Reviewing concepts in the immunopathogenesis of psoriasis *

Imunopatogênese da psoríase: revisando conceitos

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Abstract: Insights into the pathogenesis of psoriasis led to the development of therapeutic tools aimed at blocking its immunological trigger. In parallel, cytokines such as the tumor necrosis factor (TNF) have been recognized as playing a crucial role in the pathogenesis of psoriasis and its associated comorbidities. Genetic and immunological studies have contributed effectively towards establishing the currently held concepts regarding this complex disease.
Keywords: Antigens, CD4; Interferon-stimulated gene factor 3; Interleukin-4; Psoriasis; Th1 cells; Tumor necrosis factor-alpha

Resumo: O conhecimento sobre a fisiopatogenia da psoríase possibilitou o desenvolvimento de ferramentas terapêuticas que visam ao bloqueio do seu gatilho imunológico. Paralelamente, citocinas como o TNF têm sido reconhecidas como integrantes da etiopatogenia da psoríase e comorbidades a ela relacionadas. Estudos genéticos e epidemiológicos contribuíram efetivamente para as conclusões a que se tem chegado atualmente sobre esta complexa patologia.
Palavras-chave: Antígenos CD4; Células Th1; Fator gênico 3 estimulado por Interferon; Fator de necrose tumoral alfa; Interleucina-4; Psoríase

INTRODUCTION

For many years, psoriasis has been recognized by its characteristic histological changes. Nevertheless, more recent immunological studies have led to a new definition of the disease based on genomic function and on gene expression analysis. These data brought singular new understanding to the processes involved in regulating inflammation in psoriasis. Therefore, the gamut of chemokines expressed in skin lesions is certainly much larger than was previously believed. Furthermore, it has now been established that the chemokines, whose expression was thought to be restricted to lymph nodes and lymphoid tissues, are present in high concentrations in psoriatic lesions. [1]

For these reasons, psoriasis began to be considered a chronic inflammation resulting from the persistent stimulation of T cells ($CD4^+$ and $CD8^+$ lymphocytes) by immunogens of epidermal origin involving innate and acquired immunity. [2,3]

PHYSIOPATHOGENESIS

When skin affected by psoriasis is compared with unaffected skin, the current models used to explain the physiopathogenesis of the disease reveal differences in cell composition and in inflammatory mediators. With respect to cell composition, whereas non-lesional skin has few immature Langerhans and dendritic cells, few CD4+ lymphocytes and rare CD8+ lymphocytes, in lesional skin there is an abundance of these and other cell types, as shown in table 1. [1]

After describing the cell populations involved in psoriatic lesions, the molecular relationships expressed by inflammatory mediators and costimulators should then be explained. In general, both at the onset of the disease and in the episodes of exacerbation, mature dendritic, myeloid and plasmacytoid cells are activated in the epidermis and dermis, producing messengers that promote the development of subclasses of T helper and T cytotoxic cells (Th1, Tc1). These T cells secrete mediators (IFN-γ), inducers of

Received on 28.06.2010.
Approved by the Advisory Board and accepted for publication on 08.02.2011.
* Study conducted at the Santa Casa de Misericórdia do Recife, Recife, PE, Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial Support: None / *Suporte financeiro: nenhum*

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Table 1: Cell populations involved in psoriatic lesions

Cells	Non-lesional skin	Lesional skin	Expression in psoriasis
Immature Langerhans cells	Few	Many	Immature dendritic cells in the epidermis.
Myeloid dendritic cells	Few	Many	Located in the dermis and derived from blood monocytes or from other myeloid precursor cells, they strongly express the major histocompatibility complex class II, which is responsible for intense stimulation of T lymphocytes due to the pronounced release of IL-12 and IL-23 (cytokine with a direct inflammatory action, which promotes the increase and activation of Th1 and Tc1 lymphocytes)
Mature dendritic cells	Absent	Large amount	Following maturation through the action of TNF-α, this lineage, which originates from the myeloid lineage, presents greater capacity for T-cell activation, unlike those that are present in normal skin.
Plasmacytoid dendritic cells	Absent	Many	Once activated, they synthesize and release large concentrations of interferon alpha (IFN-α), thus stimulating T lymphocytes in the lesion.
CD4+ T lymphocytes	Few	Large amount	They are predominant in the dermis and express cutaneous lymphocyte antigen, which acts selectively on the inflammatory lesions.
CD8+ T lymphocytes	Scarce	Large amount	Located in the epidermis, they express alpha and beta-7 integrins, which bind to E-cadherin, thus avoiding the formation of desmosomes among the keratinocytes.
Natural killer T lymphocytes	Absent	Large amount	Recruited from the circulating blood by chemotaxis, they synthesize large amounts of IFN-α.
Neutrophils	Absent	Frequent	Migrate towards the lesion following recruitment through the action of IL-8. Despite their presence in the lesion, neutrophils are not considered a primary cause of psoriasis.
Macrophages	Absent	Large amount of activated macrophages	Essential for the activation of B-lymphocytes.

