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# Psoriasis – Types, Causes and Medication

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54728>

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## 1. Introduction

Although the skin disease psoriasis was first recognized as a distinct disease as early as 1808 [1], its pathogenic mechanisms have eluded investigators for decades, its definition by Ferdinand von Hebra as a distinct entity dates back only to the year 1841 and estimates of its prevalence around 2-3% of the general population, and is characterized by an exaggerated proliferation of keratinocytes secondary to an activated immune system. The incidence is highest at the age of 20–39 years in males and 40–59 years in females, with an equal male-to-female ratio [2]. Psoriasis clinically manifests as raised, well defined erythematous plaques with irregular borders and silvery scales, affecting the upper and lower extremities equally, but with a predilection for the elbows, knees, scalp, and trunk. Psoriasis vulgaris or plaque psoriasis accounts for almost 90% of the dermatological presentation of the disease, but several other forms, including guttate, inverse, erythrodermal, pustular, and palmoplantar psoriasis may occur, as well as nail involvement. Psoriasis may have significant systemic involvement, which is underscored by the coexistence of various clinical disorders, including eye, cardiovascular, and intestinal problems, metabolic syndrome, and joint inflammation. It has a very high negative impact on quality of life, requires long-term treatment which usually has a high social and economic impact and is also associated with a decreased life span [3] [4].

## 2. Psoriasis types

### Psoriasis classification

No one classification of psoriasis satisfies all the mentioned requirements. Usually, criteria are intermingled (Table 1), and subclasses are nonexclusive. Similar problems exist with the clinical classification of psoriatic arthropathy [5].

Morphologic aspects of elementary lesions	Pustular, non-pustular but also plaque, nummular, guttate, gyrate, rupioid, elephantine, ostraceous, etc.
Degree of inflammation	Mainly inflammatory vs mainly hyperkeratotic
Pattern distribution	Extensory, inverse, seborrhoeic, widespread
Extent	One site (scalp, nail, etc.), many sites, generalized
Time of first onset	Early vs late onset
Velocity of propagation	Stable, unstable, eruptive

**Table 1.** Features which have been considered in different classifications of psoriasis [6]

Classification criteria based on purported etiology rank higher in formalization compared with purely morphological ones.

### 2.1. Classifying psoriasis: The spectrum of clinical varieties

Psoriasis, a papulosquamous skin disease, has several different types, including: **psoriasis vulgaris** (common type), **guttate psoriasis** (small, drop like spots), **inverse psoriasis** (in the folds like of the underarms, navel, and buttocks), and **pustular psoriasis** (pus-filled, yellowish, small blisters). When the palms and the soles are involved, this is known as **palmoplantar psoriasis**.

### 2.2. Psoriasis vulgaris (chronic stationary psoriasis, plaque-like psoriasis)

The commonest type of psoriasis, accounting for 90% of all cases, is psoriasis vulgaris, in which papulosquamous plaques are well-delineated from surrounding normal skin. The plaques are red or salmon pink in color, covered by white or silvery scales and may be thick, thin, large or small (Figure 1). They are most active at the edge: rapidly progressing lesions may be annular, with normal skin in the centre. Plaques are usually distributed symmetrically, and occur most commonly on the extensor aspects of elbows and knees; scalp (where they rarely encroach beyond the hairline), lumbosacral region, and umbilicus. Active inflammatory psoriasis is characterized by the Koebner phenomenon, in which new lesions develop at sites of trauma or pressure [7].

#### 2.2.1. Classification of psoriasis vulgaris according to phenotype: plaque-type psoriasis

There is also variation of features of psoriasis dependent on anatomical sites. Until the reasons for this variation are fully understood, they are proposed to be recorded as a phenotypic entity, although subsequently they may be shown to be part of a common pathogenetic mechanism. A further distinction arises according to the age of onset of plaque psoriasis [8]. Henseler and Christophers are credited with identifying two ages of onset: type I occurring at or before the age of 40 years—this accounts for approximately 75% of patients; and type II presenting after the age of 40 years, with a distinct peak at 55–60 years [9].

### 2.2.2. *Plaque-type psoriasis: Chronic plaque psoriasis*

As a consequence, chronic plaque psoriasis is the form of the disease entered into clinical trials and the object of the majority of investigations of genetics and pathogenesis of psoriasis. It is characterized by red, scaly, discoid lesions varying in size from 0.5 cm in diameter to large confluent areas on the trunk and limbs (Figure 1). There is a sharp line of demarcation between a plaque and clinically normal, uninvolved skin. Longitudinal studies of individual plaques have demonstrated that plaques are dynamic [10] with an active and expanding edge, sometimes to the extent that the advancing edge may become annular (Figure. 2) leaving clinically normal skin in the centre of the original plaque. The variety of plaque is characterized by well-demarcated plaques with a loosely adherent silvery-white scale, which preferentially affect the elbows, knees, lumbosacral area, intergluteal cleft, and scalp. Occasionally, pustular lesions may appear in the plaque (so-called psoriasis with pustules). Chronic plaque psoriasis is the most common variety of psoriasis, representing about 70% to 80% of psoriatic patients [11].



**Figure 1.** Typical plaque of Psoriasis Vulgaris.



**Figure 2.** Annular psoriasis showing clearance in centre of plaque.

Under the heading of plaque psoriasis, it is proposed to include, as subdivisions, a new, more logical nomenclature of phenotypes associated with specific anatomical sites, distribution, size and thickness of plaques [8].

### 2.2.3. Site-specific variants of Psoriasis Vulgaris (PV)

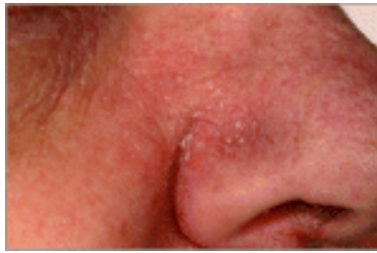
Site-specific variants of psoriasis vulgaris exist. Flexural (inverse) psoriasis in intertriginous sites is shiny, red, and typically devoid of scales (figure 3); seborrheic psoriasis, which can be confused with seborrhoeic dermatitis, has greasy scales and occurs in eyebrows, nasolabial folds, and postauricular and presternal sites. Psoriasis vulgaris will probably prove to be several closely related but phenotypically and genotypically distinct conditions [8].

**Flexural/intertriginous:** Inverse psoriasis (Flexural Psoriasis or Psoriasis of the Skin Folds) is usually located in the skin folds: i.e. armpits, under the breasts, skin folds around the groin and between the buttocks. It is particularly subject to irritation from rubbing and sweating because of its location in skin folds and tender areas (Figure 3). Plaques are thin, have minimal scale and a shiny (nonscaly) surface commonly accompanied by secondary fissuring and/or maceration. The major clinical manifestation of inverse psoriasis is sharply demarcated erythematous plaques, with varying degrees of infiltration, which often tend to itch and burn [12]. The most common lesions are found in inguinal, submammary, intergluteal, umbilicus and genital folds, whereas the popliteus and axillae are rarely involved. The humidity and heat typical of these sites, together with the combination of local traumatic factors often associated with infections caused by dermatophytes and *Candida albicans*, together contribute to the development of psoriasis in accordance with the Koebner phenomenon. The Koebner phenomenon is an indicator of disease activity, may have a prognostic value, and is associated with early onset of psoriasis [13]. The Koebner phenomenon was first described by Heinrich Koebner (1838–1904) and refers to the fact that in people with certain skin diseases, especially psoriasis, trauma is followed by new lesions in the traumatized but otherwise normal skin, and these new lesions are clinically and histopathologically identical to those in the diseased skin [14].



