Supplement-Psoriasis

Pathophysiology of psoriasis

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ABSTRACT

Psoriasis is a chronic inflammatory papulosquamous disease characterized by multiple remissions and relapses. For long, it was believed to be primarily a disorder of keratinization. However, the successful use of traditional immunosupressants and newer immunomodulatory agents in the treatment of psoriasis led to the belief that psoriasis is primarily a disease of Th1 cell immune dysregulation. Recent developments have brought up several new findings such as the role of Th17 cells and evidence of skin barrier dsysfunction in psoriasis, akin to atopic dermatitis. The present review aims to focus on these new developments and explain the pathogenesis of psoriasis on the basis of currently available information.

Key words: Psoriasis, pathogenesis, skin barrier dysfunction, Th17 cells

INTRODUCTION

Psoriasis affects nearly 2-3% of the world's population and presents as erythematous, indurated, scaly plaques over the skin sometimes with involvement of the nails and joints.[1] It is characterized by exaggerated and disordered epidermal cell proliferation and keratinization. Though tremendous leaps have been made in our understanding of the disease, the chain of events that culminates in this aberrant keratinization has not yet been elucidated. A host of abnormalities seen in psoriasis, like increased levels of cyclic – adenosine monophosphate (cAMP), epidermal growth factor receptor binding, protein kinase C and transforming growth factor-α (TGF-α), collectively point to a disturbance in T cell function. Currently, the most accepted hypothesis is that psoriasis is an immune-mediated inflammatory skin disease that manifests in a genetically predisposed person exposed to certain environmental agents or triggers. This view has been reinforced by the efficacy of various immunomodulatory agents in the treatment of psoriasis.[2-4]

Recent findings such as the presence of a barrier defect in psoriasis and the proinflammatory role of NLR/CATERPILLAR (nucleotide binding domain) family of genes and microbial flora have again shifted the focus from T lymphocytes to keratinocytes as the cells of prime importance in the pathogenesis.[5] Figure 1 shows the factors that favor the lymphocyte centric or keratinocyte centric theory of pathogenesis of psoriasis. It can be argued that psoriasis results from interplay between genetic susceptibility, skin barrier defect and dysregulation of innate and adaptive

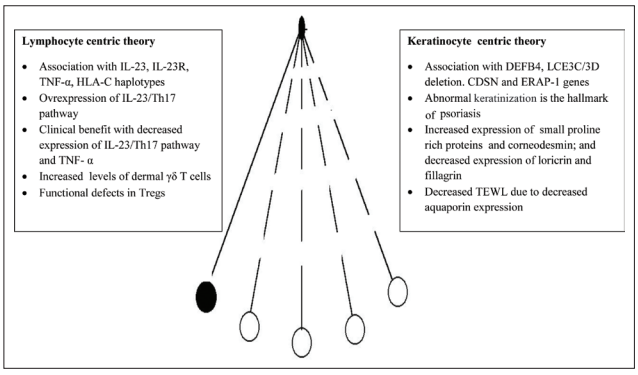

Figure 1: Evidence favouring lymphocytes or keratinocytes central to pathogenesis of psoriasis

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immunity. This review aims to discuss the role of various factors, genetic, environmental and immunologic, that are central to the pathogenesis of psoriasis.

ROLE OF GENETIC FACTORS

There is considerable evidence that genetic factors play a key role in the development of psoriasis. In a north Indian study, 9.8% of children had a family history of psoriasis;[6] the figure was as high as 28% in another study from Kuwait.[7] If only one parent has psoriasis, then the risk for the child developing psoriasis is 16%. It increases to a 50% chance if both parents have psoriasis.[8] Twin pair analysis has revealed 72% concordance among monozygotic twins compared to 22% concordance among dizygotic twins.[9] Due to genomic imprinting, men are more likely than women to transmit psoriasis to the offspring.[10] Psoriasis has been associated with many (human leukocyte antigen) HLA haplotypes. By using linkage analysis and genome-wide association studies, at least nine candidate loci have been identified: 6p (PSORS1), 17q25 (PSORS2), 4q34 (PSORS3), 1q21 (PSORS4), 3q21 (PSORS5), 19p13 (PSORS6), 1p32 (PSORS7), 16q (PSORS8) and 4q31 (PSORS9).[11] A few non-major histocompatibility complex (MHC) susceptibility loci have also been identified, but they may be of limited value in disease prediction as they confer a low risk towards disease development. Recently, Chen *et al*. developed a psoriasis global genetic risk score (GRS) using ten single nucleotide polymorphism (SNP) previously confirmed psoriasis susceptibility loci and observed that of the 10 SNPs evaluated, the strongest signal was found at the *HLA-C* locus at rs10484554, with a 206% elevated risk of psoriasis.[12] They did not find any association between weighted GRS (wGRS; which weights each risk allele by the logarithm odds ratio) and psoriatic arthritis and a marginally significant association between wGRS and guttate psoriasis. In a study from western India, Umapathy *et al*. showed a strong association of HLA-A2, B8, and B17 antigens with psoriasis.[13]

