Chapter 4

Pathophysiology of Psoriasis: Current Concepts

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Additional information is available at the end of the chapter

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1. Introduction

The word 'psoriasis', is derived from the Greek word "psora" meaning "itch" or "scurf" or "rash", although most patients suffering from the condition do not complain of itching. It has been known since ancient times and was originally considered a type of leprosy. For quite some time now, it is one of the most common human skin diseases. Up to a few decades back, psoriasis was considered to be a chronic inflammatory dermatosis with albeit, genetic factors involved in the pathogenesis.

It is now considered a multifactorial disorder that has several factors like genetic predisposition, environmental, immunologically mediated inflammation and several modifying factors including obesity, trauma, infection and a possible deficiency of the active forms of vitamin D3. Different subsets of T lymphocytes, antigen presenting cells (APC's), keratinocytes, Langerhans' cells, macrophages, natural killer cells, an array of Th1 type cytokines, certain growth factors like vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF) etc are involved [1].

Psoriasis was long-considered either a disorder of keratinocyte growth or a chronic inflammation. However, advancement in immunologic techniques and in genetic analyses over the past four decades have resulted in a reappraisal of the pathophysiology involved. Some consider psoriasis as an organ-specific autoimmune disease that is triggered by an activated cellular immune system and is similar to other immune-mediated diseases such as Crohn's disease, rheumatoid arthritis, multiple sclerosis and juvenile-onset diabetes. All of these fit the definition of an autoimmune disease as "a clinical syndrome caused by the activation of T cells and B cells, or both, in the absence of an ongoing infection or other discernable cause" [2]. From the many factors postulated to be involved in the pathophysiology of psoriasis and psoriatic arthritis, it is obvious that the mechanism leading to the development of the symmetrically present discoid plaques with silvery scales, is still not understood clearly. In spite

of the plethora of research studies into its pathogenesis, psoriasis still poses a challenge to the scientific community to, once and for all, establish how and why it occurs and consequently to develop the magic drug to treat it.

2. Role of genetic factors

The idea that psoriasis has a genetic component has been there for over a 100 years but it was Lomholt's classic epidemiologic study in 1963 that really established the genetic component in psoriasis. He investigated more than 11,000 of the 30,000 inhabitants of the Faroe islands and studied psoriatic patients and their unaffected relatives. He found a clear genetic basis as the incidence of psoriasis was much greater amongst first- and second degree relatives of patients with psoriasis. Lomholt however, was unable to establish a particular inheritance pattern [3].

Further studies performed in Sweden and later in Germany supported Lomholt's data. Hellgren published extensive data showing the prevalence of psoriasis to be 7.8% in first degree relatives compared with a prevalence of 3.14% in matched controls, and 1.97% in the overall population [4].

3. Racial & geographic variations

Although, psoriasis occurs worldwide, its prevalence is highest in Scandinavian countries and Northern Europe (3%); in contrast, its prevalence in North America and the UK its prevalence is ~2%, while in Japan its prevalence is ~0.2% of the population. Far more interesting is the fact that it is rare in Native American Indians although it is much more prevalent n the USA where 3 million office visits for psoriasis are made each year, costing over $3 billion [5]. It contributes to approximately 1-5% of all skin disorders in Saudi Arabia [6].

3.1. Establishing a genetic component

Over the past two decades or so, cumulative evidence establishing a substantive role for genetic factors in respect to disease susceptibility and expression is based on family based investigations; population based epidemiological studies, association studies with human leucocyte antigens (HLAs), genome-wide linkage scans, and candidate gene studies within and outside the major histocompatibility complex (MHC) region [7 & 8].

3.2. Concordance

There is marked variation in concordance for monozygotic twins in various studies: 35-73% and the concordance never approaching 100% raises the possibility that genetic factor probably act with environmental ones = 12-14 Fitz. The concordance of psoriasis in monozygotic twins approached 65–72%, versus 15–30% in dizygotic twins. Determination of concordance in older twin pairs from a national twin registry in Denmark revealed nearly 90–100% herit-

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ability [5]. However, in an Australian study the monozygotic twin concordance rate was found to be considerably lower (35% for monozygotic twins and 12% for dizygotic twins), giving an estimated heritability of 80% [9].