**Figure 3.** Flexural psoriasis, notes the relative lack of scale.

**Seborrhoeic:** Seborrhoeic psoriasis ('sebopsoriasis'), so called because of its similarity in morphology and anatomical distribution to seborrhoeic dermatitis, may occur either in isolation or associated with plaque psoriasis elsewhere. Sites of involvement are the nasolabial folds (Figure 4), medial cheeks, nose, ears, eyebrows, hair line, scalp, presternal and inter-scapular regions. Characteristically the lesions are thin, red and well-demarcated (somewhat like intertriginous psoriasis) with variable degrees of scaling.



**Figure 4.** Seborrhoeic psoriasis, nasolabial, 'greasy' appearance and finely scaled.

**Scalp:** The scalp is frequently the site of initial presentation and is the commonest anatomical site to be involved by psoriasis. Morphologies range from discrete plaques to total scalp involvement with either thick plaques or scaly nonthickened areas almost identical to seborrhoeic dermatitis. Sites of predilection include the immediate postauricular area and occiput. An important and fascinating observation is that the scalp lesions rarely extend > 2 cm beyond the hairline. Compared with psoriasis elsewhere, scalp involvement is frequently asymmetrical (Figure 5).



**Figure 5.** Psoriasis of the scalp.

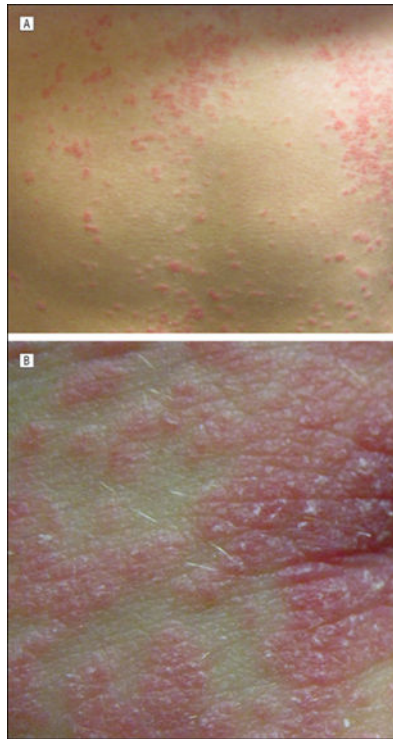
**Palms/soles (nonpustular):** Palmoplantar pustulosis, consisting of yellow-brown, sterile pustules on palms and soles, is still described in textbooks of dermatology as a subtype of psoriasis. About 25% of people with palmoplantar pustulosis also have chronic plaque psoriasis. The disease has different demographics to psoriasis vulgaris in that patients are predominantly women (9:1 female: male ratio) and either current or previous smokers (95%) and onset occurs in the 4th or 5th decades of life (Figure 6) [15].



**Figure 6.** Plantar involvement by plaque psoriasis.

### 2.3. Guttate psoriasis

Psoriasis affects approximately 2% of the world population, and of these cases, 2% manifest as guttate psoriasis [16]. Guttate means "drop" in Latin; aka Teardrop Psoriasis, Raindrop Psoriasis or Psoriasis Exanthematic) is the second most common type of psoriasis. Guttate psoriasis (GP), an important clinical variant, most frequently occurs in adolescents and young adults. It is characterized by the sudden onset of widely dispersed small red scaly plaques mainly over the trunk and proximal limbs. The symptoms of GP are numerous small, red, drop-like spots which cover a large portion of the skin. Spots have an abundant scaling. Lesions are usually located on the trunk, arms, legs and scalp. GP can clear up without treatment or disappear and resurface in the form of plaque psoriasis. GP is especially common in children or young adults with a family history of psoriasis and follows streptococcal infection and/or acute stressful life events [17]. Guttate flares in patients with established psoriasis vulgaris (PV) are also frequently observed. These observations, taken together with investigative studies, indicate an important pathogenetic link between GP and PV [15]. GP is often associated with a preceding streptococcal throat infection or a rise in anti-streptococcal serum titer [16] [18]. Bacterial streptococcal infections (strep throat, chronic tonsillitis) or a viral respiratory infection usually precede and trigger the first signs of Guttate Psoriasis in persons predisposed to psoriasis. Herein, Dr. Loh in 2012 reports a case that suggests such an association. This 15-year-old girl presented with a case of acute guttate psoriasis shortly after the onset of mononucleosis. The structural characteristics of her eruption and her skin biopsy findings are consistent with guttate psoriasis (Figure 7).



**Figure 7.** Clinical photographs of the abdomen with guttate psoriasiform papules and plaques. A, Unmagnified image. B, Image at higher unspecified magnification [19].

#### **2.4. Pustular psoriasis: In a population survey of psoriasis, pustular lesions were reported at any time during the course of psoriasis by about 20% of patients [11]**

**Generalized pustular psoriasis:** Patients with generalized pustular psoriasis (GPP) may have preexisting plaque psoriasis or develop it after pustular episodes. Acute episodes may be triggered in patients with plaque psoriasis by irritating topical therapy or abrupt corticosteroid withdrawal [20]. At the onset of an attack of acute GPP (von Zumbusch type) the skin becomes very red and tender. There may be fever and systemic symptoms such as anorexia and nausea. Within hours, myriads of pinhead-sized pustules appear, studding the erythematous background (Figure 8). Pustules may become confluent, producing lakes of pus. Subsequently, the pustules dry out, and the skin peels off, leaving a glazed, smooth erythematous surface on which new crops of pustules may appear [21]. GPP should be distinguished from acute generalized exanthematic pustulosis, a self-limiting febrile drug reaction usually resolving in 2 weeks after withdrawal of the suspected agent, characterized by pinpoint nonfollicular pustules on erythematous patches mainly involving folds. Single necrotic cells in the epidermis, eosinophils, and vasculitic changes in the dermis are peculiar pathologic features [22] [23].



**Figure 8.** Early phase of generalized pustular psoriasis with edematous plaques and pustules.

**Localized pustular psoriasis:** Besides so-called psoriasis with pustules (sometimes referred to by the misleading term “localized form of generalized pustular psoriasis”), 2 main clinical varieties are reported as localized pustular psoriasis: acrodermatitis continua of Hallopeau and palmoplantar pustulosis.

**Acrodermatitis continua**, also known as dermatitis repens, is a rare, chronic, pustular eruption of the fingers and toes (Figure 9). Often, it begins after a localized trauma starting at the tip of a single digit [24].

