Factors Involved in the Pathogenesis of Psoriasis

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Abstract

Psoriasis is thought to be an autoimmune disease. Both innate and adaptive immune factors are involved in pathogenesis. Innate immune factors include neutrophils, dendritic cells, mast cells and keratinocytes as well as receptors that they express and cytokines they produce, and the coagulation and complement systems. The adaptive immune factors include mainly the T-lymphocyte subsets and their cytokines. Cytokines produced in both arms of the immune response and appear to play a major role in pathogenesis are TNF and IL-17. Innate and adaptive immune responses are interdependent and this review covers both arms of the immune response with respect to what is known about the pathogenesis of psoriasis.

Keywords: innate immunity, adaptive immunity, TNF, IL-17

Psoriasis is a chronic inflammation of the skin. Several types have been defined based on clinical grounds. They include guttate, plaque, inverse, pustular, erythrodermic,
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Arthritis occurs in 5-30% of cases [21]. Since about 65% of patients with the guttate form develop the plaque form later, it is thought that these types appear to be linked to one another [61]. Psoriasis is thought to be an autoimmune disease, but the provoking antigen is yet to be identified. The disease is characterized by elevated scaly lesions due to abnormal proliferation of keratinocytes.

Pre-disposing genetic factors aided by environmental factors are implicated in the disease. Genetics of psoriasis is complex. There are several susceptibility genes implicated in psoriasis and they vary among different ethnic groups (Table 1) [9, 17, 62, 64]. Recently, Jordan et. al. [16] reported that the predisposing genetic factor for plaque and possibly pustular and arthritic psoriasis is due to mutations in the caspase recruitment domain 14 (CARD14) gene. CARD 14 gene codes for a protein that belongs to the membrane-associated guanylate kinase (MAGUK) family. This protein induces the phosphorylation of BCL10, a promoter of apoptosis, and activates the transcription factor, NF-kB. This finding might resolve the genetic complexity of the disease.

Environmental risk factors include viral and bacterial infections such as HIV and streptococcal pharyngitis, high stress levels, medications such as beta blockers, ACE inhibitors, lithium and hydroxychloroquine and obesity have been associated with psoriasis.

The pathogenesis of psoriasis involves both innate and adaptive immune responses followed by inflammation and proliferation of keratinocytes. Factors that contribute to exaggerated or unwanted immune and inflammatory responses in psoriasis will be covered in this review.

I. Innate Immune Response

A. Cells and their receptors

1. Receptors

Innate immune mechanisms thought to be involved in psoriasis pathogenesis include different cell types and humoral factors. Ligand engagement to receptors expressed by these cells usually result in their activation. Three groups of cell receptors that have been studied are Toll-Like Receptors (TLR), nucleotide-binding domain leucine-rich repeat containing receptors (NOD-Like Receptors, NLR) and Protease-Activated Receptors (PAR).

a. Toll-Like Receptors (TLR)