3.3. Inheritance pattern

Despite all the work on psoriasis, the inheritance pattern has not been ascertained and psoriasis has by various authors, been considered a single gene disorder with an autosomal dominant inheritance with its variable expressivity and reduced penetrance or an autosomal recessive disorder because of multiple affected individuals in a family. Patients with more dominance of genetic factors have more severe disease and in a younger age group. The risk for a person of developing psoriasis is 41% if both parents affected; 14% if 1 parent is affected, 6% if one sibling is affected and only 2% when no parent or sibling is affected [10].

However, Swanbeck et al presented empirical data that may be of more relevance for genetic counseling. After assessing over 3000 families in which one or both parents had psoriasis, the calculated lifetime risk of getting psoriasis if no parent, one parent, or both parents have psoriasis was found to be 0.04, 0.28, and 0.65, respectively. If there was already one affected child in the family, the corresponding risks were 0.24, 0.51, and 0.83, respectively [11].
Possession of certain HLA class I antigens, particularly HLA-Cw6, is associated with an earlier age of onset and with a positive family history. This finding led to the proposal that two different forms of psoriasis exist: type I psoriasis, with age of onset before 40 years and HLA-associated, and type II, with age of onset after 40 years and lacking HLA associations, although many patients do not fit into this classification. There is no evidence that type I and type II psoriasis respond differently to different therapies. So far, between 10 and 20 chromosome regions have been proposed to harbour psoriasis genes but less than a handful of genes have been identified. This is due, in part, to their low-risk effects and the limitations in the number of patients and families that have been studied. One locus consistently identified in studies of psoriasis is the class I region of the major histocompatibility locus antigen cluster. However, it's low penetrance — about 10% — indicates that other genetic and environmental factors are also involved. The identity of psoriasis susceptibility 1 (*PSORS1*) remains controversial. Although its association with human leukocyte antigen (HLA) Cw6 and psoriasis was reported more than 25 years age, the extensive linkage disequilibrium across the class I region and its complex evolutionary history has made identification of the susceptibility variant(s) very difficult. Genes within this region lying about 160 kilobases telomeric to HLA-C, such as corneodesmosin (*CDSN*) and the α-helical coiled-coil rod (*HCR*), have been proposed as contenders. A consensus is now beginning to emerge that supports the location of *PSORS1* as being closer to the region harboring HLA-C/HLA-B and excluding *CDSN* and *HCR.* However, whether *PSORS1* is a classical MHC allele, or a regulatory variant within this region, has not yet been agreed upon. Other predisposing polygenes might affect the immune system or be involved in keratinocyte differentiation. Common variants in the SLC9A3R1/NAT9 region and loss of a potential RUNX binding site have been described that could potentially affect regulation of the immune synapse [12].PSORS1 is located in the major histocompatibility complex (MHC, chromosome 6p21.3), home of the

HLA) genes.[17] Multiple HLA alleles have been associated with psoriasis, particularly HLA-B13, HLA-B37, HLA-B46, HLA-B57, HLA-Cw1, HLA-Cw6, HLA-DR7, and HLA-DQ9.[10] Many of these alleles are in linkage disequilibrium with HLA-Cw6 (i.e., found together on the same chromosome more often than would be predicted by chance). HLA-Cw6 has consistently demonstrated the highest relative risk for psoriasis in Caucasian populations [13].