Many authors classify psoriasis as a genetically complex disease as it shares features like the pattern of inheritance, environmental influence and immune dysregulation with diseases such as diabetes mellitus and Crohn's disease.[14] One school of thought is that psoriasis results from the interplay of multiple genes. The drawback of this hypothesis is that although the psoriasis susceptibility genes are located in numerous loci throughout the genome, these locations vary among different populations and families, and the results are difficult to replicate. Goilhou *et al*. hypothesize that the same genes may be present at these different loci as "jumping genes or retrotransposons".[14] This implies that a sequence may be present as multiple copies in the human genome and the disease manifests when one or several copies are activated. Human endogenous retroviruses (HERVs) may fit this criterion. HERVs are the sequences in genome that were probably derived from the viruses many million years ago which then integrated into the human genome and became its integral component during the evolutionary process. These highly repetitive and moderately repetitive sequences are transmitted as Mendelian genes and through retrotransposition.[15] Moreover, since these HERVs can be activated spontaneously during meiosis or by environmental factors like UV radiation, they may account for the phenomenon of genomic imprinting.

PSORS1 is present in the HLA Class I region of chromosome 6p and accounts for 35-50% of heritability of the disease. HLA-C-*06 is the most likely susceptibility gene in the PSORS1 region and given its important role in antigenic presentation, the association reflects the role of the adaptive immune response in psoriasis.[16] The locus also harbours the corneodesmosin (CDSN) gene, which encodes a protein expressed in differentiated keratinocytes and is considered a genetic risk factor for psoriasis development. Since PSORS1 harbours both the CDSN gene and HLA-C-*06, it is quite possible that both adaptive immunity and defective barrier function are involved in the pathogenesis of psoriasis.[17] Table 1 enumerates the various genetic loci that have been implicated in the pathogenesis of psoriasis.[17]

Significant associations have also been found in gene regions involving specific inflammatory pathways, namely, IL-23 signaling (IL-23A, IL-12B and IL-23R), modulation of Th2 immune responses (IL-4 and IL-13), and nuclear factor (NF) κB signaling.[18,19] Other associations include epidermal defense genes, DEFB4 (copy number variation [CNV] of a genomic segment on chromosome 8p23.1 harboring a cluster of DEFB genes, encoding β-defensins), and late cornified envelope proteins 3B (*LCE3B*) and 3C (*LCE3C*) (a CNV in the PSORS4 region on chromosome 1q21 encoding their deletion).[19-21] These genes are expressed in epithelial cells but not on immunocytes. Epistatic interactions involving HLA-C-*06, endoplasmic reticulum aminopeptidase 1

(which encodes a protease that has an important role in MHC class 1 peptide processing) and *LCE3C-LCE3B-del* have also been documented. Marrakchi *et al*. observed that homozygous missense mutation in the IL36RN gene on chromosome 2q13-q14.1, encoding for IL-36 receptor antagonist was associated with an unregulated secretion of inflammatory cytokines and an increased predisposition to develop generalized pustular psoriasis.[22]

The role of the NLR/CATERPILLAR (nucleotide binding domain) family of genes in psoriasis has also been studied. These encode important mediators of innate immunity and are concerned with maintaining epidermal barrier function and initiating pathogenic responses to environmental microbes.[23,24] NLR genes have also been implicated in the causation of Crohn's disease, Blau's syndrome, early onset sarcoidosis, familial cold urticaria, familial Mediterranean fever, Muckle-Wells syndrome and chronic infantile neurologic cutaneous syndrome. NLR products can be divided into those with N-terminal coiled-coil structures and those with N-terminal Toll like receptors (TLR)/IL-1 receptor domains. NLR gene products like Nod 1, Nod 2 and Ipaf proteins are involved in intracellular recognition of bacterial components and regulation of chemokine secretion and defensin release.

