Chapter 1

INTRODUCTION
1.1 Brief Introduction:

The word “Psoriasis” is derived from the Greek word Psora meaning ‘to itch’. It is a chronic, immunologically mediated, inflammatory skin disease that can be quite resistant to treatment. It affects approximately 1% to 3% of the world population (1), (2), (3). Environmental and genetic factors are both implicated in the aetiology of psoriasis. T-cells, dendritic antigen presenting cells and cytokine networks are recognized as playing a major role in the pathogenesis of psoriasis (4).

The major manifestation of psoriasis is localised chronic inflammation and hyperproliferation of the skin which is characterized by disfiguring, scaly, erythematous plaques that may be painful or sometimes pruritic. The other clinical presentations of psoriasis are inverse psoriasis which occurs in flexures unlike psoriasis vulgaris which is commonly seen on the extensor aspects, erythrodermic psoriasis, pustular psoriasis, guttate psoriasis which is commonly seen in children, nail disease and psoriatic arthritis (5). In the recent years psoriasis has been recognized as a systemic disease with multi organ abnormalities and complications among which cardiovascular disorders and vascular accidents have emerged as the most studied and researched association.

Comorbidity refers to the occurrence of one or multiple disorders in association with a given disease and often appears to be related to a common pathogenic pathway (6). Risk factor is something that increases a person’s chance of developing a disease.

Over the last decade many studies world over have shown that people with psoriasis often have co morbidities like diabetes, hypertension and lipid abnormalities (7) (8),(9). In 2006 an article authored by Mallbris et al discussed the metabolic disorders in patients with psoriasis (10). Around the same time Sommer DM et al also showed that metabolic syndrome (MetS) was more prevalent in patients with psoriasis (11). In 2007 Gisondi et al
showed an increased prevalence of MetS in patients with psoriasis (12). Since then there have been many studies from various parts of the world substantiating the same findings (13).

Another important co-morbidity is non alcoholic fatty liver disease (NAFLD). NAFLD is now regarded as the hepatic manifestation of metabolic syndrome, as it is largely dependent on the underlying insulin resistance (14), (15). A few recent studies have found an increased prevalence of NAFLD in patients with psoriasis (16), (14). The exact pathomechanisms remain unclear, but are likely to be related to the high prevalence of obesity and metabolic syndrome within this psoriatic patient population (17). Current data although inadequate suggests that a routine work up for NAFLD is warranted in patients with psoriasis more so in those patients where hepatotoxic drugs are being considered as the main modality of treatment.

Treatment options that are currently available are either incompletely effective or associated with toxic effects (18). Adding to this is a host of comorbidities which are being increasingly reported and hence have to be taken into consideration while choosing the apt management protocol for the subjects with moderate to severe psoriasis.

1.2 Psoriasis in the Indian context:

Psoriasis is a common dermatological disorder in India. However there is a paucity of data on the epidemiology of psoriasis in India. From the current data it is inferred that the prevalence of psoriasis is between 0.44% and 2.8% (19) almost paralleling the world scenario. There have been very few Indian studies so far on the risk factors and co-morbidities in psoriasis (20). Most of these are observational descriptive studies. Only one recent study from Kashmir, a case control study; investigated the prevalence of MetS in patients with psoriasis. This study consisted of 150 patients with psoriasis (21).
So far epidemiological studies relating to co morbidities in Indian patients with psoriasis are inadequate. There are no Indian studies so far on the prevalence of NAFLD in patients with psoriasis. Our study was undertaken to fill in these lacunae.

To further our understanding on the common pathogenesis of psoriasis and MetS and the role of adiponectin, an adipocytokine in potentiating psoriasis we studied the expression of adiponectin receptors in keratinocytes as an extension of our study. The presence of co morbidities has important implications in the global approach of patients with psoriasis. By identifying the various co morbidities and the risk factors, patients with psoriasis can be encouraged into behavioural change to correct their modifiable cardiovascular and hepatic risk factors. In particular obesity, alcohol consumption and smoking habits when controlled can improve their quality of life and the outcome of psoriasis.

1.3 The disease

Definition:

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over the extensor surfaces and the scalp. The disease is enormously variable in duration and extent with periods of flares and remission. Morphological variants are common.