4. Immunological factors in psoriasis

Both innate and acquired immune changes are thought to be responsible for the development of psoriatic plaques. Different types of helper T subsets, dendritic cells, plasmacytoid dendritic cells as well as Langerhans cells have been found to play a role in psoriasis. Research had already suggested the role of T cells in psoriasis. Further studies led to the successful use of T-cell immunosuppressant cyclosporin A in the treatment of psoriasis The concept that T cell activation is a key event in psoriasis was further strengthened with the successful use of anti-T cell specific drugs in the form of anti-CD3 and -CD4 monoclonal antibodies in treatment. There is also the possibility that psoriasis may be an organ-specific autoimmune disease with similarities to rheumatoid arthritis and multiple sclerosis and the recent use of so-called “etio-pathogenetic” drugs like methotrexate, and alefacept suggests autoimmunity as a major factor in pathogenesis. [14].

5. Histologic features of psoriasis and their Immunological basis

Light Microscopic features of psoriasis include three predominant groups of changes: i) epidermal hyperplasia ii) inflammatory infiltrate and iii) vascular changes. All of these changes must be explained satisfactorily by any hypothesis, to withstand a critical scrutiny. The epidermal changes include keratinocyte hyperplasia, an attenuated or absent granular cell layer and impaired keratinocyte differentiation and maturation. The combination of these epidermal changes leads to the thick scaly plaques characteristic of psoriasis [15]. The inflammatory infiltrate in the dermis is seen to invade the epidermis (exocytosis) and is mainly composed of Th1 helper T cells as well as the cytotoxic CD8+ cells. In addition there is an infiltration of neutrophils that go on to form the diagnostic histologic features spongiform pustule of Kogoj and Munro microabscess. The third change is vascular and consists of increased number of the vessels in the superficial vascular plexus with tortuosity of vessels and most interestingly venulization of the capillary network so that the vessels become HEV (High Endothelial Venules) [16].

The presence of T cells in the inflammatory infiltrate in psoriatic plaques obviously indicated an immune-mediated or an autoimmune basis for the pathogenesis of psoriasis. The evidence of an immune basis comes from research in the laboratory with experimental animals as well as from clinical research and particularly the significant regression of the disease with the use immunosuppressive agents like cyclosporine which act against T cells.

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6. Mouse models of psoriasis and the immune basis of the disease

There is no animal model where psoriatic lesions may be produced de novo. Initially humanized mouse models in which psoriatic skin was xenografted onto immunodeficient mice was used as a means to study the immune pathways leading to the development and resolution of psoriatic lesions. When non-lesional (normal-looking) skin from psoriatic patients was injected with superantigen-activated leukocytes and subsequently grafted onto these mice, there was development of new lesions on the transplanted skin. This provided strong evidence that T cells play a key role in the pathology of the disease. Later, a new model of xenotransplantation was developed. This entailed non-lesional skin from psoriatic patients being engrafted onto AGR129 mice (lacking T and B cells and with severely impaired NK cell responses). It was seen that the non-lesional skin grafts transplanted onto AGR129 mice spontaneously converted to lesional skin, suggesting that all of the elements required for the development of psoriasis lesions are present in non-lesional skin. This conversion was associated with enhanced proliferation of T cells that are resident in non-lesional skin and increased TNF-α production. All this argued in favor of a dominant role of cytokines and T cells in the pathogenesis indicating an immune or autoimmune basis [17].

Valdmarson et al discovered that an early event in the evolving lesions of guttate psoriasis was an intrepidermal influx of activated T cells that were HLA- DR+, CD4+, while on the other hand, resolving plaques of psoriasis showed a reduced intraepidermal infiltration [18].

However, evidence was produced by other researchers showing that CD8+ T cells were predominant in psoriatic epidermis and that the decrease in the number of these cells was more closely related to resolution of the plaques following treatment. But regardless of the phenotype of these T cells, it was agreed that they were activated and that they were HLA- DR+, expressed the IL-2 receptor CD25 and also secreted cytokines IL-2 and γ-IFN both of which are involved in the activation of T cells [19]. It was also deduced from the presence of activated and proliferating dermal dendritic antigen-presenting cells the presence of activated and proliferating memory T cells, that the signals for these changes were derived from the skin itself [20].

