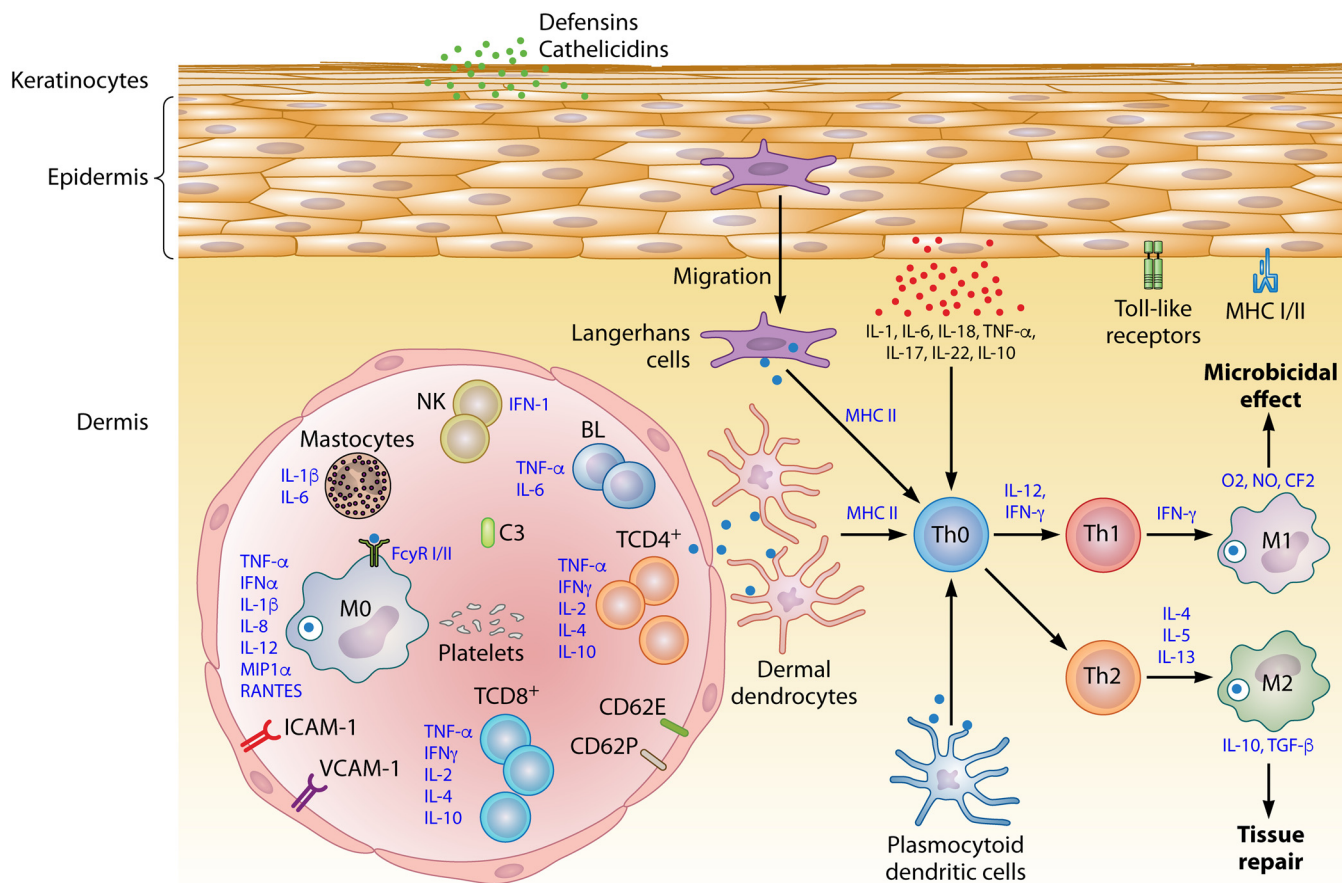


FIG 5 Integrated view of the association between the host cells and infectious agents in the context of the skin's *in situ* immune response. Note that the triggered mechanisms culminate in the activation of professional and nonprofessional immune cells, such as keratinocytes, which can, however, interfere with the immune response cascade against various harmful agents. These cells act as a mechanical barrier and can interfere with the immune response in the skin. Endothelial activation is required for the migration of immune cells from the blood to the tissue.