HLA-DR production in the keratinocytes, reactivating the process, which contributes to the epidermal and vascular alterations found in psoriasis. [2]

The initial process of activating the T cells occurs via antigen-presenting cells, matured by antigenic peptides presented by HLA-I or HLA-II on the surface of these cells, with the participation of molecules such as lymphocyte function-associated antigen-1 (LFA-1), an integrin composed of CD11a and CD18, and intracellular adhesion molecule-1 (ICAM-1), which encourage the maintenance of this adhesion. This link counts on the participation of biochemical signaling and the co-participation of other agents, particularly the CD28 glycoprotein, located on the surface of the T lymphocytes, and CD80 and CD86, located on the surface of the dendritic cells, resulting in an increase in mRNA and the transcription of cytokines such as IL-2, IFN-γ, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are crucial for T lymphocyte activation. If the costimulation promoted by CD28 fails to occur, T lymphocyte activation is partial (Figure 1). [4]

Another important interaction takes place between the B7 molecules and cytotoxic T-lymphocyte antigen 4 (CTLA-4). The B7-CD28 interaction is activating, whereas the B7-CTLA-4 link emits a signal that suppresses activation of the T lymphocytes. In collaboration with the activation, there are some proteins on the surface of antigen-presenting cells that, when bound to the T lymphocyte, release other accessory signals (Figure 1). [1]

Furthermore, the release of IL-2 and IL-12 by the mature dendritic cells contributes respectively to mitotic activation and to the differentiation of the T

lymphocytes. The mature dendritic cells, important in the lymphocyte activating process, achieve this condition after capturing the antigen, mediated by cytokines such as GM-CSF, IL-4 and TNF-α; however, the later stages of its differentiation are regulated by contact with the T lymphocytes. [1,2]

The communication between CD40 and CD40L autoregulates CD40 expression in the dendritic cell. This interaction also stimulates B7 synthesis in the antigen-presenting cells and favors the synthesis of elevated IL-2 levels, contributing towards the activation and differentiation of the T lymphocytes (Figure 1). [1,5]

The tumor necrosis factor-related activation-induced cytokine (TRANCE) of the TNF family is synthesized by the T cells and, when bound to the dendritic cell (TRANCE-R) inhibits its process of apoptosis. In view of all these interactions, the relationship between the T lymphocytes and the dendritic cells may be considered to represent a continuous dialogue and not a short monologue.

Activation of the mature dendritic cells (myeloid and plasmacytoid) initiates the inflammatory cascade, with differentiation of the lymphocytes in the Th1 and Tc1 lineages by costimulation, consisting of the interaction of non antigen-specific cells. If this costimulation fails to occur, the T lymphocytes suffer apoptosis and become anergic; however, when this occurs, the psoriatic plaque develops. [6]

The antigen-presenting cells in the lymph nodes trigger the specialization of the CD4 and CD8 T lymphocytes by MHC class I and MHC class II, respectively through the synthesis and release of interleukin-12 (IL-12). This stimulation promotes the conversion of the CD4+ T cells into Th1 and the CD8+ T cells into Tc1, cells that are able to synthesize and release other cytokines including: interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), as well as the granulocyte-macrophage colony-stimulating factor (GM-CSF) and epidermal growth factor (EGF) (Figure 2). [2]

During their maturation process, the T cells produce new surface proteins that enable their passage from the vessels to the skin. The most important is probably the cutaneous lymphocyte antigen (CLA), an adhesion molecule which, with the help of cytokines, exerts an effect on maturation and lymphocyte chemotaxis, as well as on the intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), which contribute to creating an avidity gradient favoring the chemotaxis of the T and B lymphocytes, as well as neutrophils and macrophages, to the lesion by activating the vascular endothelium. The lymphocyte function-associated antigen-1 (LFA-1) and CD2 also act in the T lymphocyte, as does the lymphocyte function-associated antigen-3 (LFA-3) in the activated antigen-presenting cell. [1]

