

Immunopathogenesis of Psoriasis

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Abstract Investigations into the cause and treatment of psoriasis remain at the forefront of basic and applied clinical research efforts around the world. The purpose for this review is to provide an up-to-date synopsis of recent progress in ten sections exploring the immunological and inflammatory basis for psoriasis. Given the breadth of this topic in investigative skin biology and frequent paradigm shifts, it should not be surprising that the bibliography contains more than 150 references; many of which have been published in the last 5 years. Whereas considerable progress has been made into the immunopathogenesis of psoriasis, many fundamentally important questions remain regarding the role of cells located in both epidermal and dermal compartments. Attempts to characterize various animal models of psoriasis, delineation of the mechanism of action for biological agents, and consideration of molecular links between skin inflammation and various extracutaneous comorbidities are likely to continue challenging investigators and clinicians for many years to come.

Keywords Psoriasis · Immunopathogenesis · Epidermal compartment · Dermal compartment

Introduction

Psoriasis is typically regarded as a chronic inflammatory reaction by which thin, clinically appearing normal, prepsoriatic or symptomless skin is converted into thick, erythematous plaques [1]. As no pathogen has been consistently identified within psoriatic plaques (indeed skin infections are rare in lesions because of antimicrobial peptides) [2], an autoimmune basis for the chronic inflammation is the dogma for this complex disorder, which may also involve the joints in about one-third of the patients [3]. Joint involvement typically occurs only after many years of skin disease activity; but this review will focus predominantly on the skin manifestations of psoriasis with a particular emphasis on recent advances regarding the molecular and cellular bases for immunological and inflammatory reactions that contribute to the onset, maintenance, and resolution of psoriatic plaques. In the penultimate section, brief mention of comorbidities associated with psoriasis such as Crohn's disease, obesity, atherosclerosis, and diabetes mellitus will be linked with the inflammatory process in skin.

Not only can psoriatic plaques persist for years (and even decades, if not treated), but either spontaneously or after appropriate therapy, the disease process is entirely reversible. That is, when the psoriatic plaques resolve, there is no scarring or other obvious evidence of preexisting disease activity at sites of inflammation [4]. Of course, if the patient experiences a clinical relapse, these same sites of skin can undergo the same cycle of induction of plaque formation, followed by resolution. Thus, for any given skin site (typically elbows, knees, scalp, and nails), there can be repeated phases of disease activity. The purpose of this review is to provide an updated summary (as our previous comprehensive analysis of the field in 2004; *ibid.*) of the most important developments of interest to clinicians and

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basic research investigators focused on cellular and molecular mechanisms of chronic inflammation, and components of innate and adaptive immunity that may contribute to the onset, maintenance, and resolution of inflammation within psoriatic plaques (and relevance to comorbidities).

During the past several years, there has been considerable progress in many different aspects of the pathophysiology and treatment of psoriasis [5, 6]. Whereas no one has yet consistently identified an antigen, the immunopathogenesis underlying psoriasis has been better understood. Hopefully, investigators focused on psoriasis will continue to make headway in delineating the distinct contributions of heredity, environment, and the healing process by which psoriatic plaques are created, resolved, and perhaps even prevented. Before proceeding further, it should also be noted that whereas in many cases, psoriasis can be inherited, the precise genetic locus or loci that convey enhanced disease susceptibility remain to be defined [7]. The primary locus is located on the short arm of chromosome 6 (PSORS1) within the HLA complex and appears to be in proximity to HLA-Cw6, but this review will not deal with the immunogenetics of the disease. The interested reader can find current viewpoints concerning HLA alleles and other results in several recent publications [5, 8–10]. Nonetheless, it remains a challenge to integrate the predisposing genes with various environmental cues that participate in the conversion of symptomless skin into chronically inflamed lesions. For example, triggering of psoriasis has been associated with group A streptococcal infections of the tonsils for over 50 years [11], but the antigen responsible for T cell activation in the skin has yet to be conclusively identified and mechanistic links between tonsillitis and skin lesions although previously investigated, remains to be fully defined [12–14]. Finally, there are diverse clinical expressions of the psoriatic process including guttate, pustular, and other variants besides the more common plaque type presentation that is the subject for this review.