adipokines, serpin E1, leptin, and resistin, which can act as a bridge between the control of the local inflammatory response and lipid metabolism in the skin (266). This ability to control the tissue immune response pattern of sebaceous glands in close association with lipid metabolism makes these glands fundamental to control of the local microbiome. Consequently, the deregulation of their physiology is linked to the pathophysiology of infectious, metabolic, and inflammatory skin diseases, such as acne, psoriasis, seborrheic dermatitis, and rosacea (266–271). The eccrine sweat glands are entangled tubular structures and comprise cells that eliminate the secreted product, without compromising the cells. They produce sweat, which is directly secreted onto the skin surface through an excretory duct and is composed of an aqueous solution of ions (Na^{2+} , K^{+} , and Cl^{-}), urea, ammonia, uric acid, and very small amounts of protein (253). The apocrine sweat glands are found in the axillary, pubic, and perianal regions. Part of the cytoplasm of the cells that constitute these glands is lost during secretion. The apocrine sweat glands produce a viscous secretion that is discharged into the hair follicle canal, rather than directly onto the surface of the skin (252, 253).

Finally, neurons, which primarily act on the somesthetic processes of the skin, interact with lymphocytes and regulate local immune responses (254, 272, 273). Riol-Blanco et al. have shown a close relationship between DDs and skin nociceptors, as these nerve endings probably induce the production of IL-23 and IL-17, which, in turn, function to control immune responses of the skin in experimental models of psoriasisform inflammation (272).

TABLE 2 Types of cell death and causes, morphology, mechanisms, or factors that lead to its induction

Type of skin cell death	Cause
Necrosis	Tuberculosis
Apoptosis	Leprosy
Autophagy	Zika virus infections
Pyroptosis	Leishmaniasis
Ferroptosis	ROS, RNS, glutathione
Necroptosis	<i>Staphylococcus aureus</i> infection

THE ROLE OF CELL DEATH IN HOMEOSTASIS AND THE CONTROL OF THE SKIN'S IMMUNE RESPONSE

The phenomenon of cell death is intrinsically linked to the cellular life cycle and aging, and it occurs as a homeostatic mechanism under both physiological and pathological conditions (274–279). Cells in general may die by two distinct mechanisms, namely, accidental cell death and regulated cell death (RCD) (274). RCD may occur in contexts that include exogenous or endogenous cellular alteration or disturbance, leading to physiological changes that cannot be reverted, and consequently lead to cell death. It may also occur in the absence of exogenous disorders and, as in this specific case, in the context of programmed cell death (PCD) during the process of cell development and renewal (274, 275). Classical studies have divided the mechanism of cell death into three types: type I cell death or apoptosis, type II cell death or autophagy, and type III cell death or necrosis, based primarily on the morphological characteristics of each of these groups (274).

Since 2005, a committee on cell death has formulated the guidelines of a classification system for the different types of cell death, based not only on morphological aspects but also on genetic, biochemical, pharmacological, and functional characteristics. This has resulted in a wider classification for the mechanisms of cell death and has furthered our understanding of the importance of these mechanisms for processes involving homeostasis and disease. This classification scheme proposes the occurrence of at least 12 distinct mechanisms of cell death, which are shown in Table 2 (274, 275).

In the skin, although cell death is related to important physiological and pathological processes, evidence suggests that it also has a prominent role in the control of immunological responses and in the pathophysiology of various skin diseases. Necrosis and apoptosis appear to be at opposite ends of a spectrum, and several mechanisms lead to cell death (257, 262, 280–282). Mechanisms such as necroptosis, pyroptosis, ferroptosis, and autophagy have received increased attention in the study of the pathophysiology of various infectious and noninfectious diseases, including in the cutaneous environment (Table 2) (257, 262, 280–287).

