Immunity
Review

# The Multitasking Organ: Recent Insights into Skin Immune Function

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The skin provides the first line defense of the human body against injury and infection. By integrating recent findings in cutaneous immunology with fundamental concepts of skin biology, we portray the skin as a multitasking organ ensuring body homeostasis. Crosstalk between the skin and its microbial environment is also highlighted as influencing the response to injury, infection, and autoimmunity. The importance of the skin immune network is emphasized by the identification of several skin-resident cell subsets, each with its unique functions. Lessons learned from targeted therapy in inflammatory skin conditions, such as psoriasis, provide further insights into skin immune function. Finally, we look at the skin as an interacting network of immune signaling pathways exemplified by the development of a disease interactome for psoriasis.

## Introduction

The skin, with its surface area of 1.8 $m^2$, is one of the largest organs in the human body and most exposed surface to the environment. Being constantly exposed to potential hazards requires the skin to perform numerous tasks in order to maintain homeostasis critical for health. Among other classical nonimmune functions, the skin provides a physical and biochemical barrier and a sensory-receptive area; it ensures adequate hydration; and it allows synthesis of vitamins and hormones. The skin is also required to serve as an immuno-protective organ that actively defends deeper body tissues. Similar to lung and gut mucosal barriers, the skin exploits the immune surveillance versatility of a well-coordinated system of epithelial and immune cells. Collectively, they ensure adequate immune responses against trauma, toxins, and infections, while maintaining self-tolerance, preventing allergy, and inhibiting autoimmunity. Long gone are the days when the skin was considered a mere passive barrier. This review portrays the skin as a multitasking organ, and by integrating recent exciting findings, from both clinical and murine models with fundamental concepts, we highlight how skin immune functions contribute to human health.

## Anatomy of the Skin

The unique ability of the skin to carry out multiple and wide-ranging roles is very closely related to its structure, which is composed of an outer epidermis overlying an inner dermis, separated by a basement membrane. From the lowermost layer to the uppermost visible part of the epidermis is the stratum basale, the stratum spinosum, the stratum granulosum, and the stratum corneum, the latter consisting of dead keratinocytes called corneocytes. The physical and biochemical skin barrier results from the combination of terminally differentiated epidermal keratinocytes (KCs) and the acidic, hydrolipidic nature of the skin, as a result of sweat, sebum, lipids, and antimicrobial peptides (AMPs). Changes in lipid composition and epidermal differentiation lead to a disturbed skin barrier, which plays a role in the pathogenesis of several immune-mediated skin pathologies, such as atopic dermatitis and ichthyosis vulgaris (Palmer et al., 2006; Smith et al., 2006). The epidermis is host not only to KCs, but also to melanocytes and immune cells such as Langerhans cells (LCs) and T lymphocytes. In addition, it hosts nerve-ending cells (Merkel cells), essential for light-touch and discrimination of shapes and texture. The dermis is composed of an upper papillary (stratum papillare) and lower reticular (stratum reticulare) dermis containing thin and thick collagen fibers, respectively. The collagen fibers offer a mechanical barrier as well as a structural framework in which to host blood vessels and many immune cells such as dermal dendritic cells (DDCs), $\alpha\beta$ T cells, $\gamma\delta$ T cells, natural killer (NK) cells, B cells, mast cells, and macrophages.

At this point it is important to highlight that anatomical and immunological differences exist between murine and human skin (Gudjonsson et al., 2007), in order to better appreciate information gleaned from murine models of skin infection, inflammation, and wounding. Mouse skin is covered by a thick layer of fur, whereas human skin has sparse hair coverage. Hair aids in waterproofing and prevention of desiccation and protects from certain fungal infections. Mouse skin is also much thinner than human skin with a faster epidermal cell turnover, resulting in fast healing of wounds. Murine skin also contains a thin superficial muscle layer, the panniculus carnosus, which allows for wound healing by contraction, leaving no scar upon healing, whereas human skin heals via re-epithelialization and granulation tissue formation, which can lead to scar formation. Immunological differences include the existence of subtypes of DCs not present or not yet identified in humans such as CD207(langerin)$^+$ CD103$^+$ dermal DCs (DDCs). Whether analogous cell types exist in human skin is currently being investigated. Moreover, mice, but not humans, possess V$\gamma$5V$\delta$1 T cells, named dendritic epidermal T cells (DETCs), for their morphology and location. Uniquely seeded to the basal epidermis during fetal development, DETCs constitute more than 90% of epidermal T cells, forming an interdigitating network with keratinocytes and overlaying LCs. Human epidermal V$\delta$1 (Toulon et al., 2009) and

skin-homing Vγ9Vδ2 (Laggner et al., 2011) have recently been attributed some of the functions exerted by DETCs in mice and will be discussed later.

The skin is not a sterile place and as many as $10^{12}$ resident bacteria/$m^2$ are sheltered and prosper in the intercorneocytic spaces. They feed on corneocyte debris and sebum and prevent other undesirable bacteria from developing. The skin microbiome is dependent on the site that is being considered and on sebum and moisture availability. A great step forward in helping us to understand how and why the skin responds to microbes in the way it does has been made by the establishment of the Human Microbiome Project and in particular the skin microbiome (Grice and Segre, 2011). Three species of bacteria are particularly well adapted to withstand the acidic pH environment and host AMPs: *Staphylococcus*, *Propionibacterium*, and *Corynebacterium*. Commensal bacteria like *Staphylococcus epidermidis* appear to act as an additional barrier against colonization of potentially pathogenic microbes and against the overgrowth of already present opportunistic pathogens, by producing their own AMPs to enhance host AMPs. They are also beneficial in maintaining inflammatory homeostasis by suppressing excess cytokine release after minor epidermal injury. *Propionibacterium acnes* has maintained a controversial link with the pathogenesis of acne in the face of being a skin-resident bacterium. *Propionibacterium* species was found to be more extensively located on the back of four subjects in the healthy skin group than in the nose and feet (Grice and Segre, 2011), again supporting clinical findings that acne is prone to occur on the backs of many patients. More advanced technologies (e.g., whole genome shotgun sequencing), able to differentiate between living and dead bacteria, will soon provide further details regarding temporary and long-term skin-resident bacteria to identify the true genetic diversity of the skin microflora (Grice and Segre, 2011).

## Skin as an Immunocompetent Organ and a Window into Tissue-Specific Immune Responses

Although skin nonimmune functions have been long known, its immune function was not formally recognized until 1978, when Streilein coined the term skin-associated lymphoid tissue (SALT) to describe the continuous trafficking of immune cells between the skin, draining lymph nodes (LNs), and the peripheral circulation (Streilein, 1983). Expansion of this innovative concept to include the vast majority of the cutaneous cellular components led to the term skin immune system (SIS) (Bos and Kapsenberg, 1986). Eventually, a detailed analysis of the dermal compartment gave rise to the dermal immune system (DIS) model in which dermal cells are crucially involved in the majority of chronic inflammatory skin disorders (Nickoloff, 1993). More recently, we have proposed a sentinel role in health and disease for a spectrum of skin-resident cells (Nestle et al., 2009a), with KCs involved in sensing pathogens and danger signals, migratory DCs capable of initiating a diverse range of immune responses, and tissue-resident memory T (Trm) cells performing crucial effector functions.

