Immunological Aspects of Cutaneous Psoriasis: A Review

Nashwa M Selim[1], Zahira M.F El sayed[1], Yasmin Ahmed Fahmy[1], Manal Fawzy[2], Rehab M. Elsaid Tash[1]

[1]Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[2]Dermatology and Venereology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author: Nashwa M Selim

E-mail: nm.selem@medicine.zu.edu.eg, nashwaselim529@gmail.com

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Abstract

Background: Psoriasis is a chronic, hyper proliferative inflammatory skin disease, which is clinically characterized by erythematous and squamous plaques. Psoriasis manifests in several ways: plaque, flexural, guttate, pustular and erythrodermic psoriasis. Overproliferation and aberrant differentiation of epidermal keratinocytes are the key features of psoriasis. Psoriasis is a multifactorial disease with multiple important components such as genetic susceptibility, environmental triggers along with immune dysfunction and skin barrier disruption. It is known to be a T-cell-mediated autoimmune skin disease.

Keywords: Psoriasis, T cells, Innate immunity, Adaptive immunity

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Introduction:

Psoriasis is a chronic, hyper proliferative inflammatory skin disease, which is clinically characterized by erythematous and squamous plaques (1). Worldwide, the incidence of psoriasis varies dramatically, and it seems to be dependent on the climate and genetic heritage of the population. It is less common in the tropics and in dark-skinned individuals. An estimated 60 million people have psoriasis worldwide. Psoriasis affects females more than males especially those with a family history. Its age of onset shows a bimodal distribution with peaks at 30–39 years and 60–69 years in men, and 10 years earlier in women (2). Psoriasis is classified into cutaneous psoriasis and systemic psoriasis. Plaque psoriasis is the most common subtype with elevated areas of more than 1 cm and presents with well-demarcated annular lesions comprising an erythematous base and thick silvery scale. These lesions are found on the extensor surfaces (elbows, knees), scalp, lumbosacral area, and intergluteal cleft (3).

1. Causes and triggers of cutaneous psoriasis

2.1 Genetic factors:

Genetics studies have shown that psoriasis patients have diverse gene polymorphisms related to immune and skin barrier dysfunction (4). More than 30 single nucleotide polymorphisms (SNPs) have been associated with psoriasis risk but only two gene mutations including interleukin 36 receptor antagonist gene (IL36RN) and the caspase recruitment domain 14 gene (CARD14) have been found to induce psoriasis by affecting both the skin and immune system. For example pustular psoriasis shows genetic association with IL36RN gene mutation (5).

Nine chromosomal loci have been discovered to be associated with psoriasis named psoriasis susceptibility loci (PSORS1 to PSORS9). However, the only region that has been identified in the genetic screens of families is the major-histocompatibility complex (MHC) region on chromosome 6 named PSORS. It is responsible for up to 50 % of genetic susceptibility to psoriasis. Multiple Human leukocyte antigens (HLAs) alleles have been associated with psoriasis, particularly HLA-B13, HLA-B37, HLA-B46, HLA-B57, HLA-Cw1, HLA-Cw6, HLA-DR7, and HLA-DQ9 (6).

2.2 Psychogenic factors:

Stress is one of the psychogenic factors that participate in the initiation and exacerbation of psoriasis. It lowers cortisol levels and elevates norepinephrine and epinephrine levels which lead to release of mast cells, disruption of skin barrier function, and upregulation of pro inflammatory cytokines (7).

2.3 Alcohol consumption and smoking:

Alcohol consumption can activate T cells and induce keratinocyte hyper proliferation by stimulating transforming growth factor α (TGFα), IL-6, and interferon gamma (IFN-γ) production (8). Smoking increases reactive oxygen species and decreases the production of antioxidants. Nicotine activates innate immune cells as macrophages, dendritic cells and keratinocytes leading to psoriasis. Cytokines released by these cells can stimulate T lymphocytes and mediate chronic inflammation (9).