1.3.1 Epidemiology:

Epidemiology is the study of the distribution (e.g. incidence and prevalence) and determinants (e.g. risk factors) of disease frequency in human populations. The incidence of psoriasis (the number of new cases occurring in a given population in a defined time)
has been assessed in only one study till now which is a population based study from Rochester. The overall annual crude incidence rate was 57.6 per 100,000 population; for men 54.4 per 100,000 and for women 60.2 (22).

The prevalence of psoriasis varies based on the geographical regions. Prevalence is defined as the proportion of individuals in a population who have the disease of interest in a specified time period. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be anywhere from 0.6% to 4.8% (23). Prevalence studies from India are mostly hospital based. Table 1.1 shows the comparative data from various epidemiological studies on psoriasis from India (19). Therefore it may be inaccurate to match it with the general population.
Table 1.1(19):

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<tbody>
<tr>
<td>Total no of patients</td>
<td>3573</td>
<td>162</td>
<td>782</td>
<td>530</td>
<td>1220</td>
</tr>
<tr>
<td>Prevalence (%) of total dermatology outpatients</td>
<td>1.02</td>
<td>0.8</td>
<td>1.4</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Male: Female</td>
<td>2.46: 1</td>
<td>2.5:1</td>
<td>2.3:1</td>
<td>2.4:1</td>
<td>2.03:1</td>
</tr>
<tr>
<td>Mean age in males and females</td>
<td>Comparable</td>
<td>Lower in females</td>
<td>Lower in females</td>
<td>-</td>
<td>Slightly lower in females</td>
</tr>
<tr>
<td>Peak onset of disease</td>
<td>Third and fourth decade</td>
<td>Third and fourth decade</td>
<td>-</td>
<td>Third and fourth decade</td>
<td>-</td>
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</tbody>
</table>
Impact of age and gender on incidence and prevalence of psoriasis:

Psoriasis can occur at any time, starting right from birth until advanced ages. Many large studies have shown that the age of onset of the disease has a bimodal distribution, i.e one peak in early adult life (late teens to 20s) and then again in later adult life (50s and 60s). (29). This bimodal distribution in psoriasis incidence represents two clinical presentations of psoriasis which is classified as type I and type II. The type I subset is believed to occur before the age of 40 years and is thought to account for more than 75% of cases whereas type II psoriasis is sporadic and mild (30). Type I psoriasis is hereditary, has a consistent association with HLA Cw-6 and is clinically more severe than type II psoriasis which is HLA unrelated (30). Data analysis from a vast majority of the studies on psoriasis shows a higher prevalence among males than females (19). However in young patients (<20 years) the prevalence of psoriasis is more in females when compared to males, suggesting an earlier age of onset in females (23).

1.3.2 Clinical patterns (30):

There are varied clinical presentations of psoriasis. It is broadly classified into pustular and non-pustular psoriasis. Most common clinical type is the classic chronic plaque type psoriasis. This clinical subtype can behave differently in different individuals.

Chronic stable plaque psoriasis

The appearance of the typical lesion is characteristic. There is a single or usually multiple well defined, erythematous plaques with silvery white scales and a sharply delineated edge. Discs and plaques of varying size are often found on the trunk and limbs. The number of lesions may vary. When multiple lesions are present, they may be symmetrically distributed (30).
**Guttate psoriasis**

Guttate psoriasis describes the acute onset of a myriad of small 2-10mm diameter scaly lesions of psoriasis. Classically guttate psoriasis occurs shortly after an acute group B β haemolytic streptococcal infection of the pharynx or tonsils. It is commonly seen in children and occasionally in adults. Guttate psoriasis accounts for 2% of the total cases of psoriasis and has a good prognosis.

**Flexural inverse psoriasis**

Psoriasis affecting the inframammary, perineal and axillary regions has a distinct morphology. Flexural lesions are devoid of scale and appear as red, shiny, well demarcated plaques. It can mimic fungal infections and underlying immune deficiency must be ruled out.

**Palmo plantar psoriasis**

Psoriasis on the palms and soles may present as typical scaly patches on which a fine silvery scale can be evoked on scratching or as less well defined plaques resembling lichen simplex chronicus or hyperkeratotic eczema.