Table 1: Genes involved in susceptibility to psoriasis Reprinted by permission from Macmillan Publishers Ltd: [J Invest Dermatol 2012;132:2320-1]

Gene/Locus	Function
Genes associated with adaptive immunity	
HLA C or MHC gene	Present antigens to naïve T cells
IL-23R or IL-23 receptor subunit	Maturation of T cells
IL-12B	Maturation of T cells
ERAP1 (Endoplasmic reticulum aminopeptidase 1)	Trimming of peptide antigens for binding to MHC1
TNF-α	Important pro inflammatory cytokine involved in psoriasis
IL-23A/STAT2 or IL-23, subunit p19	Regulation of T-cell activation
IL-23A, α-subunit p19	Regulation of T-cell activation
Genes associated with innate immunity	
IFIH1 (Interferon induced helicase C domain), MDA5	Rig like helicases, involved in recognition of RNA viruses
TNFAIP3 (Tumour necrosis factor-α induced protein 3)/ A20	TNF-α inducible zinc-finger protein that temporarily limits immune response by inhibiting NF-κB signalling
FBXL19 (F-box and leucine rich repeat protein 19)	Inhibition of demethylase activity to activate NF-κB
Genes associated with skin barrier function	
LCE3B and *LCE3C*	Barrier of skin function
CDSN	Component of cornified envelope
DEFB cluster or β-defensins	Antimicrobial and chemotactic function
GJB2 (Gap junction protein β2), connexin26	Involved in gap junction formation

HLA: human leukocyte antigen, MHC: major histocompatibility complex , STAT: signal transduction and transcription, MDA: melanoma differentiation-associated protein, RNA: ribonucleic acid, DEFB: defensin β:, NF: Nuclear factor, LCE3B: Late cornified envelope proteins 3B, TNF-α: Tumour necrosis factor-α, CDSN: Corneodesmosin

ENVIRONMENTAL FACTORS

It is clear that environmental factors are involved in the expression of the disease. Several factors, such as physical trauma, psychological stress, drugs[25] and infections, may trigger the disease in a genetically predisposed individual [Tables 2 and 3].[26-30]

Drugs can cause drug triggered psoriasis (i.e., induction

Table 2: Drugs known to induce or trigger psoriasis[25]

Drug	Mechanism of action	Comments
Beta-blockers	A delayed type hypersensitivity reaction, an immune mediated response and a decrease in intraepidermal cAMP and a consequent increase in epidermal cell turnover	Both cardioselective and non-cardioselective drugs have been implicated but the frequency is higher with the latter. Also with topical timolol, reported to induce psoriasis and to transform psoriasis vulgaris into psoriatic erythroderma
Lithium	Acts directly by blocking cell differentiation and leading to dysregulation of inflammatory cytokines and indirectly by ↓ cAMP levels	Provokes or induces chronic plaque psoriasis, localized or generalized pustular psoriasis and even psoriatic erythroderma
Antimalarials	May trigger psoriasis by inhibiting the enzyme transglutaminase	Do not induce psoriasis although they are known to trigger psoriasis in 18% of patients
NSAIDs	Inhibit the cyclo-oxygenase pathway, leading to accumulation of leukotrienes and hence may exacerbate psoriasis	
Tetracyclines	May provoke psoriasis either by inhibiting cAMP or by inducing Koebner's phenomenon due to their photosensitizing potential	