2.4 Trauma:

Psoriasis lesions can be triggered by physical injury of the skin in susceptible patients (the koebner response) (10).

2.5 Drugs:

The most widely accepted drugs are β-blockers, lithium, anti-malarial drugs, interferons, imiquimod, angiotensin-converting enzyme inhibitors, terbinafine, tetracycline, nonsteroidal anti-inflammatory drugs, and fibrate drugs. The mechanisms of drug-related psoriasis still remain to be fully elucidated and the molecular mechanisms are complicated. However, some drugs have been known to affect keratinocyte hyperproliferation and the IL-23/IL-17 axis. The symptoms of psoriasis are rarely exacerbated during biologic therapy. However, psoriasis can also be triggered by biologics, and this is recognized as paradoxical reactions. Most of the paradoxical reactions

reported have been associated with the use of either tumor necrosis factor alpha (TNF-α) inhibitors such as infliximab or other biologics targeting IL-23 and IL-17 (11).

2.6 Climatic conditions:

Patients reported improvement in summer and deterioration in winter. Cold and dry conditions sap the natural moisture from the skin and dry skin can cause flares. Also in the winter, most people get very little natural exposure to UV light because they spend so much time indoors or with skin covered up with warm clothing (12).

2.7 Endocrinal factors:

Hypoparathyroidism and Hypocalcemia have been reported to trigger generalized pustular psoriasis as intracellular calcium plays an important part in the regulation of proliferation and differentiation of keratinocyte (13).

2. Pathophysiology

Psoriasis is the best understood autoimmune skin disease that is mediated by both innate and adaptive immune systems cells. The innate immune factors include neutrophils, dendritic cells and keratinocytes as well as their expressed receptors and their produced cytokines. The adaptive immune factors include mainly the T lymphocyte subsets and their cytokines (14).

3.1 Role of innate immunity :

One important feature of psoriasis is abnormal activation of dendritic cell (DC) in the dermis leading to downstream T-cell mediated autoimmune cascade. Plasmacytoid DCs (pDCs) producing type I IFNs appears to be important in this process. PDC- derived IFNs activate conventional DCs which activate autoimmune T cells to move into epidermis. These T cells produce Th17 cytokines, which initiate keratinocyte proliferation and abnormal epidermal differentiation (15).

Natural killer (NK) cells are a subset of $CD56^{+}CD16^{+}$ cells which are able to kill cancer cells and virally infected cells. However, NK cells play a role in psoriasis by releasing cytokines as TNF, IFN-γ and IL-22. Natural killer T (NKT) cells are different group of innate cells which have features of both NK cells and T cells. 3 subsets of NKT have an important role in psoriasis by releasing cytokines as IFN-γ (16).

Neutrophils are found in stratum corneum of psoriatic skin. Circulating neutrophils are recruited to inflammatory sites following inflammatory signals. They are then activated to generate and release large amounts of reactive oxygen species (ROS) in a phenomenon known as respiratory burst. In response to the overproduction of ROS, DCs are stimulated to present antigens to the T cells which results in an imbalance of T helper cell (Th)1 and Th2 cells, stimulation of keratinocytes proliferation, and promotion of angiogenesis (17).

In psoriasis, there is marked proliferation of keratinocytes, leading to thickening of epidermis. There are changes in the differentiation and rapid maturation of keratinocytes. There is absence of granular layer and rete redges become elongated. There is marked angiogenesis and many immune cells infiltrating the skin. The cell cycle is 8 times shorter than normal (36 vs 311 hours) and keratinocytes production in psoriasis is 28 times more than normal epidermis (18).