**Palmoplantar pustulosis:** is characterized by hyperkeratosis and clusters of pustules over the ventral aspects of hands and/or feet (Figure 10). Classification of palmoplantar pustulosis within the spectrum of psoriasis is controversial. The disease predominates in women (more than 70% of patients are women) and is much more strongly associated with smoking than plaque psoriasis [25]. Palomar-plantar pustulosis (PPP) generally appears between the ages of 20 and 60. PPP causes large pustules to form at the base of the thumb or on the sides of the heel. In time, the pustules turn brown and peel. The disease usually becomes much less active for a while after peeling.





**Figure 9.** Acrodermatitis continua showing crops of pustular lesions at the tips of the fingers.



**Figure 10.** Palmoplantar pustulosis.

## 2.5. Erythrodermic psoriasis

As already mentioned, plaque psoriasis is a rather stable disorder. The transition to a more extensive involvement, due to frequently unidentifiable triggering factors, is frequently marked by the onset of an inflammatory phase with predominant erythema and limited scaling associated with itching and rapidly progressing lesions. This unstable psoriasis may sometimes evolve to whole-body involvement. The erythrodermic phase is dominated by generalized erythema, loss of peculiar clinical features of psoriasis, and skin failure, that is, inability to maintain homeostatic functions [26]. Erythrodermic psoriasis characterized by severe scaling, itching, and pain that affects most of the body, erythrodermic psoriasis disrupts the

body's chemical balance and can cause severe illness (Figure11). This particularly inflammatory form of psoriasis can be the first sign of the disease, but often develops in patients with a history of plaque psoriasis.



**Figure 11.** Erythrodermic psoriasis.

## 2.6. Nail psoriasis

Approximately 50% of all patients with psoriasis develop characteristic nail changes as a clinical correlate of psoriatic inflammation of the nail matrix and/or nail bed. The most frequent signs of nail psoriasis are pitting and distal onycholysis [27]. Clinical manifestations range from pitting, yellowish discoloration, and paronychia, to subungual hyperkeratosis, onycholysis, and severe onychodystrophy (Figure 12) [28].



**Figure 12.** Yellowish discoloration of fingernails.

## 2.7. Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease occurring in 6–39 % of patients with psoriasis with a prevalence of PsA in the general population of about 0.1–0.25 % [29] [30]. Based on the several common clinical and radiological features, PsA is considered as a member of the family of spondyloarthritides [31]. This type of arthritis can be slow to develop and mild or it can develop rapidly. PsA can be a severe form of arthritis with prognosis similar to that of rheumatoid arthritis (RA) [32]. Psoriatic arthritis (PsA) is characterized by focal bone erosions mediated by osteoclasts at the bone–pannus junction. Importantly, 80% of patients with psoriatic arthritis have nail psoriasis (Figure13) [33]. Recognition of bone as an active organ that interacts with its environment is a relatively new development. In the pathogenesis of bone destruction associated with rheumatoid arthritis, the synovium is a site of active interplay between immune and bone cells. The interaction between T cells and osteoclasts is a critical issue in the field of osteoimmunology [34]. Further differentiate mechanisms of bone resorption and repair in PsA and RA and likely will uncover additional therapeutic targets [35].



**Figure 13.** Psoriatic arthritis hand changes over time.

## 3. Psoriasis causes

### Psoriasis – Pathogenesis

Today, psoriasis is recognized as the most prevalent autoimmune disease caused by inappropriate activation of the cellular immune system. There are two main hypotheses about the process that occurs in the development of Psoriasis. The first considers psoriasis as primarily a disorder of excessive growth and reproduction of skin cells. The problem is simply seen as a fault of the epidermis and its keratinocytes and is characterized by hyperproliferation with incomplete differentiation of epidermal keratinocytes and decreased keratinocyte apoptosis. The second hypothesis sees the disease as being an immune-mediated disorder (immunosuppressant medications can clear psoriasis plaques) in which the excessive reproduction of skin

cells is secondary to factors produced by the immune system. T cells become active, migrate to the dermis and trigger the release of cytokines which cause inflammation and the rapid production of skin cells. It is not known what initiates the activation of the T cells. That work initially pointed towards a major role of T lymphocytes as inducers of the disease phenotype and the pathogenic contribution of this cell type has now been tested through clinical studies of more than a dozen immune modifying biological agents in patients with psoriasis. The inflammatory cytokines such as tumor necrosis factor (TNF) are likely to play major pathogenic roles in this disease and that other types of inflammatory leucocytes may also serve key pathogenic functions. Here we will review some recent works on psoriasis that advances our overall understanding of disease pathophysiology regarding neuroendocrine immunology. The concept of Psoriasis & Supersystems considers site of recognition, skin barrier in the sympathetic nervous (beta2 adenoceptors) and immune systems.

### **Psoriasis & supersystems**

The brain and the immune system, or the “supersystems”, a term recently coined by Tada (1997), are the two major adaptive systems of the body [36]. Although the immune system has been often regarded as autonomous, the last two to three decades provided strong evidence that the central nervous system (CNS) receives messages from the immune system and vice versa messages from the brain modulate immune functions. Thus, the brain and the immune system are involved in functionally relevant cross-talk, whose main function is to maintain homeostasis [37]. In psoriasis it seems that the most important components of these supersystems are  $\beta$ 2 adenoceptors and tumor necrosis factor alpha (TNF $\alpha$ ). Recent studies show that the  $\beta$ 2-adrenergic receptor is specifically associated with the homeostasis of skin barrier. Ca has critical role in this function. Increasing evidences indicate that TNF may have immunosuppressive effects, since long-term exposure to TNF can directly prevent the activation of T cells.  $\beta$ 2-adrenergic receptor interacts with TNF $\alpha$  which is evaluated in below, respectively.

### **3.1. Skin's barrier function**

#### *3.1.1. Homeostasis of skin barrier: Self-referential system*

The skin barrier homeostatic function is a self-referential system because it is always monitoring its original function, i.e., water impermeability. This function is regulated by the peripheral function [38]. Epidermal homeostasis is understood as the maintenance of epidermal tissue structure and function by a fine tuned regulatory mechanism balancing proliferation and cell loss by desquamation and apoptosis [39]. Stem cells of the basal layer or stratum basal in the epidermis have a crucial role in maintaining tissue homeostasis by providing new cells to replace those that are constantly lost during tissue turnover or following injury [40]. cAMP and calcium influence the formation and maintenance of barrier function [41].

#### *3.1.2. Skin: An indispensable and protective barrier*

The first protective barrier is provided by the skin, our largest organ. It serves as the interface between the organism and the outside world and it serves many functions, such as the retention

of body fluids, maintenance of body temperature, and protection against UV-light, chemical influxes, wounds, and the invasion of micro-organisms. The protective barrier function is performed by the keratinocytes of the epidermis, which are continuously produced by proliferating stem cells of the basal layer or stratum basal and differentiate during a 14 day journey towards the surface [42].