Baker et. al [12] reported that TLR-1, 2 and 5 were expressed by normal keratinocytes and their expression by psoriatic keratinocytes was altered. However, the relevance of such alterations in psoriasis was not determined. De Pita et. al. [55] compared TLR-1 and 2 expressions by keratinocytes obtained from psoriatic patients treated with adalimumab (TNF inhibitor) and patients on systemic conventional therapies. Clinical improvement of patients on adalimumab concurred with recovery
of TLR 1 and 2 on keratinocytes. Calprotectin, an endogenous ligand of TLR-4 is up-regulated in the epidermis and serum in psoriasis. Up-regulation of calprotectin was correlated with disease activity [34]. There was an increase in gene expression of TLR-4 and to a lesser extent TLR-2 on peripheral blood mononuclear cells in patients with psoriasis. Increased expression correlated with increased levels of serum pro-inflammatory cytokine levels and an increased level of calprotectin [68]. Gilliet et al. [42] reported that imiquimod, a TLR-7 agonist, when applied topically, caused aggravation and spreading of psoriatic plaque, accompanied by massive induction of Type 1 interferons in the lesions. Since plasmacytoid dendritic cells (PDCs) are naturally producing Type 1 interferons, they compared the number of PDCs in psoriatic and atopic dermatitis lesions, and normal skin. The number of PDCs were high in psoriatic lesions, low in atopic dermatitis and were absent in normal skin. Lande et al. [63] detected high levels of LL37, a defensin in psoriatic plaques. PDC cannot take up self-DNA. However, in addition to its antimicrobial property LL37 functions as a carrier for self-DNA, delivering it into the endosomal compartment of PDC where it engages TLR-9 expressed by PDC. Morizane et. al. [69] reported that exposure of normal keratinocytes to LL-37 resulted in an increase in the expression of TLR-9. Treatment of keratinocytes with LL-37 followed by a TLR-9 ligand resulted in increased production of Type I interferons. They conclude that keratinocytes recognize and respond to DNA and contribute to the immunological pathogenesis of psoriasis. Furthermore, it was suggested that Type I interferons are involved in the pathogenesis of psoriasis since there was an increased sensitivity of psoriatic T-cells to these cytokines [39]. Another defensin, β-defensin 2 (HBD-2) is up-regulated when TLR-2 and/or 4 are engaged by their ligands. HBD-2 is an endogenous ligand for TLR-4, thus it enhances the production of cytokines by activating both the MyD88 dependent and independent pathways [1, 14, 45]. A synthetic DNA compound, IMO-8400, TLR-7, 8 or 9 antagonists suppressed the occurrence of psoriasis in a mouse model. Psoriasis was induced in C57BL/6 mice by the intradermal injection of IL-23 or LL37 and treated with subcutaneous injection of IMO-8400. The authors suggested that IM-8400 can be considered for the treatment of psoriasis [72].

Most of the afore mentioned reports indicate that excessive production of Type I interferons plays a major role in the pathogenesis of psoriasis. Perhaps monoclonal antibodies to Type I interferons receptors that inhibits Type I interferons activity could be considered for therapy [58]. However, nowadays TNF and IL-17 cytokines are thought to play the major role.

In addition to pro-inflammatory cytokines, nitric oxide is generated when a ligand engages its TLR [28, 41]. Nitric oxide on one hand is involved in killing microorganisms and on the other hand excess production is thought to contribute to hypotension and septic shock [35]. Serum nitric oxide levels in patients with chronic plaque, erythroderma and pustular psoriasis were compared to that in normal controls. It was reported that levels were significantly higher in the patients group. Moreover,
in the chronic plaque group NO levels increased with the duration of the disease [51]. Serum levels of NO in normal controls, psoriatic patients prior to, and after treatment with methotrexate were compared. NO levels in patients prior to treatment were higher than that in controls and patients after treatment. Based on their results the authors suggest that NO is possibly a mediator in the pathogenesis of psoriasis and the use of NO inhibitors might be considered for treatment [52]. Perhaps antimicrobial agents could be used. Gentamycin, tobramycin, imipenem, azathioprim and isoniazid were shown to suppress physiological levels of NO as well as levels induced by LPS in mice. In doing so, both NO levels would be suppressed and possibly infectious agents that provoke the disease would be eliminated [26, 27].

b. NOD-Like Receptors (NLRs)
Muramyl dipeptide, a constituent of the cell wall of both Gram positive and negative bacteria is a ligand for NLR 2 and TLR-2. Ligand engagement to its receptors results in signaling pathways leading to the production of the pro-inflammatory cytokines. Baker et. al. [11] have suggested that the peptidoglycan-containing muramyl peptide is a major etiological factor for psoriasis. The engagement of muramyl peptide to NLR-2 and TLR-2 would probably result in an additive or synergetic effect on production of the pro-inflammatory cytokines.

c. Protease-Activated Receptors (PAR)
Serine proteases including thrombin and trypsin are ligands for PAR. The ligand for PAR 3 and 4 is thrombin and trypsin is a ligand for PAR-2. Upon ligand engagement PARs that are coupled with G-proteins would initiate signal transduction resulting in the transcription of genes, the products of which are involved in the immune response and inflammation [49]. Iwakiri et. al. [37] reported that there was an extensive expression of human airway trypsin-like protease (HAT) in psoriatic epidermis and concluded that HAT might promote PAR-2 mediated IL-8 production leading to the accumulation of inflammatory cells in the epidermal layer of psoriatic lesions. It was shown that a PAR-2 agonist, SLIGKVNH(2) enhanced the production of the 2 chemokines, CXCL1 and CXCL8, their production of which is induced by IL-17. This enhanced effect was suppressed by PAR-2-specific siRNA, cyclosporine A, vitamin D3 and glucocorticosteroids. It is concluded in this study that the production of pro-inflammatory chemokines induced by IL-17 is enhanced by the activation of PAR-2 in keratinocytes [66]. In 2000 Nakanishi-Matsui et. al. [46] reported that PAR-3 was a co-factor for PAR-4 activation by thrombin. According to these authors PAR-3 and PAR-4 are expressed on mouse platelets.