Among other actions, TNF-α acts by: a) increasing cytokine release by the lymphocytes and chemokines by the macrophages; b) increasing the expression of ICAM-1 in the keratinocytes and of vascular cell adhesion protein-1 (VCAM-1) in the endothelial cells, with the consequent imprisonment and increased activation of the T lymphocytes for being exposed to the circulating cytokines and chemokines for longer periods of time. Furthermore, TNF-α promotes an increase in the proliferation of the keratinocytes and endothelial cells, with formation of neocapillaries and an increase in lymphocyte recirculation, favoring and maintaining lymphocyte diapedesis, which perpetuates the inflammatory process. [7]

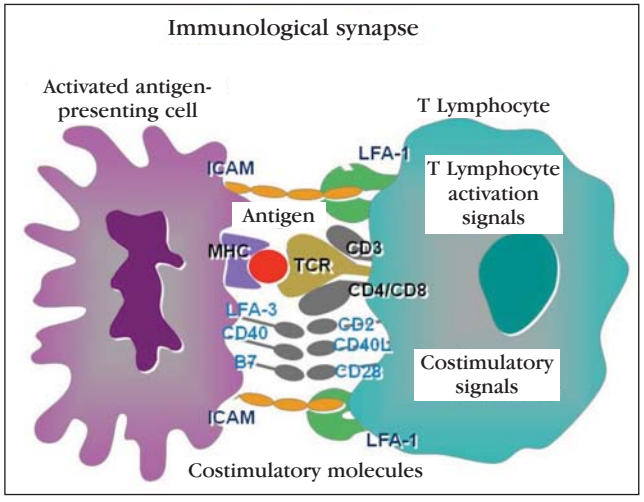

Figure 1: Immunological synapse model between Langerhans and dendritic cells in the skin and T lymphocyte at the onset of the psoriatic immune response

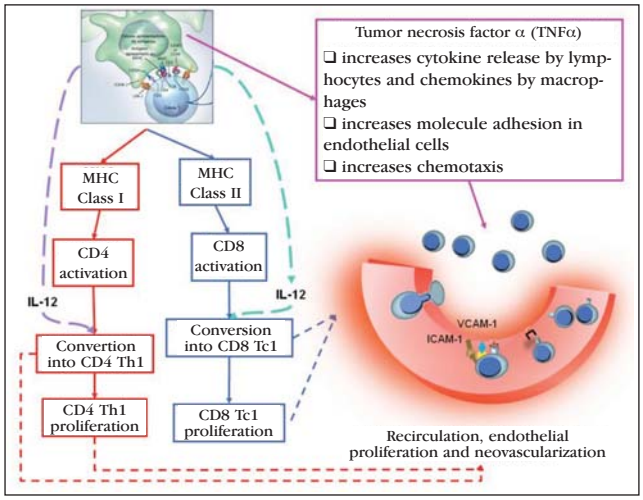

Figura 2: Interleukin-12 activity in promoting synthesis of tumor necrosis factor
Legend: MHC – major histocompatibilty complex

Other important factors for the formation of lesions in psoriasis are: a) IFN-γ, which promotes hyper-proliferation of keratinocytes by inhibiting apoptosis, as well as increasing ICAM-1 expression in the endothelial cells, facilitating lymphocyte circulation; and b) IL-17, which interacts with IFN-γ to increase the synthesis of proinflammatory cytokines by keratinocytes such as IL-6 and IL-8, increasing the influx of T cells into the skin, which contributes towards maintaining the psoriasis plaque. [1,4]

The keratinocytes, activated by the cytokines synthesized by the CD4+ and CD8+ lymphocytes also release inflammatory cytokines of which the following have already been identified: a) TNF-α; b) IL-6, which stimulates the proliferation of keratinocytes; c) IL-8, which, in addition to stimulating the proliferation of keratinocytes, increases neutrophil chemotaxis, promoting the rupture of the desmosomes in the keratinocytes and the formation of Munro's microabscess, as well as maintaining the differentiation of the T lymphocytes into Th1; and d) Growth transforming factor, responsible for angiogenesis and vascular hyper-permeability. [7,8]

The participation of stimulating cytokines such as IL-1, IL-6, IFN-γ and the presence of T cells among the keratinocytes provoking damage to the plasma membrane are some of the mechanisms that result in the hyper-proliferation of the epidermis seen in psoriasis. Furthermore, the release of cytokines by the T cells stimulates the differentiation and release of IL-8 by the keratinocytes and the consequent recruitment of neutrophils, triggering further damage in the keratinocytes (Figure 3). [4]

This immunological process is associated with an epidermal hyper-proliferation characterized by a two-fold increase in the number of mitoses, by an approximately 8-fold reduction in the keratinocyte cycle and, consequently, by incomplete maturation. This reduces lipid synthesis for the formation of desmosomes by the keratinocytes. On the other hand, the Tc1 lymphocytes (CD8+) attack the site of the psoriasis lesions by releasing cytokines and succeed in penetrating the intercellular spaces of the keratinocytes, facilitating the inflammatory process. [9]