It was also noted by different researchers that the T cells in present in psoriatic plaques of different patterns of psoriasis based on two different groups of cytokines secreted. Mossman for example found that a Th1 profile is indicated by a predominance of IL-2, IL-12 and γ-interferon while a Th2 profile is indicated by the predominance of IL-4, IL-5 and IL-10 [21].

7. Innate immunity in psoriasis

The role of the innate immune system in psoriasis is increasingly seen as important. Neutrophils are found in the stratum corneum of psoriatic skin [22]. Since neutrophils have a short life span (about 3 days), their persistent presence in the epidermis suggests that they are continually recruited. Dendritic cells (DCs) are increased in psoriatic lesions and also appear to play their part in the T-cell response [23 & 24].

Subsets of DCs not usually found in the skin are also observed to be present in psoriatic skin lesions. Plasmacytoid DCs are potent producers of IFN-α, which is thought to be a key cytokine in triggering lesion development, and myeloid DCs, with the ability to secrete TNF-α and inducible nitric oxide synthase, have been also been observed in psoriatic skin. There are increased numbers of mature and activated DCs in psoriatic lesions implying that these cells may be stimulating other aspects of the immune response. Innate immunity is associated with the production of proinflammatory or primary cytokines. The most important of them are IL-1α and TNF-α. The role of IL-1α is unclear as detection in psoriasis lesions has given conflicting results. TNF-α is increased in lesional skin of psoriasis patients and in synovium of patients with psoriatic arthritis [25].

8. Natural Killer (NK) cells and psoriasis

NK cells are lymphocytes that are generally considered to be part of the innate immune system. They are best known for their ability to kill virally infected and cancer cells; however, they also produce a range of cytokines including IFN-γ, TNF-α, and TGF-β. They can be defined phenotypically by the presence of particular surface antigens: either NKp46 or $CD56^{+}CD3^{-}$cells. While the role of NK cells in psoriasis still remains relatively unstudied, there is mounting evidence that these cells may contribute to disease. Ottaviani et al. found that the inflammatory infiltrate into psoriatic skin consisted of 5–8% cells that expressed the NK cell phenotype of $CD56^{+}CD3^{-}$. Most of these were of the $CD56^{bright}$ subset of NK cells. Thought to represent more immature cells, $CD56^{bright}$ cells are less cytotoxic and more proficient at cytokine secretion compared to $CD56^{dim}$ NK cells. The cells present in the infiltrate found by Ottaviani et al. also expressed the activation antigen, CD69, and produced large quantities of IFN-γ *in vitro* in response to IL-2 stimulation. Supernatants from these IL2-stimulated NK cells induced activation of keratinocytes causing upregulation of MHC class I molecules and induction of the expression of ICAM1 and HLA-DR receptors. The keratinocytes were also observed to secrete chemokines that are known to attract NK cells (CXCL10, CCL5, and CCL20) thereby providing a mechanism of NK cell recruitment to the skin [26].

More weight is added to the possibility of a dysregulated immune system playing a role in psoriasis by the impressively good response following treatment with TNF-α neutralizing modalities. For example, one course of infliximab (Remicade®) results in an impressive Psoriasis Activity and Severity Index (PASI) 75 of 80%, meaning that at least 80% of patients have a decrease of at least 75% of their psoriasis skin symptoms [27]

9. Neutrophils and psoriasis

Although psoriasis is a chronic disease, the skin lesions often contain groups of neutrophils within small spongiotic foci in the superficial part of the stratum spinosum of the epidermis as well as intermittently within the stratum corneum. Thus, there is an element of acute in-