There are many and diverse processes by which infectious agents interact with host cells to induce injury (284). Often, these agents trigger a process that culminates in immunosuppression. Among these mechanisms, apoptosis is commonly used by diverse infectious agents to negatively control immune responses by inducing cell death in inflammatory cells (280–287). The high-affinity recognition of autoantigens by T lymphocytes (when these are constantly stimulated by antigens) can lead to apoptosis (280, 288–297). There are two major apoptotic pathways, and both involve the deletion of peripheral and mature immune cells. Cell death by apoptosis may present mitochondrial changes, which are regulated by the Bcl-2 family of proteins; this family has pro- and antiapoptotic members (284). Changes in the permeability of the outer membranes of mitochondria may be induced by Bcl-2 proteins, or these proteins may interact with a caspase activation inhibitor (280). The extrinsic pathway occurs by activation of death receptors and is the second most important apoptosis activation route in the deletion of immune cells. Death receptors, which are homologous to TNF receptors, may be activated by TNF-like ligands, leading to the oligomerization of an adapter protein (280, 284). This protein activates a caspase cascade or induces the translocation of a proapoptotic member of the Bcl-2 family to the mitochondria,

leading to a change in their permeability and to the activation of a caspase (280, 284–287).

Some studies have suggested the occurrence of apoptosis in the control of the immune response in lepromatous leprosy and cutaneous leishmaniasis, as well as in several viral diseases (298–301). Lytic, caseous, or liquefactive necrosis can occur in inflammatory or infectious skin diseases as a consequence of the action of viruses, bacteria, or helminths (302). Moreover, the innate immune response pattern may underlie the occurrence of cell death by pyroptosis, implying that this type of cell death is important in innate immune responses to infectious or noninfectious skin agents (255, 303).

Necroptosis is a type of necrotic cell death that involves fine control of plasma membrane permeability, and it is activated by the formation of RIPK1/RIPK3/MLKL complexes (necrosomes), which activate a pronecrotic protein termed MLKL (285, 304). After this phase, the propagation of cell death by the release of DAMPs, with activation of cellular immune responses, takes place, leading primarily to the activation of macrophages, DCs, and NK cells (305), inducing the pinocytosis of compromised or infected cells. This leads to the activation of a cascade of cell death where the presence of TNF- α may also contribute to the induction of chronic inflammation and to the presence of more lesions (305, 306). Some infections have been associated with cell death by necroptosis, as reported for infectious processes induced by a suspension of *Staphylococcus aureus* diluted in phosphate-buffered saline (PBS) and inoculated into mice in experimental models of infections (169, 284, 307, 308).

Cellular autophagy occurs through the accumulation of autophagosomes in the cellular cytoplasm, with the degradation and recycling of cellular components that may have been damaged by aging, chemical agents, infections, or inflammation (257, 262, 309, 310). Experiments on the interaction between Zika virus and skin cells have shown that infected fibroblasts form autophagosomes in the cytoplasm, suggesting that during viral replication, autophagy is stimulated in cutaneous cells (311–313).

Characterized by the occurrence of lipid peroxidation products and ROS release from iron metabolism, ferroptosis is a type of RCD with morphological characteristics such as diminished mitochondria and condensation of mitochondrial membranes that induces reduction in numbers of cristae and the rupture of the outer mitochondrial membrane (314–327). Ferroptosis can be induced in keratinocytes, mainly in processes related to DNA or mitochondrial damage mediated by ROS or nitrogen radicals, as well as by potentially toxic chemical compounds, which can be produced in abundance in the presence of infectious diseases (265, 326, 327). These compounds can cause injury and induce cell death by diverse mechanisms, including apoptosis, necroptosis, and ferroptosis, depending on the activity of xenobiotic biochemical pathways involving glutathione and vitamins C and E (314–327). The types of cell death and their relation to infectious and noninfectious causes, as well as their stimuli, mechanisms, and morphology, are shown in Tables 2 and 3.

OVERVIEW OF THE RELATIONSHIP BETWEEN SKIN IMMUNE SYSTEM AND THE EVOLUTION OF INFECTIOUS CUTANEOUS DISEASES

I have already discussed the general organization of the cutaneous immune system, so in the present section I specifically address the mechanisms inherent in compartmentalized responses to infectious agents of diverse nature, with emphasis on local skin immune responses, tissue immune responses, or *in situ* immune responses.