Validating the Cytokine Network Theory of Psoriasis

Before the recognition of cytokines as the primary mediators of cutaneous inflammation in psoriasis, investigators had focused on defining the role for proinflammatory products derived from the arachidonic acid pathway such as prostaglandins and leukotrienes [15]. When the primary cytokines such as TNF- α and various interleukins were detected in psoriatic lesions, investigators switched from examinations of arachidonic acid-based cascades to identifying and localizing many different types of cytokines within normal and diseased skin [16]. Pioneering work by Mosmann and Sad involving the characterization of immune responses in mice led to the notion that there were two distinct types of cytokine-

mediated responses known as type I (e.g. TH-1) and type 2 (e.g. TH-2) reactions [17]. Whether human immune responses would also fall into discrete cytokine categories was quickly answered in the affirmative by numerous groups studying several diseases in many different organ systems.

In 1991, the initial version of the cytokine network theory of psoriasis was proposed by which dermal dendritic cells producing TNF- α were placed center stage [16]. This theory integrated existing data at that time by which TNF- α could induce relevant adhesion molecules, growth factors and chemotactic polypeptides. Whereas highly simplistic, the essence of this proposal postulated a key role for TNF- α in the immunopathogenesis of psoriasis. During the past 15 years, an incredibly complex and long list of cytokines, chemokines, and growth factors have been found to be present within psoriatic plaques [18, 19]. To untangle the complex web of cytokines, and establish cause-effect relationships, various *in vitro* and animal models were employed. But the most definitive evidence supporting the hypothesis that the pathophysiology of psoriasis was dependent on cytokines such as TNF- α emerged from the clinic in which highly specific reagents targeting TNF- α were observed to improve skin, and in some circumstances, joint disease activity [20, 21]. It has been these clinical results that have led to the current viewpoint that by simply neutralizing the biological activity of a single cytokine, the skin and joint-based clinical activity is often reduced. It should be noted that TNF- α has pleiotropic biological effects and has overlap or redundancy with other cytokines. Such complexities may have led to the incorrect prediction that targeting a single cytokine could not achieve clinically significant beneficial effects in diseases such as psoriasis. Nonetheless, the inflammatory role for TNF- α in psoriasis is now on firm clinical ground. However, it should also be noted that not every patient responds to TNF- α inhibitors and some patients experience amelioration of joint, but not skin disease, activity [22].

From a T cell perspective, there are several reports indicating that the persistent T cell activation within psoriatic plaques resemble the conventional TH-1 type lymphocyte [23–26] although unconventional T cells coexpressing natural killer receptors (e.g. NK-T cells) have also been implicated in the immunopathogenesis of psoriasis and psoriatic arthritis [27–31]. Even natural killer cells have been hypothesized to play a role in psoriasis [32, 33]. Whether psoriasis represents a disease of innate versus adaptive immune system is a currently hot topic [34, 35]. As will be described below, a new perspective has been advanced that includes consideration of T cells producing IL-17, which have been recently identified within psoriatic plaques [36].

In the next section, a review of recent animal model-based experimental results in which the TH-1 cytokine model for autoimmune responses has been modified (e.g. TH-17 type responses) to take into account yet another

pathway, will be presented. The recent *in vivo* data has also been accompanied by *in vitro* data pointing to more complex interactions than previously believed involving TH-1, TH-2, TH-17, and Treg subsets that contribute to the maintenance and severity of inflammatory responses and autoimmunity. Before leaving this section, it should also be noted that during the past few years, several other cytokines have been implicated in psoriasis, including IL-15, and IL-19, and IL-20 [37–40], to name a few.

New TH-17 T cell Paradigm and Potential Relevance to Psoriasis

Currently, most immunodermatologists regard psoriasis as being a T cell-driven inflammatory skin disease. Whereas initial viewpoints favored the epidermal keratinocyte as the primary cell of importance in the pathogenesis of psoriasis because of the prominent alterations involving hyperkeratosis, parakeratosis, acanthosis, elongation of the rete ridges, etc., the clinical experience in which the immunosuppressant agent cyclosporine A shifted the paradigm away from keratinocytes and more towards immunocytes—specifically T cells [41]. As the serendipitous entry of cyclosporine into the armamentarium for psoriatic patients (this agent works extremely well in clearing skin lesions, but does not improve the arthritic component; and causes renal failure as its principal side effect limiting its use for psoriasis), there are several other lines of evidence that support a viewpoint focusing on the pathogenic role for T cells in psoriasis.