2. Cells
a. Neutrophils
Neutrophils are attracted to psoriatic lesions by the chemokines IL-8 and Gro-α (CXCL1) produced by keratinocytes and C5a generated by activation of the alternative pathway of the complement system. They are located under the stratum
Factors involved in the pathogenesis of psoriasis

Factors involved in the pathogenesis of psoriasis include the corneum of psoriatic lesions [71]. Rahmoun et al. [47] reported that keratinocytes in psoriatic lesions that express on their surface carcinoembryonic antigen related cellular adhesion molecule 1 (CEACAM1) might contribute to the persistence of neutrophils in lesions by delaying their elimination by apoptosis. Neutrophils can produce extracellular traps. These traps are composed of DNA, histones, and antimicrobial peptides. Traps are meant to kill invading microorganisms and prevent tissue damage [50]. Neutrophils are induced to produce traps by IL-23 and IL-1β. During the formation of traps neutrophils release IL-17, a cytokine that plays a major role in psoriasis pathogenesis [10]. The psoriatic condition of a patient improved when he developed neutropenia due to treatment with ticlopidine, an anti-platelet drug. When treatment was terminated and the neutrophil count became normal the psoriatic lesions reappeared [22].

b. Mast cells
There is an increase in number of dermal mast cells in psoriatic lesions and it is thought that they play a role in augmenting the inflammatory process. They are attracted to the lesion by the chemokine, IL-8 that is produced by keratinocytes [73]. Like neutrophils, mast cells are induced to produce extracellular traps by IL-23 and IL-1β, and produce IL-17. The major source of IL-17 is thought to be from neutrophils and mast cells and not Th17 cells [10].

c. Antigen presenting cells (APCs): dendritic cells
Some reports have emphasized the major role of dendritic cells rather than Th1 and Th17 cells in the pathogenesis of psoriasis. There are at least 2 subsets of mature dendritic cells; plasmacytoid (PDC) and myeloid (MDC). Immature and mature PDC are present in psoriatic lesions. They are natural producers of Type I interferons and as mentioned earlier this property is augmented by self-DNA-L37 complexes engaging TLR-9. They also process and present antigens to T-lymphocytes, therefore although they are considered as part of the innate immune system they are needed to generate the adaptive immune response. In an animal model of psoriasis it was demonstrated that inhibiting the ability of PDC to produce Type I interferons prevented T-cell-mediated psoriasis [25]. Clodronate is a non-toxic bisphosphonate. Within liposomes it is taken up by APCs. It is eventually released from the liposome within the APC and induces cell death by apoptosis. Ward et al. [53] reported that the psoriatic skin phenotype in KC-Tie2 mice was reversed by intradermal injection of clodronate liposomes. They showed that mice depleted of APCs resulted in the resolution of the acanthotic skin phenotype, decreased dermal angiogenesis and return to normal (control levels) levels of IL-1α, IL-6, IL-23, TNF and CD8-positive T cell numbers, and modest reduction in γ-interferon and IL-17 levels. They suggested that APC-derived IL-23 and TNF play the major role in maintaining psoriatic skin lesions in the mice and they underscore the role of Th1 and Th17 cells generated in the adaptive immune response. CD91 is a receptor for Heat Shock Protein (HSP)-70. Boyman et al. [54] reported that the majority of CD91-positive cells in human and
mouse psoriatic lesions were TNF- producing dermal dendritic cells. These dendritic cells were in contact with lesional keratinocytes that expressed HSP70. Again, it appears that they are underscoring the role of Th1 and Th17 cells in pathogenesis, in favor of dendritic cells and keratinocytes.