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flammation changes in the disease which often persists for decades. Thought to be recruited and subsequently activated by a high gradient of chemotactic factors like chemokines, IL-8 and Gro-a released by the stimulated keratinocytes, and particularly C5a/C5a des-arg produced via the alternative complement pathway. Initially, the presence of neutrophils in psoriatic epidermis was considered a secondary and rather passive phenomenon. However, Terui et al proposed "a neutrophil-associated inflammation-boosting loop" and suggested that this may well explain the localized ''acute'' inflammatory changes scattered over the ''chronic'' psoriatic plaques as well as in the acutely inflamed lesions of pustular psoriasis. They proposed that these neutrophils may actively increase the activation of T cells and that the activated T cells in turn release cytokines to stimulate epidermal keratinocytes to produce IL-8 and C3 that facilitates complement activation as well as PMN accumulation. The neutrophils forming the intra-corneal Munro microabscess may also influence keratinocytes to induce disturbances of epidermal keratinization and underlying hyperproliferation. They also express HLA-DR under the influence of IFN-g and GM-CSF in turn to potentiate T cells. Thus, PMNs infiltrating into the lesional skin may play a pivotal role in eliciting the acute inflammatory and hyperplastic responses in classic psoriatic plaques [28].

10. Acquired immunity & psoriasis

In contrast to neutrophils which are not persistently present in all psoriatic lesions, increased numbers of T lymphocytes are a highly consistent finding in psoriasis biopsies. With immunohistochemical staining, T lymphocytes are found interspersed between keratinocytes throughout the epidermis and in somewhat larger quantities in the dermis. In fact, a significant fraction of dermal ''mononuclear'' inflammatory cells seen in routine sections is due to T cell infiltration. T cell subsets are not uniformly distributed in psoriasis lesions. Epidermal T cells are chiefly CD8+ T cells, with a significant fraction of these cells specialized for homing to epithelia through expression of the integrin aeb7, which binds E-cadherin associated with desmosomes. Dermal T lymphocytes are a mixture of CD4+ and CD8+ cells, with a CD4+ predominance similar to that seen in peripheral blood. Most T cells in skin lesions are memory cells that express cutaneous lymphocyte antigen (CLA), the skin addressin. [27] In contrast, only, 10% of circulating T lymphocytes are CLA+. Hence, CLA+ T cells are impressively and selectively targeted to inflammatory psoriasis lesions [29].

Although a case report in 1979 suggested that cyclosporin A could clear psoriasis, this disease was generally considered to be a primary disorder of keratinocytes in the early eighties. A direct role of T cells in the pathogenesis of psoriasis was first suggested in 1983, and it was independently demonstrated that the eruption of psoriatic skin lesions coincided with epidermal influx of dendritic cells (DCs) and T cells and that resolution of psoriatic lesions during phototherapy was preceded by depletion of T cells, especially from the epidermis. The efficacy of cyclosporin A in psoriasis was subsequently confirmed in two independent studies and trials with anti-CD4 monoclonal antibodies and an interleukin-2-toxin conjugate further supported that psoriasis is a T cell-mediated disease. These T cell-specific treatments resulted in the normalization of the keratinocyte proliferation and epidermal thickening.

The key role of T cells in psoriasis was conclusively demonstrated in 1996 when psoriatic lesions were induced by injecting autologous T cells into uninvolved psoriatic skin transplanted to SCID mice. It was further shown in this model that psoriatic lesions could be induced by injecting purified CD4+ T cells into uninvolved psoriatic skin but no changes were seen when purified CD8+ T cells were injected. Although CD4+ T cells therefore seem to be essential for initiating psoriatic lesions, CD8+ T cells may also have an important role in the pathogenic process as uninvolved psoriatic epidermis contains an increased number of CD8+ T cells that may be able to proliferate locally with the help of IL-7 and IL-15, cytokines that are produced by keratinocytes [30].

11. Pathogenesis of vascular changes in psoriasis

Vascular endothelial growth factor (VEGF) has been implicated in the pathologic angiogenesis observed in psoriasis and other chronic inflammatory skin diseases that are characterized by enhanced expression of VEGF by epidermal keratinocytes and of VEGF receptors by tortuous microvessels in the upper dermis. In addition, the number of mast cells in the upper dermis was significantly increased in transgenic skin. Highly increased leukocyte rolling and adhesion in postcapillary skin venules that were both inhibited after injection of blocking antibodies against E- and P-selectin were also seen in experimental studies. It was also revealed that VEGF is a growth factor specific for blood vessels, but not lymphatic vessels, and that chronic orthotopic overexpression of VEGF in the epidermis is sufficient to induce cardinal features of chronic skin inflammation, providing a molecular link between angiogenesis, mast cell accumulation, and leukocyte recruitment to sites of inflammation.