Other therapeutic agents targeting T cells that improve psoriasis [42] include anti-CD4 ab [43], an IL-2 conjugated-diphtheria toxin [44], a drug that interferes with T cell costimulation (e.g. CTLA4lg) [45], and a drug that targets the CD11a (e.g. LFA-1; efalizumab) surface antigen [46, 47]. In addition, clonal derived T cell clones with distinct TCR rearrangements have been noted in the skin and joints of psoriatic patients [48, 49]. Some of these clones may originate in the tonsillar tissue and represent an antibacterial (e.g. streptococcal) tissue response [14]. As will be discussed in more detail in the following section on macrophages and psoriasis, it has been suggested that macrophages in the tonsillar tissue may ingest bacterial wall fragments including peptidoglycans that are recirculated into the skin where they may activate a T cell response, thereby provoking psoriatic lesions [50]. There may also be molecular mimicry such that T cell clones originally generated in response to strep tonsillitis or pharyngitis are then reactivated in the skin because of a cross-reactive epitope derived from hyperproliferative epidermal keratinocytes such as keratin 16 or keratin 17 [51]. Another theory implicates the role of bacterial-derived superantigens in the immunopathogenesis of psoriasis [52–54]. Finally, the ability

to transfer the disease using the experimental SCID-Hu animal model in which bacterial-derived superantigens were used to activate CD4+ T cells that could convert symptomless skin into full-fledged psoriatic plaques after engraftment supports a T cell-driven process [55]. Whether true autoantigens exist in psoriatic plaques remains to be determined [56].

Another interesting set of observations has recently emerged regarding the role of resident T cells versus T cells recruited from the circulation as regards the immunopathogenesis of psoriasis. We and others have begun defining the presence and significance of T cell subsets in normal healthy skin as well as in prepsoriatic skin [57–60]. Although nonlesional skin appears uninfamed, there are actually a remarkable number of resident T cells in the epidermal and dermal compartments. It has been estimated that in a normal healthy adult, there may be approximately 2×10^{10} T cells in the skin, which is approximately twice the total number of T cells in the blood [58]. These resident T cells may not be proliferating *in situ*, but possess a remarkable T cell receptor repertoire and capacity to undergo rapid proliferation and cytokine production *ex vivo* [58, 59]. After mitogenic stimulation, these resident T cells appear to be preprogrammed with a TH-1 cytokine secretion bias [58]. Recognition of resident T cells in prepsoriatic skin was highlighted by the findings that engraftment onto immunodeficient AGR mice resulted in T cell dependent spontaneous psoriatic lesion formation, indicating that resident immunocytes were necessary and sufficient to create lesions [61]. These results are more than of academic interest as they suggest that targeting endothelial cell molecules that mediate trafficking of circulating cells may not be an appropriate therapeutic strategy given that resident cells alone appear to suffice in lesion formation [58, 62, 63].

In the past, the TH-1 type T cell response highlighted key roles for IL-12 and IFN- γ . Using animal models in which specific cytokines and/or their receptors could be genetically deleted, it became possible to more directly assess the relative contribution of specific cytokine pathways. Because animal models were available to serve as tools for probing the molecular and cellular basis for autoimmune disease processes such as multiple sclerosis and inflammatory bowel disease, they were selected for genetic manipulations and the subsequent phenotypic effects were examined [64–69]. Such studies have led to the proposal that a distinct “inflammatory axis” exists featuring key roles for IL-23 and IL-17 [70]. Indeed, the new paradigm for autoimmunity in these mouse models revolves around the TH-17 type of T cell [71]. These recent developments have not escaped the attention of immunodermatologists interested in psoriasis because early clinical trial results indicate that an antibody which targets the p40 subunit shared between IL-12 and IL-23 can improve psoriatic lesions [72, 73].

The subunit composition for IL-12 and IL-23 is important for understanding the immunobiology of these cytokines [66]. As mentioned above, they share a common p40 subunit and are distinguished by IL-12 possessing the p35 subunit, whereas IL-23 contains the p19 subunit. Within psoriatic plaques there is increased expression of IL-23 p19 and p40 subunits [74], and compared to normal skin, psoriatic plaques have enhanced IL-23 levels [75]. By selectively depleting either distinct subunit, the relative roles for IL-12 versus IL-23 could be appreciated in animal models of autoimmunity. From these studies, it has been proposed that the simple TH-1 versus TH-2 type T cell immune responses should be modified to take into consideration a TH-17 type response. In this scenario, the traditional TH-1 T cell response features key roles for IL-12 and IFN- γ ; whereas the TH-17 T cell pathway is dependent on the roles for IL-23 and IL-17. These new results are particularly interesting because these new pathways not only impact each other, but they may also influence the involvement of regulatory type T cells (which will be further explored near the end of this review).