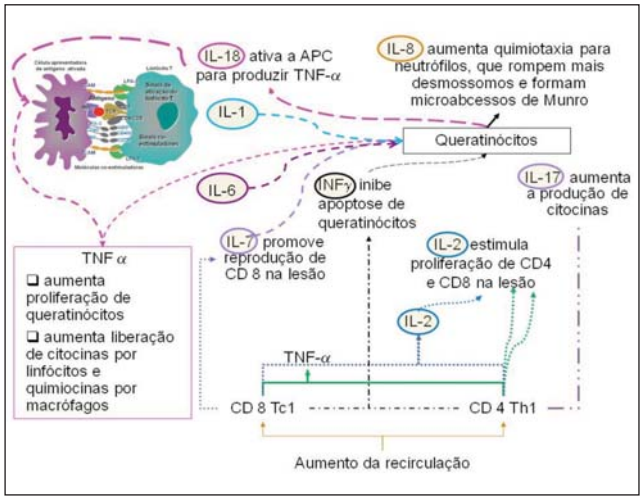

Figure 3: Psoriatic inflammatory cascade involving keratinocytes

Studies into the physiopathogenesis of psoriasis have revealed findings similar to those identified in rheumatoid arthritis and in Crohn's disease. Given the immunomediated inflammatory nature of these diseases, it became evident that it was characterized by high concentrations of TNF-α and interleukin-1 at the site of the lesions. This finding gave rise to the hypothesis that drugs capable of blocking the effect of TNF-α could be useful in the treatment of this disease, although at that time it was not possible to evaluate the risks of this therapy. [10] To do so, it was necessary to find out more about the functions of this cytokine and those of the lymphotoxins, which were believed to exert an important effect on normal skin and on skin affected by psoriasis.

The role of TNF-α and the lymphotoxins on inflammatory reactions

TNF-α is a pleiotropic inflammatory cytokine produced by various cells including the activated T and B cells and NK cells. When inflammation is present, it is primarily synthesized by macrophages in response to various proinflammatory stimuli. It is found in high levels in the skin, joints and plasma of patients with psoriasis and is related to the activity of the disease. [11]

TNF-α is referred to as a sentinel cytokine because it initiates defense in response to local injury. [12] At low concentrations in the tissues, it exerts beneficial effects such as increasing the host's defense mechanisms against infections. In high concentrations, it may lead to excess inflammation and organ damage such as, for example, in septicemia when an intense release of TNF-α results in septic shock. [13]

In general, TNF-α increases in pathogenic processes, promoting the production of other mediators of inflammation and tissue destruction, taking on the principal role in the inflammatory cascade in innate and acquired immunity; however, it should also be considered an important proinflammatory cytokine that participates in an intricate network, more than just a member of the inflammatory cascade. [14]

The nomenclature TNF has changed over time. The molecules previously known as TNF-α and TNF-β have come to be known as TNF and lymphotoxin-alpha (LTα), respectively, since the congress on TNF

held in 1998, although the term TNF-α is still widely used. The denomination TNF includes: soluble TNF (sTNF) and transmembrane TNF (tmTNF), whereas the denomination LT refers to the members of a family of lymphotoxins composed of monomeric alpha and beta helixes, L3 being the most important in the context discussed here. [14]

The mechanism of action of TNF consists of various modifications, as shown in Figure 4. TNF is released from the synthesizing cells (macrophages, T cells, mastocytes, granulocytes, NK cells, fibroblasts, neurons, keratinocytes and smooth muscle cells) in soluble form (formed by three 17 kDa monomers), which is then converted into tmTNF, the precursor of the form bound to the cell membrane, under the effect of the TNF-a converting enzyme (TACE). The sTNF and tmTNF forms are biologically active and their concentration depends on tissue stimulus, on the type and state of activation of the cells involved in the defense reaction, on the concentration of active TACE and on the TACE inhibitors such as the metalloproteinases-3. [15]

TNF synthesis by the cells may be induced by a variety of stimuli. Macrophages synthesize TNF in the presence of bacteria, viruses, immunological complexes, cytokines (such as IL-1, IL-7, GM-CSF, IFN-γ), complement, tumor cells, irradiation, ischemia, hypoxia and trauma. These stimuli trigger mRNA transcription, pro-TNF protein synthesis, which is incorporated into the cell membrane as tmTNF. Once present in the membrane, tmTNF induces the synthesis of other cytokines such as IL-1, IFN-α and IL-2, which in turn regulate TNF production. Nevertheless, TNF is able to induce the synthesis of regulating factors such as IL-10, prostaglandins and corticosteroids, which inhibit its transcription and block further release of this cytokine (Figure 4). [14]