d. Keratinocytes

Keratinocytes are thought to be one of the key players in the pathogenesis of psoriasis. They are the predominant cell type in the epidermis. Their normal function is to form a barrier against foreign intruders such as infectious agents. When activated by intruders they produce chemokines that attract leukocytes to the site. Calcium ions are needed for their normal differentiation and proliferation. It is thought but not confirmed that some transient receptor potential cation channels (TRPC) regulate the entry of calcium ions into cells [40]. Some reports indicated that a defect in calcium intake results in abnormal differentiation and proliferation of keratinocytes. Leunert et. al. [38] reported that there were substantial defects in calcium ion influx in psoriatic keratinocytes that was associated with down regulation of TRPC 1, 4 and 6. They suggested the use of TRPC channel antagonists for the topical treatment of psoriasis. Man et. al. [74] reported that calcium ions upregulated the expression of vascular endothelial growth factor receptor (VEGFR) by psoriatic keratinocytes. Angiogenesis induced by keratinocytes has been implicated in pathogenesis. As reviewed by Creamer et. al. [18] there is an increase in the proliferation of endothelial cells in the microvasculature of psoriatic lesions. Lesional keratinocytes produce vascular endothelial growth factor (VEGF), a cytokine that promotes the proliferation of endothelial cells, and thymidine phosphorylase (TP), an endothelial chemotactic factor. Moreover, there is an upregulation of VEGF receptors (VEGFR) on the lesional psoriatic microvasculature. Keratinocyte-derived VEGF is a potent mitogen for human microvascular endothelial cells. Thus, engagement of VEGF with its receptor on endothelial cells will lead to their proliferation and formation of new vessels. These new vessels will provide the necessary needs for keratinocytes to pursue their replication. Besides the production of new vessels that provide keratinocytes with their needs, keratinocytes are resistant to apoptosis. Mechanism involved in resistance is yet to be determined. One mechanism as reported in a review by Kastelan et. al. [44] is an overexpression of IL-15 by keratinocytes that engages IL-15 receptors (IL15R) expressed in psoriatic epidermis. Another proposed mechanism is that TNF influences apoptosis by regulating the Bax/Bcl-2 ratio. Bcl-2 may block apoptosis and Bax promotes it. Perhaps a mechanism for the inhibition of apoptosis will be related to the recent report by Jordan et, al. [16] who determined that a mutation in CARD 14 is associated with psoriasis. CARD 14 gene codes for a protein that belongs to the membrane-associated guanylate kinase (MAGUK) family. This protein induces the phosphorylation of BCL10, a promoter of apoptosis, and activates the transcription factor, NF-kB.
In summary, most reports on innate cellular mechanisms underscore the role of Th1 and Th17 cells and favor the roles of neutrophils, PDC, mast cells and keratinocytes in the pathogenesis of psoriasis. However, Tsuruta [19] reported that both innate cellular elements and T cells were involved. Activation of NF-kB in either one of the cell types alone did not produce psoriatic lesions while activation in both cell types did.