AMP: Antimicrobial peptide, NSAIDs: non-steroidal anti-inflammatory drugs

Table 3: Role of environmental factors in inducing or triggering psoriasis

Diet	Not been proven conclusively
	Beneficial effect of EPA/DHA (eicosapentanoic acid/ docosahexanoic acid) or fish oil supplementation not confirmed in randomized controlled trials[26]
	Excessive alcohol intake exacerbates psoriasis due to alcohol abuse associated immune dysfunction, increased production of inflammatory cytokines, such as cyclin D1 and keratinocyte growth factor, and an increased susceptibility to superficial infections and trauma[27]
	Cigarette smoking is associated with exacerbation of palmoplantar pustulosis and a poor response to treatment. It modifies the expression of HLA-Cw6, HLADQ*0201, and CYP1A1 and is associated with stimulation of MAPK and NF-κB.[28]
	Nicotine may provoke psoriasis by neo-angiogenesis and stimulation of neutrophil chemotaxis.
Trauma	A well known trigger factor[29,31]
Stress	Leads to altered hypothalamic-pituitary-axis activity with lowered serum cortisol levels and an increase in disease activity[30]
Infections	Toxins from β-haemolytic streptococci act as superantigens which may cause polyclonal activation of T-cells.[32-35]

HLA: Human leukocyte antigen, HLA-DQ: Human leukocyte antigen-DQ, CYP: Cytochrome, MAPK: Mitogen activated protein kinase, NF-κB: Nuclear factor κB

of psoriatic lesions on clinically uninvolved skin in patients with psoriasis) as well as drug induced psoriasis (i.e., precipitation of the disease in genetically predisposed individuals). Although a plethora of drugs have been implicated in provoking psoriasis, the strongest evidence is for lithium, beta-blockers, anti-malarials, non-steroidal anti-inflammatory drugs and tetracyclines. In addition, angiotensin-converting enzyme inhibitors, interferons, digoxin, clonidine, carbamazepine, valproic acid, calcium-channel blockers, granulocyte-colony stimulating factor, potassium iodide, ampicillin, penicillin, progesterone, morphine and acetazolamide have been reported to exacerbate psoriasis.

There is considerable evidence that guttate psoriasis may be preceded by tonsillar *Streptococcus pyogenes* infection, whereas disease exacerbation has been linked with skin and/or gut colonization by *Staphylococcus aureus*, *Malassezia* and *Candida albicans*. In one study, staphylococcal superantigens were isolated from 17% of a group of 111 patients who showed a sudden onset or aggravation of psoriasis.[32] The close relationship between streptococcal infections and psoriasis has made streptococcal superantigens the main candidates responsible for activating T cells. As the superantigens from *S. aureus*, streptococci, and Candida can cause polyclonal activation of T-cells, it is possible that T cell stimulation by superantigens is responsible for pathology of psoriasis. However, psoriatic lesions are characterized by an oligoclonal T cell expansion, which points towards an antigen-specific T cell response. It was suggested that streptococcal M protein may be this antigen, due to its mimicry with type 1 keratin.[33] A few other autoantigen candidates, such as peroxiredoxin 2 and heat shock protein 27, show homology to streptococcal antigens. Baker *et al*. suggest that streptococcal peptidoglycan is more likely to be the candidate than M protein as it is a strong proinflammatory immunogen and the genes encoding the peptidoglycan recognition receptors are located within the linkage sites associated with psoriasis.[34] Thorleifsdottir *et al*. note that tonsillectomy may improve chronic psoriasis because the palatine tonsils generate effector T cells that recognize keratin determinants in the skin.[35]

Psoriasis is one of the dermatosis where the occurrence of Koebner's phenomenon (KP) has been well documented and studied in detail. The time interval between injury and onset of psoriasis varies from 3 days to 2 years. The factors that contribute to Koebnerisation include season (seen more frequently in winter than in summer) and disease severity (more in unstable or flaring disease).[31] It has been suggested that trauma has to cause both epidermal cell injury and dermal inflammation to produce KP. The onset of KP may be a two step process. The first step is of nonspecific inflammation, which initiates the production of inflammatory mediators, including cytokines (specially IL-23), stress proteins (mainly nerve growth factor and basic fibroblastic growth factor), adhesion molecules and autoantigens and the second step is characterized by disease-specific reactions, by T cells, B cells, autoantibodies, and immune deposits under the restriction of genetic backgrounds. *LCE3B* and *LCE3C* genes are also induced after minor skin trauma and deletion of these proteins leads to incomplete barrier repair after minor trauma which in turn causes penetration of various antigens and induction of inflammatory response.