Analysis of clinical specimens and animal models of skin inflammation and infection have contributed to the definition of Trm cells as critical components of organ-based immunity (Figure 1; Sheridan and Lefrançois, 2011; Woodland and Kohlmeier, 2009). Initial views of skin immune surveillance greatly emphasized the role of circulatory memory cells, trafficking between skin-draining LNs and skin, poised to react quickly to a secondary challenge (Kupper and Fuhlbrigge, 2004; Streilein, 1983). Effector T cells gain tissue-specific tropism by the DC-imprinted expression of tissue-specific homing markers, determining and directing T cell migration to the tissue from which the cognate antigen is originally derived. For instance, imprinting for intestinal migration results in the expression of the gut-homing markers α4β7 and CCR9, whereas the α1β1 integrin very late antigen-1 (VLA-1) is involved in T cell migration to the lung. Expression of cutaneous leukocyte antigen (CLA), CCR4, and CCR10 determines T cell cutaneous tropism (Sheridan and Lefrançois, 2011). It has been suggested that skin DCs can metabolize vitamin $D_3$ to $1,25(OH)_2D_3$ through which they "imprint" T cells with a skin-homing signature via upregulation of CCR10 (Sigmundsdottir et al., 2007).

There is increasing evidence to support the concept of skin-resident T cells, in keeping with other barrier sites such as the lung and gut. The skin is thought to harbor a subset of Trm cells that do not circulate but are strategically positioned in both epidermis and dermis as the first-line defense in the tissue (Boyman et al., 2007; Clark, 2010). It has been estimated that the skin of a normal adult individual contains approximately 20 billion T cells, nearly twice the number present in the entire circulation. More importantly, 98% of $CLA^+$ skin-homing lymphocytes in the body reside in the skin under physiological conditions (Clark et al., 2006). Our own model of T cell-mediated skin inflammation strongly implies the existence of a Trm cell compartment with a critical functional role, because upon xenotransplantion of human nonlesional psoriatic skin onto immunodeficient mice, fully fledged psoriatic lesions develop in the absence of T cell recruitment from blood (Boyman et al., 2004). Development of skin inflammation depends on the ability of locally activated skin Trm cells, present in the initial graft, to migrate into the epidermis via VLA-1 binding to collagen IV (Conrad et al., 2007). Elegant studies of herpes simplex virus (HSV) skin infection clearly implicate Trm cells in long-term peripheral immunity (Gebhardt et al., 2009; Wakim et al., 2008), as indicated by the fact that HSV-1-specific $CD8^+$ Trm cells are retained in latently infected ganglia and are able to proliferate in situ and to contain virus reactivation with $CD4^+$ Trm cell help (Wakim et al., 2008). HSV-1-specific $CD8^+$ skin Trm cells expressing CD103 and VLA-1 are also retained in healed skin where they promote long-lasting and effective protection against local reinfection (Gebhardt et al., 2009).

Important differences between $CD4^+$ and $CD8^+$ T cell subsets in terms of tissue localization and migratory capacity have also been highlighted (Gebhardt et al., 2011). Once infection has resolved and immunological memory has taken place, memory $CD8^+$ T cells remain sequestered in the epidermis, in close proximity to the original infection site. In contrast, memory $CD4^+$ T cells rapidly traffic through the dermis, re-enter the circulation, and rapidly reach previously uninvolved skin in the case of secondary infection (Gebhardt et al., 2011). Therefore, the well-known division of labor between helper $CD4^+$ and cytotoxic $CD8^+$ T cells seems to also include a spatial compartmentalization. Besides these animal models, the existence of a population of virus-specific T cells that increases in number during subclinical HSV reactivation has been documented in humans