Returning to the relative roles for IL-12 versus IL-23, several points of potential relevance to human inflammatory

disease processes are worth highlighting. It has been reported that IL-12 can upregulate expression of the skin homing receptor, CLA on T cells [76], although this finding may not be applicable to psoriasis [77]. It will be important to determine the location of IL-17 versus IFN- γ producing T cells within normal skin, symptomless skin, and within psoriatic plaques. It is also important to determine the potential additive, synergistic or antagonistic biological responses for TNF- α , IFN- γ , and IL-17 alone and in combination on various cell types within the skin, as has been done in synovial tissues. The biology of IL-17 is also rapidly emerging as the types of cells that can produce IL-17 are characterized and the responses of various cells to IL-17 are defined. IL-17 can promote the accumulation of neutrophils and also impact barrier function [78]. Several groups have explored the ability of IL-17 to influence keratinocyte proinflammatory cytokine and chemokine levels with two reports finding IL-17 enhances proinflammatory mediators [36, 79], whereas one report observed that IL-17 may alleviate chemokine-mediated skin inflammation [80].

A simplified overview of the interactions that have been found to date involving TH-1, TH-2, TH-17, and Tregs is provided in Fig. 1. Note that the differentiation pathways

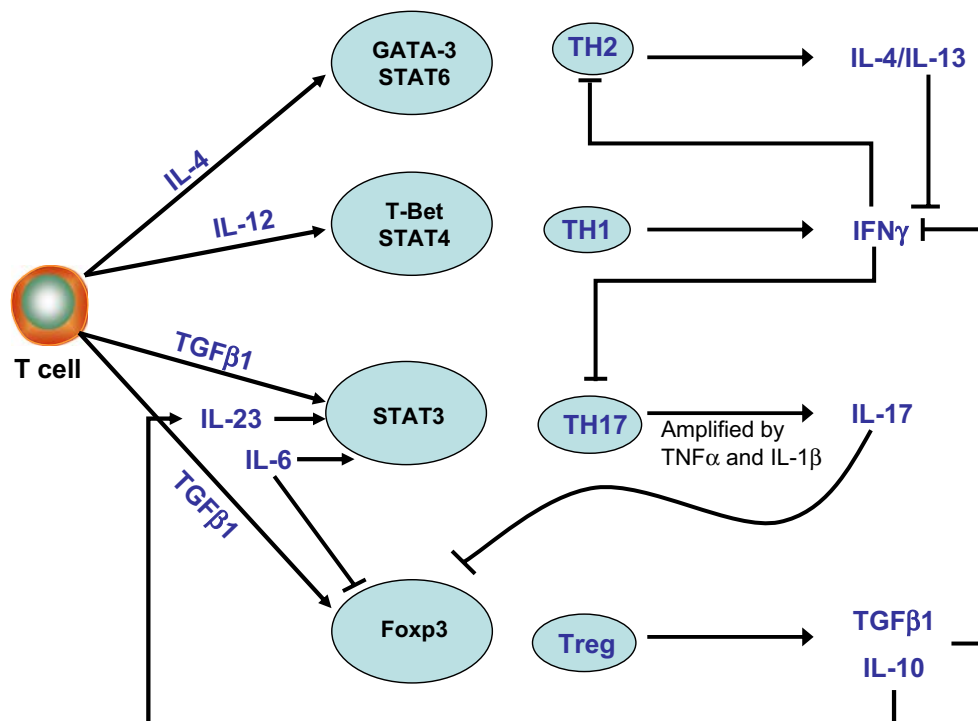


Fig. 1 Overview of potential interaction between various T cell subsets that may contribute to the immunopathogenesis and chronic inflammation of psoriatic skin lesions portrayed in a summary figure adapted from Tato et al. [84] and Cua et al. [152]. The final or net cytokine network operative in psoriatic plaques can be considered as resulting from a balance of a variety of different T cell subsets that are differentially regulated by various upstream cytokines such as IL-4,