**Erythroderma**

The more serious version in which the patient presents with total or subtotal involvement of the skin by active psoriasis is known as erythroderma. In this form thermoregulation is compromised leading to hypothermia and protein loss in scales. High output cardiac failure, metabolic changes including hypoalbuminemia, and anaemia are the other complications associated with this condition.
**Pustular psoriasis**

Pustular psoriasis can either be generalised or localised to the palms and soles. Generalised pustular psoriasis is rare and represents active unstable disease. Precipitants include withdrawal of systemic or potent topical corticosteroids and infections. The patient is pyrexial, with red, painful, inflamed skin studded with monomorphic sterile pustules which may coalesce to form sheets. Patients with generalised pustular psoriasis frequently require hospital admission for management.

Localized palmoplantar pustular psoriasis presents with erythematous and scaly plaques studded with sterile pustules over palms and soles which may coalesce. The disease is chronic and resistant to treatment.

**1.3.3 Psoriatic arthritis**

Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy associated with psoriasis. The proportion of patients with psoriasis who develop psoriatic arthritis ranges from 6% to 40%. Arthritis is the most common association, which was first recognized by Jean Louis Alibert in 1818 (31).

In 1973, Moll and Wright clearly defined psoriatic arthritis as a distinct entity under seronegative spondyloarthropathies and gave simple criteria for its diagnosis which include; an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis); presence of psoriasis; absence (usually) of serological tests for rheumatoid factor. They also described its five main clinical patterns viz:

- distal interphalangeal (DIP) arthritis,
- arthritis mutilans (destructive),
- symmetric polyarthritis,
• asymmetric oligoarthritis and
• spondyloarthropathy.

Other manifestations of psoriatic arthritis include enthesitis, tendonitis, fasciitis, and dactylitis (32). Psoriatic arthritis can develop at any time including childhood but commonly appears between the age of 30 and 50. Characteristic radiographic features of psoriatic arthritis include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including “pencil in cup” deformity, acro-osteolysis, ankylosis, spur formation and spondylitis (33). Long term systemic therapy is required with or without other biologicals to treat such patients.

**Classification:**

The recently developed CASPAR criteria (classification criteria for psoriatic arthritis) consists of established inflammatory arthritis, defined by the presence of tender and swollen joints and prolonged morning or immobility-induced stiffness, with a total of at least 3 points from the features listed in the table below (table1.2). The CASPAR criteria below has a specificity of 98.7% and sensitivity of 91.4% for diagnosing psoriatic arthritis (34).
Table 1.2: CASPAR criteria for the diagnosis of psoriatic arthritis (modified)

<table>
<thead>
<tr>
<th></th>
<th>The CASPAR (classification criteria for psoriatic arthritis) criteria consist of established inflammatory articular disease* with at least 3 points from the following features:</th>
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<tbody>
<tr>
<td>A</td>
<td>Current psoriasis (assigned a score of 2; all other features are assigned a score of 1)</td>
</tr>
<tr>
<td>B</td>
<td>A personal history of psoriasis (unless current psoriasis is present)</td>
</tr>
<tr>
<td>C</td>
<td>A family history of psoriasis (unless psoriasis or history of it is present)</td>
</tr>
<tr>
<td>D</td>
<td>Current dactylitis or history of dactylitis recorded by a rheumatologist</td>
</tr>
<tr>
<td>E</td>
<td>Juxta-articular new bone formation</td>
</tr>
<tr>
<td>F</td>
<td>Rheumatoid factor negativity</td>
</tr>
<tr>
<td>G</td>
<td>Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis</td>
</tr>
</tbody>
</table>

*Prolonged morning or immobility-induced stiffness, and tender and swollen joints suggest an inflammatory joint disease

**Psoriatic arthritis in India:**

There are only a few studies on psoriatic arthritis from India (35), (36). A study by Prasad et al including 472 patients with psoriasis showed a prevalence of 8.47% (37). Peak incidence in Indian patients was 5th and 6th decade of life as per these studies. In most of the studies male patients were more frequently diagnosed with psoriatic arthritis than females, when compared to rheumatoid arthritis which is more common in females. Ray et al. and Rajendran et al. also found polyarticular pattern simulating rheumatoid arthritis as the most common pattern whereas most common pattern of psoriatic arthritis reported in
Western literature is asymmetric oligoarticular (38). Isolated DIP arthritis was uncommon and arthritis mutilans was rare (35). Psoriasis lesions preceded the onset of psoriatic arthritis in more than 70% of the cases (36).