### 3.1.3. Skin: Epidermal barrier capacity (lipid/protein polymer structure)

#### **Stratum corneum (SC) & Ceramides (family of lipid molecules)**

Epidermal barrier capacity is controlled by lipids that fill the extracellular space of the skin's surface layer—the stratum corneum. Lipid synthesis for skin barrier function takes place within the keratinocytes in all nucleated epidermal layers. Lipids are stored within the epidermal lamellar bodies (secretory organelles) or keratinosomes, which are ultrastructurally visible at the level of the upper spinous layer and in the granular layer. In the outermost granular layer, the contents of lamellar bodies are secreted into the intercellular domains of the stratum granulosum–stratum corneum interface. Lamellar bodies mainly contain phospholipids, glucosylceramides and cholesterol as well as hydrolytic enzymes, which convert phospholipids, glucosylceramides and sphingomyelinase to free fatty acids and ceramides. Then, lamellar bodies cause in the formation of an impermeable, lipid-containing membrane that serves as a water barrier and is required for correct skin barrier function. The Stratum Corneum (SC) contains three types of lipids -- ceramides, cholesterol and free fatty acids. These lipids have different chemical compositions and different functions throughout the body. There are nine different types of ceramides in the Stratum Corneum, conveniently named ceramide 1 through ceramide 9, and they account for 40-50% of the lipids in this outermost layer. A ceramide is composed of sphingosine and a fatty acid. Ceramides are found in high concentrations within the cell membrane of cells. They are one of the component lipids that make up sphingomyelin, one of the major lipids in the lipid bilayer. Ceramide can actually act as a signaling molecule. The most well-known functions of ceramides as cellular signals include regulating the differentiation, proliferation, programmed cell death (PCD), and apoptosis (Type I PCD) of cells [43]. The proliferation rate of keratinocytes to corneocytes is matched by the shedding of old corneocytes at the SC [44] and skin tissue maintains a steady number of SC layers regardless of age [45].

**Desquamation**, the process of cell shedding from the surface of the stratum corneum, balances proliferating keratinocytes that form in the stratum basale. These cells migrate through the epidermis towards the surface in a journey that takes approximately fourteen days. During cornification, the process whereby living keratinocytes are transformed into non-living corneocytes, the cell membrane is replaced by a layer of ceramides which become covalently linked to an envelope of structural proteins (the cornified envelope). This complex surrounds cells in the stratum corneum and contributes to the skin's barrier function [41]. SC serves as the principal barrier against the percutaneous penetration of chemicals and microbes and is capable of withstanding mechanical forces [46].

Stratum corneum (SC) & Proteases (kallikrein family of serine proteases)

Interestingly, two major proteases of stratum corneum SCCE/KLK7/hK7 and SCTE/KLK5/hK5 together can destroy three major components of the corneodesmosomes: DSC1, DSG1 and CDSN [47]. These enzymes belong to kallikrein family of serine proteases. Their expression starts in suprabasal keratinocytes where their inactive precursors undergo a processing by an unidentified trypsin-like protease [48]. In stratum corneum, these enzymes appear in the intercellular spaces suggesting their involvement in the desquamation [49]. Recent discoveries have highlighted the importance of various proteases, protease-inhibitors, and protease targets as key players in epidermal barrier function [50]. It has become clear in recent years that serine proteases have an important role in epidermal homeostasis, and the signaling cascades are gradually being identified [41].

#### 3.1.4. Skin: Epidermal proteases

The specific differentiation program in stratified skin requires a specialized proteolytic system to detach the corneocytes from each other without causing a barrier defect. A number of different proteases have been reported to be involved in the desquamation process and to contribute to the barrier function of the skin. Based on their proteolytic domain, proteases are classified into serine, threonine, cysteine, aspartate, metallo, and glutamate proteases. Especially serine proteases (SPs) seem to be involved in epidermal permeability barrier homeostasis as it was reported that SP activity was increased after acute barrier disruption and that blockade by topical SP inhibitors accelerated barrier recovery after acute abrogation [51].

#### 3.1.5. Skin: Adherent junction proteins (Epidermal junction)

The Epidermal junction (EJ) plays a crucial role in the formation and maintenance of epithelial and endothelial barriers. The EJ is a complex basement membrane synthesised by basal keratinocytes and dermal fibroblasts. It plays a fundamental role as a mechanical support for the adhesion of the epidermis to the dermis and regulates the exchanges of metabolic products between these two compartments; besides, it serves as a support for keratinocytes migration during wound healing, and is traversed by various cell types (LC, lymphocytes...) during immunologic and inflammatory processes [52]. Basal keratinocytes are connected to adjacent cells by several types of intercellular junctions (including gap and adherens junctions), the most characteristic of which are the desmosomes. Formation of adherens junctions and desmosomes requires extracellular calcium [53].

### Summary 1: Psoriasis & skin's barrier function

Although the Psoriasis is a multifactorial disease, the studies show that disruption the homeostasis in skin's barrier is the main factor. Several factors interfere of hemostatic establishment in skin. 1) Heterogeneous Structure (lipid/protein) of this barrier that is the main cause of hemostasis. This two compartment structures is renewed continuously and when the barrier function is damaged, it is repaired immediately. 2) Several proteases important for desquamation (skin shedding). 3) The Epidermal junction (EJ) plays a crucial role in the formation and maintenance of epithelial and endothelial barriers. Formation of adherens junctions and desmosomes requires extracellular calcium. Raising the calcium concentration

in the cell culture medium from 0.05 to 1.2mM [53] stimulates keratinocytes to form strong cell-cell adhesions in vitro. 4) In epidermal keratinocytes, both extracellular and intracellular  $Ca^{++}$  is reported to be important to cell differentiation and proliferation.

### 3.2. Skin's sympathetic fibers: Neuroendocrin regulation

The skin is a complex organ containing afferent and efferent neural networks, glands, blood vessels, smooth muscle elements, connective tissues and immune cells, many of which are modulated by catecholamines and glucocorticoid hormones. Glucocorticoids and catecholamines reach skin tissues as circulating hormones and catecholamines are released in skin by projections of the sympathetic nervous system. The sympathetic division of the autonomic nervous system within the skin is supplied by postganglionic fibers of the paravertebral chain ganglia. Catecholamines also are produced locally by keratinocytes [54] [55].

#### 3.2.1. Skin's Beta2 adrenergic receptors ( $\beta$ -ARs)

Beta2 adrenergic receptors were identified in keratinocytes more than 30 years ago, but their function in the epidermis continues to be elucidated [56]. The  $\beta$ -adrenergic ( $\beta$ -ARs) agonists are capable of modulating the two distinct components of keratinocyte directional migration via divergent signaling pathways: 1) migration rate via a cAMP-independent, mitogen-activated-protein-kinase-dependent pathway [57] and 2) galvanotaxis by a cAMP-dependent one. Previous data have shown that both endogenous and exogenous catecholamines act to attenuate the permeability response to various inflammatory mediators via  $\beta$ 1- [58] and  $\beta$ 2-adrenoceptors [59] [60] [61] [62]. Additionally, because  $\beta$ -adrenergic agonists and antagonists modulate both keratinocyte migration and galvanotaxis, they could be valuable tools for controlling reepithelialization and restoration of barrier function, an essential component of the wound healing process.

