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Insights into the Pathogenesis and Treatment of Psoriasis

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1. Introduction

By virtue of the dynamic nature of the scientific process, the description of the pathogenesis of a disease is always a work in progress. Each day new research shapes and refines our understanding of disease processes; an attempt to describe the current scientific understanding provides merely a snapshot of a body of knowledge that is constantly changing. However, characterizing a disease using homeostatic and physiological terms allows the creation of a framework to convey the most up-to-date theories while maintaining the potential for their evolution.

The complex nature of psoriasis can similarly be unveiled through understanding the historical context of our current understanding, examining prevailing hypotheses, and extrapolating horizons for new research. To develop a framework for understanding the pathogenesis of psoriasis and its evolution, the first perception to be changed is the prevalent view of the immune system. The general notion of the immune system as a defense arrangement that protects us against the microorganisms must be changed. This view results from a reduction of the process itself and, as mentioned by Dr. Nelson Vaz, are features derived from the birth of the immunology (Vaz et al., 2006). Immunology, as scientific field, is new in the history of medicine. Immunology developed in a century marked by the First and Second World War and Cold War tension. Hence, many models to exemplify the immunological concepts were simplified and described in relation to war affairs to facilitate the understanding of this science. In this model, if a microorganism attacks a human being, the individual advocates the use of the immune system to counteract. Another simple aspect is the teleology that prevails in the immune science. For example, the T lymphocyte exists to kill cells infected with intracellular parasites. This model full of logic and consequences does not apply in many other areas of medical and non-medical sciences. As such, it is necessary to move to a new approach to describing the relationship between the immune system and environment. In this new paradigm, the

immune system does not react, but rather interacts with the environment, and this contact is made through the skin and mucous membranes. This interaction, causal or not, can have different results. In most cases, there is a balance, imperceptible to other sensory systems, which is characterized by the integrity of what we call health. Thus, homeostasis disorders or imbalances lead to disease. This seems obvious when written, but this search for stability has continuity for the duration of the life of a given organism. If we consider the immune system a sensorial system, it interacts with the modifications of the environment, detects this information of change, and responds with adjustments to maintain homeostasis. You might reduce this view by comparing it to an engine that runs under different types of fuel mixture. It detects the different fuel composition and changes the compression ratio of the cylinder for better efficiency to keep the car moving.

For better observation of this psoriasis pathogenesis, we will make a technical simulation of the immune system in a specific situation. This simulation will cover various aspects of immune response, spanning from the beginning of the inflammatory response, to specific immune response through the development of psoriasis. Here, under a historical perspective and comparing with a chess game, the main objective is to provide insights on the central role of some of these cytokines and immunological pathways in psoriasis pathophysiology. Through this, the aim is to explain some facts of modern immunodermatology that might be useful for clinicians to understand the basis of the immunology of psoriasis. Moreover, an important goal is to dispel some misinformation that might have a negative impact on the use of new immunomodulators and medications available for use by physicians. Treatment basis and therapeutic response experience strongly supports the use of immunomodulators as important modalities in the treatment of psoriatic arthritis and plaque psoriasis. Studies with these therapeutic agents, which act in different steps of the psoriatic inflammatory cascade, have also shown significant efficacy. (Scarpa et al., 2010).

Directly targeting this inflammatory cascade, blocking specific cytokines is a modern treatment option for psoriasis and other autoimmune diseases (Lima et al., 2009b). The rationale for this therapy arises from pathophysiology; in different autoimmune diseases there is an increase in production of proinflammatory cytokines by the immune system. Inflammatory cytokines, like many other cytokines, have an important role in both maintaining health and participating in disease manifestation (Feldmann et al., 1998). This chapter discusses the pivotal role of some of these cytokines in psoriasis pathophysiology, how our understanding of its mechanism evolved, and how blocking the effect of a specific cytokine might substantially improve the disease condition.

2. Pre-biologic immunological history of psoriasis

Psoriasis is a common skin disease with extra-cutaneous manifestations. It is characterized by chronic inflammation of the skin with changes in the maturation of keratinocytes, which is manifested by the hyperproliferation of the epidermis. Moreover, inflammatory reaction can be found in other systems of the same patient. However, this disease is mediated by T lymphocytes, orchestrated by orchestration multigenic and environmental factors. The altered immune system is essential for the inflammation present in both the skin and other organs. A concept of a multi-systemic disorder involving different organs of the patient is

actual and reflects a better understanding of the complex pathophysiology of this disease (Scarpa et al., 2010).

The concept of biological therapy for psoriasis has been derived from its etiopathogenesis. As in a chess game, these new forms of treatment have evolved from an integration of the knowledge of interactions between the immune system cells (pieces) and its cytokines (movements) that initiates the pathologic processes and ultimately leads to the development of the clinical features of psoriasis.

In ancient records, the initial causes of psoriasis were attributed to multiple sources ranging from the divine power to racial associations (Squire, 1873). An unknown infectious organism was indicated as a source of psoriasis in 1927 (Heaney, 1927). Later, its etiology was described as primarily and essentially an epidermal problem, independent of immunologic phenomena (Ingram, 1953). The main objective of cytotoxic drugs developed in the 20th century, such as methotrexate, was to reduce keratinocyte proliferation. Immunological studies on psoriatic patients identified changes in humoral immune reactions as part of the overall problem but not the cause (Aswaq et al., 1960; Harber et al., 1962). Efficacy of the cytotoxic drugs in the late 1960s paved the road for ideas about the role of the immune system in psoriasis (Harris, 1971; Landau et al., 1965). Further investigations in the 1970s revealed the role of immunologic factors in psoriasis. However, the dominant thought was that psoriasis was a disease of faulty epidermopoiesis due to impaired autocontrol mechanisms (Shuster, 1971). Hunter *et al.* wrote "More work on cell turnover and its regulation will give the clue to psoriasis" (Hunter et al., 1974).

Other studies in the 1970s revealed the role of immunologic factors in psoriasis. Histopathologic examination of psoriatic lesions showed a striking resemblance to cellular inflammatory reactions observed in allergic contact dermatitis (Braun-Falco & Christophers, 1974). A selective immunosuppressant effect was the initial hypothesis used to describe the pathological cellular immune response (Krueger et al., 1978). Soon thereafter, the discovery of a soluble factor that played an important role in keratinocyte proliferation helped to form the cytokine-based theory for the induction/maintenance of the inflammatory and proliferative cascades of psoriatic lesions (Krueger & Jederberg, 1980). Subsequently, an integrated theory explaining the etiopathogenesis of psoriasis came into play: in a genetically susceptible patient, immunological factors trigger rapid turnover in the epidermis resulting in development of psoriasis (Champion, 1981).