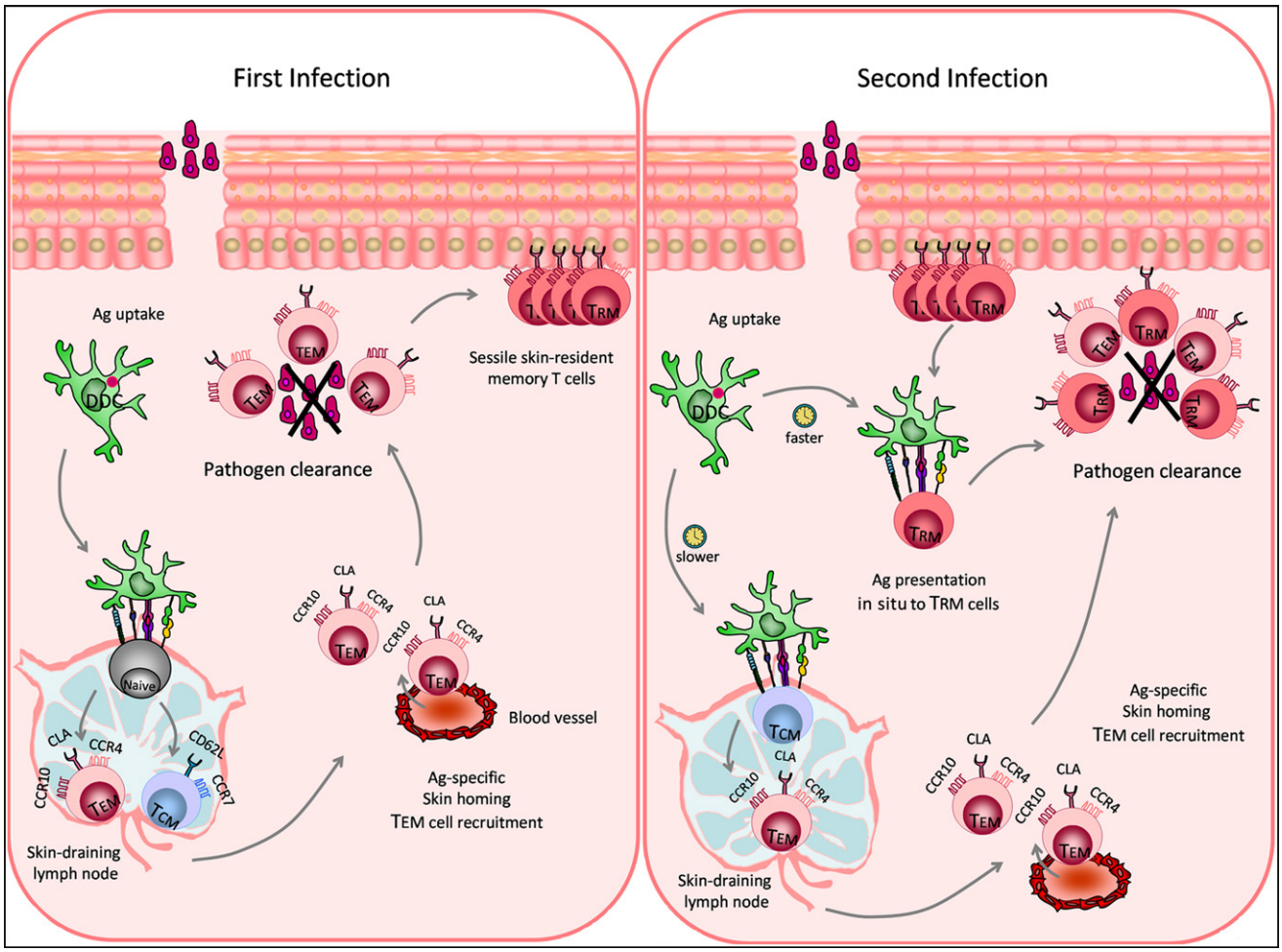


**Figure 1. Tissue-Resident Memory T Cells Provide Long-Term Peripheral Immunity in Human Skin**
After first skin infection (left) with a pathogen, dermal dendritic cells (DDCs) take up foreign antigens (Ags) and present them to naive T cells in the skin-draining lymph node, initiating an adaptive immune response. Ag-specific central memory T (Tcm) cells, expressing CCR7 and CD62L and mainly residing in lymph nodes, and effector memory T (Tem) cells, expressing cutaneous leukocyte antigen (CLA), CCR4, and CCR10, are generated. Tem cells migrate to sites of skin infection and remain there after the pathogen has been cleared to become tissue-resident memory T (Trm) cells. Upon second encounter with the same Ag (right), DDCs present Ag in situ to skin Trm cells, allowing a quick response to local reinfection. Moreover, DDCs present Ag to Tcm cells in skin-draining lymph nodes, giving rise to another population of Tem cells that migrate into skin and contribute to clearance of infection.

(Zhu et al., 2007). Further studies are required to clarify whether the different migration pattern of $CD4^+$ and $CD8^+$ T cells holds true for tissues other than skin and most importantly whether this can be exploited for therapeutic application.

## Skin Immune Network Ensures Host Defense and Tissue Repair against Chemical and Physical Insults

Having discussed the skin as an immune-competent organ, capable of rapid response to danger, we will now explore the vast array of signals that can trigger this response. Damaging the skin physical barrier may have severe detrimental effects on deeper body tissues, and therefore, the skin reacts to exposure to chemicals and to physical trauma by mounting a robust inflammatory response that prevents further damage and ultimately attempts to restore tissue function.

Exposure to irritant xenobiotic compounds triggers the activation of the skin innate immune system and results in the skin inflammatory condition known as irritant contact dermatitis (ICD). This nonspecific inflammatory reaction is characterized by an abundance of KC-derived proinflammatory mediators, neutrophil and macrophage infiltrate, and KC apoptosis and/or necrosis followed by compensatory proliferation (Nosbaum et al., 2009). ICD is usually self-limiting and spontaneously resolves, but in some individuals the contact irritant can act as a hapten, resulting in an allergic contact dermatitis (ACD) (discussed later).

The primary immunological task of the skin is to maintain body homeostasis and is most evident in the physiologic process of wound healing after tissue injury. Wound healing occurs in three sequential stages: inflammation, new tissue formation, and tissue remodeling. Within seconds of the injury, a well-orchestrated cascade of inflammatory events take place. Exposed collagen activates the coagulation cascade leading to an initial platelet plug, which is sealed and solidified by fibrin, and eventually leads to a blood clot at the skin surface, which prevents further loss of blood and fluid and serves as a scaffold for

incoming immune cells. Neutrophils arrive within an hour of wounding and launch the immune response. Although they may be dispensable for proper tissue repair, in animal models of artificial and sterile wounds (Martin and Leibovich, 2005), they kill bacteria and produce chemokines, cytokines, and proteolytic enzymes that encourage monocyte, pDC, and lymphocyte recruitment and activation (Nathan, 2006). Two days after injury, neutrophils are outnumbered by incoming monocyte-derived macrophages. In mice, two distinct monocyte subpopulations have been described (Auffray et al., 2009) as giving rise to wound macrophages with different kinetics (Brancato and Albina, 2011). Inflammatory monocytes, characterized as Ly6C$^{hi}$CCR2$^{hi}$CX3CR1$^{lo}$, migrate into sites of inflammation, early after injury, to produce proinflammatory cytokines and clear wound debris by phagocytosis. A second population, defined as Ly6C$^{lo}$CCR2$^{lo}$CX3CR1$^{hi}$, egresses from the circulation later and produces transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF). In humans, CD16$^{+}$ cells highly expressing CX3CR1 are considered the ortholog of Ly6C$^{lo}$CCR2$^{lo}$CX3CR1$^{hi}$ murine monocytes, whereas CD16$^{-}$CCR2$^{+}$CX3CR1$^{lo}$ monocytes resemble Ly6C$^{hi}$CCR2$^{hi}$CX3CR1$^{lo}$ murine monocytes (Auffray et al., 2009). That macrophages undergo temporal evolution as the wound matures is supported by a recent study uncovering their rather complex phenotype, sharing traits associated with both alternative and classical activation (Daley et al., 2010). In contrast to an early mouse model of macrophage deficiency suggesting a detrimental role for macrophages in promoting scar formation (Martin and Leibovich, 2005), three recent reports (Goren et al., 2009; Lucas et al., 2010; Mirza et al., 2009) depleting monocytes and macrophages during wound healing strongly confirm their essential role as main orchestrator of the tissue repair. Macrophage depletion results in delayed re-epithelialization and impaired angiogenesis, associated with increased expression of inflammatory mediators and reduced expression of VEGF and TGF-β1. Thus, it is likely that macrophages modulate wound closure and dermal healing, in part by regulating the cytokine environment of the healing wound. Nonetheless, their role is probably multifaceted and further studies are required to understand their contribution to the different stages of the healing process.

Other leukocytes to enter the wounded area in the inflammatory stages include plasmacytoid DCs (pDCs). pDCs are a unique subset of DCs, normally absent in skin and characterized by extraordinary secretion of type I interferons (IFNs) via toll-like receptor-7 (TLR7)- and TLR9-dependent recognition of nucleic acids (Conrad et al., 2009). Two studies on a murine model of tape stripping-induced mechanical skin injury have recently uncovered a previously unappreciated role for pDCs in wound healing. pDCs were found to infiltrate skin wounds as early as neutrophils and to react to self nucleic acids released by dying cells as a result of coupling with the cathelicidin LL37, and thereby inducing the typical type I IFN gene signature (Gregorio et al., 2010; Guiducci et al., 2010). pDCs also contribute to the early inflammatory responses and the re-epithelization of injured wound by releasing IL-6 and promoting the production of IL-17A and IL-22 by T cells. Of interest, a similar course of events after skin injury also occurs in humans (Gregorio et al., 2010).

Skin-resident T cells residing in the epidermis have a crucial role in promoting wound healing. In mice, Vγ5Vδ1 DETCs act as fast, early responders to skin damage promoting tissue repair (Havran and Jameson, 2010). After wounding, DETCs respond to an as-yet-unknown antigen, expressed on damaged or stressed KCs, by proliferating and producing proinflammatory cytokines, chemokines, and KC growth factors. DETCs are critical in skin repair as shown by the fact that mice lacking DETCs exhibit a delay in wound closure. DETCs also modulate conventional αβ T cell and macrophage recruitment to the skin by enhancing the deposition of extracellular matrix (ECM) molecules (Havran and Jameson, 2010). As mentioned earlier, DETCs are not present in humans and γδ T cells are rare in normal healthy skin, representing about 2%–9% of dermal and 1%–10% of epidermal T cells. It has long been speculated whether or not humans have a population of epidermal T cells capable of aiding in wound healing. Toulon et al. (2009) have recently reported that in humans, both αβ "conventional" and Vδ1 "unconventional" epidermal T cells are able to produce insulin-like growth factor-1 (IGF-1) upon activation and to promote wound healing in a skin organ culture model. Epidermal T cells isolated from patients with chronic wounds are refractory to stimulation and do not produce IGF-1. Moreover, we have recently shown that a population of skin-homing Vγ9Vδ2-expressing T cells, able to produce the same spectrum of mediators, is rapidly attracted into perturbed skin (Laggner et al., 2011). Thus, both recruited and skin-resident human γδ T cells act as early effector sentinels upon trauma.