The psychological impact of psoriasis cannot be underestimated. Studies have reported that patients with skin diseases have poorer Health Related Quality of Life than the general population. No differences were found between men and women. However, patients with Psoriatic Arthritis had significantly poorer Health Related Quality of Life than and psoriatic patients (39). The increased presence of the risk factors for cardiovascular diseases among patients with psoriasis i.e alcohol consumption, smoking and obesity could be secondary to the presence of psychological depression among the chronic sufferers. Counseling and regular psychological assessment will go a long way in the management of psoriasis (40).

1.3.4 Genetics:

The genetic basis of psoriasis has been established earlier. Lomholt from his epidemiologic study of psoriasis concluded that “......psoriasis is genetically determined ...beyond doubt...” (41). Susceptibility loci for psoriasis (43) PSORS1: It has been estimated that HLA-associated allele PSORS1 accounts for 30% to 50% of the genetic contribution to psoriasis, but its identification has been difficult. PSORS2: The linkage of psoriasis to 17q24-q25 has been shown in various studies in Caucasian populations from US, Sweden, and Ireland (43).
Other psoriasis linkages:

Linkage of psoriasis susceptibility with regions other than 17q and HLA has been reported in multiply affected families from different geographic locations: 4q10 (PSORS3) in a set of Irish families; 1q21 (PSORS4) in families from the Lazlo region of Italy and the US; 3q21 (PSORS5) in a set of Sweedish families; 19p13 in German families, and 16q in a large Icelandic family.

Overlap of psoriasis loci with other autoimmune loci

The overlap of psoriasis susceptibility loci with loci for other autoimmune diseases has been described. These are loci for atopic dermatitis on chromosomes 1q21,3q21 an 17q24-q25 (44) and for rheumatoid arthritis on chromosomes 3q21 and 17q24-q25 (45). A locus on chromosome 16q also shows evidence of linkage to both psoriasis and Crohn’s disease (46). These overlapping regions of linkage suggest that at least in some instances the same gene is responsible for two autoimmune diseases. Psoriasis susceptible loci are given in table 1.3.

Table 1.3: Potential psoriasis-susceptibility loci (47)

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Approximate location</th>
<th>Association with other inflammatory diseases</th>
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<tbody>
<tr>
<td>PSORS1</td>
<td>6p21</td>
<td>Asthma</td>
</tr>
<tr>
<td>PSORS2</td>
<td>17q25</td>
<td>Eczema, Rheumatoid arthritis</td>
</tr>
<tr>
<td>PSORS3</td>
<td>4q34 -</td>
<td></td>
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<tr>
<td>PSORS4</td>
<td>1q21</td>
<td>Eczema</td>
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<tr>
<td>PSORS5</td>
<td>3q21</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>PSORS6</td>
<td>19p13 –</td>
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1.3.5 Immunopathogenesis of psoriasis:

Psoriasis as has been proved and many of its co morbidities have an underlying immuno pathogenesis. To understand the common pathophysiology the immunomechanism of psoriasis must be elaborated. It was originally thought that the primary cause of psoriasis was excessive keratinocyte proliferation, leading to abnormal differentiation and impaired barrier function (48).

In the late 1970s and early 1980s, T-lymphocytes and macrophages were identified as the major cell types in the dermal inflammatory infiltrates and thus the view of the pathogenesis of psoriasis shifted to that of an immune mediated disease (49).

**T-cell subsets:**

T-cells are mainly activated memory T cells that express the skin homing receptor CLA (cutaneous lymphocyte antigen). T cells are mainly activated type-1 helper T cells (Th1) and type-1 cytotoxic T cells (Tc1) (50). CD8+ T cells are the major subset of T cells within the epidermis, where they trigger keratinocyte hyperproliferation through cytokine production. CD4 cells have also been implicated in the appearance of psoriatic plaques. In experiments using the severe combined immunodeficient (SCID) mouse model, it was shown that injection of highly purified CD8+ T cells did not produce psoriatic plaques, while similarly purified CD4+ cells did (51). These experiments suggested that CD4+ cells could contribute to activating dormant intra-epithelial pathogenic CD8+ T cells, or function more directly as effector cells.