The fundamental confirmation that any defect of the skin is not sufficient by itself to maintain a psoriatic lesion occurred in the subsequent decade. Some studies confirmed that T cells and soluble factors could stimulate keratinocyte proliferation. Immunophenotyping of psoriatic lesions showed mixed T lymphocyte (TL) cell populations (CD4 and CD8) and Langerhans cells (LCs) distinct from normal skin (Bos et al., 1983). This cellular infiltrate changed with topical or systemic treatment (Baker et al., 1985; Bos & Krieg, 1985). In another study, failure of plasma exchange and leukapheresis ruled out the major participation of humoral immune system in the pathogenesis of psoriasis (Lieden & Skogh, 1986). Thus, the cellular arm of the immune system was implicated in psoriasis for the first time during the 1980s (Valdimarsson et al., 1986).

During the 1990s, research on immunopathogenesis of psoriasis thus focused on the cellular and the cytokine components of the immune system. Researchers observed that an influx of

activated T lymphocytes, mainly CD4+, HLA-DR+, Interleukin (IL)-2 receptor - CD25+ T cells, was one of the earliest events of psoriasis (Schlaak et al., 1994). Based on Mosmman and Coffman's publication (Mosmann et al., 1986), these T lymphocytes were classified as T helper (Th) type 1 cytokine producers (Th1) (Austin et al., 1999). They produce Interferon (IFN)-γ, IL-2, and Tumor Necrosis Factor (TNF)-α cytokines and implied that a cellular type 1 reaction was responsible for psoriasis (Figure 1). The observation of the historical evolution of the extra-cutaneous manifestations of psoriasis and their pathogenesis confirms the idea of a multi-organ disease with complex immunological pathways (Scarpa et al., 2010).

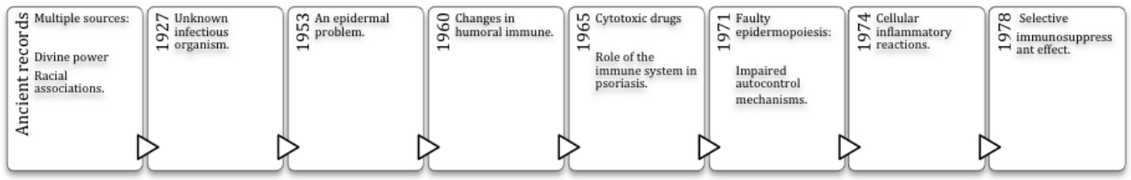

Fig. 1. Time line of development of psoriasis pathophysiology: From unknown by epidermal problem until Immunological disease.

3. Psoriasis: Many pieces and movements on a complex chessboard

Psoriasis plaque is induced and maintained by multiple interactions between cells of the skin and immune system. It seems that the pathogenesis of psoriasis could involve a stage of cellular infiltration resulting in epidermal (keratinocyte) proliferation. Each inflammatory pathway (IL-12/Th1, IL-23/Th17, and IL-22/Th22) has its impact on psoriasis development (Kagami et al., 2010). The different pathways are based on the fact that T helper cells can be skewed towards mutually exclusive subtypes on the basis of the cytokine environment (Abdi, 2002; Vanaudenaerde et al., 2010). The process of T lymphocyte reactivation results from interaction of T cells with the resident antigen presenting cells (APCs) found in plaque psoriasis, which in turn determines the cytokine environment and Th1/Th17/Th22 pathway.

The primary etiopathogenesis of an autoimmune disease, or the activation of Th1/Th17/Th22 pathways, is the dysregulation of immune system activation since the development of autoreactive lymphocytes occurs in the same basic manner as lymphocyte activation. The understanding of this process or processes is very important to maintain the balance of the normal performance of the immune system. Briefly, it is comparable to the process to find the moment where one player lost the chess game based on the retroactive analysis of his moves. Cytokines are the possible moves of different pieces of the game. Many pieces can produce the same movement but with different results. The moves are the key players in generating/establishment of a specific immune system reaction. Therefore, blocking cytokines that maintain autoimmune activity has become one the most successful strategies for autoimmunity therapy. A new balance can be established with the removal of a key piece or blocking of a lethal move so that the critical players are removed from the chessboard of an autoimmune response.

As with any other disease involving the immune system, psoriatic manifestation begins with Antigen-Presenting Cells (APC) activation by an unknown trigger. Different factors

including infections, trauma, medications, and emotional stress can initiate the initial phase of the disease. Such factors can activate keratinocytes to release cytokines such as IL-1 and TNF-α, initiating the effector phase of psoriasis by activating resident skin macrophages and Dendritic Cells (DCs). DCs migrate to the regional lymph node, which initiates T lymphocyte activation in response to the stimuli. This is part of the working model of the immune synapse of T cells in psoriasis, integrating T cell signaling pathways in autoimmunity (Nickoloff & Nestle, 2004). This association leads to the production of IL-12/Th1/IFN-γ pathway. Many molecules in the plasma membrane of both cells, other than the Major Histocompatibility Complex (MHC) and T Cell Receptor (TCR), are involved in this phase and can be used as a target molecule for the treatment of psoriasis. The most important molecules are ICAM-1, LFA-3, and CD80/CD86 in the DC and LFA-1, CD2, and CD28 in the T cell, respectively. Alefacept, a fusion protein used for psoriasis treatment, blocks T cells activation by interfering with CD2 on the T cell membrane, thereby blocking the costimulatory molecule LFA-3/CD2 interaction (Kraan et al., 2002). Furthermore, it has recently been discovered that IL-27 suppressed macrophage responses to TNF-α and IL-1β, thus identifying an anti-inflammatory function of IL-27 (Kalliolias et al., 2010).