The *in situ* pattern of the skin's response to infections is complex and involves several cellular and humoral factors (Table 1 and Fig. 5). The immune response to various infectious agents in the tissue environment requires the activation of innate and acquired types of immunity, which are closely linked and interregulated (Fig. 5) (328–332). Infectious agents of diverse nature can reach the skin tissue either through direct inoculation at a break in the physical barrier of the epidermis or through blood vessels and activation of the endothelium (5, 333, 334). In the latter context, endothelial cells play an important role in the migration of microorganisms

TABLE 3 Mechanisms of cell death in the skin and their relationship with various infectious agents and chemical inducers of irreversible cell damage^a

Type of cell death	Cause	Mechanism	Morphology	Occurrence
Necrosis	Stress or toxic agents with low ATP concentration or impaired ATP generation	ATP concentration or impaired, ATP generation	Dilation of organelles, dissociation of ribosomes from the endoplasmic reticulum, cell nucleus disintegration, chromatin condensation.	Infections, ischemia
Intrinsic apoptosis	Intracellular microenvironment perturbations (DNA damage, ERE, ROS, mitochondrial alterations, mitotic defects, etc.)	MOMP controlling and antiapoptotic members of the Bcl-2 family	Cytoplasmic shrinkage, pyknosis, karyorrhexis, plasma membrane blebbing, apoptotic bodies	DNA damage, hypoxia, viral infection, toxins, hyperthermia, growth factor withdrawal, infections
Extrinsic apoptosis	Death ligand binding to receptors of the TNF superfamily (e.g., FasL/FasR, TNF- α /TNFR1, Apo3L/DR3, Apo2L/DR4, Apo2L/DR5)	DISC activation with activation of caspase cascade; absence of activation of survival receptor with activation of caspase cascade	Cytoplasmic shrinkage, pyknosis, karyorrhexis, plasma membrane blebbing, apoptotic bodies	Cancer, thymus involution, infections
MPT-driven necrosis	Severe oxidative stress, cytosolic Ca ²⁺ overload	MPT with abrupt loss of the impermeability of the IMM to small solutes resulting in rapid potential dissipation	Necrosis morphology	Ischemia with reperfusion injury in neuronal, cardiac and renal tissue, infections
Necroptosis	Intracellular microenvironment perturbations with activation of death receptors (Fas, TNFR1, TLR3, TLR4, etc.)	Phosphorylation and oligomerization of MLKL proteins that insert into and permeabilize the plasma membrane	Necrosis morphology	Homeostasis of adult T cells, development, infections
Ferroptosis	Intracellular microenvironment perturbations with severe lipid peroxidation, ROS generation and iron availability	Unchecked lipid peroxidation and oxidative lipid fragmentation normally opposed by GPX4	Electron microscopy: shrunken mitochondria, chromatin condensation, cytoplasmic and organelle swelling, plasma membrane rupture, formation of double membrane vesicles	Antineoplastic agents, ROS, RNS
Pyroptosis	Pyroptosis is a form of RCD triggered by perturbations of extracellular or intracellular homeostasis related to innate immunity	Activation of one or more caspases, including CASP1, associated with IL-1 β and IL-18 secretion, and hence mediates robust proinflammatory effects	Cell lysis, cell swelling, pore formation, DNA fragmentation	Intracellular pathogen infection, inflammation
Parthanatos	UV, alkylating agents (e.g., MNNG), Ca ²⁺ influx, ROS	Hyperactivation of poly(ADP-ribose) polymerase 1; release of apoptosis-inducing factor into the cytoplasm; activates endonuclease	Chromatin condensation, nuclear fragmentation	Neuronal cell death, neurodegeneration
Entotic cell death	Entosis is a form of cell cannibalism that occurs in healthy and malignant mammalian tissues, involving the engulfment of viable cells by nonphagocytic cells of the same (homotypic) or a different (heterotypic) type.	Detachment of epithelial cells from the extracellular matrix and consequent loss of integrin signaling	Actomyosin chains accumulate at the cortex of internalizing cells, cortical plasma membrane blebbing, entotic cell-containing vesicles and promote their fusion with lysosomes	Cancer

(Continued on next page)

TABLE 3 (Continued)