IL-12, TGF β 1, IL-23, and IL-6 that influence transcription factors such as GATA-3, STAT6, T-Bet, STAT3, and Foxp3. The relative roles for TH-2 cells versus TH-1 cells versus TH-17 cells versus Tregs depend upon complex interactions (both positive and negative) that culminate in the chronic inflammatory response. Precise details as to the initiation, propagation, and resolution of psoriatic lesions are likely to involve many (if not all) of these different types of T cell subsets

by which naïve CD4⁺ T cells are converted to functionally and immunophenotypically distinct subsets are controlled by specific transcription factors and cytokines. Also note the self-reinforcing and mutually antagonistic pathways appear to be very complicated; nonetheless, such feedback loops and cross-talk are essential for proper regulation of such an important process as inflammation. As can be appreciated, the field has moved quickly from the initial two observations by which cross-talk was appreciated between only TH-1 versus TH-2 subsets [81]. These early observations included the ability of IL-4 (a TH-2 type cytokine) to downregulate the IL-12R β 2 (involved in promoting TH-1 responses) and the ability of IFN- γ (a TH-1 type cytokine) to block TH-2 development. After the establishment of the TH-1 and TH-2 cytokine production, paradigms for polarized T cell responses in which TH-1 responses were viewed as providing defense against intracellular pathogens and the TH-2 responses provided defenses against parasites, the field of immunology became enamored with the characterization of regulatory type T cells (e.g. so-called Tregs) that could control inflammatory and immune-mediated responses. Whereas we will cover the topic of Tregs in a subsequent section, at this point, the emergence of the TH-17 paradigm will be continued as the focal point because new evidence is emerging to explain the interrelationships amongst these different subsets that may be highly relevant to psoriatic immunopathology.

It has been observed that Tregs are unable to suppress T cell proliferation *in vitro* in the presence of an inflammatory stimulus such as lipopolysaccharide. Thus, rather than there being a simple relationship between Treg and TH-1 type cells, it has become recognized that in the context of an inflammatory cytokine milieu, CD4⁺T cells may emerge with a distinct phenotype that is currently designated as TH-17 cells [82–85]. These proinflammatory cells may not be as easily influenced by Tregs (or the products they secrete such as TGF- β 1). Indeed, as shown in Fig. 1, cytokines such as TGF- β 1 play important roles (in concert with other cytokines such as IL-23 and IL-6) in the differentiation of TH-17 cells. Furthermore, there is amplification of TH-17 cells by the presence of TNF- α and IL-1 β . It may well be the presence or expansion of TH-17 cells over the TH-1 cells or Tregs that tip the balance in favor of a more severe or persistent inflammatory state that characterizes human chronic inflammation, as exemplified by psoriatic plaques. Future investigations will dissect the precise functional role of TH-17 cells and its potential driver IL-23 in psoriasis. In the next section, the roles for dendritic cells in the pathogenesis of psoriasis will be highlighted because dendritic cells strongly influence the behavior of T cells and act as go-betweens for both innate and adaptive immune responses by direct contact and expression of costimulatory molecules, as well as by secreted factors such as IL-12 and IL-23, not to mention TNF- α and IFN- α .

Update on Roles for Dendritic Cells in Psoriasis

Ever since the original observation in which psoriatic plaque-derived dermal dendritic cells were found to promote autologous resting T cell proliferation and cytokine release [86], investigators have probed the role for dendritic cells (DCs) in the pathophysiology of psoriasis. Currently, a confederacy of DC subsets has been found to be present within psoriatic plaques. Beginning in the epidermis, the immature Langerhans cells (LCs) in the plaques have a reduced density and altered distribution pattern [87]. However, after treatment with adalimumab, a rapid increase in the density of epidermal LCs was observed with a normalization of their intraepidermal pattern of distribution [88]. As LCs possess ATPase activity, they may play an antiinflammatory role by degrading the proinflammatory ATP [89], and hence their reduction in psoriatic plaques may thereby contribute to the prolonged inflammatory reaction. It is interesting to note that it has been found that LCs possess a markedly diminished capacity to leave the epidermis of symptomless skin compared to normal healthy skin [90]. Thus, the mechanism by which a reduced number of LCs were seen in the untreated psoriatic plaques requires further study [91]. One possible mechanism may involve TNF- α , as this cytokine is overexpressed in psoriatic lesions, and TNF- α can promote migration of LCs out of human skin explants. Presumably, when TNF- α is neutralized by adalimumab, the overall kinetics regulating the movement of LCs into and out of the epidermal compartment are normalized. It is also possible that there is a self-renewing pool of epidermal LCs within human skin that can contribute to the net density and distribution of LCs in psoriatic plaques [92]. In addition to LCs, there are also “inflammatory dendritic epidermal cells (IDECs)” that have been predominantly characterized in lesional skin of atopic dermatitis patients [93]. A recent report indicates that mast cells can influence the mobilization of LCs in response to bacterial peptidoglycan [94].