Natural killer T cells (NK- T cells), a separate lineage of T cells that bears a number of NK-cell markers (CD161+, CD94+) has been identified among epidermal infiltrating immunocytes in close apposition with keratinocytes. As classical NK-T cells may play an immunoregulatory role for recognition of both self and foreign antigens and are implicated...
in the pathogenesis of autoimmune and inflammatory diseases, it was hypothesized that this subset could have a pathogenic action in psoriasis.

**Dendritic cell subsets in psoriasis**

Dendritic cells are also increased in psoriatic skin. Cutaneous dendritic cells belong to different subsets: immature dendritic cells (iDC), mature myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs) (52). Immature DCs function in antigen detection, uptake and processing, whereas mature DCs primarily function in antigen presentation as well as cytokine production (53). In psoriasis Langerhans cells retained within the epidermis could contribute to sustained activation of effector T cells, leading to the inflammatory process (54).

**Keratinocytes**

The proinflammatory cytokines that are secreted by the T cells and the dendritic cells appear to be responsible for keratinocyte hyperproliferation. Inflammatory cytokines such as IL-1, IL-6, IL-8, INF-\(\gamma\), and TNF-\(\alpha\) are known to trigger epidermal hyperplasia through direct or indirect pathways. Keratinocytes also produce inflammatory mediators such as IL-1, IL-6, IL-8, IL-15, IL-18, IL-19, IL-20, IL-23, TNF-\(\alpha\), VEGF (vascular endothelial growth factor), amphiregulin, TGF-\(\alpha\),CCL20 and CCL27. Most of the mediators belong to the Th-1-inducing family of cytokines. Thus keratinocytes are also active participants in the pathogenesis of psoriasis (54).
Immune activation Pathways:

The immune mechanisms involved in the formation of a psoriatic plaque are as follows:

**Antigen uptake & processing:**

The exact mechanism of the activation of T cells is unknown. Either an exogenously derived stimulus such as trauma, or an endogenous stimulus such as HIV-1, neuropeptides, or ingested medications, was thought as triggering a plexus of cellular events by inciting a cascade of cytokines. It is also unknown whether the inciting antigen is self-derived (thereby qualifying psoriasis as an autoimmune disease) or is of non-self origin (47).

Following antigen recognition at peripheral sites, immature DCs perform antigen capture and processing through mechanisms including receptor-mediated endocytosis, phagocytosis, and macro pinocytosis (55). Once antigens are captured and within the cell, processing occurs within endosomes as the molecules are degraded into peptides that are subsequently complexed with MHC class II molecules.

**Dendritic cell migration:**

Following antigen uptake and processing, DCs migrate to secondary lymphoid tissues for presentation to T-cells. DC trafficking to draining lymph nodes is orchestrated through a complex interplay of pro-inflammatory cytokines (TNF-α, IL-1 beta, IL-18), chemokine and chemokine receptors (CCL19, CCR2, CCR6, CCR7), leukotrienes, and cell adhesion molecules (e.g. E-cadherin down-regulation) (56). Psoriatic lesions may serve as potential sites for chronic T-cell activation through lymphoid-organizing chemokines that are found at increased levels in psoriatic lesions. It has been proposed that these chemokines are capable of organizing DCs and T-cells into lymphoid-type tissues that can possibly support ongoing, peripheral APC–T-cell interactions that are usually confined to the
lymph nodes or spleen (58). Pictorial representation of the immunological synapse is given in figure1.1.