Among T cell-derived mediators involved in wound healing, a prominent position is occupied by IL-22, in keeping with a similar homeostatic role at other barrier surfaces, such as lung and gut (Sonnenberg et al., 2011). An increasingly expanding variety of adaptive (Th1, Th17, Tc17, "Th22," and "Tc22") and innate-like (LTi-like, γδ T, NK, NKT) cell types have been reported to produce IL-22 (Sonnenberg et al., 2011). To date only Th1, Th17, and the recently described skin-homing IL-22-producing "Th22" cells (Duhen et al., 2009; Eyerich et al., 2009; Trifari et al., 2009) have been reported to produce IL-22 in inflamed human skin (Eyerich et al., 2009). Although named after their signature cytokine, these IL-22-producing cells still lack the attribution of a master regulator transcription factor to be formally recognized as a distinct T helper cell lineage. The aryl hydrocarbon receptor (AHR), involved in Th17 cell differentiation (Stockinger et al., 2011) and recently shown to be an essential regulator of murine DETCs and intraepithelial lymphocytes in the gut (Kadow et al., 2011; Li et al., 2011), has been suggested as the putative master regulator, but this has not been conclusively proven as yet. Nevertheless, we will henceforth refer to them as Th22 cells.

IL-22 exerts its effects only on epithelial cells, in keeping with the expression pattern of the IL-22R complex (Wolk et al., 2004). The early identification of genes selectively regulated by IL-22 in KCs reveal its involvement in tissue repair (Boniface et al., 2005). Regulated genes include those coding for keratinocyte differentiation-associated protein, mobility and migration-regulating proteins, and AMPs. More recently, transcriptome profiling of Th22 clones shows selective expression of growth factors (FGFs) and chemokines involved in tissue remodeling, angiogenesis, and fibrosis (Eyerich et al., 2009). Supernatants from Th22

clones are able to upregulate KC expression of chemokines (CXCL9, CXCL10, and CXCL11), T cell growth factors (IL-7 and IL-15), and AMPs and to enhance wound healing in vitro. Hence, IL-22 functions promote the formation of new tissue in the second stage of the wound healing process. This stage occurs 2–10 days after injury and is characterized by proliferation and migration of different cell types. KCs migrate over the injured dermis, proliferate in response to growth factors produced by γδ T cells, and terminally differentiate in response to IL-22 to ultimately restore the barrier function of the epithelium. At 2–3 weeks after injury, the majority of the inflammatory cells undergoes apoptosis or exit from the wound, and fibroblasts become the key players. Fibroblast-derived ECM, mainly collagen, forms the bulk of the mature scar while differentiated myofibroblasts bring the edges of the wound together. Increased angiogenesis is also a prominent feature promoting fibroblast activity and scar formation. The remodeling phase, a stage lasting up to 2 years and involving reorganization of collagen fibers, terminates the healing process with the wound progressively contracting near its surface. Such a controlled and tightly regulated cascade of events ultimately results in an uncomplicated fine scar with little fibrosis and the return to near-normal tissue architecture. However, if these events are not controlled and occur out of sequence, the wound does not heal, resulting in chronic wounds (such as in diabetic patients), which can be accompanied by excessive fibrosis, resulting in an impaired skin structure and thus compromising its functional integrity.

## Skin Provides First Line Defense against Pathogens

Keratinocytes can be considered the first immune sentinels encountered by pathogens and they need to be quick and efficient in sensing and responding to danger (Nestle et al., 2009a). On first encountering a microbe, KCs are alerted to potential danger by recognizing conserved microbial structures known as pathogen-associated molecular patterns (PAMPs) via their pattern recognition receptors (PRRs) (Takeuchi and Akira, 2010). One major group of PRRs are Toll-like receptors (TLRs), which keratinocytes express on their surface (TLR-1, TLR-2, TLR-4, TLR-5, and TLR-6) and in their endosomes (TLR-3 and TLR-9). TLR engagement triggers activation of nuclear factor-kappa B (NF-κB) and interferon regulatory factor (IRF), which in turn induces immune and inflammatory genes, namely, tumor necrosis factor (TNF) and type I IFNs.

Another way in which KCs try to curtail the immediate microbial threat is by releasing an abundant supply of proinflammatory cytokines as a result of activating a large multiprotein oligomer complex, within the cytoplasm, called the inflammasome (Feldmeyer et al., 2010). This in turn activates the enzyme caspase 1, which cleaves unprocessed pro-interleukin-1β (pro-IL-1β) and pro-IL-18, stored in KCs, into the active IL-1β and IL-18. Activated keratinocytes release processed IL-1 (Dombrowski et al., 2011), enabling neighboring epithelial cells to respond by amplifying the signal through further production of IL-1α, in addition to IL-1β, TNF, and IL-6.

Another critical role fulfilled by KCs in the defense against invading microorganisms is the induction of numerous AMPs. There are many cationic AMPs, such as the cathelicidin (LL-37), defensins, and S100 family proteins (Harder and Schröder, 2005). These cationic molecules destroy bacteria by creating holes in their anionically charged cell walls or by sequestrating iron required for bacterial growth (Gläser et al., 2005). Proinflammatory cytokines (IL-1α, IL-1β, IFN-γ, TNF) differentially regulate the expression of genes encoding for a number of AMPs, and IL-17A, IL-17F, and IL-22 are potent inducers of AMPs (Sonnenberg et al., 2011).

The important role that AMPs play in the cutaneous defense against infection is apparent in patients with AD, who are highly susceptible to cutaneous bacterial and viral infections as a result of decreased amounts of β-defensins and cathelicidins (Ong et al., 2002), whereas skin infections are not common to a disease like psoriasis associated with increased production of AMPs. Overall, the general increase in cytokines and chemokines, such as CXCL9, CXCL10, CXCL11, CCL27, and CCL20, resulting from activated KCs (Albanesi et al., 2001) leads to an increase in the neutrophil and macrophage infiltrate in addition to T lymphocyte recruitment.

As mentioned earlier, pDCs are normally absent in peripheral nonlymphoid organs but migrate to the skin after viral infections. pDCs produce large quantities of type I IFNs that limit the spread of viral infections and induce maturation and activation of DCs, thereby promoting cell-mediated protective immunity (Conrad et al., 2009). Upon activation, pDCs lose their plasmacytoid morphology and the ability to produce type I IFNs and differentiate into cells with a dendritic morphology expressing major histocompatibility complex (MHC) and T cell costimulatory molecules. However, even in their mature status, pDCs are less efficient than DCs in antigen presentation, especially in priming naive T cells, and most probably do not have cross-presentation capacity. Nevertheless, pDCs sustain protective responses at sites of infection and display functional plasticity in promoting almost every type of effector T helper subsets in vitro, including differentiation of skin-homing Th22 cells, via IL-6 and TNF (Duhen et al., 2009).