Moving from the epidermis to the dermis, the density and distribution patterns for DC subsets have also been evaluated in psoriatic plaques. Compared to symptomless skin, there are increased numbers of DCs expressing factor XIIIa and HLA-DR originally designated as dermal dendrocytes [95]. Besides these dermal dendrocytes, human skin contains several other types of DCs [96], including myeloid DCs expressing CD11c [97, 98]. The newest DC subsets found within psoriatic skin are the TNF- α inducible nitric oxide synthases-expressing DCs [99] and the plasmacytoid DC [100]. As regards proinflammatory TNF/iNOS producing DCs, one group has found these cells to be important in mouse models of bacterial infection [101]. The plasmacytoid DCs produce high levels of IFN- α and can be activated by the TLR7 agonist, imiquimod [102]. In the

AGR-Hu animal model, injecting either neutralizing antibody against IFN- α or the cell surface marker BDCA-2, prevented the induction of psoriatic lesions after xenotransplantation [103]. A role for IFN- α in triggering psoriasis is supported by the clinical observations that patients receiving IFN- α injections for the treatment of warts experienced a flare of psoriatic lesions at the sites of injection [104]. It will be interesting to test if blocking IFN- α has a prophylactic or therapeutic effect in psoriasis.

Update on Role for Macrophages in Psoriasis

Besides dendritic cells, another common type of mononuclear cell in the dermal infiltrate of psoriatic plaques is the macrophage [105–108]. Whereas the initial recognition of macrophages was characterized by the capacity to phagocytose particulate material, it is now clear that there are many subsets of macrophages with distinct immunophenotypes and functional characteristics. Originally, macrophages were considered as either belonging to a classical or an alternatively activated category. As summarized by Mantovani et al., macrophage subsets can be classified as either type 1 or type 2. At least 4 different subsets of macrophages have been defined, reflecting a vast diversity of functions that these important cell types must oversee in the skin [109]. It should be noted that the M1 or classically activated macrophage is most closely linked to psoriatic plaques, as these mononuclear cells are proinflammatory by virtue of their production of cytokines such as TNF- α , IL-6, IL-12, IL-23, as well as reactive oxygen species and inducible nitric oxide synthase [4]. There is a growing interest in defining the molecular pathways by which macrophage activation occurs after barrier perturbation in the skin and at other organ sites [110]. Of particular note [111] are the vast arrays of exogenous pathogen-associated molecular patterns (e.g. PAMPs) and endogenous ligand recognized through pattern recognition receptors (e.g. PRRs).

As regards pathogen-associated products that can impact macrophages implicated in the pathogenesis of psoriasis, it has been observed that there are increased macrophage-like cells containing a major cell wall compound of gram-positive bacteria, peptidoglycan [50]. Similar macrophages containing peptidoglycan have been found in the tonsillar tissue [112], and hence it has been postulated for psoriatic patients that such macrophages may circulate from the oral cavity into the skin and trigger a TH-1 type cellular immune reaction leading to psoriatic lesions [50, 113]. Further studies are indicated to determine whether such immune responses generated against macrophages bearing bacterial peptidoglycans are responsible for initiating or perpetuating psoriatic skin lesions.

A direct role for macrophages in contributing to cutaneous inflammation was established by the local elimination of

macrophages that led to disease resolution [114]. As will be further discussed in the animal model section, several groups have provided evidence also supporting an important role for macrophages in cutaneous inflammation. More direct evidence linking macrophages to psoriasis will await future clinical trials in which direct targeting of these important mononuclear cells is accomplished.