Type of cell death	Cause	Mechanism	Morphology	Occurrence
NETotic cell death	Extrusion of a meshwork of chromatin-containing and histone-containing fibers bound to granular and cytoplasmic proteins known as neutrophil extracellular traps	Signaling pathway that involves Raf-1 proto-oncogene, serine/threonine kinase (RAF1), mitogen-activated protein kinase kinases, and extracellular signal-regulated kinase 2, culminating with NADPH oxidase activation and consequent ROS generation	Chromatin-containing and histone-containing fibers bound to granular and cytoplasmic proteins known as neutrophil extracellular traps (NETs)	Diabetes, cancer, inflammation, bacterial and fungal infections
Lysosome-dependent cell death	Perturbations of intracellular homeostasis and demarcated by the permeabilization of lysosomal membranes	Cell death proceeds upon lysosomal membrane permeabilization, resulting in the release of lysosomal contents, including proteolytic enzymes of the cathepsin family, to the cytoplasm	Degradation of intracellular contents and organelles	Inflammation, tissue remodeling, aging, neurodegeneration, cardiovascular disorders, and intracellular pathogen response
Autophagy-dependent cell death	Cell death that relies on the autophagic machinery or components thereof	Upregulation of Atg5 and Atg6; autophagosome and autolysosome formation	Large-scale sequestration of cytoplasmic contents in autophagosomes and autolysosomes	Treatment with etoposide, staurosporine, thapsigargin, viral infections, bacterial infections
Immunogenic cell death	Adaptive immune response to specific endogenous (cellular) or exogenous (viral) antigens expressed by dying cells	Release of a series of DAMPs, whose recognition by PRRs expressed by innate and adaptive components of the immune system warns the organism of a situation of danger, resulting in the elicitation of an immune response	Can present a varied morphology of apoptosis, necrosis or autophagy	Viral infection, bacterial infections, anthracyclines, bortezomib, specific forms of radiation therapy

^aERE, endoplasmic reticulum stress; MOMP, mitochondrial outer membrane permeabilization; MPT, mitochondrial permeability transition; IMM, inner mitochondrial membrane; DISC, death-inducing signaling complex; MLKL, mixed lineage kinase domain-like; ROS, reactive oxygen species; RNS, reactive nitrogen species; RCD, regulated cell death; DAMP, damage-associated molecular pattern; PRR, pattern recognition receptor.

from blood to the cutaneous environment, as well as in the migration of leukocytes to the focus of infection (335). It should be emphasized that endotheliocytes allow the transmigration of cells from the blood into the infected tissue in order to elicit a specific immune response during the course of an infection (Fig. 5) (336–338). It has already been shown that the endothelial phenotype can influence the evolution of chronic and spectral infectious diseases such as leprosy and leishmaniasis, depending on the pattern of cells that migrate to the focus of infection (336–338). Furthermore, the capillaries of the dermis maintain a close anatomical relationship with the DDs and probably participate, together with endotheliocytes, in the first stages of the immune response to infectious agents of the skin (Fig. 5) (339–342). Although LCs are the main type of immune cells in the epidermis, as already mentioned, keratinocytes can participate in the control of the immune response in the tissue microenvironment (343). They do so by releasing antimicrobial peptides, presenting antigens, or participating in innate or adaptive immunity by releasing cytokines that control the cascade of proteins in the immune response to microorganisms (Fig. 5) (343). The first cytokine identified as being released by keratinocytes was IL-1. Subsequently, other cytokines were identified: IL-6, IL-8, IL-10, TNF- α , and TGF- β (38–41, 344). Keratinocytes are also able to express MHC-I and MHC-II and participate in the immunopathogenesis of various infectious viral, bacterial, and protozoal diseases, including leishmaniasis, leprosy, and herpes (Fig. 5) (38–41). In infections with flaviviruses such as Zika virus, West Nile virus (WNV), and dengue virus, keratinocytes possibly play key roles in the early stages of immune responses, which are mediated by IFN- β , IFN- γ , and antimicrobial peptides (345).

DCs contribute to the development of an effective and specific adaptive immune response against infectious agents through the processing and presentation of antigens (13, 61–64). Several studies have demonstrated the importance of this group of cells in specific immune responses to bacteria, fungi, protozoa, and viruses in the skin tissue environment (89). These studies have indicated the importance of antigen presentation by DCs in the evolution of infectious diseases such as leprosy, leishmaniasis, paracoccidioidomycosis, lacaziosis, and infections with flaviviruses such as dengue and Zika viruses (89, 313). In several arthropod-borne infections, the interaction of infectious agents with the dermal immune system, in particular with LCs and adjacent keratinocytes, represents the first stage of interaction with the host and one of the determining factors in the clinical evolution of disease, as well as in maintaining transmissibility cycles (345). Several mosquitoes responsible for transmitting infectious agents produce saliva with substances that generally exhibit anticoagulant, angiogenic, and anti-inflammatory properties, inhibiting local T cell proliferation and suppressing the expression of cytokines such as TNF- α , IL-2, and IFN- γ , as well as stimulating the secretion of IL-4 and IL-10, both in the tissue environment and in experimental models (345).

