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INFLAMMATORY SKIN DISEASES, T CELLS, AND IMMUNE SURVEILLANCE

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Skin is the primary interface between the body and the environment. The spectrum of insults to which skin is susceptible includes disorders caused by chemical and microbial agents, thermal and electromagnetic radiation, and mechanical trauma. The most damaging consequence of the disruption of skin is invasion by pathogenic microorganisms, and the need for an effective means of protection against this challenge has been a fundamental force behind the evolution of the immune system. The translation of insults into cutaneous inflammation (innate immunity) and the recruitment of memory T lymphocytes that have clonally expanded in response to antigens encountered at the cutaneous interface with the environment (acquired immunity) are both required for successful cutaneous immune surveillance.

Certain memory T cells appear to remember the anatomical site where they first encountered antigen. Specifically, there is an identifiable subgroup of memory T cells with the ability to circulate preferentially to the skin. These memory T cells, identified by a marker known as cutaneous lymphocyte antigen (CLA), are generated in lymph nodes draining skin and are recruited back to the skin during inflammation. Although their primary function is cutaneous immune surveillance, CLA-positive T cells have been implicated in the pathogenesis of relatively rare skin diseases, such as cutaneous T-cell lymphoma and graft-versus-host disease after allogeneic bone marrow transplantation. CLA-positive T cells also mediate many common skin diseases, including allergic contact dermatitis, psoriasis, atopic dermatitis, alopecia areata, vitiligo, drug-related eruptions, and lichen planus. The patterns of T-cell movement and migration that mediate cutaneous immune surveillance are central to an understanding of the clinical and pathological features of T-cell–mediated skin diseases.

T CELLS AND IMMUNE SURVEILLANCE

Whereas antibodies recognize three-dimensional conformations of macromolecules, T-cell antigen receptors recognize antigens as fragments of macromolecules bound to antigen-presenting proteins on the surface of antigen-presenting cells. These cell-surface proteins include class I (HLA-A, B, and C) and class II (HLA-D) major histocompatibility complex molecules, which bind peptide antigens for presentation to CD8+ and CD4+ T cells, respectively, and CD1 molecules, which bind nonpeptide antigens for presentation to a different subgroup of T cells. T-cell antigen receptors are heterodimeric proteins composed of α/β or γ/δ chains. These receptors are encoded by four genes containing a large number of discrete genetic elements that recombine during intrathymic differentiation, generating an almost unlimited repertoire of T-cell receptors, each with a unique specificity. This great diversity is both a strength and a weakness. Although there may be a T-cell antigen receptor that is specific for every possible peptide antigen from a pathogen, establishing conditions in vivo under which a T cell will encounter the antigen for which its unique antigen receptor is specific represents a substantial logistic challenge.

The migratory behavior of T cells allows the immune system to overcome this logistic challenge. T cells that have never been activated by antigen (naive T cells) efficiently migrate from blood into lymph nodes and return to blood through efferent lymphatics. The mechanisms by which these T cells enter lymph nodes from blood involves specific combinations of adhesion molecules and chemokines on specialized postcapillary venules in the endothelium (high endothelial venules), as well as L-selectin and other adhesion molecules and chemokine receptors on the T cells. Naive T cells lack the specific combinations of adhesion molecules and chemokine receptors required to enter extranodal tissues from blood (Fig. 1).

The presentation of antigen to T cells, which is necessary for their activation, requires both the binding of the antigen–HLA or antigen–CD1 complex with the T-cell antigen receptor and additional costimulatory signals delivered by the antigen-presenting cells. Dendritic cells are specialized antigen-presenting cells that express high levels of costimulatory molecules and are uniquely capable of activating naive T cells in lymph nodes. Skin contains large numbers of dendritic cells, in both the epidermis (Langerhans' cells) and the dermis. Macromolecules (including those derived from microorganisms) introduced after the skin has been disrupted are efficiently internalized by dendritic cells. After enzymatic processing in the endosomes of these cells, the antigens are bound to antigen-presenting molecules, and the resulting complex is expressed on the cell surface for presentation to T cells. These dendritic cells

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migrate through afferent lymphatics and collect in lymph nodes replete with naive T cells that have recently entered the lymph nodes from the blood. In this fashion, antigens derived from a large surface area of skin are concentrated at a single specialized site (the lymph node), where they come into contact with naive T cells, making it likely that an interaction between antigen and T-cell antigen receptor will occur (Fig. 1).