ROLE OF ADAPTIVE AND INNATE IMMUNITY: IS PSORIASIS A TH1- OR A TH17-MEDIATED DISEASE?

The successful use of cyclosporine in the treatment of psoriasis nearly three decades ago first brought into focus the role of the immune system in the pathogenesis of psoriasis.[36] Activated T cells are believed to be the primary modulators in the pathogenesis of

psoriasis.[37-39] Disordered cellular immunity involving inflammatory cytokines (IL-1, IL-6, Tumour necrosis factor-α [TNF-α]) and proinflammatory transcription factor (NF-κB, signal transduction and transcription and AP-1) has also been implicated.[40-42]

Naïve T-cells can differentiate into any of the four types of inflammatory cells (viz. Th1, Th2, Th17 or T regulatory cells) depending on the presence of TNF-α, TGF-β and IL-6.[43] In the presence of TGF-β and IL-6, naive T-cells transform into Th17 cells.[44,45] These activated cells enter the circulation and extravasate through the endothelium to the sites of inflammation in skin where they produce the Th1-Th2-Th17 imbalance. The role of the IL-23/Th17 pathway has been intensely researched in recent years. IL-23, a heterodimer composed of p19 and p40 subunits, is produced by dendritic cells and macrophages.[46,47] It causes activation of Th17 cells to produce IL-17 and IL-22. Psoriatic skin lesions contain high mRNA IL-23 levels compared to normal skin. Th17 cells are CD4+ effector cells distinct from the classic Th1 and Th2 lineages and are responsible for providing both innate and adaptive immunity against pathogens. IL-17 (also known as IL-17A) is part of a group of cytokines, called the IL-17 family, consisting of six ligands (A to F), and with five receptor family members. IL-17 cytokines are probaby critical for the pathogenesis of psoriasis. IL-17A and IL-17F are the predominant cytokines released by Th17 cells, but are also produced by γδ T cells, whereas IL-17C is produced by keratinocytes. The effect of IL-17 cytokines is mediated via the adaptor protein connection to IκB kinase and stress-activated protein kinases (CIKS)/Act1.[48] This is confirmed by the association of psoriasis with the gene encoding CIKS. IL-17A and IL-17F act on keratinocytes to stimulate the production of β-defensins and antimicrobial peptides (AMPs), and chemokines such as IL-8, CCL20 and CCL2. In addition, the IL-17 system may also play a role in antimicrobial defense via maintenance of mucocutaneous immunity.[49]

Elevated levels of IL-17 result in an increase in levels of pro-inflammatory cytokines like S-100, A7, β-defensins and lipocalin. In addition, increased levels of β-defensins are associated with relative resistance to infections.[50,51] Increased levels of IL-17 also promote keratinocytes to produce CXC-chemokines and CCL-20, both of which attract neutrophils to the site of inflammation.[52] Increased IL-22 levels lead to epidermal acanthosis and abnormal keratinocyte differentiation. Ustekinumab, a monoclonal antibody that inhibits the p40 subunit of IL-17, is effective in the treatment of psoriasis. Similarly, Apilimod, an orally administered compound that selectively suppresses synthesis of IL-12 and IL-23, leads to substantial improvement in psoriasis.[53] Analogous to psoriasis, the role of Th17/IL-23 pathway has been investigated in psoriatic arthritis. However, a definite involvement of Th17 cells and related cytokines in human arthritic disease remains to be conclusively proven. Although initial studies with IL-17 antagonists and IL-23 monoclonal antibodies have shown a favourable response in psoriatic arthritis, these results need to be compared with TNF-α inhibitors.[54]

Apart from Th-17 cells, the role of a new subtype of cells, Th-22 cells, is also considered important in the pathogenesis of psoriasis. These cells, on activation by TNF-α, IL-6 and CCL20, exclusively produce IL-22 and are involved in epidermal immunity and remodeling. They express CCR10, CCR6 and CCR4 receptors on their surface.[37] Different dendritic cell subsets might also regulate the Th17 versus Th22 activation with CD11C+ dermal DC's promoting Th17 cells while epidermal Langerhans cells stimulate the Th22 cells.[55]