#### 3.2.2. $\beta$ -ARs signaling cascade

In skin, it has been proposed that epinephrine activates keratinocyte beta2AR to modulate calcium influx and begin the differentiation cascade crucial to the native architecture of the epidermis [54]. The beta2AR desensitizes upon repeated activation through several mechanisms, including downregulation of the number of beta2AR receptors [63] [64]. Indeed, beta2AR expression is more highly expressed at the basal layers of the epidermis and decreases in expression toward the stratum corneum [54], suggesting that epinephrine may be activating the receptor to increase intracellular calcium levels and induce differentiation.

#### 3.2.3. $\beta$ 2 adrenergic receptor ( $\beta$ -ARs): Phosphodiesterase

The cyclic nucleotide phosphodiesterases comprise a group of enzymes that degrade the phosphodiester bond in the second messenger molecules cAMP and cGMP. They regulate the localization, duration, and amplitude of cyclic nucleotide signaling within subcellular domains. The PDE superfamily of enzymes is classified into 11 families, namely PDE1-PDE11, in mammals. PDEs have different substrate specificities. Some are cAMP-selective hydrolases (PDE4, 7

and 8); others are cGMP-selective (PDE5, 6, and 9). A phosphodiesterase type 4 inhibitor, commonly referred to as a PDE4 inhibitor, is a drug used to block the degradative action of phosphodiesterase 4 (PDE4) on cyclic adenosine monophosphate (cAMP). It is a member of the larger family of PDE inhibitors. The PDE4 family of enzymes is the most prevalent PDE in immune cells. They are predominantly responsible for hydrolyzing cAMP within both immune cells and cells in the central nervous system [65]. Since the late 1980s, PDE4 inhibitors have been under investigation as anti-inflammatory therapies against asthma and chronic obstructive pulmonary disease. Due to the broad anti-inflammatory activity of PDE4 inhibitors, their possible use in the treatment of atopic dermatitis and psoriasis was examined.

#### 3.2.4. $\beta_2$ adrenergic receptor ( $\beta$ -ARs): cAMP & Calcium

In psoriasis, keratinocytes within the psoriatic lesions demonstrate a low cAMP response to  $\beta_2$ -AR activation [66]. These findings point to a role for the cutaneous  $\beta_2$ -AR network in maintaining epidermal function and integrity. Moreover, it has also been shown that  $\beta_2$ -AR density in the human epidermis depends on the calcium concentration [67] [54], where undifferentiated keratinocytes express approximately 7500 AR per cell and differentiated keratinocytes express only 2500 receptors underlining an important function for the 2-AR in the differentiation process in human skin [68]. Stimulation of the beta2-AR leads to a transient increase in the keratinocyte intracellular calcium concentration [69] [70] and this likely occurs through several signaling cascades. The mean increase in intracellular calcium of psoriatic keratinocytes was significantly reduced compared with control keratinocytes when intracellular calcium stores were mobilized from endoplasmic reticulum with thapsigargin (an inhibitor of the endoplasmic reticulum  $\text{Ca}^{2+}$  ATPase was used to empty the  $\text{Ca}^{2+}$  stores from endoplasmic reticulum) [71].

#### Summary 2: Psoriasis & $\beta_2$ adrenergic receptor ( $\beta$ -ARs)

It has already been established that the skin is an important peripheral neuro-endocrine-immune organ that is tightly networked to central regulatory systems. These capabilities contribute to the maintenance of peripheral homeostasis. Skin cells and skin as an organ coordinate and/or regulate not only peripheral but also global homeostasis. Activation of the sympathetic system is the most common studied in literature, but other possibilities have to be considered, like impairment of epidermal barrier function, which is already described.  $\beta_2$ -AR density in the human epidermis depends on the calcium concentration and calcium plays an important part in the regulation of proliferation and differentiation of keratinocytes.

### 3.3. Skin's immunity function: Keratinocytes as immune sentinels

Keratinocytes can sense pathogens and mediate immune responses to discriminate between harmless commensal organisms and harmful pathogens. Keratinocytes are continuously in contact with external stimuli and have the capacity to produce several soluble mediators. Pathogen-associated molecular patterns (PAMPs) are recognized, among others, by Toll-like receptors (TLRs). Epidermal keratinocytes express several TLRs, located either on the cell surface (TLR1, TLR2, TLR4, TLR5 and TLR6) or in endosomes (TLR3 and TLR9) [72]. Kerati-



nocytes are also an important source of chemokines and express chemokine receptors, and therefore can modulate an immune response by attracting different cell types into the skin.

### 3.3.1. *Keratinocytes as a secretory organ of cytokines*

Keratinocytes produce a wide array of cytokines, including tumor necrosis factor and interleukin 1 $\alpha$  (IL-1 $\alpha$ ), IL-1 $\beta$ , and IL-6. Disruption of the permeability barrier increases the expression of these cytokines [73] [74]. Studies in mice deficient in these cytokines or their receptors have shown delays in permeability barrier recovery after acute disruption, suggesting that the increased cytokine production facilitates barrier repair [75] [76]. Cytokines are well known to stimulate lipid synthesis and metabolism, and one could anticipate that an increase in epidermal lipids induced by cytokines could facilitate lamellar body formation and permeability barrier recovery [75] [77] [78].

### 3.3.2. *Sympathetic regulation of innate immunity*

Activation of the sympathetic nervous system (noradrenergic nerves and adrenal medulla) exerts a potent anti-inflammatory action upon the innate immune system. Adaptive immune cells are known to express primarily the  $\beta$ 2AR, while innate immune cells appear to express the  $\beta$ 2AR,  $\alpha$ 1AR, and  $\alpha$ 2AR. In the case of adaptive immune responses, however, signals from the brain are transmitted back to the periphery, primarily via activation of the HPA and the SNS [79]. The magnitude of an adaptive immune response appears to be regulated by the release of norepinephrine within the direct vicinity of activated CD4+ T cells and B cells located within lymphoid tissue. The released norepinephrine stimulates the  $\beta$ 2AR expressed on the immune cells to regulate the level of gene activity. The immune cell self-regulated immune response develops and progresses normally with the participation of norepinephrine to regulate the level of the response in an attempt to maintain immune homeostasis [80]. The importance of sympathetic nervous system has been studied in skin disorders. In vitiligo, there is a dysregulation of catecholamine biosynthesis with increased plasma and epidermal noradrenaline levels associated with high numbers of  $\beta$ 2-ARs in differentiating keratinocytes and with a defective calcium uptake in both keratinocytes and melanocytes. In atopic eczema, a point mutation in the  $\beta$ -AR gene could alter the structure and function of the receptor, thereby leading to a low density of receptors on both keratinocytes and peripheral blood lymphocytes [81]. In psoriasis,  $\beta$ -ARs are downregulated, because the increased circulating levels of catecholamines have been observed in psoriatic patients [82] [83] [84] and a 10-fold increase in the expression of the Phenylethanolamine N-methyltransferase (PNMT), the epinephrine synthetic enzyme is also found in basal keratinocytes in involved psoriatic epidermis [85]. It is tempting to propose that long-term exposure to increased levels of catecholamines, in the circulation or locally derived by the keratinocytes themselves, in combination with increased desensitization of beta 2AR in individuals, may predispose to psoriasis. Catecholamines regulate the immune system at regional, local and systemic levels via adrenergic receptors expressed on immune cells [86] and interestingly,  $\beta$ -AR blockers may cause this inflammatory autoimmune skin disease [87] [88].