Once these T cells have been activated by an antigen, they proliferate and express activation molecules, undergoing the transition to memory T cells. During this transition, the T cells acquire new molecular keys that allow them to exit the blood vessels in extranodal tissues. Lymph nodes that drain different epithelial interfaces with the environment (e.g., skin and the gastrointestinal tract) generate phenotypically distinct memory T cells that can exit the ves-
sels at these specific extranodal sites. The best-studied T-cell component mediating this phenomenon is CLA, a glycoprotein molecule first expressed during the transition of T cells from previously unactivated cells to memory cells in lymph nodes that drain the skin.\(^5\) The expression of CLA by T cells involves the induction of glycosylation enzymes that modify a pre-existing protein (P-selectin glycoprotein ligand 1) in a highly specific fashion.\(^6\) Thus, memory T cells in inflammatory skin diseases express CLA on their surface; in contrast, T cells in inflammatory diseases involving tissues other than skin are predominantly CLA-negative.\(^3\)

CLA is more than just a marker that identifies skin-specific T cells. It is an adhesion molecule that mediates the initial tethering of T cells to the endothelium in cutaneous postcapillary venules.\(^15,16\) This step is required for the subsequent slowing, arrest, and extravasation of the T cells, allowing them to overcome the substantial forces exerted by blood flow.\(^15,16\) E-selectin, the endothelial ligand for CLA, is expressed constitutively at low levels on cutaneous microvessels, but its expression is strongly up-regulated during cutaneous inflammation.\(^17\) The preferential expression of E-selectin in skin helps select for CLA-positive T cells under both normal and inflammatory conditions. Although interactions between CLA and E-selectin are required as the initial step in the extravasation of T cells from the blood into the skin, the activation of T cells through chemokines and the firm adhesion of T cells to the endothelium through interactions between integrin and cell adhesion molecules are also required\(^18\) (Fig. 2). The expression of unique chemokine receptors by CLA-positive T cells and the preferential expression of their respective chemokine ligands by skin cells increase the specificity of these T cells for skin.\(^19\)

**CUTANEOUS INFLAMMATION, CYTOKINES, AND NUCLEAR FACTOR-κB–MEDIATED PATHWAYS**

Interleukin-1 and tumor necrosis factor α, which have been called primary cytokines, have broad effects that are relevant to inflammation and immunity.\(^20\) The epidermis is a storehouse of interleukin-1α and can produce large amounts of interleukin-1β and tumor necrosis factor α.\(^20,21\) After binding to their receptors, these cytokines activate several cellular signaling pathways, including the nuclear factor-κB (NF-κB) pathway.\(^22\) Among the many genes regulated by NF-κB in skin cells, those that are central to the initiation of cutaneous inflammation include the genes for E-selectin, chemokines and cytokines, defensins (antibacterial peptides), intercellular adhesion molecule 1, and vascular-cell adhesion molecule 1.\(^22\)

Cytokines are not the only means of inducing NF-κB responses in skin. Plants, insects, and mammals share a family of innate immune-cell surface receptors that signal through NF-κB (or its plant and insect homologues).\(^23\) In humans, these are known as Toll-like receptors (receptors that resemble the drosophila Toll protein).\(^24\) Rather than binding cytokines, these receptors recognize conserved molecules derived from microbes; Toll-like receptor 2 was recently identified as a signal-transducing receptor for gram-negative bacterial lipopolysaccharide, as well as gram-positive bacterial lipoteichoic acid.\(^25,26\) Although their extracellular ligands are different, Toll-like receptors use multiple intracellular molecular elements in common with primary cytokine receptors, culminating in the translocation of NF-κB to the nucleus\(^22\) and the transcription of genes that play an important part in cutaneous inflammation (Fig. 3). Many Toll-like receptors have been described, but the ligands for most of them are unknown.\(^23\)