Continuing the evolving complex immunological chess game, the activated T lymphocyte Th1 cytokine producers leave the lymph node and migrate to the skin where cytokines like TNF-α, produced by keratinocytes and activated DCs, facilitate T lymphocyte diapedesis into the dermis and epidermis (Philipp et al., 2006). The TNF-α induces the skin immune cell infiltration by inducing chemokines and upregulating adhesion molecules on the endothelial cells of dermal vessels. Adhesion molecules such as CLA and LFA-1 on the T lymphocyte membrane and E-selectin and ICAM-1 on the endothelial cell membrane are involved in this process. Efalizumab, a Humanized Anti-CD11a, Anti-LFA-1 molecule has been used in psoriasis treatment by blocking the TL migration to the skin (Sobell et al., 2009). In summary, dendritic cells and effector T-cells are important in the development of the psoriastic lesion, and cytokines produced by these cells stimulate keratinocytes to proliferate and increase the migration of inflammatory cells into the skin, promoting epidermal hyperplasia and inflammation (Monteleone, G. et al., 2011).

3.1 The chessboard: The skin influence on psoriasis development

The primary cause of psoriasis was not found. Factors such as genetics and environmental exposure are now recognized to play a role in psoriasis development. Certainly, autoimmunity does not appear the only and necessary component to the development of psoriasis. However, psoriasis is a manifestation of skin immune reactions. Inflammation is a key feature of pathogenesis, with all inflammatory cell types implicated in psoriasis pathology by multiple interactions between cells of the skin or from other organs and immune system. Nonetheless, the etiology of psoriasis as an epidermal problem or a disease of faulty epidermopoiesis due to impaired autocontrol mechanisms is not completely wrong. Keratinocyte-derived inflammatory molecules amplificate skin immune responses associated with psoriasis, and contribute to the disease process and clinical phenotype (Albanesi & Pastore, 2010). Psoriatic keratinocytes respond aberrantly to cytokines and show altered intracellular signaling pathways (Endo et al., 2006).

Heterogeneous functions of other skin resident cells, such as fibroblasts and endothelial cells, may also contribute to the pathogenesis of psoriasis (Albanesi et al., 2007).

Furthermore, leukocytes that infiltrate skin lesions have been shown to be involved in the pathogenesis of this disease (Chen et al., 2010). Despite parallels to the chicken and egg causality dilemma, all of these accounts for what later clinicians observe in patients suffering from psoriasis.

4. The initial biologic treatments for psoriasis and implications on the understanding of immunological mechanism of psoriasis

Psoriasis was defined as Th1 type of disease based on the early understanding of the T helper subsets. The initial belief was that infiltrating T cell subpopulations derived from the draining lymph node regulated the development of the inflammatory responses in the skin by producing IFN-γ and TNF-α (Albanesi et al., 2005). The Th1-derived cytokines produced by these infiltrating Th1 favors further Th1 cell access, upregulates keratinocyte chemokine production, and supports dermal DC myeloid type (DC11c+) activation. In response to this cytokine activation, keratinocytes and other cells produce a plethora of immune mediators, which induce and amplify inflammatory responses in the skin (Lowes et al., 2007).

As a result, two logical biologic therapeutic approaches were tested: one was the administration of counter regulatory type 2 cytokines and the second was the blocking of type 1 cytokines. The use of monoclonal antibodies or fusion proteins to neutralize cytokines started to be used on a large scale because of their efficacy and practicality.

These studies have proved to be a useful biological model and test ground for evaluation of the skin immune system and psoriasis. Although these drugs were not initially developed in the treatment of psoriasis, but rather in rheumatoid arthritis and Crohn's disease, the observation that Crohn's disease patients with psoriasis were improving while on anti-TNF therapy profoundly influenced the studies that were to come (Schon & Boehncke, 2005).

Although clinical response to anti-TNF suggested a role for Th1 cells in psoriasis, evidence coming from other studies demonstrated that Th1/Th2 paradigm and key role of TNF were not sufficient to explain the full pathogenesis of psoriasis. At this point some academic resistance to an immunological pathogenesis for psoriasis was raised (Nickoloff et al., 2000). However, the main interpretation was that an important piece of the immunological cytokine puzzle was missing. Many other pieces would be involved in such a complex game.

5. The IL-12/23 and its role in the immunopathogenesis psoriasis

The initial quest for the missing cytokines was the search for pathway inducers. Researchers first noted that IL-12 is crucial for Th1-cell differentiation (Okamura et al., 1995). IL-12 signaling via its receptor activates Stat4 (signal transducer and activator of transcription 4), which upregulates IFN-γ. IFN-γ activates Stat1, which enhance T-bet (T-box expressed in T cells), the leading TH1 transcription factor, further enhancing IFN- γ production and downregulating IL-4 and IL-5 expression (Biedermann et al., 2004). IFN-γ mediates many of the pro-inflammatory activities of IL-12. Phagocytes and Dendritic Cells (DCs) are the main producers of IL-12 in response to microbial stimulation (Macatonia et al., 1995), and this relationship links innate resistance and adaptive immunity. The main function of IL-12 is resistance to infections with bacteria and intracellular parasites. However, it plays an

important role in the Th1 response that sustains organ-specific autoimmunity (Trinchieri, 1998). The use of anti-IL-12 mAb (monoclonal antibody) in an experimental model of psoriasis also suggested the therapeutic value of blocking IL-12 in humans (Hong et al., 2001), although side effects of the drug limited further development in this area.

For many years, the IL-12-dependent Th1 cells were thought to be essential for the induction of autoimmunity. However, during the Th1/Th2 paradigm studies, an IFN-γ-independent mechanism responsible for the pathogenesis of many inflammatory diseases and psoriasis was found (Hong et al., 1999). IL-12 and IL-23, as discovered previously from human DNA sequence information, share the subunit p40 (Monteleone, I. et al., 2009). The use of anti-IL-12/23p40 and anti-IFN mAb ultimately established at least part of the solution to the riddle. Only neutralization of p40, but not of IFN-γ, ameliorated chronic inflammatory reactions. This finding suggested that the latter cytokine, IL-23, accounted for the IFN-γ-independent mechanism of inflammation.