Upon activation by trigger factors, such as skin trauma and pathogens (i.e., streptococci) or drugs, keratinocytes become a source of innate immune mediators. The latter include cationic antimicrobial peptides (AMP), cytokines of IL-1 family, and chemokines active in the recruitment of leukocyte subpopulations of innate immunity, such as pDC, neutrophils, mast cells, and macrophages. Among AMP, the cathelicidin LL37 has been associated with the development of psoriasis, through its capacity to activate pDC and myeloid DC (mDC), with consequent initiation of the adaptive immune phase. DC drive expansion of T lymphocytes, typically Th17 and Th22 in the initial phase and IFNγ producing T cells during the chronic phase of the disease (19).

3.2 Role of T cell :

Over the past few decades, scientific research has helped us to reveal that innate and adaptive immune cells contribute to the chronic inflammatory pathological process of psoriasis. In particular, dysfunctional helper T cells (Th1, Th17, Th22, and Treg cells) are indispensable factors in psoriasis development. When stimulated by certain triggers, APCs can release pro-inflammatory factors (IL-23, IFN-α and IL-12), which further activate naive T cells and polarize them into distinct helper T cell subsets that produce numerous cytokines, such as TNF, IFN-γ, IL-17 and IL-22, which act on keratinocytes to amplify psoriatic inflammation (20).

IFN-γ induces thickening of epidermis and causes macrophages to release other inflammatory cytokines as TNF-α. TNF-α has a direct inflammation promoting activity so it plays a role in the inflammatory response in psoriasis. It increases the production of pro-inflammatory molecules e.g. IL-1, IL-8, IL-6, Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) , vasoactive intestinal peptides and adhesion molecules (e.g. intercellular adhesion molecule-1 (ICAM-1), P-selectin and E- selectin (21).

The discovery of a new subset of human T cells expressing IL-17 has led to the suggestion that these cells have a major role in psoriasis, as well as other autoimmune epithelial disorders such as Crohn's disease. This IL-17 has contributed to the increased production of keratinocyte-derived antimicrobial (22), which may serve as psoriasis auto antigens and further promote disease progression. In response to DC-derived IL-23 stimulation, Th17 and Th22 cells induce the production of IL-19, IL-36, and IL-22 in the lesional psoriatic skin (23).

IL-36 is expressed in the skin, lung and gut, and has been shown to induce cellular inflammation through the activation of NF-κB and mitogen-activated protein kinase (MAPK) (24). Similarly, IL-19 is expressed in the skin and is strongly regulated by IL-17. In response to IL-17, keratinocytes produce increased amounts of IL-19 and IL-22, which stimulate epidermal hyperproliferation and the upregulation of proinflammatory signals, including antimicrobial peptides. IL17 also activates neutrophils, B cells, monocytes, and macrophages (25).

3.3 Role of angiogenesis :

Psoriasis is characterized by various endothelial vascular changes in the dermal layer as angiogenesis, dilation and high endothelial venule formation. Several angiogenic factors have been identified in psoriatic epidermis, including IL-8, TGF-α, TNF-α, endothelial cell stimulating angiogenesis factor (ESAF), thymidine phosphorylase, and vascular endothelial growth factor (VEGF). VEGF

is an endothelial specific growth factor, potent angiogenic agent, and very potent hyperpermeability factor being 50, 000 times more potent than histamine. VEGF has a potential role in causing aberrant angiogenesis and vascular leakage in upper dermis. It may also contribute to keratinocyte proliferation and epidermal barrier homeostasis. In psoriatic skin, VEGF receptors, VEGFR-1 and VEGFR-2, are detectable and functional in keratinocytes (26).

3.4 Role of streptococcal infection :

An association between streptococcal throat infection and acute guttate psoriasis (an early onset) has been demonstrated in various studies (27). Chronic plaque psoriasis is also exacerbated after these infections. It has been reported that the psoriasis patients have a 10-fold higher frequency of streptococcal throat infections than age-matched controls. Streptococcal antigens are the main activator to immune cells. The molecular mimicry is the main mechanism responsible for T cell activation in the skin due to the highly similar structure of streptococcal M protein and type I keratins (28).

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