NF-κB-mediated inflammation in skin appears to be a final common pathway for the translation of environmental insults into inflammation and is a crucial element of innate immunity (Fig. 3). Even ultraviolet radiation from sunlight induces ligand-independent clustering and activation of interleukin-1 and tumor necrosis factor receptors,\(^27\) leading to NF-κB–mediated inflammation.

**CLA-POSITIVE T CELLS AND CUTANEOUS INFLAMMATION**

CLA-positive T cells represent 10 to 15 percent of all circulating T cells in peripheral blood, and although they have some features in common (e.g., their expression of CLA and certain chemokine receptors), their T-cell antigen-receptor specificities are quite heterogeneous. Furthermore, CLA-positive T cells may be positive for either CD4 or CD8, and once activated, they may be capable of producing either type 1 T-cell cytokines (interferon-γ, interleukin-2, and lymphotoxin) or type 2 T-cell cytokines (interleukin-4, 5, 10, and 13). This heterogeneity of phenotype and function is likely to be important for a successful and flexible host response to the plethora of distinct pathogens encountered in skin.

How do insults to the skin trigger immune surveillance and immunity mediated by CLA-positive T cells? NF-κB transcriptional activation induces inflammation,\(^22\) favoring the recruitment of CLA-positive T cells to skin through E-selectin, chemokines, and cell adhesion molecules. Thus, cutaneous inflammation preferentially recruits memory T cells that have been activated by skin-related antigens. Because circulating CLA-positive T cells have previously encountered antigens in lymph nodes draining skin,\(^3\) this mechanism of immune surveillance mediated by memory T cells is based on the principle that common things occur commonly — in this case, that antigens encountered previously in skin may be responsible for (or at least associated with) the new insult.

Extravasation of CLA-positive T cells into skin does
Figure 2. Extravasation of a CLA-Positive Memory T Cell into Inflamed Skin.