Another aspect of macrophage-related biology involves consideration of these cells in the termination phase of inflammatory responses. A number of endogenous anti-inflammatory mediators have been identified that are produced by macrophages including interleukin 10 (IL-10), as well as transforming growth factor beta (TGF β), lipoxins and prostaglandins, reviewed by Gilroy et al. [115]. Besides these mechanisms, additional antiinflammatory pathways may include CD200L [116] and TGF β 2 treated macrophages [117]. More recently, tissue macrophages have also been identified that are involved in the generation of antigen specific efferent regulatory T cells in various mouse models of delayed-type hypersensitivity reactions [118]. Taken together, it is entirely worth exploring the diversity of macrophage subsets in psoriatic skin to better delineate both proinflammatory and antiinflammatory roles for these abundant mononuclear cells.

Role for Regulatory T cells in Psoriasis

Besides the presence of pathogenic T cells, the emergence or maintenance of psoriasis can also be viewed as an absence or relative paucity of T cell subsets with regulator type function. Recently, the critical role of regulatory T cells (Tregs) in the maintenance of immune tolerance to self and in the control of autoimmunity is in the spotlight of contemporary immunological research [119]. From a developmental perspective, regulatory type CD4 $^{+}$ T cells can be considered as existing in two general categories: a naturally occurring subset and an induced subset [120]. The generation of regulatory T cells is genetically controlled, and can influence autoimmune and inflammatory diseases by direct contact with antigen presenting cells [121] or by providing soluble mediators such as IL-10 [122] or TGF- β 1 [123]. Tregs represent between 1% and 5% of peripheral blood CD4 $^{+}$ T cells and exhibit strong suppressive capabilities, as well as control T cell homeostasis [124–127]. Immunophenotypic markers for Tregs include CD4, CD25, and Foxp3. Whereas Tregs expressing such markers have been identified in psoriatic lesions, they do not appear to be functioning properly [128]. Given the growing interest in the immunobiology of Tregs, determining why existing Tregs within plaques may be dysfunctional, and devising methods to expand Tregs indicate that new therapeutic opportunities are likely to emerge in this active

area of research. It is interesting to note that another report found that 1,25-dihydroxyvitamin D₃, an effective therapeutic compound for psoriasis, could promote dendritic cell mediated induction of CD4⁺Foxp3⁺Treg cells [129], paving the way for manipulating Treg cells for psoriasis treatment.

Defining the Mechanisms for Terminating Chronic Inflammation

In this section, rather than focusing on the role of cytokines and immunocytes that contribute to the initiation of inflammatory reactions leading to the creation and maintenance of psoriatic lesions, an examination of the mechanisms that are responsible for terminating inflammation will be highlighted. In the setting of an infection, it is rather straightforward to assume that once the inciting antigens from the organism are effectively eliminated by the host immune response, the inflammation would subside in a somewhat passive fashion. However, in many clinical settings, it is becoming well-documented that there are many control points within an inflammatory setting [130] and that active processes are critical for proper resolution of inflammatory reactions. Indeed, a recent collection of articles was devoted to the review of progress made in delineating active processes that are engaged early on after the onset of inflammation that contribute to the termination of inflammation [131]. The interested reader is referred to this website for further discussion: <http://www.nature.com/nature/index.html>. As alluded to earlier, many mechanisms are being elucidated by which inflammatory processes are terminated (see the “Update on Role for Macrophages in Psoriasis” section). With the more widespread use of biological agents that can reliably reverse many aspects of the psoriatic lesion, investigators have new tools to better understand the mechanism of action by which neutralizing TNF- α , for example, can improve the skin lesions. Whether neutralizing TNF- α leads to a passive resolution of the inflammation or triggers an active, reparative process remains to be determined. Such considerations could lead to even better and more targeted therapeutic approaches in the future if active reparative processes were found to be engaged by administration of anti-TNF- α agents. In the next section, a brief review of recent developments pertaining to animal models of psoriasis is presented.