3. Humoral Factors
   a. Coagulation system
Psoriasis is associated with increased thrombosis and cardiovascular disease [24, 56]. The coagulation system is an integral part of the innate immune system and inflammation. It includes platelet activation/ aggregation and the interplay of two pathways, the intrinsic (Contact Activation) and extrinsic (Tissue Factor) leading to the production of fibrin that strengthens the platelet aggregate. When a vessel is injured, the collagen that is exposed will activate/aggregate the platelets at the site of the injury. The activated/aggregated platelets release from their granules a number of biologically active substances including adenosine phosphate (ADP) and thromboxane A2 that induce further platelet aggregation, serotonin that increases vascular permeability, lysozyme and beta-lysin that are antibacterial agents, prostaglandin E2 and F2α that modulate inflammation, and Platelet Factors III, IV and V that are involved in the extrinsic and intrinsic pathways, initiated simultaneously with platelet activation. In as much as the platelet aggregate is concerned, the fibrin produced strengthens the platelet plug at the site of the vessel injury [7]. Tissue Factor (Thromboplastin) initiates the extrinsic pathway which results in the production of thrombin that in turn converts fibrinogen to fibrin. Thrombin is the most important product of these pathways. It has a number of properties [70] (Table 2). Thrombin is both a procoagulant and an anticoagulant. As a procoagulant it activates platelets and converts fibrinogen to fibrin. As an anticoagulant, with thrombomodulin and protein S it activates protein C. Activated protein C regulates the activity of Factors V and VIII, both of which are needed to produce fibrin. It has been reported that the two cytokines, TNF and IL-17 that play a major role in the pathogenesis of psoriasis, in combination, promote pro-coagulant and pro-thrombotic effect on blood vessels. IL-17 promoted the production of Tissue Factor that is needed for the generation of fibrin, and decreases the level of thrombomodulin that controls the production of FactorV and VIII, both of which are needed for the generation of fibrin [5]. Statins are used to decrease cholesterol levels and hence to cut down on the probability of developing cardiovascular disease. In one study it was demonstrated that atorvastatin (Lipitor) decreased the levels of γ-interferon and IL-4 in mice immunized with egg albumin [13]. However, TNF and IL-17 levels were not determined but perhaps it could be assumed that TNF and IL-23 (propagates Th17 cells that produce IL-17) levels were declined as well, since γ-interferon activates macrophages that will produce a number of cytokines including TNF and IL-23. Hot et. al. [4] reported that Simvastatin or rosuvastatin inhibited the pro-inflammatory
effects of IL-17 and TNF on endothelial cells. Probably, in addition to their effect on cholesterol levels, the inclusion of statins in the therapeutic regimen for psoriatic patients might reduce their lesions.

b. The Complement System
The complement system consists of a group of serum proteins. When activated, a number of substances are generated that are involved in inflammation. There are 4 pathways by which the system can be activated. The classical pathway that is activated by antigen-antibody (IgG or IgM) complexes, activated Factor XII of the coagulation system or Plasmin of the fibrinolytic system, the alternate pathway activated by bacterial LPS or polysaccharide and the lectin pathway activated by bacteria-containing mannan. A 4th pathway is initiated by thrombin that is generated in the coagulation system [43]. Substances produced include chemokines, opsonins, anaphylatoxins, kinins and a lytic factor. Levels of serum C4d, iC3b and Bb fragments generated when the complement system is activated were determined in 16 patients with psoriasis and compared to levels in 12 healthy controls. The levels were significantly higher in the patients group. The highest levels were seen in patients with erythrodermic pustular psoriasis [23]. C3, C4 and Factor B cleavage products were determined in 55 patients with psoriatic arthritis before and after 22 weeks of treatment with entanercept or adalimumab, both are anti-TNF agents. It was concluded that the levels of C3 and C4 fragments were significantly higher in the pre-treated psoriasis group and declined to normal levels following anti-TNF therapy. It was suggested to use complement levels to monitor anti-TNF therapy [48]. The Complement system appears to play a role in the production of excessive amounts of TNF. Activation of the Complement system by the alternate pathway was a prerequisite for the increase in TNF production induced by Streptococcus Group B infection. Serum from C3 deficient mice had a significantly reduced ability to induce release of TNF from macrophages in the presence of Group B Streptococcus. C3 and Factor B, both components of the alternate pathway were needed for the increase in TNF release [57]. Anti-TNF therapy which has been proven to be effective reduces complement activation and it is suggested to use complement inhibitors as therapeutic agents [20].

II. Adaptive Immune Response
A. Antigen and Superantigen
The adaptive immune response is generated getting help from the innate immune response, in particular APCs and cytokines generated. One proposed mechanism states that APCs in the dermis are activated by TNF and process the yet unidentified antigen. The APCs then migrate to the lymph nodes where they activate T-lymphocytes. The activated T lymphocytes (possibly Th1, Th17, Tc, T reg, NKT cells and γ/δ T cells) attach to endothelial cells by the adhesion
molecules LFA-1 expressed on T lymphocytes binding to ICAM-1 expressed on endothelial cells and migrate into dermal and epidermal tissue. The T-cells are again exposed to antigen in the dermal and epidermal tissue and TNF among other cytokines are produced [33].