Skin injury or infection results in the activation of the nuclear factor-κB (NF-κB) pathway through cytokine receptors (interleukin-1 or tumor necrosis factor α [TNF-α]) or Toll-like receptors. Microbial products may directly activate this pathway. The result is the transcription of many genes that contain κB sites in their promoters in a variety of skin cells. In endothelial cells, these include the adhesion molecules E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular-cell adhesion molecule 1 (VCAM-1). To extravasate into skin, T cells must slow their velocity in the circulation. To do so, they use CLA—P-selectin glycoprotein ligand 1 (CLA—PSGL-1) cell-surface molecules, located on the tips of microvilli, to bind to E-selectin and P-selectin on the luminal surface of the cutaneous postcapillary venules, a process called “tethering.” Once tethered, the T cells roll on the endothelial surface in the direction of the blood flow, but much more slowly. This exposes much of the surface of the T cells to the surface of the endothelium, where chemokines that have been produced on the abluminal side of the vessel by resident skin cells and transported to the luminal surface of the endothelial cells can be displayed. The binding of chemokines to specific receptors on T cells results in a modification of the structure of the α4β1 integrin (lymphocyte-function–associated antigen 1 [LFA-1]) and the α4β1 integrin (very late antigen 4 [VLA-4]) so that they can bind to ICAM-1 and VCAM-1, respectively. Not only is the integrin binding of sufficiently high affinity to arrest the CLA-positive T cells, but it also favors the flattening of the lymphocytes in preparation for their extravasation through the endothelial layer. Once extravasated on the abluminal side of the vessel, the T cells are no longer subjected to shear forces from blood flow, and they can respond to chemotactic gradients emanating from the site of injury or infection. If these T cells encounter antigen in tissue, they will become activated. The subsequent release of T-cell cytokines will modify and expand the inflammatory infiltrate.
Figure 3. Shared Pathways in Primary Cytokine (Interleukin-1 and Tumor Necrosis Factor α) and Toll-like–Receptor Signaling.
Activation through Toll-like receptors, the interleukin-1 receptor, and the tumor necrosis factor (TNF) receptor all culminate in NF-κB gene transcription and the production of inflammatory mediators. Toll-like receptors bind microbial products and initiate signaling by recruiting MyD88, an adapter protein also used by the type I interleukin-1 receptor after ligand binding. This leads to the recruitment of interleukin-1-receptor–associated kinases (IRAK) 1 and 2, also known as innate immune kinases. TNF-receptor–associated factor 6 (TRAF-6) is recruited to this complex, which then activates NF-κB–inducing kinase (NIK). NIK is similarly activated by TNF-receptor–associated factor 2 (TRAF-2), which is recruited to the signaling complex of the TNF receptor and its adapter proteins TNF-receptor–associated death domain (TRADD) and receptor-interacting protein (RIP) after ligand binding to the receptor. NIK phosphorylates the IKK complex, which in turn phosphorylates the cytoplasmic complex of IκB and NF-κB. This leads to the degradation of IκB in the cellular proteosome and allows free NF-κB to migrate into the nucleus. NF-κB–mediated gene transcription induces the expression of E-selectin, intercellular adhesion molecule 1, and vascular adhesion molecule 1 in cutaneous endothelial cells. It also induces primary cytokine production and chemokine production in keratinocytes, fibroblasts, and other resident skin cells. Collectively, these signals recruit CLA-positive T cells (as well as other leukocytes) from skin.
not by itself require antigen recognition by T cells. For T cells to perform effector functions in skin, however, they must recognize antigen through their antigen receptors. They then become activated, producing effector molecules, including type 1 or type 2 T-cell cytokines. Therefore, only CLA-positive T cells that actually encounter the antigen for which their antigen receptor is specific will be activated during a given episode of cutaneous inflammation. The cutaneous microenvironment favors antigen presentation; antigen-presenting cells are abundant in skin, and blood dendritic cells and monocytes can also be recruited from blood in response to cutaneous inflammation, resulting in an expanded pool of these cells. It is the activation of T cells by antigen, and the subsequent release of type 1 and type 2 T-cell cytokines and other effector molecules, that result in clinically apparent, T-cell–mediated skin disease. Type 1 T-cell cytokines induce resident skin cells to produce chemokines that recruit monocytes and additional type 1 T cells. Type 2 T-cell cytokines induce a different set of chemokines that favor the recruitment of eosinophils and type 2 T cells.

Although it facilitates the process dramatically, inflammation may not be an absolute requirement for the extravasation of CLA-positive T cells into the skin. Because cutaneous postcapillary venules express low levels of E-selectin and intercellular adhesion molecule 1 constitutively, activated CLA-positive circulating T cells may not require chemokines to extravasate in the absence of cutaneous inflammation. Alternatively, if low levels of chemokines are constitutively expressed on postcapillary venular endothelium in uninfamed skin, even resting CLA-positive T cells may undergo the process of tethering, activation, and adhesion required for extravasation into normal skin. This may represent an additional component of immune surveillance mediated by CLA-positive memory T cells.

What is the fate of the large numbers of CLA-positive T cells that successfully extravasate but do not encounter the antigen for which their antigen receptor is specific during a given episode of inflammation? These cells do not become activated through their antigen receptors, and they appear to leave the skin through afferent lymphatics, traveling to a lymph node and then through efferent lymphatics back to the blood. They then rejoin the circulating population of CLA-positive T cells (Fig. 1) and continue to mediate cutaneous immune surveillance.