Lessons Learned from Animal Models

In this section, a focus on what has been learned from mice that may be applicable to psoriasis is highlighted. Perhaps the most widely discussed animal model for the past few

years was reported in *Nature* (accompanied by a prominent cover illustration) by Zenz et al. [132]. By generating conditional knock-out mice in which both *JunB* and *c-Jun* loci were inducibly deleted in the epidermis, erythematous skin lesions, and joint disease were observed, accompanied by upregulation of TNF- α and IL-1 β levels. The joint lesions appeared to be more dependent on T cells than the skin lesions, and whereas some phenotype functions resembled psoriasis, the conclusion that psoriatic plaques are characterized by downregulation of the AP-1 subunit *JunB*, the relationship between this mouse model and psoriasis has been challenged by several subsequent publications [41, 133, 134]. Along the lines of mouse models questioning the relevance of T cells in the immunopathogenesis of psoriasis, one other independent group created transgenic mice that develop inflammatory skin diseases (by deleting IKK2) that appear to be more dependent on non-T cells for TNF- α production driving the cutaneous pathology [135]. On the other hand, two other groups created psoriasis-like models that were dependent on T cells (i.e. CD18 hypomorphic PC/J mice [136] and STAT3c mice [137]). Besides these transgenic mice, other interesting transgenic models were reported by targeting regulators of angiogenesis [138] and lymphatic endothelial cell decoy receptors [139]. Such inside-out approaches targeting dermal-based reactions rather than outside-in approaches targeting epidermal-based reactions emphasize the current conundrum as to the fundamental cellular basis for psoriasis (i.e. epidermal-based versus dermal-based cell types [41]).

Besides the transgenic approach, additional progress has been made using human skin xenograft models and immunodeficient mice. From the SCID-Hu model, a role for natural killer cells as inducers of psoriatic lesions was proposed [33]. Using the AGR-Hu model, a role for IFN- α -producing plasmacytoid cells was also proposed [103]. Interested readers are referred to our recently completed and more extensive update of animal models of psoriasis (Nestle and Nickoloff, submitted for publication). Taken together, it is clear that we still have a long way to go in fully understanding the pathogenic basis for psoriatic skin lesions, and for each animal model under consideration, an objective and reproducible assessment method for evaluating the model is urgently required [140].

Comorbidities and Psoriasis

Before we summarize the field as regards psoriatic skin lesions, it is worth mentioning some of the developments that pertain to the disease processes observed in psoriatic patients beyond the skin [141]. These extracutaneous diseases include a distinctive form of arthritis, as well as

other comorbidities that may be shared by patients with psoriasis such as inflammatory bowel disease (i.e. Crohn's disease [142]), obesity, atherosclerosis, type II diabetes, fatigue, and depression [143]. Whereas a complete discussion of these complex, multifactorial diseases is beyond the scope of this journal, a few points are relevant to the theme of this report. Despite the diverse clinical phenotype for these aforementioned comorbidities, it is becoming clear from colleagues working in these other nondermatological areas that important lessons can be learned—including the recognition of the important roles of inflammatory cells, such as activated macrophages, and inflammatory cytokines, such as TNF- α . Indeed, activated macrophages are clearly linked to the development of Crohn's disease in the gastrointestinal tract [144]; formation of atherosclerotic plaques involving oxidized forms of LDL [145, 146]; and migratory macrophages and TNF- α are linked to obesity-induced insulin resistance [147, 148]. As regards fatigue and depression, cytokines generated by skin lesions such as TNF- α and IL-1 have receptors detected on various cell types in the central nervous system that may play a role in these comorbidities [149, 150]. It will be interesting to determine if and how biological therapies targeting TNF- α influence these other comorbidities in the long-term [151].

Conclusion and Future Directions

As can be appreciated by this review, considerable progress and new insights into the immunopathogenesis of psoriasis has been made during the past 5 years. Yet many fundamentally important questions remain regarding the relative role of cells located in the epidermis, such as keratinocytes, versus cells located in the dermis, such as T cells, NK-T cells, natural killer cells, plasmacytoid dendritic cells, myeloid dendritic cells, macrophages, and endothelial cells. The relative role for regulatory T cells and possible mechanisms by which they are dysfunctional in psoriatic skin requires further study, as does delineating the mechanism of action by which effective biological agents such as the TNF inhibitors improve psoriatic lesions. Perhaps of greatest need is a highly reductionist perspective and model system that will permit more definitive cause–effect relationships to be discerned involving the dialogue between immunocytes and epidermal keratinocytes and dermal endothelial cells. Finally, a better appreciation and approach is needed to understand not only the pathogenesis of psoriatic skin lesions, but also the other related diseases that occur beyond the skin, such as psoriatic arthritis, Crohn's disease, diabetes, cardiovascular disease, fatigue, and depression. All of these issues are complex and multifactorial and will likely continue to challenge investigators and clinicians for many years to come.

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