### 3.3.3. Psoriasis & immune system

Psoriasis is a chronic inflammatory, immune-mediated skin disease, which affects 2%-3% of the population worldwide [89]. Psoriasis was until recently regarded as a T-cell-driven disease with presumed (auto) immune mechanisms as its primary cause [90] [91].

### 3.3.4. Psoriasis & the innate immune system

The innate immune system provides the first line of defense against infection by detecting the presence of invading pathogens in a non-specific manner. Cells of the innate immune system include macrophages, dendritic cell (DC), monocytes, neutrophils, mast cells, natural killer (NK), NKT cells and  $\gamma\delta$  T cells. Innate immune cells recruit additional leukocytes to the site of inflammation by releasing cytokines and chemokines. Many innate immune cells can also directly kill invading pathogens. In addition, the innate immune system plays a crucial role in the initiation and direction of the adaptive immune response. Mechanisms regulating barrier integrity and innate immune responses in the epidermis are important for the maintenance of skin immune homeostasis and the pathogenesis of inflammatory skin diseases [92].

### 3.3.5. Is psoriasis a result of the bidirectional communication between the nervous and immune systems?

The existence of an association between the brain and immunity has been documented. Data show that the nervous and immune systems communicate with one another to maintain immune homeostasis. Activated immune cells secrete cytokines that influence central nervous system activity, which in turn, activates output through the peripheral nervous system to regulate the level of immune cell activity and the subsequent magnitude of an immune response. One key mechanism responsible for such coordination involves the autonomic nervous system (norepinephrine), which serves as the messenger from the mind to the body for all organ systems, including the immune system [93]. The antigen-activated immune system regulates CNS activity through the release of cytokines that bind to receptors located peripherally on the vagus nerve or sympathetic nerve terminals or centrally within the CNS or at the blood-brain barrier. Subsequently, the CNS communicates back to the immune system by activating the SNS or the HPA to release the neurotransmitter norepinephrine or a corticosteroid hormone, respectively. Lymphocytes express receptors that bind norepinephrine and corticosteroids, providing a mechanism for these ligands to activate intracellular signaling pathways, which regulate the level of immune cell activity. A bidirectional communication between the nervous and immune systems is to maintain homeostasis, whether this requires an increase or decrease in immune cell activity. Also, skin-brain axis fMRI studies on patients with psoriasis have revealed that the processing of facial expressions of disgust is significantly impaired in subjects with psoriasis as compared with normal controls in that blood flow in the anterior insular cortex is reduced. This appears to be a coping mechanism [94].

### Summary 3: Psoriasis & neural immunoregulation

The brain and the immune system are the two major adaptive systems of the body. During an immune response the brain and the immune system “talk to each other” and this process is essential for maintaining homeostasis. Two major pathway systems are involved in this cross-

talk: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This overview focuses on the role of SNS in neuroimmune interactions, an area that has received much less attention than the role of HPA axis. Evidence accumulated over the last 20 years suggests that norepinephrine (NE) fulfills the criteria for neurotransmitter/neuromodulator in lymphoid organs. The immune cell self-regulated immune response develops and progresses normally with the participation of norepinephrine to regulate the level of the response in an attempt to maintain immune homeostasis. Catecholamines regulate the immune system at regional, local and systemic levels via adrenergic receptors expressed on immune cells.

### **3.4. Psoriasis comorbidities: Overactivity of sympathetic nervous system**

The more common comorbidities include psoriatic arthritis and anxiety/depression disorder [95] [96]. More recently, psoriasis has also been reported to be associated with metabolic disorders including obesity, dyslipidaemia and diabetes [97] [98]. Moreover, an increased mortality from cardiovascular disease in patients with severe psoriasis has been documented, and psoriasis may confer an independent risk of myocardial infarction especially in young patients [99].

#### *3.4.1. Psoriasis & metabolic syndrome*

Recent studies of epinephrine stimulation at the  $\beta_2$  adrenergic receptor reveal important potential long-term beneficial effects in the metabolic syndrome [100]. The association between psoriasis and metabolic disorders such as obesity, dyslipidemia, and type 2 diabetes has shown that severe psoriasis might be associated with increased mortality rate due to cardiovascular disorders [97] [98] [101].

#### *3.4.2. Psoriasis & cardiovascular disease*

The study by Gelfand et al. in 2006 indicated that patients with psoriasis are more likely than the general population to have diabetes, high cholesterol, and other “traditional” risk factors for heart disease [99] [102]. Recent studies suggest that psoriasis, particularly if severe, may be an independent risk factor for atherosclerosis, myocardial infarction (MI), and stroke. Mehta et al. in 2010 conducted a cohort study using the General Practice Research Database to determine if severe psoriasis patients have an increased risk of cardiovascular (CV) mortality [103].

#### *3.4.3. Shared risk factors*

The existence of shared risk factors between psoriasis and both CV and metabolic conditions has been shown in several epidemiological studies which demonstrate that the same comorbidities are present in psoriasis patients, regardless of age or ethnicity [104] [105].

### **Summary 4: Conclusive remarks**

This review shows that the overactivity of sympathetic nervous system occurs in Psoriasis disease. Abnormalities of  $\beta$ -ARs in their expression, signaling pathway, or in the generation of endogenous catecholamine agonists by keratinocytes have been implicated in the patho-

genesis of cutaneous diseases such as atopic dermatitis, vitiligo and psoriasis. These studies suggest that mainly the localization of Beta2-adrenergic receptors in the epidermis and play an important part in the calcium dynamics and barrier homeostasis of epidermal keratinocytes [106]. The decrease expression of beta2 adrenergic receptor mRNA in involved psoriatic epidermis shown by RT-PCR [107]. Together, these findings suggest that the downregulation of the number of beta adrenergic receptors, rather than an inherent defect in the receptor itself, is the mechanism that is responsible for the reduced beta-adrenergic responsiveness seen in psoriatic epidermis. This decreased response to endogenous agonists then results in a decrease in intracellular cAMP and thus an increase in keratinocyte proliferation. This downregulation can be about overactivity of sympathetic nervous system. Polimorphism studie show that inactivity of Beta2 adrenoceptor is the main cause in this disorder. Beta2 antagonists wreck this condition and reduction of cAMP could cause disruption in skin barrier hemostasis. Freund et al. in 2012 have used boron-based molecules to create novel, competitive, reversible inhibitors of phosphodiesterase 4 (PDE4). The co-crystal structure reveals a binding configuration which is unique compared to classical catechol PDE4 inhibitors, with boron binding to the activated water in the bimetal center. These phenoxybenzoxaboroles can be optimized to generate submicromolar potency enzyme inhibitors, which inhibit TNF- $\alpha$ , IL-2, IFN- $\gamma$ , IL-5 and IL-10 activities in vitro and show safety and efficacy for topical treatment of human psoriasis [108]. However, it may be that currently utilized therapies also work by modifying this signaling pathway. For example, vitamin D, currently used as a topical treatment of psoriasis, has been shown to increase the generation of cAMP in response to betaAR agonists [109] Glucocorticoids, the mainstay of topical therapy for psoriasis, increase both the expression of beta2AR in keratinocytes, and the generation of cAMP in response to agonists [110]. UVB irradiation, another mainstay in the treatment of psoriasis, has been shown to increase beta2AR-mediated cAMP accumulation [111].