T-CELL–MEDIATED SKIN DISEASES

Psoriasis

Psoriasis affects more than 2 percent of the world’s people. It is characterized by scaly, red cutaneous plaques that contain inflammatory infiltrates and epidermal hyperproliferation (Fig. 4). The serendipitous observation that treatment with cyclosporine dramat-ically improved psoriasis provided the first strong evidence that the disorder had an immune cause, an idea that had previously been suggested by its association with certain HLA class I haplotypes. The role of T cells in this disorder has been demonstrated by the remission of severe psoriasis after treatment with a drug consisting of diphtheria toxin and the receptor-binding domain of interleukin-2 (DAB interleukin-2), which creates a toxin specific for activated T cells. Cutaneous T cells in psoriatic lesions express CLA, whereas those found in the joints of patients with psoriatic arthritis do not express CLA. Although CD4+ T cells may help initiate the skin lesions, CD8+ T cells that produce type 1 cytokines (interferon-γ) are responsible for the persistence of the lesions. The role of CD8+ T cells explains the paradox that psoriasis can worsen dramatically even as CD4+ T-cell counts fall in patients with human immunodeficiency virus infection. There is increasing support for the idea that psoriasis is an autoimmune disease; however, the antigen or antigens responsible for activating the CD8+ cells in the epidermis are not known.

The development of new psoriatic lesions on injured skin, known as the Koebner phenomenon, is consistent with the immune-surveillance paradigm. Normal human epidermis contains preformed interleukin-1α, which is released from keratinocytes after minor trauma. CLA-positive T cells are recruited from peripheral blood by interleukin-1α–initiated inflammation, and CLA-positive T cells whose antigen receptor is specific for the putative psoriatic autoantigen in skin will be activated in situ. The subsequent release of type 1 T-cell cytokines results in further inflammation, the recruitment of additional CLA-positive T cells, and ultimately the development of psoriatic lesions in susceptible persons. The prevalence of psoriasis on the elbows, knees, and other sites of repetitive trauma is consistent with this model. Another potential connection with the innate immune system involves the association of acute exacerbations of established psoriasis with bacterial and fungal infections of skin. This interesting clinical observation may have as its basis the activation of Toll-like receptors by infectious microorganisms in skin cells, which induces NF-κB–mediated inflammation and the recruitment of CLA-positive T cells.

Although activated T cells are necessary for the development and persistence of lesions, psoriasis is difficult to explain solely on the basis of T-cell activation. For example, the activation of CLA-positive T cells that produce type 1 cytokines in the epidermis is probably a common response to environmental antigens in persons in whom psoriasis never develops. Whether this paradox can be explained by the existence of a unique subgroup of cytokines produced by T cells in patients with psoriasis or whether resident skin cells from patients with psoriasis have
an aberrant response to cytokines or other effector molecules is not known. The clinical heterogeneity of psoriasis and the apparent multigenic pattern of inheritance suggest that a combination of variables are involved in its development.

Therapies for psoriasis, in particular, and for T-cell-mediated skin diseases in general, tend to have a remittent effect (inducing long-term remission) or a suppressive effect (improving lesions but with a prompt recurrence when the treatment is discontinued). The differences in remittent and suppressive therapies for psoriasis are correlated with the clinical and histologic features of the disease, such as T-cell apoptosis. For example, treatment with ultraviolet B radiation or psoralens plus ultraviolet A radiation (PUVA) greatly reduces the number of activated T cells in the epidermis and dermis of psoriatic skin by inducing T-cell apoptosis, often resulting in long-standing remissions. Systemic treatments with agents such as methotrexate and DAB interleukin-2 preferentially induce apoptosis of activated T cells, both in blood and in skin. In contrast, treatment with topical corticosteroids or cyclosporine inhibits the production of cytokines by intralesional T cells. Although such suppressive therapies efficiently reduce both inflammation and hyperproliferation of keratinocytes, they rarely reduce the number of lesional T cells to a level below 50 percent of the pretreatment levels. As a result, psoriasis often recurs soon after the cessation of suppressive therapies. Both remittent and suppressive therapies have toxic effects that may limit their use.