Superantigens do not need processing or second signals to activate T-cells. One end of the superantigen binds to the MHC-II molecule expressed on the APC at a site other than the groove and from the other end it binds to the lateral surface of the Vβ region of the T-cell antigen receptor (TCR). Intracellular signaling results in proliferation and excessive production of pro-inflammatory cytokines by both APCs and T-lymphocytes, and possibly the activation of self-reactive T-lymphocytes since several T cell clones are generated. Superantigens include microbial products and their constituents. They are believed to be involved in the activation of T lymphocytes in psoriasis. Enterotoxins produced by *Staphylococcus aureus* and pyrogenic exotoxins produced by *Streptococcus sp.* are superantigens. *S. aureus* is found in the nasopharynx of 20 – 40% of normal adults and over the skin surface of 80% of individuals with psoriasis or other forms of dermatitis. Streptococci have been detected on the skin of individuals who later developed impetigo [65]. Rather than the APC carrying a yet non-identified antigen to the lymph nodes, it would carry a superantigen. Another possible mechanism is that the circulating antigen or superantigen activates both APCs and lymphocytes in the lymph nodes and the activated APCs and T lymphocytes migrate to the dermis and epidermis where cytokines are produced. In one study *S. aureus* was isolated from the throat of 11 psoriatic patients. Enterotoxin A and/or C genes were detected by PCR in 9 isolates. None of the isolates from healthy volunteers possessed enterotoxin genes. Moreover, Vβ expansions determined by RT-PCR were detected in all patients [60]. In an extension of this study Streptococcus B pyrogenic toxin gene was detected in five Streptococcus isolates obtained from psoriatic patients [32].

**B. Cells**

1. **Th-lymphocytes (CD4-positive T-lymphocytes).**

There are a number of Th lymphocyte subsets. The subset that is to be activated depends in part on which cytokine is present in abundance and the transcription factor that is activated (Table 3). Th lymphocytes are located mainly in the dermis of lesions. There is a number of Th lymphocyte subsets that have been detect in psoriatic lesions. Earlier reports indicated that activated Th1 cells in psoriatic lesions that produced γ-interferon, TNF and IL-2 were mainly involved in the pathogenesis of psoriasis. Later, other CD4-positive subsets including Th17 and Treg were detected in psoriatic lesions and it was reported that they also are involved in pathogenesis. Ghoreschi et. al. [36] reported that both activated Th1 and Th17 lymphocytes produce a series of pro-inflammatory cytokines including γ-interferon, IL-8, IL-17, and TNF,
all of which contribute to the inflammation seen in psoriasis. Treg lymphocytes usually play the role of a regulator of the immune response and as such inhibit autoimmune responses. However, it has been reported that the Treg lymphocytes in psoriatic lesions are converted into IL-17A producing cells (normally produced by Th17 cells). This conversion was induced by IL-23, a product of activated dendritic cells and macrophages. The transcription factor activated in Treg cells is FOXP3 and that in Th-17 cells is RORγt (Table 3). This differentiation was linked to a decline in FOXP3 and an increase in RORγt expression. Moreover, triple positive cells (IL-17A/FOXP3/CD4+) were detected in the psoriatic lesions [31].

2. Tc-lymphocytes (CD8-positive cells)
They are present mainly in the epidermis of psoriatic lesions and some are found in the dermis. Most reports had indicated that activated Th1 and Th17 cells were the main contributors to the pathogenesis of psoriasis until it was observed that some patients with AIDS who were deficient in CD4+ T-cells had psoriasis. Boyenschen et al. [29] studied the T-cell subsets in psoriatic lesions of patients treated with clobetasol-17 propionate ointment. They reported that all the CD4+ T-cell subsets were reduced following treatment, but CD8+ lymphocytes were not affected. They suggested that the CD8+ cells might be responsible for disease relapse. Ortega et. al. [15] reported that CD8+ cells obtained from psoriatic lesions produce IL-17, TNF, γ-interferon, IL-21 and IL-22. All these cytokines have been reported to be involved in the pathogenesis of psoriasis. Furthermore, Res et. al. [59] reported that IL-22 is produced in addition to IL-17A by CD8+ cells obtained from psoriatic lesions.

3. Natural Killer T cells (NKT) and γδ T-cells.
NKT cells are a heterogeneous group of cells that express markers present on T-lymphocytes and Natural Killer (NK) cells. In addition they express an invariant T cell antigen receptor (TCR) that is limited in diversity. They recognize self and foreign lipids associated with CD1d expressed on APC. They have been implicated in the pathogenesis of psoriasis. Koreck et. al. [6] reported that circulating NKT cells of psoriatic patients were significantly less than that in controls. Following treatment, the level of circulating NKT cells in patients increased but did not reach the level in controls. They conclude that NKT cells might be involved in the development of autoimmune diseases.