**T-cell and dendritic cell interaction:**

In mature lymphocytes, T cell receptor (TCR) signaling is mediated by formation of a multimolecular complex at the T cell–APC interface, referred to as the immunological synapse. The immunological synapse is a discrete cluster of molecules formed between a T cell and an APC that facilitates immune cell interactions (58). Key molecular components include the TCR and, surrounding it, a ring of adhesion molecules, such as LFA-1, which can bind to ICAM-1 expressed by the adjacent cell, e.g., a keratinocyte or APC. While the immunological synapse controls T cell activation, additional contributory molecules, including other adhesion molecules and costimulatory molecules, also influence T cell responsiveness. For example the cell surface molecular pairs CD2:LFA-3 and CD28:CD80/CD86 (59).
Figure 1.1: Immune synapse–related signaling pathway and autoimmune diseases. A possible role for genetic mutations involved in several autoimmune diseases is highlighted, including ZAP-70 rheumatoid arthritis (RA); SLC9A3R1 and NAT9 (psoriasis); PDCD1 (systemic lupus erythematosus [SLE]); and SLC22A4 (RA and Crohn disease). T lymphocytes contain both surface receptors and intracellular signalling components that become activated when the TCR is engaged by interactions with an appropriate APC in which antigen is presented in the context of MHC molecules. The APC is displayed in the upper portion of this schematic view. The TCR mediates signalling in conjunction with molecules located in the plasma membrane, including CD3 and ζ-chains, which contribute to the formation of an immunological synapse and a lipid raft, leading to activation of proximal, intermediate, and distal signalling components. Several but not all components are portrayed in this figure. Ultimately, transcription
factors become activated and bind to respective promoter regions to either enhance or suppress target gene expression. Potential mechanisms linking the genetic findings to functional components of the immunological synapse are shown by solid bold lines.

**Formation of psoriatic plaque**

An extensive cytokine network generated by activated DCs and T-cells mediates the formation of psoriasis lesions. Collectively, DCs have been shown to secrete numerous cytokines that are implicated in psoriasis including TNF-α, IFN-α, IL-12, IL-23, and IL-15. IFN-α, which is produced by pDCs that are present within psoriasis plaques, plays a key role in the stimulation and proliferation of T-cells as well as the formation of psoriatic skin (60). IL-23 activates T-helper cells that subsequently produce IL-17 and IL-22; this latter cytokine contributes to dermal inflammation and epidermal hyperplasia characteristic of psoriasis (61). Similarly, IL-15 is a pro-inflammatory cytokine that induces T-cell proliferation as well as skin hyperplasia (62). Activated T-cells secrete IFN-γ and TNF-α, which are essential players in the potentially self-perpetuating type 1 pathway of psoriasis. Summary of the immune pathways in psoriasis is given in table 1.4. Diagrammatic representations of the immunopathogenesis of psoriasis are given in figures 1.2, 1.3, 1.4.
**Table 1.4: Summary of the immune pathway in psoriasis:**

<table>
<thead>
<tr>
<th>Activating stimuli</th>
<th>Antigen uptake and processing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1) <em>Microbial products</em> (e.g. CpG motifs, lipopolysaccharide) stimulate <em>pattern-recognition receptors</em> (i.e. lectin receptors, Toll-like receptors) and subsequent antigen internalization</td>
</tr>
<tr>
<td></td>
<td>(2) Antigen processing occurs through <em>proteolysis by endocytic proteases</em>, and results in the generation of peptides that are loaded on to MHC molecules</td>
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| DC migration | (1) *Pro-inflammatory chemokines, leukotrienes, cytokines, and other chemotaxins* (e.g. C5a and PAF) facilitate DC migration to inflammatory sites |
|             | (2) Up-regulation of *lymphoid chemokine receptors* (CCR7) and down-regulation of pro-inflammatory chemokine receptors correlate with DC migration to secondary lymphoid tissues |

| T-cell activation | (1) DCs produce *IL-12p70*, which helps generate T-helper cell type 1 (Th1) responses; IL-12p70 acts as a “third signal”, while enhancing CD8+ T-cell survival, clonal expansion, and effector functions; other possible stimulatory cytokines include IL-15, IL-18, IL-23, and IFN-α. |
|                  | (2) Mature DCs exhibit surface *MHC - peptide complexes* for presentation to T-cells |
|                  | (3) *Co-stimulatory signals* (CD80 and CD86) and *adhesion molecules* (DC intercellular adhesion molecule-1 binds to T-cell leukocyte-function-associated antigen-1) facilitate DC–T-cell interactions |
|                  | (4) Heat shock proteins and their corresponding receptors (CD91) stimulate: the upregulation of DC costimulatory molecules; DC activation of T-cells; DC production of cytokines, which induce T-helper cell proliferation |
|                  | (5) *Cross-presentation* and priming of cytotoxic T-lymphocytes |
Figure 1.2: Comparison of immune cells in normal versus psoriatic skin illustrating how genetic risk factors could trigger and perpetuate epidermal inflammation and proliferation. 