**Allergic Contact Dermatitis**

Allergic contact dermatitis, also known as contact hypersensitivity, is a T-cell-dependent skin disease with the kinetics of a delayed-type hypersensitivity response (Fig. 4). This disorder is even more prevalent than psoriasis, and although it is rarely life-threatening, the costs to society of occupation-related allergic contact dermatitis are high. In this disorder, the offending antigen is introduced epicutaneously through intact skin. The sensitizing antigens are typically unstable reactive molecules that can form complexes with host proteins. In addition, potent contact-sensitizing antigens induce dose-dependent cutaneous irritation that is independent of their antigenicity. This injury-mediated triggering of the innate immune system may operate through the production of cytokines by resident cells of the epidermis and dermis or through direct activation of the NF-κB pathway in the endothelium. In both cases, endothelial adhesion molecules are expressed and inflammatory chemokines are produced, allowing the recruitment of circulating CLA-positive T cells. These signals also favor the migration of Langerhans’ cells bearing contact-sensitizer--modified proteins from the epidermis into draining lymph nodes for presentation to naive T cells.

Within days after the initial cutaneous contact with the sensitizing antigen, newly generated CLA-positive memory T cells specific for this antigen exit the cutaneous lymph nodes and appear in the peripheral blood. Repetitive exposure to the sensitizing antigen is likely to increase the number of antigen-specific CLA-positive memory T cells circulating in the peripheral blood, until a level is reached that results in allergic contact dermatitis on subsequent exposure. These newly generated CLA-positive T cells extravasate at the site of irritation from the sensitizing antigen, recognize the antigen in situ, and become activated. Their cytokines (and possibly direct cell-mediated injury of keratinocytes) induce the clinical pattern of cutaneous inflammation that is characteristic of allergic contact dermatitis. Subsequent encounters with the contact-sensitizing antigen, even months later, will again lead to the recruitment of CLA-positive T cells from peripheral blood, which now include antigen-specific memory T cells (generated from previous encounters with the contact-sensitizing antigen). T-cell extravasation, followed by antigen-receptor activation and release of T-cell cytokines, leads to the “recall” development of full-fledged clinical allergic contact dermatitis. If the contact-sensitizing antigen is a compound in the workplace that is impossible to avoid or that cannot be identified, the problem may lead to an inability to work in that environment.

**Atopic Dermatitis**

Atopic dermatitis can be viewed as an exaggerated cutaneous immune response to environmental allergens. Patients with this disorder have a humoral response characterized by IgE antibodies associated with T cells that produce type 2 cytokines (Fig. 4). The antigens that induce such responses are termed allergens, and the allergens frequently responsible for atopic dermatitis are derived from the house-dust mite *Dermatophagoides pteronyssinus*. Atopic dermatitis can be associated with asthma and allergic rhinitis, and there is a strong though incompletely defined genetic component of this disease.

Many lines of evidence suggest that naive, allergen-specific T cells in patients with atopic dermatitis are preferentially induced to develop into CLA-positive T cells that produce type 2 cytokines and migrate to the skin after encountering antigens in skin-draining lymph nodes. CLA-positive CD4+ memory T cells specific for such allergens are found in blood from patients with atopic dermatitis but not in blood from normal subjects. Type 2 T-cell cytokines promote the growth and activation of eosinophils (interleukin-5), a switch in the antibody isotype from IgM to IgE (interleukin-4 and interleukin-13), and a reduction in cell-mediated immunity (interleukin-10). Patients with atopic dermatitis have diminished resistance to cutaneous infections because of this relative cellular immunodeficiency. For example,
Psoriasis is characterized clinically by scaly erythematous plaques (Panel A) and histologically by epidermal hyperplasia, elongation of dermal papillae, subcorneal neutrophilic pustules, and a dermal and epidermal infiltrate of T cells and monocytes (Panel B; hematoxylin and eosin, ×62). The disorder is mediated largely by CLA-positive, CD8+ T cells with type 1 cytokines (interferon-γ, interleukin-2, and lymphotoxin); these cells may be activated by an autoantigen in skin. Psoriasis is a chronic, persistent, often lifelong disease.