Identified from human DNA sequence information, IL-23, like IL-12, is also a heterodimeric cytokine composed of the same subunit p40 paired with the unique p19 (Oppmann et al., 2000). It has been reported that IL-12 and IL-23 are up-regulated in psoriatic skin (Lee et al., 2004). Human studies with anti-IL-12p40 have shown that this treatment not only ameliorates psoriasis, but also down-regulates type 1 cytokines and IL-12/IL-23 in lesional skin (Toichi et al., 2006). Besides sharing the subunit p40 and signaling through similar receptors, IL-23 and IL-12 are responsible for driving different T-cell subsets. Moreover, presence of abundant IL-23$^+$ dendritic cells as well as elevated mRNA expression for both subunits of IL-23 (IL-23p19 and IL-23p40) in psoriatic lesions supports the role of IL-23 in the pathogenesis of psoriasis (Lee et al., 2004; Lillis et al., 2010; Piskin et al., 2006; Wilson et al., 2007). Genetic studies have revealed that polymorphisms in IL-23p19, IL-12/23p40, and IL-23R are associated with increased risk of psoriasis (Capon et al., 2007; Cargill et al., 2007; Nair et al., 2009). Furthermore, in an animal xenograft model of psoriasis, Tonel G *et al* showed that treatment with anti human IL-23 mAb causes statistically significant reduction of acanthosis and papillomatosis index in grafts of mice in comparison to isotype controlled mice. Moreover, they found comparable efficacy of anti human IL-23 mAb with anti TNF-α (infliximab) in blocking the development of psoriasis. They also showed a significant decrease in CD3+ T cells mainly in the epidermis of mice treated with anti human IL-23 mAb in comparison to control mice (Tonel et al., 2010).

IL-23 could also mediate and sustain late-stage chronic inflammation by the production of IL-17 by Th17 (Aggarwal et al., 2003). IL-23 plays an important role as a central growth factor (Korn et al., 2009; Miossec et al., 2009; Romagnani et al., 2009). In presence of TGF-β and IL-6, IL-23 helps in development of Th17 cells whereas TGF-β is inhibitory to production of IL-22 (Ghoreschi et al., 2010; Volpe et al., 2008; Zheng et al., 2007) (Figure 2).

The IL-23/Th17/IL-17 immune axis was initially elucidated when IL-17 gene expression was induced by *B. burgdorferi* independent of IL-12 (Infante-Duarte et al., 2000). The IL-17–producing CD4+ T cells distinct from those producing either IL-4 or IFN-γ were called Th17 (Harrington et al., 2005). Patients with psoriasis have increased Th17 cells as well as increased expression of mRNA for Th17 cytokines (IL-17A; IL-17F; TNF-α; IL-21 and IL-22) and chemokines (CCL20) (Boniface et al., 2007; Harper et al., 2009; Johansen et al., 2009; Lowes et al., 2008; Zaba et al., 2007). In psoriasis, Th17 cytokine IL-17A mainly induces cytokine and chemokine production by keratinocytes (Albanesi et al., 2000; Harper et al.,

2009; Nograles et al., 2008), whereas IL-22 induces proliferation of keratinocytes and production of antimicrobial peptides by keratinocytes (Liang et al., 2006; Sa et al., 2007; Wolk et al., 2006; Zheng et al., 2007). The role of IL-23 and IL-17 in psoriasis was further substantiated in some animal studies with recombinant IL-23 and anti IL-17A. In wild type (WT) mice, injection of recombinant murine (rm) IL-23 induces epidermal hyperplasia (Chan et al., 2006; Kopp et al., 2003), whereas, in IL-17 -/- mice showed less epidermal hyperplasia after repeated injection of rmIL-23. A recent publication by Rizzo et al showed that WT mice do not show epidermal hyperplasia to injection of rmIL-23 if they were treated with anti IL-17A antibodies (Rizzo et al., 2011). A redundant cytokine model has emerged as the evolving explanation for psoriasis pathogenesis. It is based on the IL-12/Th1/ IFN-γ - TNF-α and the IL-23/Th17/IL-17 immune pathways (Figure 3). The effectiveness of the anti-TNF treatment of psoriasis validated the first axis. The efficacy of anti-p40 (anti-IL12/23) treatment confirms the other (Nestle et al., 2009).

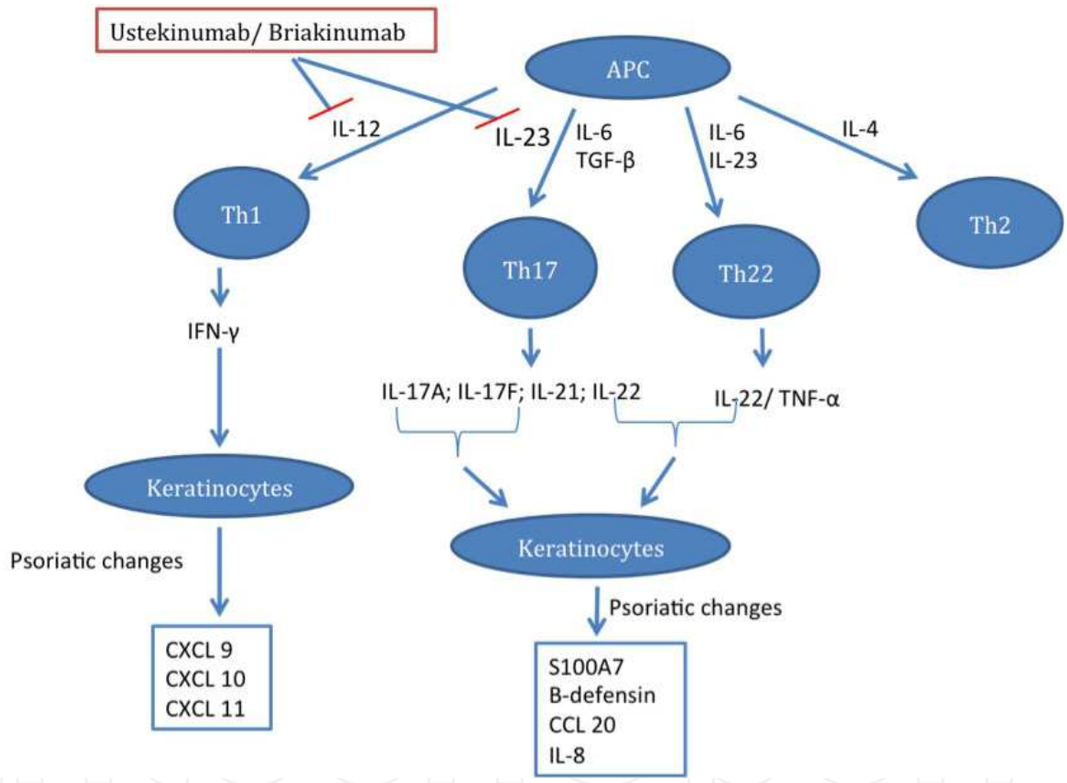

Fig. 2. The pivotal role of some of IL-12 and IL-23 in psoriasis etiopathogenesis: How blocking the effects of these cytokines substantially improve the disease condition.