Initiation of adaptive immune responses against pathogens that gain access to the skin requires pathogen-derived antigen capture, processing, and presentation by DCs followed by DC-mediated priming of naive T cells. Epidermal LCs extending dendritic processes to the stratum corneum have traditionally been regarded as the typical peripheral DCs patrolling the cutaneous barrier (Schuler and Steinman, 1985). LCs are in an immature state, yet well equipped with a series of innate receptors to sample the environment. PAMPs trigger migration toward skin draining lymph nodes where LCs acquire a mature phenotype and the functional ability to present antigens to naive T cells. However, this view, known as the "LC paradigm," has been challenged by a number of murine studies that have led to a re-evaluation of the role of LCs in pathogen-induced immune responses (Kaplan, 2010; Merad et al., 2008; Romani et al., 2010). Recently identified murine $CD207^+CD103^+$ DDCs (Bursch et al., 2007; Ginhoux et al., 2007; Poulin et al., 2007) have been shown to perform some of the tasks previously attributed to LCs, such as cross-presentation (Bedoui et al., 2009; Henri et al., 2010), despite other studies having shown cross-presentation by LCs in vitro and ex vivo (Flacher et al., 2010; Klechevsky et al., 2008). Recently, two studies shed some light on the role of LCs in adaptive immunity (Bennett et al., 2011; Igyártó et al., 2011). By using a TLR agonist-induced graft versus host disease (GvHD) model, Bennett et al. (2011) showed that LCs are not

required for T cell priming but are necessary to license effective cytotoxic responses. Finally, Igyártó et al. (2011) have investigated LC function in a skin model of recombinant *Candida albicans* infection. Confirming previous findings, they have found that $CD207^+CD103^+$ DDCs, but not LCs, are necessary and sufficient for cross-presentation of exogenous antigen to $CD8^+$ T cells in vivo. However, direct antigen presentation by LCs is required for Th17 cell differentiation promoted by LC-derived IL-6, IL-1β, and IL-23. Taken together these two studies suggest that LCs do play a specific and nonredundant role in antigen-specific responses.

Previously overlooked on the assumption that all $CD207^+$ DCs found in the dermis were LCs en route to draining LNs, $CD207^+CD103^+$ DDCs have raised considerable interest since their identification (Kaplan, 2010). They have been consistently identified in mice as the only skin-derived DC subset able to cross-present viral antigens and self-protein expressed by keratinocytes in both in vitro and in vivo settings (Bedoui et al., 2009; Henri et al., 2010). Moreover, $CD207^+$ DDCs promote antigen-specific cytotoxic T lymphocytes (CTL) and Th1 cells while inhibiting LCs and $CD207^-$ DDC-induced Th17 cells (Igyártó et al., 2011). Counterparts of $CD207^+CD103^+$ DDCs are also found residing at other mucosal sites, including the lung and small intestine (Heath and Carbone, 2009), further supporting a putative sentinel role at barrier surfaces. Despite the growing number of murine DC subsets identified to date, $CD207^+CD103^+$ DDCs share their cross-presenting capability only with splenic CD8α DCs. Because both cell subsets depend on the transcription factor Batf3 for their development, similar ontogeny and functions for these subsets can be hypothesized. No human equivalent of dermal $CD207^+CD103^+$ DDCs has been identified so far. Human $CD207^+$ DDCs are scarce, representing less than 5% of DDCs in human skin (Chu et al., 2011; Romani et al., 2010), and whether they correspond to the $CD207^+CD103^+$ DDCs described in mice remains to be investigated.

An additional subset of dermal DCs involved in building immunity to infection is a population of monocyte-derived DDCs (mo-DDCs) that patrol the skin during inflammation. They are important for adequate immune response against pathogens, e.g., inducing protective Th1 cell responses against *Leishmania major* (León et al., 2007). Interestingly, inflammatory mo-DDCs and DDCs found in steady state display similar phenotypic features, hinting to a monocytic origin for DDCs (López-Bravo and Ardavín, 2008). A formal identification of inflammatory mo-DCs during infection in human is still lacking. A population of "inflammatory DDCs," characterized as $CD11c^+CD1c^-$, has been identified in inflamed psoriatic lesions (Zaba et al., 2009b) and is believed to be the equivalent to mouse splenic TNF- and inducible nitric oxide synthase (iNOS)-producing DCs (TIP-DCs) found in infection models.

After presentation of the cognate antigen by DCs and according to the surrounding cytokine milieu, naive T cells differentiate into effector cells endowed with critical effector functions, such as cytokine production and cytotoxicity. All $CD4^+$ Th cell lineages identified to date contribute to provide protective cutaneous immunity against a range of intracellular and extracellular pathogens. Cytotoxic $CD8^+$ T cells, producing type 1, 2, and 17 cytokines, also occur. Among $CD4^+$ T cells, Th17 cells perform an essential first-line defense against a number of fungal and bacterial skin infections (Miossec et al., 2009). Mice lacking IL-23 show impaired Th17 cell response to *Candida albicans* infection (Kagami et al., 2010). In humans, genetic defects in a variety of Th17 cell-related genes, such as those coding IL-12p40, IL-12Rβ1, STAT-3, IL-17RA, and IL-17F, cause severe immunodeficiency and dramatic susceptibility to and recurrence of bacterial and fungal infections, as seen in Job's syndrome and chronic mucocutaneous candidiasis (de Beaucoudrey et al., 2008; Puel et al., 2011), respectively. Lack of Th17 cytokines observed in these patients is likely to impair recruitment of neutrophils, activation of macrophages, and production of AMPs by KCs and neutrophils, thus interrupting the crosstalk between adaptive and innate immunity required for full pathogen clearance. Other important sources of IL-17A at barrier sites come from innate immune cells and unconventional T cells (Cua and Tato, 2010). In the lung, γδ T cells have been identified as important IL-17A producers in mice and patients infected with tuberculosis (Cua and Tato, 2010). In the skin DETCs (Cho et al., 2010), a recently identified dermal-resident γδ T cell subset (Cai et al., 2011; Gray et al., 2011; Sumaria et al., 2011) as well as skin-homing Vγ9Vδ2 T cells (Laggner et al., 2011) produce IL-17A. As to which is the primary source probably depends on the triggering pathogen. Dermal γδ T cells are motile, able to proliferate in situ and orchestrate the immune surveillance program by recruiting neutrophils and promoting $CD4^+$ T cell expansion (Sumaria et al., 2011), and thus link innate and adaptive immunity.

## Skin as the Site for Immune-Mediated Inflammatory Pathologies

A critical task for skin is to ensure that active defense and tolerogenic and/or regulatory mechanisms are in place to maintain the homeostatic balance between appropriate beneficial immune response and unnecessary immune responses to self-antigens, harmless microorganisms, and environmental chemicals.