Finally, angiogenic factors produced by epidermal keratinocytes are now recognized as drivers of abnormal dermal vascular proliferation and angiogenesis. Levels of vascular endothelial growth factor are raised in psoriatic plaques.[56,57]

The role of innate immune T cells and effector cells like γδ T cells and natural killer cells has also been investigated. Cai *et al*. identified a new subset of γδ T cells in the dermis which, unlike epidermal γδ T cells and conventional αβ T cells, express IL-23R, CCR6 and transcriptional factor RORγt, and release IL-17.[58] These act as the first line of defense against foreign pathogens and on activation, release mediators that promote and maintain inflammation. Dermal γδ T cells are elevated in psoriasis plaques and may be important in the pathogenesis of psoriasis due to their role in amplifying the adaptive immunity. Mabucchi *et al*. showed that IL-23 failed to induce inflammation in T cell receptor (TCR) δ-deficient mice.[59] Laggner *et al*. found another novel Vγ9Vδ2 T cell subset, which expressed cutaneous lymphocyte associated antigen, to be increased in psoriatic lesions but decreased in the peripheral blood.[60] Functional defects in regulatory T cells (T_{reg}) have been found in psoriasis. This may partly be due to the high levels of IL-6 in psoriatic

lesions, which suppress T_{reg} activity and which in turn results in unopposed activity of pathogenic T cells.

ROLE OF IMPAIRED SKIN BARRIER IN PSORIASIS

The hallmarks of psoriasis are hyperproliferation and abnormal differentiation of epidermal keratinocytes, infiltration of T lymphocytes, and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilatation, and high endothelial venule (HEV) formation. The skin acts as a two-way barrier to prevent the inward or outward passage of water and electrolytes. The barrier is largely situated in the epidermis, isolated epidermis being as impermeable as whole skin, whereas once the epidermis is removed the residual dermis is almost completely permeable. The epidermal barrier is localized to the stratum corneum. The barrier depends on both the cornified material of the keratinocytes and the intercellular material, particularly lipids. A two-compartment model of the stratum corneum as a barrier is currently accepted, in which protein-rich cells, the corneocytes, are embedded within a continuous lipid-rich matrix. An intact stratum corneum prevents invasion of the skin by normal skin flora or pathogenic microorganisms. Minor injury in the skin and skin diseases can provide portals of entry to microorganisms, particularly Streptococci or Staphylococci. AMPs, peptides present on the epidermis and its appendages, act as the first line of immune defence. The two major groups of AMPs, defensins and cathelicidins, provide a chemical barrier to infection where a physical barrier is absent or limited.

Psoriasis is associated with epidermal defensin genes. Out of 7 β-defensin genes, 6 genes (except *DEFB1* gene) are located on chromosome 8p23.1 over a large repeat unit that can vary in copy number. Case control studies have shown a significant association between psoriasis and increased CNV of the β-defensin gene cluster.[61,62] Psoriatic lesions are characterized by increased levels of hBD-2 β-defensin.[63] While high defensin levels may account for the lower incidence of skin infections in psoriatic plaques, they also possess potent proinflammatory activity. They may account for the KP as high β-defensin copy numbers increase the intensity of inflammatory response to minor stimuli. Similarly, cathelicidin LL-37 is overexpressed in inflamed skin in psoriasis, binds to extracellular self-DNA released from dying cells, and converts self-DNA into a potent stimulus for plasmacytoid dendritic cells (pDCs).[46] Subsequently, pDCs secrete type I interferons and trigger an auto-inflammatory cascade.