Allergic contact dermatitis is characterized clinically by intense pruritus, erythema, and vesiculation (Panel C) and histologically by spongiosis (intraepidermal edema) and a mononuclear infiltrate (Panel D; hematoxylin and eosin, ×87). It is mediated by CLA-positive, CD8+ effector T cells that recognize contact-sensitizing antigens (small reactive molecules that enter through the epidermis). The activated T cells have a variable cytokine profile (e.g., both type 1 and type 2 cytokines).

Atopic dermatitis is characterized by intense pruritus and erythema and, in its chronic form, by scaling and lichenification (thickening of the epidermis) (Panel E). The characteristic histologic finding is a mononuclear dermal infiltrate in association with epidermal hyperplasia (Panel F; hematoxylin and eosin, ×95). Atopic dermatitis is initiated by CLA-positive, CD4+ T cells with type 2 cytokines (interleukin-4, 5, 10, and 13). T cells that produce type 1 cytokines may be involved in persistent lesions. Environmental allergens, such as proteins from the house-dust mite, *Deratophagoides pteronyssinus*, trigger the disorder.

Cutaneous T-cell lymphoma is usually manifested clinically as erythematous patches and plaques with minimal scale (mycosis fungoides) (Panel G), though there may be other clinical manifestations (e.g., erythroderma). The transformed T cells are found throughout the dermis and in the epidermis (Panel H; hematoxylin and eosin, ×79), where they may accumulate with Langerhans' cells (Pautrier's microabscesses). Many reactive (nontransformed) CLA-positive T cells are also present in lesions. Mycosis fungoides is a tumor of CLA-positive, CD4+ T cells.

Cutaneous graft-versus-host disease is a complication of allogeneic bone marrow transplantation. The acute form of the disease is...
characterized by a maculopapular exanthem (Panel I), whereas the chronic form may be characterized by marked dermal sclerosis (not shown). Dermal lymphocytic infiltration is associated with characteristic cytopathic changes in keratinocytes (Panel J; hematoxylin and eosin, ×63). CLA-positive T cells producing type 1 cytokines (in acute disease) or type 2 cytokines (in chronic disease) are present in lesions. The disease is caused by the recognition of antigens on host tissue by T cells transferred with the allograft. The photograph in Panel A was provided by Dr. Selim Aractingi, the photograph in Panel C by Dr. Stephan Grabbe, and the photomicrograph in Panel H by Dr. Isabelle Moulonguet.
reactivation of herpes simplex virus infection in such patients can lead to generalized cutaneous disease, requiring systemic antiviral therapy.

A variety of factors may stimulate the inflammation that recruits the T cells that initiate and perpetuate atopic dermatitis.\textsuperscript{49-51} Proteases secreted by mites may cause epidermal injury, leading to the production of primary cytokines and NF-\(\kappa B\)–induced inflammation, and the binding of IgE on mast cells to allergens induces inflammation through the degranulation of the mast cells. Additional triggers may be bacterial activation of Toll-like receptors by cutaneous bacteria and the release of stored interleukin-1\(\alpha\) from skin in response to the trauma induced by scratching or rubbing severely pruritic skin.

**Cutaneous Graft-versus-Host Disease**

Cutaneous graft-versus-host disease is a common and debilitating complication of allogeneic bone marrow transplantation. This disease is mediated by T cells transferred with the bone marrow allograft (Fig. 4).\textsuperscript{52} The two organs most often affected by graft-versus-host disease — the skin and gastrointestinal tract — are associated with different subgroups of memory T cells that home to these locations. T cells in lesions of cutaneous graft-versus-host disease are positive for CLA, whereas those in the inflamed gastrointestinal tract are negative for CLA but are positive for \(\alpha 4\beta 7\) integrin.\textsuperscript{2} A hypothesis currently being tested is that the memory T cells that mediate cutaneous graft-versus-host disease have previously been exposed to antigen in lymph nodes that drain the skin, whereas the memory T cells that mediate gastrointestinal graft-versus-host disease have been exposed to antigens in mesenteric lymph nodes.