Skin DCs and regulatory T (Treg) cells play a critical role in orchestrating extrinsic mechanisms of peripheral tolerance. Murine $CD207^+CD103^+$ DDCs are able to mediate T cell tolerance, possibly in the context of their cross-presentation (or rather "cross-tolerance") capability by which they present exogenous self-antigens in the steady state to induce unresponsiveness of self-reactive $CD8^+$ T cells (Lutz and Kurts, 2009). In humans, the majority of circulatory $CD4^+CD25^{hi}Foxp3^+$ Treg cells bear skin-homing receptors (Hirahara et al., 2006) and make up 10% of the resident T cells in normal skin. Accordingly, lack of skin-homing molecules CD103, CCR4, and P- and E-selectin ligands severely affects the migration and/or retention of Treg cells within the skin and results in impaired pathogen clearance and skin-specific autoimmunity (Campbell and Koch, 2011). Moreover, Treg cells prevent unnecessary immune responses to harmless antigens applied onto the skin and control the magnitude of the inflammatory reaction (Cavani, 2008).

A break of self-tolerance and failure of regulatory mechanisms may contribute to the development of immune-mediated inflammatory skin diseases such as ACD and psoriasis. Special emphasis will be given to psoriasis because of the recent progress made in understanding its complex pathogenesis as a result of the success of targeted biologic therapies.

## Allergic Contact Dermatitis

ACD is a typical delayed-type hypersensitivity (DTH) reaction to a sensitizer agent, characterized by two distinct phases. The sensitization, or induction, phase occurs at the first contact of skin with a strong hapten able to form complexes with host proteins and trigger activation of the innate immune system, similar to ICD. However, in ACD this leads to the generation of hapten-specific T cells in LNs and their migration back to the skin. Re-exposure of sensitized individuals with the same hapten results in the elicitation phase of ACD. Hapten-specific T cells are activated in skin and mediate adaptive immunity responsible for the cutaneous lesions. This inflammatory reaction persists for only a few days and rapidly resolves thanks to downregulatory mechanisms. Because only a minority of exposed individuals develop ACD, genetic predisposition is likely to play a role; however, data so far are inconclusive and genome-wide association studies (GWASs) are still not available. TLRs and the inflammasome mediate the initial innate inflammation in murine contact hypersensitivity (CHS) (Martin et al., 2011), the experimental model of ACD, with TLR4 identified as the receptor for nickel in a recent study (Schmidt et al., 2010). Identification of which skin DC subset is responsible for initiating the hapten-induced adaptive response has been the subject of extensive work (Kaplan, 2010; Romani et al., 2010). In keeping with the "LC paradigm," epidermal LCs are traditionally considered the initiators of CHS. This concept was first challenged by classical depletion experiments, showing enhanced CHS in the absence of LCs (Grabbe et al., 1995). Later, inducible or constitutive LC ablation in transgenic mice did not abrogate but rather resulted in CHS of similar (Kissenpfennig et al., 2005) or even enhanced (Kaplan et al., 2005) magnitude, depending on the ablation strategy used. Finally, $CD207^+CD103^+$ DDCs are found to induce CHS reactions in vivo and to compensate for LC absence (Bursch et al., 2007). Recently, functional redundancy of LCs and $CD207^+CD103^+$ DDCs has been proposed, depending on hapten accessibility. In the presence of a high concentration of hapten, which makes it accessible to both epidermal LCs and $CD207^+CD103^+$ DDCs, the latter compensate for the absence of LCs, although LCs are necessary to induce CHS in the presence of lower hapten doses (Honda et al., 2010; Noordegraaf et al., 2010). However, mice lacking the transcription factor Batf-3, and therefore lacking $CD103^+CD11b^-$ DCs in skin, develop a normal CHS response (Edelson et al., 2010). A tolerogenic role for LCs in damping CHS reactions has also been postulated with possible mechanisms involving interaction with cognate T cells and production of IL-10 to inhibit expansion of hapten-specific T effector cells (Igyarto et al., 2009; Kaplan, 2010). Therefore, further studies are required to address the relative contribution of different DC subsets to CHS.

Both CHS models and studies on nickel ACD individuals show that hapten-specific $CD8^+$ T cells are the main effector cells of CHS with $CD4^+$ T cells mainly playing a regulatory role. KC-targeted cytotoxicity, enhanced by the combined release of IFN-$\gamma$ and IL-17A (Pennino et al., 2010), is a key pathogenic mechanism by which $CD8^+$ T cells mediate disease. Resolution of ACD relies on a number of regulatory mechanisms, including apoptosis of effector T lymphocytes, release of immunosuppressive cytokines (IL-10 and TGF-$\beta$), and induction of Treg cells (Cavani, 2008). Defective regulatory function of Treg cells correlate with the development of ACD to nickel, suggesting their critical role in dampening T cell activation at the site of hapten application in allergic individuals.

## Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by highly inflamed and sharply demarcated scaly plaques (Nestle et al., 2009b). Histological features consist of marked epidermal hyperplasia with dysregulated KC differentiation, prominent inflammatory infiltrate, and increased vascularization. A combination of environmental (streptococcal pharyngitis, stress, skin trauma, and certain drugs) and genetic (gene variants conferring disease susceptibility) factors trigger the immuno-histological changes seen in the skin. Human leukocyte antigen-C (HLA-C) within the MHC and at least 23 more genes, mainly belonging the IL-23-Th17 axis, the NF-$\kappa$B pathway, and the epidermal differentiation complex (EDC), are identified to date as conferring susceptibility to psoriasis (Nair et al., 2009; Strange et al., 2010). Researchers have long debated whether psoriasis is an epidermal or an immune-mediated disease, torn between the most prominent epidermal changes and the unexpected efficacy of serendipitously administered immunosuppressive agents. Evidence, ranging from the presence of clonally expanding T cells in the lesions to the clinical benefit obtained with specific anti-T cell therapies to humanized mouse models relying on T cells for disease development, consistently points toward T cells as critical effectors. Analogous to other autoimmune-mediated pathologies, psoriasis has long been considered a Th1 cell-mediated disease. However, insights from targeted therapies, combined with genetic and experimental data, recently identify a critical role for the IL-23-Th17 axis (Di Cesare et al., 2009). It is increasingly more apparent that a pathogenic crosstalk between innate and adaptive cells underpins the dysregulated immune response leading to the aberrant epidermal proliferation.

The extraordinary success of biologic drugs targeting TNF as well as IL-12 and IL-23 has dramatically changed patient care. TNF-neutralizing agents used for psoriasis therapy are etanercept, a human TNF receptor Fc fusion protein, and two TNF monoclonal antibodies, infliximab and adalimumab. Cellular and genomic analysis of etanercept-treated patients shows that TNF blockade downregulates both innate and adaptive genes (Gottlieb et al., 2005; Zaba et al., 2007). Patients rapidly downmodulate innate cell-derived and Th17 cell-driving genes, such as *IL12B*, *IL23A*, and *IL1B* as well as Th17 cytokines. Th1 cytokines are also reduced but late in disease resolution (Zaba et al., 2009c). Ustekinumab, a fully human monoclonal antibody directed against the common p40 subunit shared by IL-12 and IL-23, is also highly effective in psoriasis, showing superior efficacy to anti-TNF therapy in a head-to-head trial (Griffiths et al., 2010).