## 4. Psoriasis – Medication

Psoriasis is skin disease with unknown etiology. There is no cure for psoriasis, but there are many treatments that can decrease the symptoms and appearance of the disease.

### Treatment options

In general, there are three treatment options for patients with psoriasis: Phototherapy, topical and systemic. A combination of therapies is often recommended. Combining various topical, systemic and light treatments often allows lower doses of each and can result in increased effectiveness.

#### 4.1. Topical treatment: Topical drugs

First line management of adult mild-to-moderate adult plaque psoriasis is with topical treatment, including vitamin D analogues and topical corticosteroids. Topical therapies are indicated for patients whose affected area is < 10% of the body surface area (BSA). Topical vitamin D analogues (VD) and topical steroids (TS) are both widely used topical treatments

for psoriasis. Calcipotriol is a vitamin D analogue that regulates epidermal cell proliferation and differentiation, as well as production and release of pro-inflammatory cytokines. TS present a wide range of biological effects such as inhibition of the recruitment and migration of inflammatory cells, modulation of cytokine synthesis, chemokines release and regulation of DNA synthesis [112]. Topical corticosteroids are available in different potencies and formulations but despite more than 40 years of experience, their use remains mostly based on individual experience. Published guidelines often specify the place of topical steroids within psoriasis treatment strategies [113] [114] [115] but not the efficacy and practical modalities of use. It should be noted that the majority of adverse events seen with topical therapies are cutaneous rather than systemic in nature and that the risk–benefit ratio for these patients is better with topical therapies than with biological [116].

#### **4.2. Light therapy (phototherapy)**

Solar ultraviolet (UV) radiation has been used since ancient times to treat various diseases. This has a scientific background in the fact that a large number of molecules (chromophores) in different layers of the skin interact with and absorb UV. These interactions may have both positive and negative biological implications. Most of the positive effects of solar radiation are mediated via ultraviolet-B (UVB) induced production of vitamin D in skin [117]. In our day's phototherapy is a valuable option in the treatment of many psoriatic and nonpsoriatic conditions, including atopic dermatitis, sclerosing skin conditions such as morphea, scleroderma, vitiligo, and mycosis fungoides [118]. UVB radiation reaches the epidermis and the upper dermis where it is absorbed by DNA, trans-urocanic acid (trans-UCA), and cell membranes [119]. Absorption of UVB by nucleotides leads to the formation of DNA photo-products, primarily pyrimidine dimers. UVB exposure reduces the rate of DNA synthesis. In addition, UVB radiation causes photoisomerization of trans-UCA to cis-UCA which has immunosuppressive effects. Furthermore, UV radiation can affect extranuclear molecular targets (cell surface receptors, kinases, phosphatases, and transcription factors) located in the cytoplasm and in the cell membranes [119]. Keratinocytes, circulating and cutaneous T lymphocytes, monocytes, Langerhans cell, mast cells and fibroblasts are all targeted by narrowband UVB [119]. Narrowband UVB induces also local and systemic immunosuppressive effects which may particularly contribute to the beneficial effects of this light source. UVA radiation penetrates more deeply into the skin than UVB, and reaches not only epidermis, but also dermis with blood vessels affecting dermal dendritic cells, dermal fibroblasts, endothelial cells, mast cells, and granulocytes [120]. UVA radiation is absorbed by pyridine nucleotides (NAD and NADP), riboflavins, porphyrins, pteridines, cobalamins and bilirubin [120]. Porphyrins and riboflavins are photosensitizers. UVA effects are dominated by indirect DNA damage caused by reactive oxygen species such as singlet oxygen. The ability of UVA radiation to cause skin erythema is approximately 103 to 104 times lower than that of UVB. As UVA-1 is even less erythemagenic than broadband UVA much higher doses of UVA-1 can be tolerated by the patients. UVA-1 phototherapy works mainly through induction of apoptosis of skin infiltrating T cells, T-cell depletion and induction of collagenase-1 expression in human dermal fibroblast [121] [122].

**Sunlight:** Already several thousands of years ago sunlight (heliotherapy) was used to treat a variety of skin conditions in Egypt, Greece and Rome [123]. Ultraviolet (UV) light is a wavelength of light in a range too short for the human eye to see.

**UVB phototherapy:** Controlled doses of UVB light from an artificial light source may improve mild to moderate psoriasis symptoms. UVB phototherapy, also called broadband UVB, can be used to treat single patches, widespread psoriasis and psoriasis that resist topical treatments.

**Narrowband UVB therapy:** A newer type of psoriasis treatment, narrowband UVB therapy may be more effective than broadband UVB treatment. It's usually administered two or three times a week until the skin improves, then maintenance may require only weekly sessions.

**Goeckerman therapy:** The combination of UVB treatment and coal tar treatment is known as Goeckerman treatment. The two therapies together are more effective than either alone because coal tar makes skin more receptive to UVB light.

**Photochemotherapy:** Photochemotherapy involves taking a light-sensitizing medication (psoralen) before exposure to UVA light. UVA light penetrates deeper into the skin than does UVB light and psoralen makes the skin more responsive to UVA exposure.

**Excimer laser:** This form of light therapy, used for mild to moderate psoriasis, treats only the involved skin. A controlled beam of UVB light of a specific wavelength is directed to the psoriasis plaques to control scaling and inflammation. Healthy skin surrounding the patches isn't harmed.

**Pulsed dye laser:** Similar to the excimer laser, the pulsed dye laser uses a different form of light to destroy the tiny blood vessels that contribute to psoriasis plaques.

### **Systemic treatment: Oral or injected medications**

Patients with moderate to severe disease generally require systemic agents (e.g. cyclosporin, methotrexate, oral retinoids, fumaric acid esters) to control their disease adequately. The severity of psoriasis traditionally has been evaluated by objective measurement of the extent of the body surface affected and consideration of the subtype of psoriasis, degree of disability, and feasibility of topical therapy [124].