As early as in the 70s Braverman had done an electron microscopic study of ultrastructure of the capillary loops in the dermal papillae of psoriatic lesions. Normal dermal papillary vessels are arterial in nature but in psoriasis these vessels change to have a venous capillary structure. Following 3 weeks of Goeckerman therapy, the morphology of psoriatic capillary loops changed from venous capillaries to arterial capillaries which are found in the papillae of normal skin. This transformation was observed to begin 48 to 72 hr after the initiation of therapy [31].

Four-fold increase of endothelial microvascular bed is reported in the psoriatic skin but not in normal skin, thus signifying the importance of angiogenesis in psoriasis. Dermal microvascular expansion with abnormal orientation and dilatation of capillaries in the biopsies of the psoriatic skin revealed that the disease was angiogenesis dependent. The keratinocytes in the psoriatic skin lesions were recognized as a source of pro-angiogenic cytokines which induce angiogenesis, namely the vascular endothelial growth factor (VEGF). Other commonly recognized cytokines were endothelial cell stimulating angiogenesis factor (ESAF), tumor necrosis factor-α (TNF-α) and platelet derived growth factors (PDGF) and newly discovered VEGF-C, NGF and vWFr [32].

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Psoriatic skin is also characterized by microvascular hyperpermeability and angioproliferation. The hyperplastic epidermis of psoriatic skin expresses strikingly increased amounts of vascular permeability factor (VPF; vascular endothelial growth factor), a selective endothelial cell mitogen that enhances microvascular permeability. Moreover, two VPF receptors, kdr and flt-1, are overexpressed by papillary dermal microvascular endothelial cells. Transforming growth factor alpha (TGF-alpha), a cytokine that is also overexpressed in psoriatic epidermis, induced VPF gene expression by cultured epidermal keratinocytes. VPF secreted by TGF-alpha-stimulated keratinocytes was bioactive, as demonstrated by its mitogenic effect on dermal microvascular endothelial cells in vitro. Together, these findings suggest that TGF-alpha regulates VPF expression in psoriasis by an autocrine mechanism, leading to vascular hyperpermeability and angiogenesis [33].

12. Role of keratinocytes in the pathogenesis of psoriasis

As mentioned earlier, it is the epidermal hyperplasia along with abnormal maturation of keratinocytes that leads to the development of the thick scaly plaques that are so characteristic of psoriasis. Gottlieb AB suggested that the epidermal changes and the inflammatory infiltrate composed of T cells with interspersed neutrophils may be linked together by the cytokines produced by both keratinocytes and leukocytes. Her proposal was based partly, on the fact that epidermal acanthosis and keratinocyte mitoses were often seen in delayed-type hypersensitivity reactions and after the intradermal injection of gamma interferon. Gamma interferon and its induced proteins have been demonstrated in active psoriatic plaques. Increased levels of the keratinocyte autocrine cytokines, transforming growth factor (TGF)-alpha and interleukin (IL)-6, have been detected in active plaques. The apparent overexpression of IL-6 in hyperplastic psoriatic tissue may explain features of psoriasis that link keratinocyte proliferation with immune activation and tissue inflammation. Both IL-6 and gamma interferon increased TGF-alpha expression in normal cultured keratinocytes. Cytokines produced during immune activation and other inflammatory processes may lead to epidermal hyperplasia. This indicated that keratinocytes have an important role to play in the pathogenesis of the disease [34].