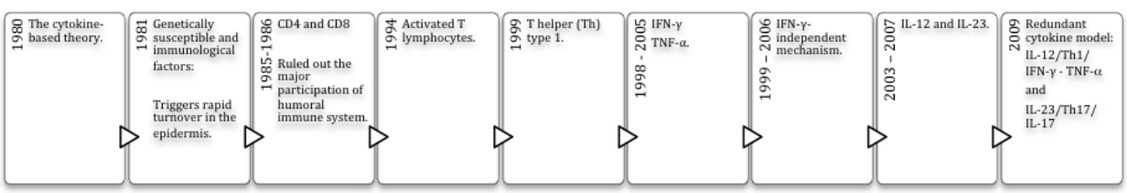

Fig. 3. Time line of development of psoriasis pathophysiology: From complex Immunological disease by genetic participation until recent advances.

6. Selective IL-23/Th17/IL-17 immune axis inhibition

IL-23 favors the proliferation of the Th17 subtype and consequent production of IL-22 and IL-6 that stimulates the proliferation of keratinocytes. IL-17 favors infiltration of neutrophils into the skin forming the typical Munro's micro-abscesses with some participation of IL-22 (Watanabe et al., 2009).

Studies have demonstrated that anti-p40 (anti-IL-12/23) treatment is highly efficacious for psoriasis. Ustekinumab anti IL-12/23 antibody showed its efficacy and safety in three phase III trials recruiting 2899 patients. From two placebo controlled trials, PHOENIX 1 and PHOENIX 2, ustekinumab showed its efficacy in ameliorating psoriatic plaques, pruritus, and nail psoriasis (Yeilding et al., 2011). (Table 1).

PASI scores	Placebo [n = 410]	Ustekinumab (45 mg) [n = 409]	Ustekinumab (90 mg) [n = 411]
PASI 50	41 (10%)	342 (83.6%)*	367 (89.3%)*
PASI 75	15 (3.7%)	273 (66.7%)*	311 (75.7%)*
PASI 90	3 (0.7%)	173 (42.3%)*	209 (50.9%)*
Physician's global assessment (Cleared)	0 (0.0%)	93 (22.7%)*	115 (28.0%)*
Physician's global assessment (Cleared or minimal)	20 (4.9%)	278 (68%)*	302 (73.5%)*
Physician's global assessment (marked or severe)	148 (36.1%)	15 (3.7%)*	10 (2.4%)*

* P <0.001 Adapted from: Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008; 371(9625):1675-1684.

Table 1. Clinical improvement at week 12 (PHOENIX II)

Remarkably, in a phase II multicenter, randomized, double-blind, placebo-controlled trial briakinumab, another human monoclonal anti-IL-12/23 antibody, 90-93% of subjects in 4 dosing groups were able to achieve a PASI 75 (Lima et al., 2009a). This finding alone confirms the centrality of this pathway because these levels of efficacy have not been previously seen in studies with other agents (Leonardi et al., 2008). Safety data for both agents is limited, but to date has been favorable.

One issue with anti-p40 therapy is that it inhibits both the classical IL-12/Th1/IFN-γ and IL-23/Th17/IL-17 immune pathways. IL-12 and IL-23 are related cytokines with differences in their biological activities. After binding to their receptors, different intracellular transcription complexes are activated (Parham et al., 2002). IL-12 predominantly acts on naïve T cells and initiates the TH1 response. In contrast, IL-23 primarily affects memory T cells and expands the initiated Th1 inflammatory response by Th17 activity and maintains

an adequate memory pool by compromising memory T cells (Oppmann et al., 2000; Parham et al., 2002; Trinchieri et al., 2003). Experimental studies suggest that IL-23/Th17/IL-17 immune axis blocking is sufficient to treat autoimmune inflammation (Monteleone, I. et al., 2009).

Another way to block both pathways is the immunoregulatory role of IFN-γ. It is well-known that the administration of anti-IFN-γ induces exacerbation of Experimental Autoimmune Encephalomyelitis (EAE) (Becher et al., 2002). One possible explanation is the inhibition of IL-12/Th1/IFN-γ axis may destroy the regulatory role of IFN-γ during chronic inflammation. TNF-α, like INF-γ, has a regulatory role in the immune system (Liu et al., 1998). This might explain the observation that anti-TNF therapies can induce psoriasis and other autoimmune diseases in some patients (Ramos-Casals et al., 2008).

An increase in efficacy and reduction of adverse events are the main drivers for new therapies. Infections, one type of adverse event, usually increase in patients receiving anti-cytokine therapy (Dinarello, 2003). Studies with anti-IL-23 therapy will require surveillance for the development of opportunistic infections. Reports from patients with IL-12 and/or IL-23 cytokine deficiency syndromes alert to these potential infections in individuals under anti-IL-23 therapy. Invasive salmonellosis and mycobacterial diseases were present more often in patients with IL-12/IL-23 deficiency indicating that immunity against these microorganisms appears to be dependent of IL-12 and/or IL-23 (MacLennan et al., 2004). However, antibodies against IL-12 and IL-23 may not cause a complete inactivity of these cytokines in a clinical scenario. For example, an experimental study showed that IL-23 plays a role in host defense against *P. carinii*, but it is not an essential one (Rudner et al., 2007). Clinical studies with anti-IL-12/23 treatment thus far have not increased the risk of non opportunistic or opportunistic infections (Shear et al., 2008). A recent study showed that blocking IL-23 with monoclonal antibodies during BCG infection does not appear to affect the bacterial burden in immunocompetent mice. In contrast, blocking TNF-α or both IL-23 and IL-12 with anti-p40 dramatically enhances mycobacterial growth. From this study, antibody blockade of IL-23 alone rather than IL-12 might be preferable in patients who have been, or may be, exposed to mycobacterial infection (Chackerian et al., 2006).

7. A new piece and a new move

As previously mentioned, the IL-23 favors the proliferation of the Th17 and consequent production of IL-22. IL-22 mRNA presence was initially described in IL-9 stimulated T-cell lines and in concanavalin A (Con-A)-activated murine spleen cells (Dumoutier et al., 2000). Further studies demonstrated that IL-22 expression can only be observed in activated immunological cells (Wolk et al., 2002). However, other reports have revealed that some T cells express IL-22 independently of IL-17 (Nograles et al., 2009). Finally, a new distinct human memory CD4+ T cell subset with skin-homing properties was identified and denominated Th22 (Duhen et al., 2009).