**Retinoids:** Several systemic retinoids (derivatives of vitamin A) have been developed for the treatment of psoriasis. Systemic retinoids are known to have immunosuppressive and anti-inflammatory activity and to modulate epidermal proliferation and differentiation [125]. As mentioned previously, clinical data suggest that combination retinoid-PUVA therapy may be more effective than either treatment alone, and may minimize the toxicities associated with each modality through dose-sparing or independent chemopreventive effects [126] [127].

**Methotrexate (MTX):** It was introduced as a therapy for psoriasis in 1958 (Edmondson et al., 1958). Taken orally, methotrexate helps psoriasis by decreasing the production of skin cells and suppressing inflammation. It may also slow the progression of psoriatic arthritis in some people. Methotrexate is generally well tolerated in low doses. Hepatic fibrosis typically occurs after total cumulative MTX doses of at least 1.5 g. [128]. The risk of

hepatotoxicity may decrease if MTX is given in short courses and rapidly discontinued after clinical improvement [129].

**Cyclosporine:** It was first used (inadvertently) for the treatment of psoriasis in 1979 [130]. Cyclosporine suppresses the immune system and is similar to methotrexate in effectiveness. Major toxicities associated with cyclosporin therapy include nephrotoxicity, hypertension and immunosuppression

**Fumaric acid esters (FAE):** Oral FAE therapy for psoriasis was first reported in 1959. Dimethylfumarate, and its metabolite monomethylfumarate, appear to be the principal active components of Fumaderm®. Treatment with dimethylfumarate and/or monomethylfumarate produces a beneficial shift towards Th2-like cytokine secretion associated with a reduction in peripheral lymphocytes (primarily T cells) [131] and inhibits the proliferation of epidermal keratinocytes in patients with psoriasis. Haematological changes, notably leucopenia, lymphopenia and eosinophilia, are frequently observed during FAE therapy [132].

**Tumour necrosis factor alpha (TNF $\alpha$ ) inhibitors:** It is known that TNF alpha is elevated in both the skin and synovium of psoriatic patients and the effectiveness of its blockade by these two agents in psoriasis and Psoriatic arthritis (PsA) confirms its role in their pathogenesis. TNFi (infliximab, etanercept and adalimumab) revolutionised the treatment of autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD) and plaque psoriasis. Anti-TNF alpha therapy has proved to have disease-reducing activity in PsA and psoriasis and appears to be well tolerated [133]. The widespread use of TNFalpha antagonists in recent years has led to the recognition of paradoxical adverse effects, defined as the onset or exacerbation of disorders that are usually improved by TNFalpha antagonists [134]. During these treatments, cutaneous adverse effects may occur like eczema, lupus, alopecia areata or psoriasis, which represents a paradoxical adverse effect. Then, therapy with TNF  $\alpha$  inhibitors can be associated with paradoxical reactions. They are considered a class effect of these drugs, and their incidence ranges from 1 to 5%, with paradoxical psoriasis (psoriasis vulgaris, palmoplantar pustulosis, scalp psoriasis and their combinations) being most frequently reported [135].

**Phosphodiesterase inhibitors:** Phosphodiesterases play a pivotal role in degrading cyclic nucleotides (cGMP, cAMP), key second messengers in all cells. Particularly cAMP plays an important regulatory role in virtually all the cell types involved in the pathophysiology of allergic and inflammatory diseases including asthma and chronic obstructive pulmonary disease, but also skin diseases including atopic dermatitis and psoriasis. Of the cAMP-degrading PDEs, PDE4 is the one that has been studied most extensively in recent years. PDE4 is abundant, and is the major cAMP-degrading isoenzyme in almost all inflammatory and immune cells. In spite of varied structural classes, highly selective PDE4 inhibitors have the same quality in suppressing several pro-inflammatory mechanisms like cytokine generation and secretion, superoxide generation, degranulation, IgE production, proliferation, histamine generation and chemotaxis [136] [137]. The PDE4 family comprises four genetically distinct subtypes (PDE4 A-D). These subtypes differ with respect to their regulatory behaviour and tissue expression patterns. The search for selec-

tive inhibitors of PDE4 as novel anti-inflammatory drugs has continued for more than 30 years and almost two decades have passed since targeting PDE4 became a focus in the development of novel therapeutics for pulmonary inflammatory diseases. The development of PDE4 inhibitors with PDE4B selectivity has been considered a promising approach because much evidence demonstrates that ablation or inhibition of PDE4B produces a broad spectrum of anti-inflammatory effects while minimizing unwanted side effects [138] [139]. Nazarian et al.'s studies in 2009 showed that AN-2728 (PDE4) is well tolerated and demonstrates significant effects on markers of efficacy, with results that were comparable to positive controls. AN-2728 appears to have good therapeutic potential, although further and larger trials are required to assess the long-term safety and characterize the broad utility of this drug [140]. Nevertheless, the impact of PDE4B-selective inhibitors on inflammatory diseases awaits further clinical trials. Several PDE4B and PDE4D selective inhibitors have been designed and synthesized, and their effects on inflammation are under investigation. Although several compounds have demonstrated therapeutic effects in diseases such as asthma, COPD, atopic dermatitis and psoriasis, none have reached the market. A persistent challenge in the development of PDE4 inhibitors has been drug-induced gastrointestinal adverse effects, such as nausea. Despite the challenges and complications that have been encountered during the development of PDE4 inhibitors, these drugs may provide a genuinely novel class of anti-inflammatory agents, and there are several compounds in development that could fulfill that promise [141]. McCann et al., in 2012 showed oral Apremilast targets PDE4 inhibitor, modulates a wide array of inflammatory mediators involved in psoriasis and psoriatic arthritis, including decreases in the expression of inducible nitric oxide synthase, TNF- $\alpha$ , and interleukin (IL)-23 and increases IL-10. In phase II studies of subjects with psoriasis and psoriatic arthritis, apremilast reversed features of the inflammatory pathophysiology in skin and joints and significantly reduces clinical symptoms. The use of an oral targeted PDE4 inhibitor for chronic inflammatory diseases, like psoriasis and psoriatic arthritis, represents a novel treatment approach that does not target any single mediator, but rather focuses on restoring a balance of pro-inflammatory and anti-inflammatory signals [142]. Now, several PDE4B and PDE4D selective inhibitors have been designed and synthesized, and their effects on inflammation are under investigation.

### **In summary: Managing psoriasis**

Currently, there is no universal standard of care for patients with moderate to severe psoriasis, and the benefits and risks of systemic therapy must be weighed carefully for each patient to ensure optimal management of psoriasis symptoms and minimization of acute and cumulative toxicities [143]. Whether the symptoms are mild, moderate, or severe, the optimal treatment plan is the one the patient is most likely to follow. For those with localized disease, topical therapy is a suitable first choice. Phototherapy is generally the first-line treatment for patients with extensive psoriasis or disabling symptoms. When phototherapy is not feasible or is ineffective, systemic treatments with conventional oral agents or biologics are indicated [144]. Psoriasis is a common skin disorder that needs



long-term management, not only because of its prevalence but also because of the profound impact it can have on quality of life.

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