The French worker Julien D also suggested most recently that since psoriasis is a polymorphous disease and is an example of an interaction of susceptibility genes, immunological mechanisms and modifying factors, it is unwise to look at the disease as either as an exclusive disorder of the immune system or in an isolated primitive change of the epithelial or stromal skin cells. According to the author, it is more likely that various combinations of selective abnormalities of these two compartments give rise to the psoriatic phenotype. Indeed, if in one hand T-cells are essential in the development of psoriatic plaques, the role of innate immunity in this process is better recognized, and numerous psoriasis susceptibility genes are linked to immunity, on the other hand some susceptibility factors related to primitive abnormalities of keratinocytes and some of the most recent murine models of psoriasis are based on modifications targeted to the keratinocytes [35].

In an exploration into the biochemical basis of the psoriatic pathway, Grove T, found anomalies in protein expression as the basis for abnormal differentiation and hyperproliferation of the keratinocytes in psoriatic lesions. At least six markers of abnormal keratinocyte differentiation have been found, and all have implications in the pathogenesis of the disease. These include aberrations of keratinocyte transglutaminase type I (TGase K), skin-derived antileukoproteinase (SKALP), migration inhibitory factor-related protein-8 (MRP-8), Involucrin, Filaggrin and keratin expression. Several possible biochemical causes for the overproduction of the keratinocytes have been found in psoriatic skin: epidermal growth factor (EGF), bone morphogenetic protein-6 (BMP-6), transforming growth factor-alpha (TGF-a), ornithine decarboxylase, activating protein (AP1) and mitogen-activated protein kinase (MAPK) [36].

13. Cytokines and chemokines in the pathogenesis of psoriasis

Once T cells are activated following possible encounters with unknown antigen, they release cytokines specific for T-helper type 1 (TH1) cells. These cells in turn, play a key role in the pathogenesis of psoriasis. Both activated CD4+ and CD8+ T lymphocytes produce TH1 cytokines. Key TH1-type cytokines involved in the pathogenesis of psoriasis are IFN-y, interleukin (IL)-2, and TNF-a. IL-2 stimulates T-lymphocyte growth, and IL-2 treatment is associated with psoriasis flares. IFN-y may inhibit apoptosis of keratinocytes by stimulating expression of the anti-apoptotic protein Bcl-x in these cells. This may be the key to the keratinocyte hyperplasia in psoriatic lesions along with TNF-α. The latter is also thought to be responsible for setting forth the release of proinflammatory cytokines from T lymphocytes and macrophages, of chemokines from macrophages, and of adhesion molecules from vascular endothelial cells. In addition, TH1 cytokines cause the release of cytokines from other cells [37]. Although the evidence for the Th1 profile was strong, IFN-γ, TNF-α, and IL-12, but not IL-4, IL-5, or IL-10, were also demonstrated within psoriatic lesions at the mRNA and protein levels. This suggested synergy between IFN-γ and TNF-α with regard to production of adhesion molecules such as ICAM-1, and chemotactic polypeptides such as IL-8 or monocyte chemotactic activating factor-1 (MCAF-1) [38]. Chemokines and chemokine receptors were also discovered to be involved in the immunopathogenesis of psoriasis. These include among many others, CCL17, MIG, CXCL9 and RANTES (CCL5). In addition, nitric oxide is present, which may contribute to an angiogenic tissue reaction, accompanied by many growth factors present at elevated levels within psoriatic plaques, including TGF-α, IGF-1, keratinocyte growth factor (KGF), VEGF, nerve growth factor (NGF), amphiregulin, and IL-20 [39].

14. Environmental factors and psoriasis

With evidence of a genetic background but the with the confounding lack of 100% concordance in monozygotic twin studies and with the eruptions of guttate psoriasis often being