A preferential production of IL-22 cytokine by T cells (Th22, Th17, and Th1) is present in psoriasis lesions (Lowes et al., 2008). Many animal models indicate the role of IL-22 in psoriasis. IL-22 over-expressed transgenic mice developed psoriasis-like skin lesions (Wolk et al., 2009a). In IL-22 -/- mice, injection of IL-23 fails to induce epidermal hyperplasia

indicating the role of IL-22 as a downstream mediator of tissue effects caused by IL-23 (Zheng et al., 2007). In a recent publication, Rizzo HL et al showed that to have IL-23 mediated epidermal hyperplasia, both IL-17 and IL-22 is required; any one of these is not sufficient to execute the effect of IL-23. They also showed that pre-treatment with anti IL-22 or anti IL-17A Abs block the rmIL-23 mediated epidermal hyperplasia in wild type mice (Rizzo et al., 2011). In reconstituted epidermis model, IL-22 produces acanthosis dose dependently, which resembles psoriasis and either one of these alone is not sufficient to execute the effect of IL-23. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis (Sa et al., 2007). In a study by Wolk K et al, a correlation was demonstrated between the plasma IL-22 levels and the severity of the disease (Wolk et al., 2006). IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes and may play a: a potential role in psoriasis (Wolk et al., 2006). Moreover, IL-22 levels correlated with IL-20 levels, which is in accordance with the IL-22-induced keratinocyte IL-20 production (Wolk et al., 2009b). This suggests that IL-22 and its downstream mediator IL-20 play an important role in the final steps of psoriasis pathogenesis. Sabat R and his group in their studies showed that IL-22 regulates keratinocyte function in several ways: a. IL-22 helps form a biological barrier of the skin by producing antimicrobial proteins (AMPs) like β-defensins, and S100 proteins. This may be one of the reasons that psoriatic patients have less skin infections. b. IL-22 interferes with physiological desquamation process of skin by inhibiting the terminal differentiation of keratinocytes. c. IL-22 plays a role in recruiting neutrophilic granulocytes in skin by inducing the production of chemokines;. d. IL-22 indirectly helps in extracellular tissue degradation by inducing production of matrix metalloproteinases 1 and 3. IL-22 induces the production of IL-20, another IL-10 family cytokine which has similar effects as IL-22, thus resulting in amplification of the effects of IL-22 (Sabat & Wolk, 2011). In a transgenic mouse model, it has been showed that IL-22 causes acanthosis, hyperkeratosis, and hypogranulosis, which are hallmarks of psoriasis. IL-22 acts through STAT-3 to impact the differentiation of keratinocytes (Wolk et al., 2009a). IL-22 induces pro-inflammatory chemokines and antimicrobial proteins (AMPs) β-defensins (BDs), and promotes epidermal acanthosis and parakeratosis of keratinocytes (Boniface et al., 2005; Wolk et al., 2004; Wolk et al., 2006). Some synergistic effect was noted with other pro-inflammatory cytokines like TNF-α; IFN-γ; and IL-17 (Sabat & Wolk, 2011). Alone, TNF- α does not have much effect on terminal differentiation of keratinocytes, but when keratinocytes were co-cultured with IL-22 and TNF- α, the effects of IL-22 were amplified. This kind of synergism was also seen with CXCL8 and IL-20 expression in keratinocytes co-stimulated with IL-22 & TNF-α. One possible explanation of this may be that TNF-α increases the expression of IL-22 receptor complex and also affects the IL-22 signaling pathway (Wolk et al., 2009a). Thus, IL-22 and IL-20, but not IFN-γ or IL-17, are the key mediators of resulting epidermal proliferation. IL-22 acts through heterodimeric receptor complex composed of IL-22R1 and IL-10R2 (Kotenko et al., 2001). IL-10R2 chain is ubiquitously expressed in all cells and is important component of receptor complexes required for IL-22, IL-10, IL-26 and IL-28 and IL-29, whereas the IL-22R1 chain is present in epithelial cells and hepatocytes (Savan et al., 2011). Between the two subunits, IL-22 binds first to IL-22R1, the high-affinity receptor, and then IL-10R2, a lower affinity

receptor (Jones et al., 2008). To produce its effect, IL-22 acts through different signaling pathways, mainly signal transducer and activator of transcription 3 (STAT-3) and mitogen activated protein kinase (Lejeune et al., 2002).

This final move induces the vicious cycle of proliferation and inflammation of the skin characterized by the hyper-proliferative phenotype of keratinocytes in psoriasis. An anti-IL-22/ IL-20 approach would have a complementary role to the neutralization of p40. However, there has not yet been a human study to demonstrate such a role or anti-IL-22 therapy in the treatment of psoriasis.

8. The other side of the chessboard: The role of Treg

Today, reading a book or scientific article on immunopathogensis, one will observe that suppressor T cells, renamed regulatory T cells (Tregs), have become a central concept in immunological vocabulary (Horwitz et al., 2002). Hundreds of publications on Tregs have validated the existence of this single line of T cells. The CD4+CD25+highFoxp3+ Treg subpopulation is developed in the thymus and may be peripherally induced during the course of a normal immune response. The model in which Tregs directly or indirectly modify activation and differentiation of pathogenic T cells by means of an effect on antigen-presenting cells is supported by *in vivo* analyses (Korn et al., 2010).

8.1 Regulatory T cells: Development of an immunological concept

Biological systems are subject to complex regulatory controls and the immune system is no exception. It is known that the immune system has the potential to generate lymphocytes against auto-antigens. Experiments, however, suggest that individuals cannot easily be immunized against their own tissues. Therefore, a suppression mechanism is necessary to control potentially pathogenic immune cells. Owen suggested that this tolerance against one's own tissues is acquired during the development of the immune system, and Burnet proposed that the clonal selective destruction of lymphocytes for auto-antigens occurs primarily in the thymus.

The destruction of auto-reactive lymphocytes is the primary mechanism that leads to tolerance, but we know that this system is not perfect. Self-reactive B and T lymphocytes can be isolated from normal individuals (Ramsdell & Fowlkes, 1990). Nishizuka and Sakakura proposed another mechanism for controlling auto-reactive cells. They observed that mice thymectomized between the second and fourth days of life developed an organ-specific autoimmune disease. This target-organ destruction can be prevented by restoring T cells from genetically identical individuals. The generation of regulator T cells was proposed in order to explain this mechanism of auto-tolerance attributed to the thymus (Sakaguchi et al., 1996).