Insights gleaned from clinical studies confirm genetic and experimental data. We and others have shown, by GWAS, that several genes of the IL-23 pathway, including *IL23R*, *IL12B*, and *IL23A*, are associated with psoriasis (Capon et al., 2007; Cargill et al., 2007; Nair et al., 2009). Moreover, we and others have recently provided a functional explanation of how the psoriasis-associated *IL23R* R381Q gene variant confers protection against Th17 cell-mediated immuno-pathologies by impairing IL-23-induced Th17 cell responses (Di Meglio et al.,

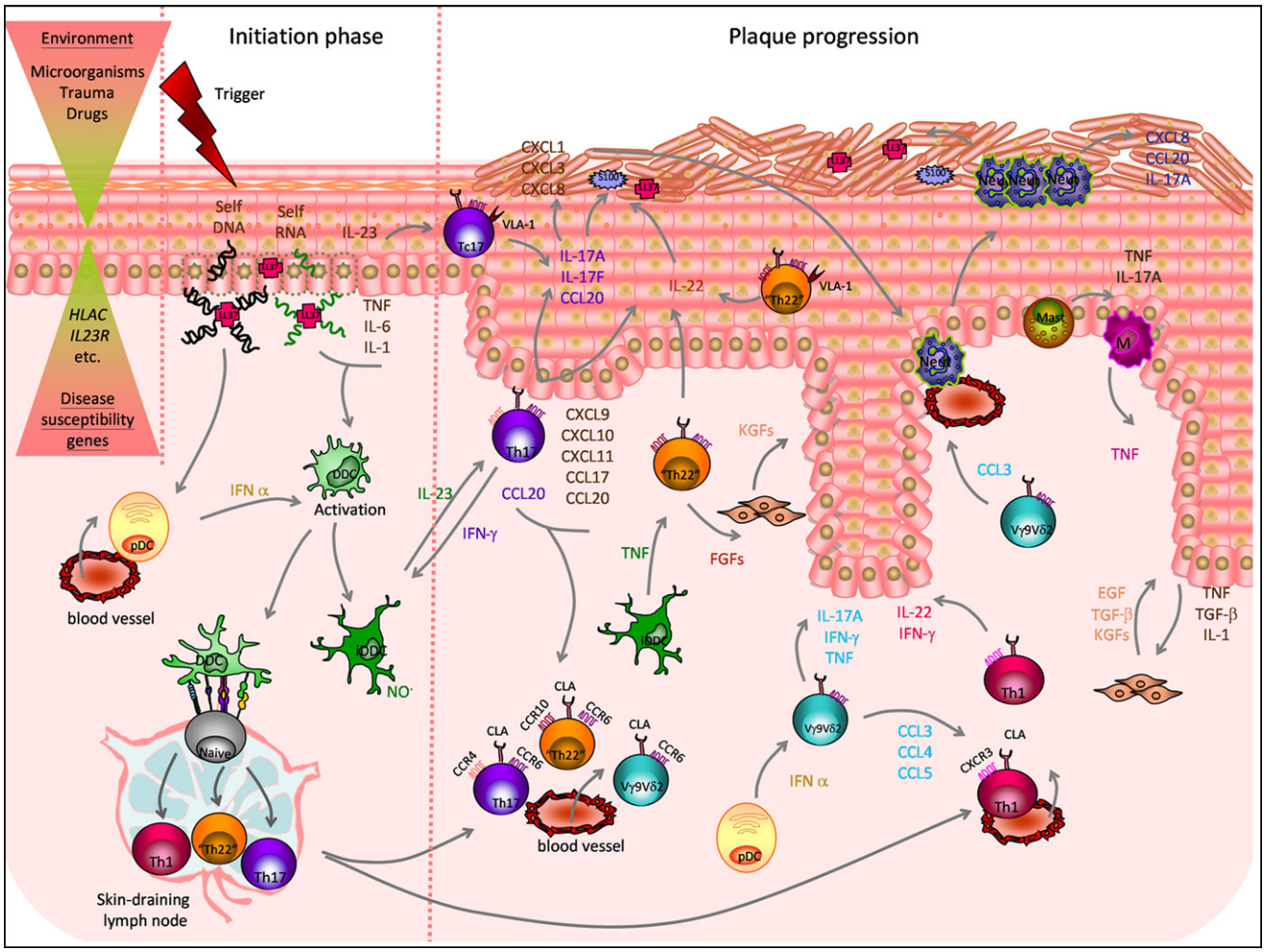


**Figure 2. Immunopathogenesis of Psoriasis**

The combination of environmental factors with psoriasis-susceptibility genes triggers an orchestrated cascade of pathogenic events leading to disease initiation and plaque formation. In the initiation phase, proinflammatory crosstalk between injured or stressed keratinocytes (KCs), releasing self-nucleic acids and LL-37, recruited plasmacytoid dendritic cells (pDCs) producing IFN-α, activated dermal DCs (DDCs), and inflammatory DDCs (iDDCs), the latter producing IL-23, TNF, and nitric oxide radicals (NO·), promoting the activation of skin-resident and newly recruited T cells that lead to plaque formation. IL-23 stimulates T helper 17 (Th17) and T cytotoxic 17 (Tc17) cells, expressing cutaneous leukocyte antigen (CLA), CCR6, and CCR4, plus very late antigen-1 (VLA-1) in the epidermis, to release IL-17A, IL-17F, IL-22, and IFN-γ. IFN-γ further activates DDCs. IL-17A and IL-17F acts on KCs promoting production of T cells and neutrophil-attracting chemokines (CXCL1,3,8-11;CCL17-20) and antimicrobial peptides (AMPs): S100 proteins and LL-37. CCL20 favors the recruitment of more Th17 cells. IL-22, also produced by Th1 cells, expressing CXCR3 and skin-homing marker CLA, and Th22 and Tc22 cells, expressing CCR6, CCR10, and CLA, induces epidermal hyperplasia by impairing KC terminal differentiation. Recruited unconventional Vγ9Vδ2 T cells, expressing CLA and CCR6, are activated by pDCs-derived IFN-α and release further proinflammatory cytokines (IL-17A, IFN-γ, TNF) as well as neutrophils (Neut) and Th1 cell-attracting chemokines (CCL3-5). Infiltrating Neut, mast cells, and macrophages (M) contribute to the proinflammatory environment producing cytokines (IL-17A, TNF), AMPs (S100 proteins, LL-37), and chemokines. Crosstalk between keratinocytes producing IL-1, TNF and transforming growth factor beta (TGF-β), and fibroblasts, which in turn release keratinocyte growth factor (KGF), epidermal growth factor (EGF), and TGF-β, and possibly Th22 cells releasing fibroblast growth factor (FGFs), contribute to tissue reorganization.

2011; Pidasheva et al., 2011; Sarin et al., 2011). Increased amounts of IL-23 (Lee et al., 2004) and IL-23R (Tonel et al., 2010; Wilson et al., 2007), essential for Th17 cell effector function and pathogenicity, as well as Th17 cytokines (Wilson et al., 2007), are detected in psoriatic skin. Both IL-23 and Th17 cytokines are downregulated after therapies (Gottlieb et al., 2005). Th17 cells and IL-17A and IFN-γ or IL-17A and IL-22 double-producing cells are also described in psoriasis patients (Eyerich et al., 2009; Lowes et al., 2008). Moreover, IL-23 induces psoriasis-like skin inflammation in murine models (Chan et al., 2006; Zheng et al., 2007). Most importantly, we have recently shown in our xenotransplantation psoriasis model that selective targeting of IL-23 alone is as effective as anti-TNF blockade (Tonel et al., 2010), strongly suggesting that the beneficial effect of ustekinumab is due to its activity on IL-23 and not IL-12. Phase I/IIa clinical trial results for secukinimab (Hueber et al., 2010), an IL-17 monoclonal Ab, further support the beneficial effects of targeting the Th17 cell axis in psoriasis.