In the process of local immune responses of skin to agents transmitted by arthropods, LCs have the ability to capture the inoculated antigens and migrate to the satellite lymph nodes, where they initiate the process of activation of T cells (345). In dengue virus infection, immunohistochemical and molecular analyses have demonstrated the presence of virus antigens in LCs, whose activation is mainly dependent on TNF- α and to a lesser extent on IL-1- β , contrary to what is observed in WNV, where the activation and migration of LCs are more dependent on IL-1- β than on TNF- α (345–348). In Zika virus diseases, some studies have demonstrated an induction of IFN- β expression by LCs (345). In another study developed by Vielle et al. (349), Zika virus infection was shown to be capable of inducing the expression of type I and II interferons in DC culture, and it was shown that the activation of these cells is mediated by the expression of MHC class II, CD40, CD80/86, or CCR7. Some data have pointed to the importance of DCs in the sexual transmission of infectious agents via mucosal surfaces through the interaction of these agents with the various subpopulations of DCs, including LCs, through the immunomodulation of the activity of these cells, a fact that is well described for the transmission of HIV and is important in the mechanisms of sexual transmission of Zika virus (350, 351). In leishmaniasis and malaria, this ability to

modulate the skin can either contribute to the elimination of these microorganisms or create an environment that stimulates the evolution of the disease into milder or more severe clinical forms (344, 352–354). This particular aspect can be observed in the clinical evolution of dengue fever and in its relationship with the phenomenon of antibody-dependent enhancement (ADE) (355). Dengue virus infection can be caused by four serotypes (dengue virus serotypes 1, 2, 3, and 4) and may result in a spectrum of clinical symptoms ranging from mild to hemorrhagic symptoms. Moreover, the pattern of this symptomatology is linked immune responses by the host (355–357). ADE is a process linked to the clinical evolution of severe forms of dengue and occurs in individuals with a history of secondary infection by a virus with a heterologous serotype. ADE triggers the activation of nonneutralizing or subneutralizing antibodies and specific previously sensitized cytotoxic T lymphocytes, which can stimulate a marked cross-immune reaction, contributing to the development of severe forms of infection. Studies have demonstrated the role of DCs in this mechanism (355–357). During ADE, mature DCs require the expression of Fc gamma receptor IIa (Fc RIIa), and the process is inversely related to the high expression levels of DC-SIGN (DC-specific intercellular adhesion molecule-3-grabbing nonintegrin) receptor present in immature DCs (355, 356). DCs stimulate the increased expression of viral proteins as well as the production of cytokines TNF- α and IL-6, which are involved in the pathogenesis of this phenomenon (355).

In cutaneous leishmaniasis and leprosy, populations of dendritic cells in the hyperergic and tuberculoid forms are more frequent than in the anergic and lepromatous forms, indicating a fundamental role for the number of DCs in cutaneous lesions in inducing effective cellular immune responses against intracellular infectious pathogens during the evolution of spectral cutaneous diseases (340, 352). These findings have been further corroborated by results obtained with other cell types such as macrophages, which are important in the presentation of antigens and in microbicidal action against *M. leprae* and leishmaniasis (358, 359).

The roles of inflammasomes in immunity to infectious agents have been characterized for some skin diseases, such as leprosy, paracoccidioidomycosis, and leishmaniasis (91, 95, 98, 359, 360). The pattern of immune responses is associated with the creation of a marked proinflammatory environment and is also involved in the induction of cell death by pyroptosis, which is related to cell deletion and induction of tissue injury in the inflammatory processes of infectious diseases (255, 303).