Other studies observed that the prevention of autoimmune diseases was diminished by the reduction of CD4+ T cells, but not of CD8+ T cells, indicating that regulatory cells belonged to the CD4+ T cell class of lymphocytes. Sakaguchi subsequently characterized these regulatory cells as natural CD4+CD25+ Tregs that express Foxp3 (Sakaguchi et al., 2001).

8.2 Suppressor T cells: Regulatory T cells are suppressor T cells

Another control point of the immune response is established when the normal immune response is initiated. A different mechanism must be set off in order to control the magnitude of the response and its subsequent termination. This regulation should contribute to limiting clonal expansion and effector cell activity. Soon after the discovery that T lymphocytes function as helper cells for B-lymphocytes, RK Gershon proposed that they could also act as cells capable of suppressing the immune response (Gershon & Kondo, 1971). This subpopulation of suppressor T cells was considered a controller of both auto-reactive and effector cells. A suppressor cell was functionally defined as a lymphocyte that inhibits the immune response by influencing the activity of another type of cell involved in a cascade of suppression factors, a network of anti-idiotypic T cells, and counter-suppressive cells (Dorf & Benacerraf, 1984).

Many of the experiments carried out contain data that support the existence of suppressor T cells. However, the mechanism responsible for these suppressive phenomena was never clearly characterized, and consequently interest in the field of suppressor T cells has gradually dwindled. The discovery of Th1/Th2 cells led researchers to abandon the concept of suppressor T cells. Suppression was instead attributed to counter-regulatory cytokines. As pointed out by Green and Webb, the letter ‘‘S'' started to resemble a foul word in cellular immunology, and its use was considered synonymous of scarce data with excessive interpretation or a mystic phenomenon (Green & Webb, 1993).

Suppressor T cells reappeared as regulatory T cells (Tregs) in the late 1990s when several subpopulations of T cells were identified as having the capacity to inhibit the proliferation of other cells. Shevach et al. were the first to call attention to the fact that regulatory T cells and suppressor T cells are the same (Shevach et al., 1998). Therefore, the term ‘regulatory' gradually replaced the term ‘suppressor'. The main problem, however, is not that cells are termed regulatory, but that they are considered to be suppressors. It is more appropriate to consider regulatory T cells as immune response directors instead of its suppressors.

9. Regulatory T cells and psoriasis

The regulation mechanism of the immune system by CD25+high Tregs is not well understood. Studies have not yet arrived at a simple mode of action. Whatever the mechanism, the homeostatic balance of the immune system is obtained by healthy cellular and humoral responses. Some inflammatory agents, whether physical, chemical, or infectious, induce an intense immune response. This immune response against them frequently results in tissue damage that could be more intense if it were not for the interference of regulatory mechanisms (Belkaid et al., 2006). As has already been specified, Treg cells help limit the damage caused by a vigorous immune response. Natural Treg cells may respond to an ample variety of auto-antigens, although there is evidence that they may also respond to antigens expressed by microbes. Induced regulatory T cells, such as TR1 or Th3, may develop from CD4+ T cells when exposed to specific conditions (Weiner et al., 2011).

Similarly, excessive activity of Treg cells may limit the magnitude of the immune response, which may result in failure to control an infection. On the other hand, the absence of the T regulator may result in intense inflammation and autoimmune dermatitis. Tissue damage

may also result from the development of effector cells against their own auto-antigens (Figure 4).

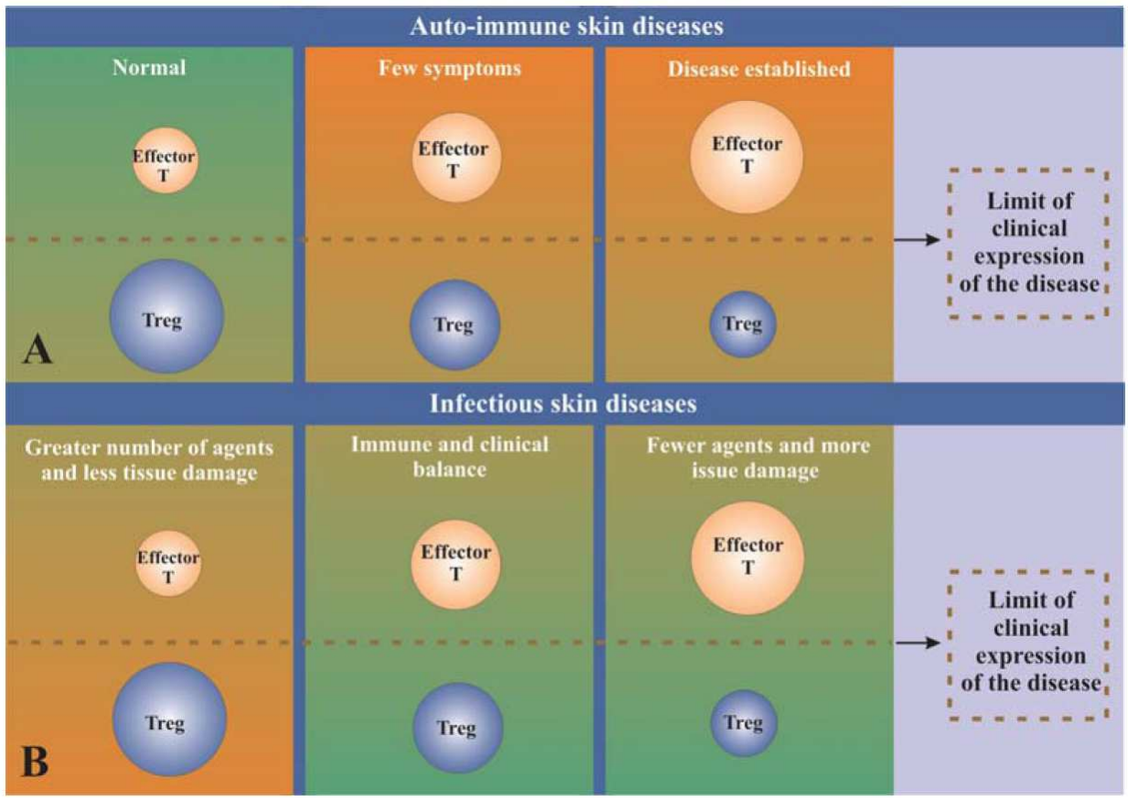

Fig. 4. Immune response regulation mechanisms. The force balance between Tregs and the effector T CD4+ cells may present in a different manner depending on being an autoantigen or a pathogen. In A portion, the clinical expression of autoimmune skin diseases is shown. In this case, there is clinical manifestation only when the number and function of Tregs are significantly reduced. B portion displays clinical manifestations that may occur in extreme cases. In case of excessive Treg function, the result shows reduction of effector lymphocytes against the pathogen, an increase in its number and less tissue damage. The contrary applies to effector cells against the pathogen that surpass the number and function of Treg. The ideal immune and clinical response occurs when there is a balance between functions