In the psoriasis model depicted in Figure 2, we integrate known environmental and genetic factors triggering the disease with established cellular and molecular effectors reported to contribute to psoriasis pathogenesis.

The exposure to unknown environmental factors of genetically predisposed individuals, carrying susceptibility psoriasis alleles, triggers disease development (Nestle et al., 2009b). In the initiation phase, LL-37 released by KCs, after trauma or infection, binds to self-DNA and self-RNA fragments (Ganguly et al., 2009; Lande et al., 2007) released by stressed or dying skin cells. These complexes of LL-37 and self-DNA activate pDCs to produce IFN-α (Lande et al., 2007). Keratinocyte-derived IL-1β, IL-6, TNF, pDC-derived IFN-α, and self-RNA-LL-37 complexes can all activate DDCs. DDCs migrate to the skin-draining LNs to present as-yet-unknown antigen (either of self or of microbial origin) to naive T cells and promote their differentiation into Th17 and Tc17 cells (Zaba et al., 2009a) as well as Th1 and Th22 cells. Skin-homing Th17 and Tc17 cells, expressing CLA, CCR4, and CCR6, migrate via lymphatic and blood vessels into psoriatic dermis, attracted by keratinocyte-derived CCL20 and CCL17. Moreover, inflammatory DCs produce IL-23A, nitric oxide (NO) radicals, and TNF (Zaba et al., 2009a). IL-23A activates recruited and skin-resident Th17 and Tc17 cells to release IL-17A and IL-17F but also IL-22 and IFN-γ. IL-17A and IL-17F stimulate KCs to produce neutrophil-recruiting chemokines and AMPs, including LL-37 and S100 family members (Wilson et al., 2007). Neutrophils infiltrating the epidermis and mast cells mainly in the dermis produce more proinflammatory mediators, including IL-17A (Lin et al., 2011), thereby contributing to the proinflammatory environment. S100A7 and S100A15 are chemoattactant for leucocytes promoting both Th1 and Th17 cell response (Wolf et al., 2010). VLA-1-expressing cytotoxic $CD8^+$ T cells accumulate in the epidermis (Conrad et al., 2007) and also produce IL-17A. Unconventional Vγ9Vδ2 T cells are recruited into the lesions via CCL20, possibly contributing to the proinflammatory milieu by releasing AMPs, IL-17A, IFN-γ, and TNF as well as neutrophils and Th1 cell-attracting chemokines (Laggner et al., 2011). Th1 cells and Th22 cells also infiltrate the lesion, attracted by KC-derived chemokines and/or activated in situ by the proinflammatory milieu. Finally, IL-22, potentially produced by Th1, Th17, and Th22 cells in the lesion (Eyerich et al., 2009), induces epidermal hyperplasia (Ma et al., 2008; Zheng et al., 2007) by impairing KC differentiation, with a possible contribution from IL-17A. This orchestrated cascade of pathogenic events ultimately leads to the formation of a psoriatic plaque characterized by acanthosis (thickening of the skin), papillomatosis (elongation of the epidermis into the papillary dermis), hypogranulosis (loss of the stratum granulosum), and parakeratosis (retention of the nucleus in the stratum corneum).

Despite knowing this sequence of events, at least 20% of patients do not respond to anti-TNF and anti-IL-12+anti-IL-23 therapy, meaning that key pathogenic mechanisms are still ill understood and the known mechanisms may not always apply to every individual. As GWASs identify more psoriasis-susceptibility genes, the next big challenge is not only their functional validation but also linkage to the environment. Finding the causative link between genetic susceptibility and environmental factors that trigger the aberrant immune response could provide additional therapeutic targets and might eventually deliver the promise of personalized medicine.

Another useful approach to unravel the immune mechanisms underlying psoriasis pathogenesis is to make use of systems immunology. This involves integrating small in vivo and in vitro data sets with in silico predictive models (Valeyev et al., 2010), as well as deconstructing large quantities of clinical and experimental data into meaningful immunology (Benoist et al., 2006). An example of the latter approach is our use of publically available data from the Genetic Association Information Network (GAIN) (Nair et al., 2009) to build up a molecular network of psoriasis, by comparing gene expression profiles from psoriasis patients against profiles from healthy controls. A molecular network, or skin interactome, has been created by looking at differentially expressed genes, genes linked to each other by similar expression profiles across samples, between patients and controls (Figure 3). Such a network can be used as a reference data set against which in-vitro- and in-vivo-derived gene expression profiles can be compared and may ultimately help to elucidate disease mechanisms, drug targets, and potential biomarkers of disease and therapeutic response (Barabási et al., 2011).

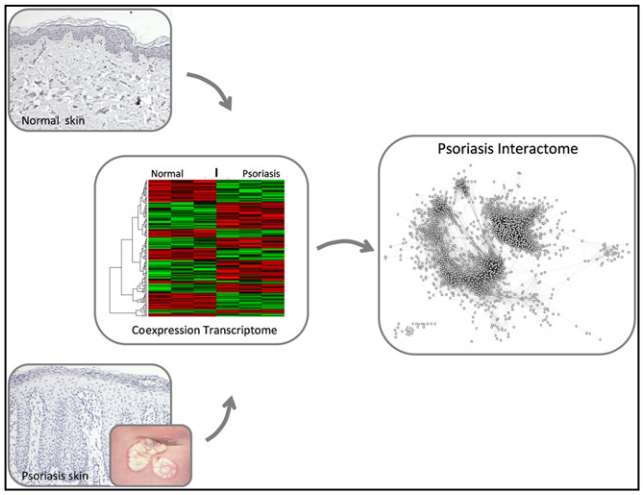


**Figure 3. A Psoriasis Interactome**
Gene expression data pooled from large patient samples can be used to generate a disease interactome. An interactome is a network of interconnected genes based on similar expression profiles across tissues. Differentially expressed genes between normal and psoriatic skin are shown as a heatmap. A coexpression interactome is created where nodes reflect genes and edges the degree of coexpression. This psoriatic interactome can be used as a disease-relevant molecular reference data set, against which differentially expressed gene transcripts generated from experimental models are assessed.

Finally, both gene-to-environment linkage and interactome studies could be of relevance to other immune-mediated inflammatory disorders at barrier sites, such as Crohn's disease, owing to shared genetic variants, immunological pathways, and therapeutic targets with psoriasis.

## Conclusions and Perspectives

The skin's exceptional accessibility makes it an ideal model system to interrogate in order to answer fundamental questions about host immunity. This, in combination with advances in technology, has led to considerable interest in cutaneous research over the past few years. Recent exciting findings have contributed to the concept of the skin as a multitasking immune organ involved in promoting health. The advantage of hosting commensal bacteria is being unraveled along with the

contribution that innate cells make toward the generation of beneficial and pathogenic immune responses. The identification of several skin-resident cell subsets, each with unique critical capabilities, expands the skin immune network and subsequently its functions. Recent findings have already been translated into therapeutic options in psoriasis and have provided a useful framework to further expand upon with regard to other barrier tissues. Finally we suggest the potential of using an integrative systems analysis to combine human data sets with experimental data sets from biological model systems.

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