Macrophages play important roles in the recognition and elimination of foreign antigens of infectious or noninfectious origin, as well as in cicatrization and in the remodeling of the extracellular matrix (Fig. 3 and 5) (264, 358, 359). In infectious diseases, macrophages are the main cells involved in immunity to infection by *M. leprae*, *Leishmania*, *Paracoccidioides*, and *Lacazia loboi* and are probably involved in antigen presentation and in the release of ROS and reactive nitrogen species (RNS) with microbicidal effects (361, 362). The microbicidal mechanism employed by macrophages is closely related to gene expression patterns such as natural resistance-associated macrophage proteins (NLRs) with regard to the efficiency of the immune response to mycobacteria, such as *M. tuberculosis* and *M. leprae* (361).

Mast cells are abundant in the intestinal mucosa and skin. Owing to their preferential location, they play a role as sentinels against microbial agents (bacteria, viruses, helminths, and fungi), triggering local inflammatory responses (132–134). Moreover, along with basophils, mast cells can affect vessels by releasing vasoactive substances that influence the flow of leukocytes between blood and tissue. They may also be associated with the action of IgE during the *in situ* immune response against infections of the skin (133, 134).

The development of an effective adaptive immune response to infectious skin agents is closely related to the clinical evolution of several diseases, such as leishmaniasis, paracoccidioidomycosis, and leprosy (363–366). The Th1 \times Th2 paradigm has been associated with the clinical evolution of several infectious diseases, and studies on leishmaniasis and leprosy have also characterized this process (Fig. 5) (179, 364). In these two diseases, predominance of the expression

of Th1 cytokines, such as TNF- α and IFN- γ , is clinically related to more localized forms of lesions, whereas predominance of the expression of Th2 cytokines, such as IL-4 and IL-10, contributes to the clinical evolution of susceptible or anergic forms (Fig. 5) (363–366), with the presence of lesions in greater quantity and more diffusely distributed in the patient's body. However, the role of recently identified immunological agents in the immune response of the skin has provided a better understanding of the evolution of these and other infectious diseases, as well as of the processes of healing and tissue remodeling (179, 362, 367). Among these new agents and cytokine profiles, Treg cells and Th9, Th17, Th22, and Th25 profile cytokines have provided us with additional data regarding the immunopathogenesis of skin infections and, above all, on complex and spectrally evolving infectious diseases (179, 363–366). For example, cytokines belonging to the Th17 profile, such as IL-6 and IL-17, probably contribute to a response mediated by a more exacerbated and efficient inflammatory profile against intracellular pathogens such as *M. leprae* and *Leishmania* (179, 368). In contrast, cytokines such as IL-10 and TGF- β effectively maintain a state of susceptibility to infection. They accomplish this either by inhibiting Th1 profile cytokines, such as IFN- γ and TNF- α , or by contributing to the differentiation of lymphocytes into Treg cells, which also negatively control immune responses (179, 369).

The Th22 profile, characterized by cytokines IL-22, IL-13, and TNF- α , in addition to fibroblast growth factor β (FGF- β), has contributed to the understanding of the complex immunopathogenesis of infections with agents such as *M. leprae* (180, 336). IL-22 has been implicated as an antimicrobial response cytokine because it interferes with the phagolysosomal maturation process, thereby inhibiting the lytic capacity of macrophages against *M. tuberculosis*. The increased participation of this cytokine in lepromatous leprosy seems to play a potentiating role in the lytic activity of macrophages, in a possible attempt to revert the susceptibility of this clinical form of the infection (180, 336). Similarly, IL-13 plays a key role in the induction of the humoral response, which is consequently ineffective in the recognition and elimination of intracellular infectious agents (336). Finally, FGF- β is probably involved in tissue regeneration associated with more aggressive infectious diseases and with increased tissue involvement. In addition to participating in the functions of Th22 lymphocytes, FGF- β (along with TGF- β) may help create a regenerative environment in lepromatous leprosy (336). Finally, the importance of Th17 profile cytokines, such as IL-17 and IL-22, should be noted, because they are capable of potentiating the release of AMPs by keratinocytes and mucosal cells. This confers on these cytokines an important role in both innate and adaptive immunity (38–41).