Psoriasis is sustained by the activation of pathogenic T cells. The regulatory expression of skin diseases discusses the action exerted by regulatory T cells, especially CD4+CD25+high Tregs on psoriasis. Various types of influence of these cells suggest that they may act by suppressing or augmenting immunity (Sabat et al., 2007; Shehata & Elghandour, 2007). The control of Treg cells may affect the results favorably or may be deleterious. There is no definitive view. In psoriasis, studies have shown that the subpopulation of CD4+ T lymphocytes in peripheral blood, phenotypically CD25+high, CTLA-4(+), Foxp3high, is deficient in its suppressor functions. This is associated with an accelerated proliferation of the CD4+ T cell response (Sugiyama et al., 2005). The presence of non-functional CD4+CD25+high Treg cells in peripheral blood and in tissues may lead to a reduced capacity to contain pathogenic T cells and to a hyperproliferation of the psoriatic plaque *in*

vivo. These findings represent a critical component of this autoimmune disease and may have implications for potential therapy by manipulation of CD4+CD25+high Tregs *in vivo*. However, other factors, such as the immune status and genotype, and the presence of concomitant diseases or other infections may also have an influence. The manipulation of this balance can be explored therapeutically.

9.1 Clinical and therapeutic consequences of regulatory T cells

An improved understanding of the role of T regulators in psoriasis may lead to the identification of new targets for treatment. More specifically, the goal is to manipulate natural regulator cells or those induced by means of an increase or decrease of their function, depending on the circumstances.

Auto-injections of regulatory T cells are a promising approach to modulation of inflammation and autoimmune diseases (Wilhelm et al., 2010). Nevertheless, there is a significant decline in the function of natural CD4+CD25+high Treg cells of peripheral blood in patients with autoimmune diseases when compared to that of healthy individuals. In order to overcome this difficulty, cytokines were used to stimulate the growth of regulator T cells. IL-15 allows a significant *in vitro* expansion of regulator cells (Ortega et al., 2009). Natural CD4+CD25+high Treg cells obtained by *ex vivo* expansion through stimulation with allogeneic antigen-presenting cells and IL-2 were capable of modulating the graft-versus-host disease (GVHD). Induction of natural CD4+CD25+high Treg cells may facilitate the establishment and maintenance of immunological tolerance. Depletion of natural CD4+CD25+high Treg cells may be an effective way of reversing the tolerance induced by malignant tumors and increasing the activity of the immune system against cancer epitopes (Yu et al., 2005)

In the field of dermatology, the stimulation of Treg cells may be important in autoimmune diseases. For example, blockage of T lymphocyte stimulation, as in the use of the antibody associated with CTLA-4 (cytotoxic T lymphocyte-associated antigen 4-immunoglobulin, CTLA4Ig), reverts the development of psoriatic plaques (Abrams et al., 2000). In the clinical context, the effect of immunomodulator drugs on these cells warrants attention. For example, tacrolimus, an inhibitor of calcineurin, increases the inhibition of Treg cells in atopic dermatitis (Sewgobind et al., 2010; Vukmanovic-Stejic et al., 2005). Fludarabine reduces the frequency and suppressive function of natural CD4+CD25+high Treg cells (de Rezende et al., 2010). Low doses of cyclophosphamide induce the inhibition of natural CD4+CD25+high Treg cells and consequently increase the immune response in an apparently paradoxical effect (Lutsiak et al., 2005). Along the same line, cyclophosphamide decreases the function, proportion, and number of natural CD4+CD25+high Treg cells that suppress the induction of contact hypersensitivity (Cerullo et al., 2011; Ikezawa et al., 2005). Currently, topical corticosteroids constitute one of the most effective treatments for psoriasis and other inflammatory skin diseases. These drugs are effective in inhibiting the function of Th2 cells, eosinophils, and epithelial cells. However, treatment with these drugs during the presentation of the epitope may result in an increased tolerance by suppressing the development of dendrite cells that secrete IL-10, which are necessary for the induction of T regulators. Therefore, treatment with corticosteroids may increase the subsequent effect of the T response and aggravate, on the long run, the course of inflammatory diseases (Stock et

al., 2005). This aspect may also be related to the rebound effect of inflammatory diseases once these drugs are removed.

10. Conclusion

In medicine, a gold standard is the intervention believed to be the best available option. Given the proven role of many cytokines in psoriasis, substantial interest exists in targeting them with neutralization immunotherapy. If Th1/Th17/Th22 pathways operate in different steps of psoriasis development, then targeted blockade place biologics as the standard-setting paradigm for therapy and understanding of the pathogenesis of psoriasis. However, large studies are needed to provide information on the therapeutic effects, adverse events of any anti-cytokine therapy, and their place in the treatment of psoriasis and other skin diseases. To complement this approach, a detailed comprehension of the associations among the various regulator cells may help in understanding the events leading to the genesis of skin diseases. Ultimately, an ability to manipulate the function of regulator T cells according to the desired therapeutic effect will be the goal. Together, an integrated immunologic approach to therapy holds great promise in reducing the burden of psoriatic disease.

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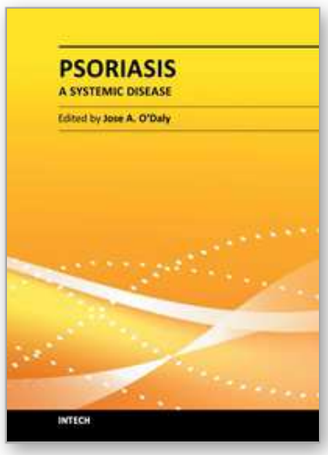

Psoriasis - A Systemic Disease

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The purpose of this book is to present a comprehensive analysis of Psoriasis, a disease that affects approximately 2-3% of humanity in all countries. Psoriasis existence is surveyed since the clay tablets of Assyrians and Babylonians 3.000-5.000 years ago, thru the middle ages, the renaissance, XIX and XX centuries.

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