Hogan et. al. [2] reported that the psoriasis area and Severity Index improved in 2 psoriatic patients treated with glucagon-like peptide-1 (GLP-1) and clinical improvement was associated with an increase in circulating NKT cells and a decrease in the psoriatic lesions compared to counts prior to treatment. The use of GLP-1 for the treatment of psoriasis was suggested. Zhao et. al. [75] studied the role of protein kinase C-zeta (PKC-zeta) that is involved in the signaling pathway created by TNF
engaging its receptor. This kinase also regulates the expression of CD1d, a molecule involved in presenting antigen to NKT cells. They showed that CD1d and PKC-zeta levels were increased in psoriatic skin. It was suggested by them that the increased CD1d expression would favor CD1d-NKT interactions in psoriatic lesions and since TNF is a major cytokine involved in psoriasis pathogenesis, agents that interfere with PKC-zeta activity could be considered for therapy. On the other hand, Bovenschen et. al. [30] reported that although there was an improvement in patients treated with dimethylfumurate there were no changes in the number of lesional NKT cells. These results might indicate that NKT cells play a minor or no role in the pathogenesis of the disease.

Reports relating γ/δ T-cells to psoriasis are scarce, in one study it was reported that in a mouse model of autoimmune encephalitis and mice infected with Klebsiella pneumoniae, IL-17A was produced mainly by NKT and γ/δ T-cells [3].

4. B-lymphocytes.

B-lymphocytes do not appear to be involved in the pathogenesis of psoriasis. However, based on one report they seem to play a preventive role. Rituximab is a monoclonal antibody directed against CD20 that is expressed by B-lymphocytes. It destroys B-lymphocytes. One of its uses is in the treatment of antibody-mediated autoimmune diseases. Daas et. al. [67] reported that 3 patients with no risk factors for psoriasis developed the disease when they were treated with rituximab. They suggested that B-lymphocytes either regulate T-lymphocytes or a sub-clinical infection provoked the occurrence of the disease.

C. Cytokines

Cytokines involved in the pathogenesis of psoriasis are produced by cells in the innate and adaptive branches of the immune response. They include Type 1 interferons, IL-1β, TNF, IL-17 and γ-interferon. In addition, VEGF and factors that block apoptosis have been implicated in pathogenesis. It appears that the main players in pathogenesis are TNF and IL-17, probably because they are produced in excess by different cell types (Table 4). Pharmaceutical companies have prepared monoclonal antibodies or fusion proteins that are TNF or IL-17 inhibitors. P40 is a polypeptide chain common to IL-12 that is needed for the activation of Th1 cells and IL-23 that is needed for the proliferation of Th17 cells. Monoclonal antibodies produced against p40 (Stelara, Ustekinumab) and monoclonal antibodies produced against TNF (Humira, Adalimumab) are being used to treat moderate to severe psoriasis. The usage of these therapeutic preparations resulted in a variation in results ranging from partial to complete disappearance of lesions. Variations might be related to type and severity of the disease.
III. Conclusion
There are those that advocate innate immune mechanisms and others that advocate adaptive immune mechanisms playing the central role in the pathogenesis of psoriasis. In immunology you cannot delineate one from the other, they are interdependent. In the case of psoriasis it all boils down to one thing; excessive production of cytokines by different cell types, in particular TNF and IL-17. Use of monoclonal antibodies for treatment have some disadvantages; they are expensive, long term treatment is required and they cause serious side effects in some individuals. Attempts are being made to produce small molecules that interfere with stages leading to the disease (Table 5) [8].

Besides the lesions that could be disfiguring and disturbing and in some cases arthritis occurs, one has to consider increased thrombosis and cardiovascular disease that is associated with psoriasis. Perhaps Activated Protein C could be used when needed in such situations. Activated Protein C proteolytically inactivates Factor Va and Factor VIIIa that are needed for the production of fibrin.