**Cutaneous T-Cell Lymphoma**

Cutaneous T-cell lymphoma, the most common form of T-cell lymphoma in adults, encompasses several discrete diseases that can have markedly different clinical courses.\textsuperscript{53-55} The most common variant is mycosis fungoides, which is classified as a low-grade T-cell lymphoma.\textsuperscript{55} Mycosis fungoides is initially manifested as an inflammatory skin disease (Fig. 4), and in early lesions transformed T cells exit the vessels and enter inflamed skin through the CLA-mediated pathway (Fig. 2). Mycosis fungoides is considered to be a lymphoma involving CLA-positive, CD4+ memory T cells that home to skin.

Therapy for mycosis fungoides depends to a large extent on the site at which the malignant T cells are most abundant. In patients with disease limited to the skin, skin-directed therapies such as the administration of psoralsens plus ultraviolet A radiation, total-skin electron-beam therapy, topical administration of nitrogen mustard, and ultraviolet B radiation often induce long-lasting remissions.\textsuperscript{55} The apparent paradox of a systemic lymphoma (e.g., blood involvement in an early stage of the disease, as determined by molecular analysis\textsuperscript{56}) that can be put into durable remission by therapies that do not extend beyond the skin probably reflects the stringent homing patterns of these cells. If most continuously recirculating mycosis fungoides cells reside in skin, with very few such cells in blood or lymph nodes, then repeated courses of skin-directed therapy for a period of weeks to months may eliminate the vast majority of the cells. This principle reflects the efficacy of skin-directed therapy in immunologically mediated, nonmalignant skin disease. In advanced stages of mycosis fungoides, the T cells have lost their strict dependence on skin, and systemic therapy is required.\textsuperscript{55} Systemic therapy, which includes interferon alfa, retinoids, DAB389–interleukin-2, and photopheresis, is often used in conjunction with skin-directed therapy. Combination chemotherapy may be palliative, but curative regimens for advanced disease have not yet been developed.

**CONCLUSIONS**

The ability to respond rapidly to a pathogen after the first encounter with it is the hallmark of acquired immunity and immunologic memory. The rapid, site-specific accumulation of CLA-positive T cells after cutaneous injury meets this criterion. CLA-positive T cells extravasate in response to inflammatory signals from skin; thus, the immune system regards insults to the skin as potential infectious challenges until proved otherwise. T-cell–mediated skin diseases such as the ones we have discussed represent a subset of this highly adaptive process. Although each of these disorders can be viewed as an example of inappropriate cutaneous immune surveillance, their clinical manifestations and courses are determined by several factors: the functional phenotype and cytokine profile of the antigen-specific T cell, the type of antigen (e.g., pathogen, autoantigen, or contact-sensitizing antigen), and the genetic background of the person. This last variable, which is the most complex and the least well defined, is the focus of much of the current research on T-cell–mediated inflammatory skin diseases.

An increased understanding of the mechanisms of cutaneous immune surveillance will almost certainly provide important insights into diseases at other epithelial interfaces with the environment, in view of the fact that microvascular beds are morphologically and functionally different in different parts of the body. This is particularly true of the high endothelial venules in lymphoid tissue,\textsuperscript{57} which favor the homing of naive lymphocytes;\textsuperscript{6} cutaneous microvascular endothelial cells with prolonged expression of E-selectin;\textsuperscript{17} and endothelial cells of the lamina propria in the gastrointestinal tract, which express an adhesion molecule that favors the homing of \(\alpha 4\beta 7\)-positive memory T cells.\textsuperscript{58,59} Preferential expression of differ-
ent chemokines in these tissues may provide for further specificity of T-cell homing.19

What we now know about the movement and function of naive and memory T cells suggests that from the perspective of the host defense against environmental challenges, regional immune responses have a central role in the body’s response to infectious challenge — the raison d’être of the immune system. Therapies directed at the movement patterns of T lymphocytes — either positively or negatively — are likely to be important elements in the future treatment of inflammatory skin diseases.

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