(a) In normal skin there are a number of resident cells of the immune system. These include specialized dendritic cells (DCs) such as Langerhan's cells and resident dermal DCs, as well as skin homing T cells and neutrophils. (b) In psoriasis lesions DCs and keratinocytes can act as antigen presenting cells (APCs) to lymphocytes via their MHC proteins. An initiating trigger could lead to enhanced production of IL-12 and IL-23 by DCs in genetically susceptible individuals. In psoriasis lesions, a subset of DCs express
high levels of tumor necrosis factor (TNF) and the enzyme inducible nitric oxide synthase (iNOS). These are termed TIP-DCs (TNF- and iNOS-producing DCs). It is thought that these DCs produce the cytokines IL-23 and IL-20, which have the potential to activate T cells and keratinocytes, respectively [24]. IL-23 triggers differentiation of Th17 cells following binding to the IL23R on naïve T cells. Production of Th17 cells would be enhanced by the presence of the IL23R genetic risk factor. Th1 and Th17 cytokines TNF and gamma interferon induce keratinocytes in psoriasis lesions to synthesize numerous proteins that can attract the array of leukocytes found in lesional epidermis. These proteins include β-defensins and the S100A7 protein also known as psoriasin. Neutrophils accumulate in small aggregates in the cornified epidermis in the form of Munro abscesses. IL-22 cytokines act on keratinocytes to increase proliferation (63).
Figure 1.3: Normal and psoriatic epidermis

Normal epidermis is made up approximately by 10 cell layers i.e basal layer, spinous layer, granular layer, and the cornified layer or stratum corneum (SC). The SC is constantly being shed and replenished by proliferation in the basal layer. Keratin proteins 5/14, 1/10 and 6/16/17 are generated in large amounts. Keratins 6/16/17 are normally induced in response to trauma. S100 proteins such as S100A7 and S100A11 are present in
the basal and spinous layers of the normal epidermis. They appear in the nucleus and cytoplasm in basal cells but are associated with the plasma membrane in spinous cells in normal and psoriatic tissue. S100A7 is also termed psoriasin and has antimicrobial functions. Terminal differentiation proteins are made in the granular layer where nuclei break down, keratins condense, and CE proteins are crosslinked by transglutaminase. Mature keratinocytes in the cornified layer are known as corneocytes, lack nuclei and are flattened and condensed. The space between cells is filled with neutral lipids that have been secreted from lamellar granules (LG) into the intercellular spaces of the upper granular layer to form intracellular lipid lamellae. The resulting organization of lipid and corneocytes has been compared to bricks and mortar and protects the organism from infection and dehydration. Defensins are stored in lamellar granules and are extruded with lipids into the intracellular space of normal skin. At the same time desmosomes are transformed into corneodesmosomes by insertion of the protein corneodesmosin into the adhesive portion of these structures. In psoriasis lesions the granular layer is often absent, and corneocytes retain their nuclei (parakeratosis). The SC is thicker and disorganized. Components of the CE are also prematurely synthesized in the spinous layer. In psoriasis lesions neutral lipids are not secreted in a normal fashion into the extracellular space. This leads to a defective water/vapor barrier and the shedding of stratum corneum fragments in large sheets called scales or flakes in psoriasis plaques. Antimicrobial peptides such as S100A7 and beta-defensin are highly upregulated in psoriasis. Connexin 26 (Cx26), is a gap junction protein that is also highly upregulated in psoriasis. Transgenic overexpression of Cx26 in mouse epidermis keeps wounded epidermis in a hyper-proliferative state and blocks the transition to remodeling. Its upregulation also leads to infiltration of immune cells (63).
Interferon (IFN)-α links innate and adaptive immunity leading to the development of psoriasis. A spatial and temporal view of psoriasis development in which IFN-α production represents an early and transient event during the psoriatic disease process and is confined to activated plasmacytoid dendritic cells (PDC) (innate immunity). Innate activation of PDC may result from the release of skin-derived products upon skin injury or infection. IFN-α stimulates the pathogenic T cell cascade (adaptive immunity) indirectly by promoting the activation and maturation of myeloid dendritic cells (MDC) or by direct stimulation of IFN-α-sensitive pathogenic T cells, leading to Th1-mediated inflammation and the development of the psoriatic epidermal hyperproliferation. (60)