The abnormal keratinization in psoriasis is seen as an increased expression of early differentiation markers such as CDSN and small proline rich proteins, cystatin A and transglutaminase 1, and decreased expression of late differentiation markers such as loricrin and filaggrin. This leads to aberrant formation of the cornified envelope that in turn affects the barrier capacity of the skin. This manifests as increased transepidermal water loss, which is directly proportional to the clinical severity. The expression of aquaporins, a family of water transporting proteins present in the plasma membrane of the stratum corneum and the stratum spinosum, is decreased in lesional and perilesional skin in psoriasis.[64] The LCE gene cluster, which is composed of six groups (LCE 1-6, with a total of 18 members) is a part of the epidermal differentiation complex. Its deletion has been strongly linked with psoriasis.[65] Deletions of *LCE3B* and *LCE3C* genes are present in 60-70% of the general population. The exact function of *LCE3B* and *LCE3C* genes is not known, but they are induced after minor skin trauma such as tape stripping. de Cid *et al*. found significantly increased expression of LCE3 genes and reduced expression of other LCE genes in psoriastic plaques.[19] de Guzman Strong *et al*. found that loss of the 32.4 kb region which functions as an epidermal specific enhancer and is present adjacent to the *LCE3B* and *LCE3C* genes, may be the initiating event in psoriasis.[66] It has been speculated that deletions of *LCE3B* and *LCE3C* genes lead to incomplete barrier repair after minor trauma, which in turn causes penetration of various antigens and induces an inflammatory response.

SOLVING THE JIGSAW PUZZLE

Figure 2 delineates the complex process that may lead to psoriasis. What is amply clear is that no single factor can account for disease causation and that genetic and environmental factors act in conjuction to produce immune dysregulation in the presence of a defective skin barrier. Interaction of damage associated molecular patterns (DAMP) and the pathogen associated molecular patterns (PAMP) with their receptors, such as TLR and NOD like receptors, causes the activation of keratinocytes and the epidermal innate immune system and thus, increased secretion of antimicrobial proteins. This interaction between DAMP/PAMP with TLR/NOD like receptors is also followed by liberation of inflammatory cytokines such as TNF-α, IL-8 and IL-1β, all of which are potent chemoattractants. In patients who carry the