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Table 1. Genes associated with psoriasis

<table>
<thead>
<tr>
<th>Genes associated with psoriasis</th>
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<tr>
<td>HLA-Cw6</td>
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<tr>
<td>Three genes involved in IL-23 signaling</td>
</tr>
<tr>
<td>Two genes that regulate NF-kB, il-4 and il-13 genes</td>
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<tr>
<td>Cornified envelope genes (LCE3B and LCE3C)</td>
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<tr>
<td>PSOR 1</td>
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<tr>
<td>PSOR 2 (CARD 14)</td>
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<td>PSOR 3 - 9</td>
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Table 2. Some properties of thrombin

<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Degrades fibrinogen into fibrin + fibrinopeptides</td>
</tr>
<tr>
<td>2</td>
<td>Activates/aggregates platelets</td>
</tr>
<tr>
<td>3</td>
<td>With thrombomodulin and protein S it activates protein C</td>
</tr>
<tr>
<td>4</td>
<td>A ligand for protease-activated receptors PARs 3 and 4</td>
</tr>
<tr>
<td>5</td>
<td>Activates the complement system</td>
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<tr>
<td>6</td>
<td>Chemokine</td>
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Table 3. Development of CD4-positive T-lymphocytes.

<table>
<thead>
<tr>
<th>T-cell</th>
<th>Cytokines needed*</th>
<th>Transcription needed</th>
<th>Factors developed T cell</th>
<th>Cytokines produced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th2</td>
<td>IL-4</td>
<td>GATA 3, IRF4</td>
<td>IL-4, IL-5, IL-9, IL-10, IL-13</td>
<td></td>
</tr>
<tr>
<td>Th9</td>
<td>TGF-β, IL-4</td>
<td>PU.1, IRF4</td>
<td>IL-9, IL-10</td>
<td></td>
</tr>
<tr>
<td>Th17</td>
<td>TGF-β, IL-6, IL-21, IL-23</td>
<td>RORγt, RORcx, IRF4</td>
<td>IL-9, IL-17, IL-21, TNF</td>
<td></td>
</tr>
<tr>
<td>Treg</td>
<td>TGF-β, IL-2</td>
<td>FOXP3</td>
<td>IL-9, IL-10, IL-35, TGF-β</td>
<td></td>
</tr>
<tr>
<td>Th1</td>
<td>IL-12</td>
<td>T-bet</td>
<td>γ-IFN, TNF, IL-2</td>
<td></td>
</tr>
<tr>
<td>Th22</td>
<td>IL-6, TNF</td>
<td>AHR</td>
<td>IL-22, TNF</td>
<td></td>
</tr>
</tbody>
</table>

*Cytokines needed in most part are produced by APCs

Table 4. Some cell types induced to produce TNF, IL-17, IL-12 and IL-23.

<table>
<thead>
<tr>
<th>Cell type that produces</th>
<th>TNF</th>
<th>IL-17</th>
<th>IL-12</th>
<th>IL-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cells</td>
<td>Neutrophils</td>
<td>Dendritic cells</td>
<td>Dendritic cells</td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td>Mast cells</td>
<td>Macrophages</td>
<td>Macrophages</td>
<td></td>
</tr>
<tr>
<td>Th1-lymphocytes</td>
<td>Th-17 lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Th-17 lymphocytes</td>
<td>NKT-lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Th-22 lymphocytes</td>
<td>γ/δ T lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cytotoxic lymphocytes</td>
<td>T-cytotoxic lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Targets of some small molecules patented for the treatment of psoriasis;

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blocking CD80-CD28 interaction/CTLA agonists</td>
</tr>
<tr>
<td>2</td>
<td>CCR5 antagonists</td>
</tr>
<tr>
<td>3</td>
<td>Blocking angiogenesis</td>
</tr>
<tr>
<td>4</td>
<td>Promoting apoptosis; Fas L-Fas agonists, BCL2 antagonants</td>
</tr>
<tr>
<td>5</td>
<td>TLR7 antagonists</td>
</tr>
<tr>
<td>6</td>
<td>IL12/23 antagonists</td>
</tr>
<tr>
<td>7</td>
<td>Inhibitors of JAK3-STAT pathway</td>
</tr>
<tr>
<td>8</td>
<td>Inhibitors of NF-kB pathway</td>
</tr>
</tbody>
</table>

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