The role of profiles such as Th9 and Th25 in infectious and noninfectious skin inflammatory diseases has not yet been extensively studied and characterized. The few available articles in the literature have indicated the proinflammatory role of Th9 lymphocytes in tuberculoid leprosy. In particular, they have focused on cytokine IL-9, or on anti-inflammatory profiles such as that observed for Th25 lymphocytes, whose cytokine IL-25 (IL-17E) is related to humoral immune responses and is therefore ineffective against intracellular infectious agents. IL-25 belongs to the IL-17 family, and unlike other members of this family such as IL-17A and IL-17F, it inhibits Th1 and Th17 cytokine production (178, 213, 218, 220, 369–372). NF- κ B activation is induced by IL-25 and triggers the expression of IL-4, IL-5, IL-9, and immunoglobulin E, as well as the degranulation of mast cells against extracellular pathogens (218).

Several studies have demonstrated the interactions between pathogen and host with regard to various types of infectious agents that have immune escape mechanisms (373, 374). In this scenario, pathogen and host factors may interact to maintain the environment. Studies have shown that factors such as TGF- β and the apoptosis phenomenon may contribute to this process (375, 376). Data collected during the evolution of certain infectious skin diseases suggest that this control is affected by apoptosis. TGF- β , which is a strong inducer of apoptosis, also seems to have a fundamental role in the process. It contributes to the differentiation of the

Treg response, inhibits macrophagic responses, and acts as an immunosuppressive cytokine (301, 375–377). Moreover, TGF- β seems to play a major role in the evolution of several infectious diseases of the skin, including leprosy, leishmaniasis, cutaneous leishmaniasis, and chromoblastomycosis (96, 359, 375, 376, 378–380). Depending on its relationship with other cytokines and humoral factors of the host's response, TGF- β has numerous roles in the tissue microenvironment. It has multiple functions and can control the immune response by direct action on the cells of the immune system, inhibiting the effector activity of lymphocytes and macrophages, and by inducing the apoptosis of macrophages (375). Apoptosis has been implicated in the negative control of the immune response because certain infectious pathogens use it as an escape mechanism (301, 375–377, 381–384). In both leprosy and cutaneous leishmaniasis, apoptosis has been identified as the most frequent mechanism of cell death in the lepromatous forms of leprosy and anergic leishmaniasis, which has implicated this phenomenon in a possible mechanism of control of the immune response in these clinical conditions (300, 301, 381–384). In addition, it is worth mentioning that other types of cell death, such as pyroptosis and autophagy, have been implicated in skin tissue responses in viral infections and in the activation of inflammasomes that induce pyroptosis in bacterial infections. This further indicates a possible role of these mechanisms of cell death in the pathogenesis and immunopathogenesis of such infections (Tables 2 and 3) (385–389).

PERSPECTIVES

Finally, it is worth remembering that the skin immune system is complex and acts in very characteristic ways against microbial agents. Moreover, many other factors might be involved in effective immune responses. The identification of new subpopulations of lymphocytes and macrophages and the characterization of other cells that may influence immune responses or act as immunogenic targets are important topics of research. Such research will certainly contribute to the elucidation of the complex mechanisms of skin immune responses and of the evolution of cutaneous diseases. Research concerning the initial stages of systemic infectious diseases with clinical courses that depend on the initial interaction between pathogen and host in the skin, such as in Zika and dengue virus infections, will also be beneficial.

The immune response to various infectious agents in the skin triggers a wide range of defense mechanisms. Nevertheless, this response is sufficiently specific to fulfill its primary role: to act as an interface between host and the environment. In recent years, an increasingly important role has been attributed to the cutaneous immune system because it is in this environment that the mechanisms of immune responses to various infectious agents begin. It is very likely that a series of immune cascades determines the host response pattern according to this first interaction. From this perspective, special emphasis has been placed on DCs, which are components of innate immunity and the first subpopulation to interact with infectious agents that enter the body through epithelia such as skin and mucous membranes. This subpopulation is also the link to the mechanisms of adaptive immunity and determines the pattern of responses to be developed against these specific agents. Recently identified mechanisms and immunological factors involved in the control of immune responses have also attracted attention in recent years, opening up promising research into both cutaneous and general immunity.

Important research topics include the role of inflammasomes in the control of local immune responses, the characterization of endoplasmic reticulum stress mechanisms in the effectiveness of the responses by DCs and macrophages, the emergence of the roles of keratinocytes, fibroblasts, and melanocytes in the control of the immune response, and the role of endothelial cells in the flux of immune cells into the skin. The characterization of this tissue environment will lead to a better understanding of the relationship between the host and the environment.

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I declare that I have no competing interests.

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