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preceded by a streptococcus pyogenes infection as well as the wealth of studies pointing to immune-mediated (possibly autoimmune-mediated) inflammation, it is no wonder that a complex disease like psoriasis has known to be associated with or possibly precipitated by environmental factors. These environmental trigger factors can be mechanical injury, ultraviolet, and chemical injury; various infections; prescription drug use; psychological stress; smoking; and other factors. The most compelling of these is infection with group A streptococci. Streptococcal throat infections frequently precede outbreaks of guttate psoriasis which can then lead to chronic plaque psoriasis. Furthermore, guttate psoriasis is more common in individuals with a family history of plaque psoriasis. A recent study of 29 patients from the UK revealed that all patients with guttate psoriasis carried the HLA-Cw*0602 allele.These same HLA associations are seen in chronic plaque psoriasis, which may also be aggravated by infection. Patients with psoriasis may also have different clinical features depending on whether they are HLA-Cw6 positive or negative. Besides possibly having a lower age of onset, HLA-Cw*0602 positive patients are reported to have more extensive plaques on their arms, legs, and trunk, more severe disease, higher incidence of the Koebner phenomenon, reported more often that their psoriasis got worse during or after throat infections, and more often had a favorable response to sunlight. In contrast, dystrophic nail changes and psoriatic arthritis are reported to be more common in Cw6-negative patients [40].

Deluvio et al (2006) explored the relationship of Streptococcus pyogenes angina with psoriasis. Using TCR analysis, they tried to identify a link between streptococcal angina and the T cell-mediated autoimmune response in psoriasis. They compared the TCR usage of psoriatic skin lesions, blood, tonsils, and tonsillar T cells fractionated according to the expression of the skin address in "cutaneous lymphocyte-associated Ag" (CLA). They found that clones of T cells in the throat of at least one of their three streptococcal patients were similar to the T cell clones in the psoriatic lesion. Because, after tonsillectomy psoriasis cleared in all three of their patients they concluded that T cells may connect psoriatic inflammation to streptococcal angina. They suggest that the chronic streptococcal immune stimulus within the tonsils could act as a source for pathogenic T cells in poststreptococcal disorders, and they may help to explain why eliminating this source with tonsillectomy may improve streptococcal-induced sequelae [41].

15. Koebner phenomenon

The Koebner phenomenon is defined as 'the development of psoriasis at sites of traumatized skin'. The 'all-or-none principle' means that, if psoriasis occurs in one area of injury, all injured areas develop psoriasis or vice versa. This principle was however, disproved by Kalayciyan et al who did a study on sixty-two patients with psoriasis. The medial aspects of both forearms, devoid of lesions, were pricked using two sets of five 30-gauge needles at an angle of 30 degrees, with 2-cm intervals. On days 14 and 28, the patients' forearms were checked for the presence of a typical psoriatic plaque of white scales on an erythematous papule. On day 28, 45 patients (72.5%) had a negative Koebner response in all prick sites whereas 1 patient (1.6%) had psoriatic papules in 10 out of 10 prick sites. The rest of the pa-

tients (n = 16, 25.8%) had between 1 and 9 papules in number. This suggests that the 'all or none' principle does not work in psoriatic patients with Koebner phenomenon [42].

16. Conclusion

For decades, the ongoing controversy on the molecular nature, choreography and hierarchy of these complex interactions e.g., between epidermal keratinocytes, T cells, neutrophils, endothelial cells and sensory nerves has served as a driving force propelling investigative dermatology to ever-new horizons. There is no question that advances in understanding the cellular immunology and biology of psoriasis, when coupled with the biotechnology revolution and rapid advances derived from human genetic studies of autoimmunity, have enhanced insights into the cause and treatment of psoriasis.

The disease starts with the activation of T lymphocyte with an unknown antigen or gene product. T cell activation depends on its binding with APC (antigen presenting cell). T cells express the cell receptor known as TCR (T cell receptor), which recognizes the peptide being presented by the APC in the grove of MHC complex. The antigen stimulated activation leads to the conversion of naive T-cells into an antigen specific cell, which may develop into a memory cell that circulate in the body. After the activation of T cells, a cascade of cytokines viz. GMCSF (granulocyte macrophage colony stimulating factor), EGF, IL-1, IL-6, IL-8, IL-12, IL-17, IL-23, Fractalkine, TNF-α etc. are secreted by the activated T Cells. Due to effect of these cytokines there is keratinocyte proliferation, neutrophil migration, potentiation of Th-1 type response, angiogenesis, up-regulation of adhesion molecule and epidermal hyperplasia [43].

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