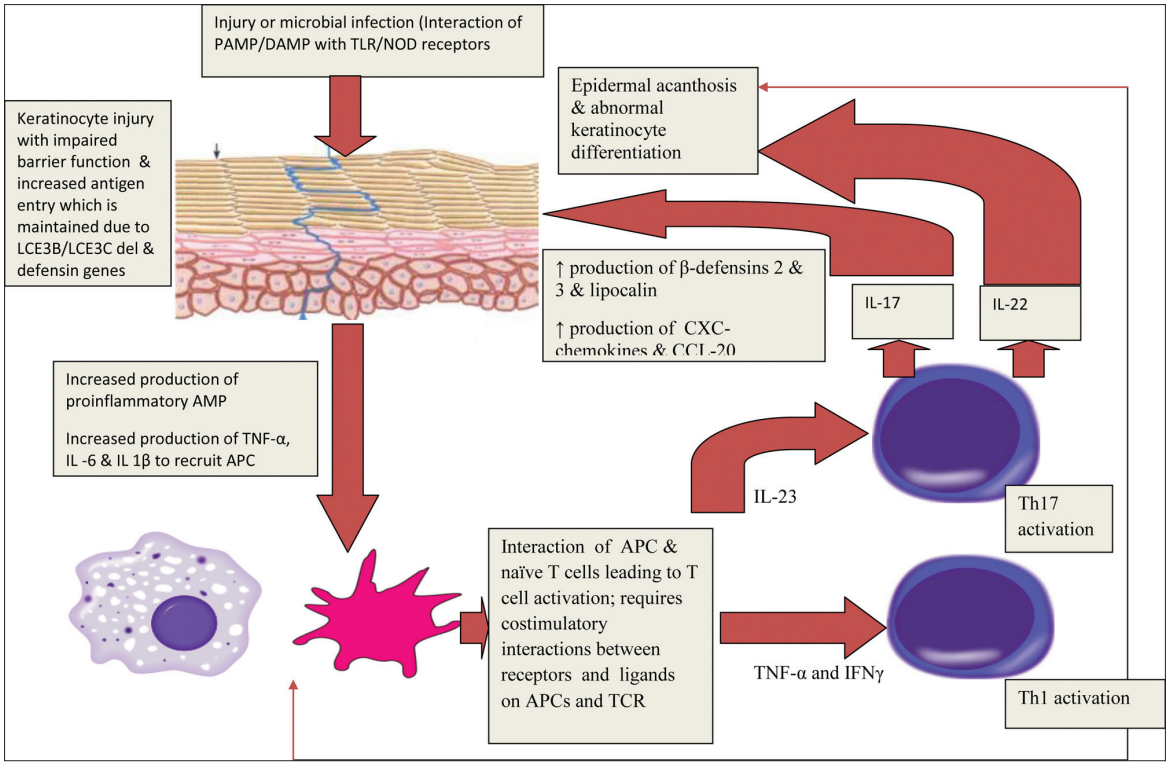

Figure 2: Pathogenesis of psoriasis – Exposure to microbial or mechanical injury damage associated molecular patterns/ pathogen associated molecular patterns leads to activaton of antigen presenting cells like macrophages and dermal dendritic cells; failure to maintain skin barrier due to late cornified envelope proteins 3C/3B deletion leads to continous exposure to such antigens. Interaction of APC and T cells leads to activation of Th1 and Th17 cells mediated by IL-23. Liberation of IL-17 and IL-22 by Th17 cells, and tumour necrosis factor-α and IFN-γ by Th1 cells further perpetuates the keratinocyte injury creating a vicious positive feedback cycle

psoriasis susceptibility genes, such as HLA-C*06, *LCE3B/LCE3C-del* or defensin genes, exposure to PAMP leads to a heightened inflammatory response and defective skin barrier repair with increased expression of keratins 6 and 17, and the LCE3 family. Aberrant skin repair allows a sustained exposure to PAMPs which are engulfed by Langerhan cells and dendritic cells.

Once the APCs engulf the inciting antigen, they migrate to the local lymph nodes where they interact with naïve T-cells, resulting in T-cell activation. This process requires interaction between the major histocompatibility complex antigens on APCs with the T-cell receptors. In addition, costimulatory interactions between receptors and ligands on APCs and TCR are important. These include interaction of lymphocyte function antigen (LFA)-3 and CD2; between intercellular adhesion molecule-1 and LFA-1; and between B7 and CD28.[67] Activation of such naïve T cells to pathogenic T cells is facilitated by the presence of polymorphisms in IL-23 genes and HLA-C*06. Sustained activation of HLA-C*06 restricted immunodominant epitopes could lead to antigen specific activation of CD8+ T cells, further amplifying the production of TNF-α and IFN-γ, although such a subtype of T cells has not been identified. Once the T cells are activated, both CD4+ and CD8+ T cells infiltrate the skin and secrete Th1 and Th17 cytokines which activate the keratinocytes. Together with IL-1

Table 4: Drugs used in the treatment of psoriasis and the key immunologfic step they inhibit

Drug involved	Key immunologic step inhibited
Methotrexate	Decreases IL-22 levels
Cyclosporine	Decreases IL-15 mediated rise in IL-17 levels
Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab	TNF-α inhibition
Alefacept	T cell inhibition by blocking the interaction between LFA-3 and CD2
Efalizumab	T cell inhibition by preventing interaction between LFA-1 and ICAM-1
Abatacept	T cell inhibition by inhibiting the binding of CD28 to CD80/CD86
Ustekinumab, Briakinumab, Apilimod	Anti IL 12/23 antibodies
Secukinumab, Ixekizumab, *Brodalumab	IL-17/IL-17R* inhibitors

TNF-α: Tumour necrosis factor-α, LFA: Lymphocyte function antigen, ICAM: intercellular adhesion molecule, CD: cluster of differentiation

and TNF-α from keratinocytes, Th17 cytokines and IFN-γ increase expression of antimicrobial peptides (AMPs). This leads to a vicious positive feedback cycle where initial activation of keratinocytes promotes immune system activation, which in turn activates the keratinocytes and is responsible for the chronic nature of the disease. Since Peroxisome proliferator activated receptors (PPAR) β/δ (PPAR β/δ), [one of three PPAR isoforms], is a key regulator of glucose and lipid metabolism, its upregulation in psoriasis may partly explain the association with metabolic syndrome.

CONCLUSION

Psoriasis is a complex disease. Three way interactions between adaptive immunity, innate immunity and skin barrier defect may best explain the pathophysiology of psoriasis. That the role of adaptive immunity is crucial to the development of psoriasis is beyond doubt, as validated by the successful use of biologic response modifiers [Table 4]. However, there is increasing evidence on the role played by innate immunity and the skin barrier function in initiating and perpetuating inflammation in psoriasis. This is likely to open up newer targets for therapeutic interventions.

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