The two forms of TNF bind to membrane receptors known as TNFR and expressed as TNFR1 and TNFR2, membrane glycoproteins that mediate different reactions. Nevertheless, there is specificity in this binding so that sTNF binds preferentially to TNFR1 and tmTNF to TNFR2, triggering different reactions depending on the metabolic state of the cell. TNFR1 is expressed in almost all the cells with the exception of the erythrocytes, whereas TNFR2 is more commonly found in the endothelial and hematopoietic cells. [11]

The primary mechanism of action of TNF (soluble or transmembrane), once internalized in the cell cytoplasm by the membrane receptors, is to synthesize nuclear factor kappa B1 (NF-κB1), a family of transcription factors that controls a great number of inflammatory genes, promoting programmed apoptosis that is dependent on the action of caspase-8 and caspase-3. Under normal conditions, this apoptosis is blocked by Fas-associated death domain (FADD)-like interleukin-1-beta-converting enzyme (FLICE). However, in a cell infected by a pathogen, apoptosis is not inhibited and the TNF-TNFR1 activation pathway is maintained (Figure 4). [16]

Lymphotoxins (LT) are also involved in inflammatory processes. LT are members of the TNF family and there are great similarities between them although molecular and biological differences exist. [16]

Figure 5 shows that the mechanism of action of the lymphotoxins is very similar to that of TNF. Lymphotoxin alpha-3 (LTα3), previously referred to as TNF-α, is structurally similar to sTNF (a trimer of 17 kDA monomers) and, unlike sTNF, binds indiscriminately to TNFR1 and TNFR2 membrane receptors. The second lymphotoxin is one that contains alpha and beta heterotrimers and for this reason is referred to as LT$\alpha\beta$ (with two variants LTα2β1 and LTα1β2, the latter in lower concentrations). LT$\alpha\beta$ binds to LTβR membrane receptors, although it may also bind to the TNFR1 or TNFR2 receptors, however, with less avidity (Figure 5). [16]

Lymphotoxin synthesis may be induced by splenic CD4+cells or by other cells from the spleen if they are stimulated by IL-4 and IL-7 or even by ligands of

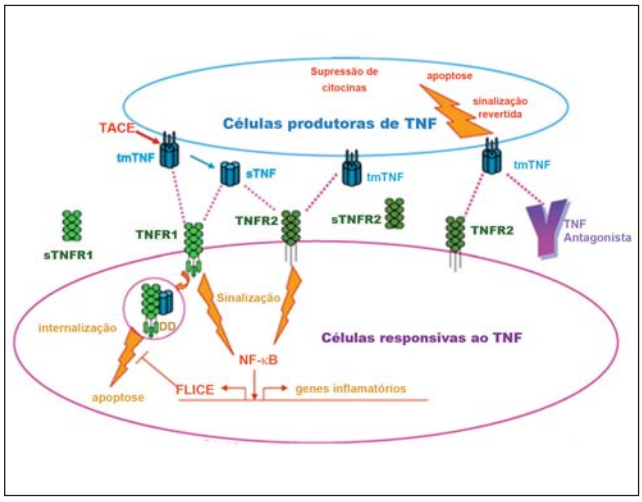

Figure 4: The biology of TNF production, receptor interaction and signaling in normal skin

Adapted source: Tracey et al., 2008 [14]
Note: The stimulation of TNF-producing cells results in the expression of tmTNF in the membrane. tmTNF is cleaved by the TNF-converting enzyme (TACE), releasing sTNF. Both may bind to TNFR1 and TNFR2 on the cell surface, initiating the signaling pathways to apoptosis and to NF-κB synthesis, triggering the inflammatory process. The activity of Fas-associated death domain (FADD)-like interleukin-1-beta-converting enzyme (FLICE) may inhibit the inflammatory and apoptotic processes

chemokines 19 and 21 (CCL-19 and CCL-21). [17]

The lymphotoxin receptors are present in stromal fibroblasts, epithelial cells and myeloid cells such as monocytes, macrophages, dendritic cells and mastocytes; however, they are absent in T, B and natural killer lymphocytes. Their ability to bind with LT$\alpha\beta$ depends on cell-cell contact between lymphocytes and surrounding stromal cells. [16]

It should be noted in Figure 5 that LT induce apoptosis and NF-κB synthesis; however, unlike the pathway of interaction of TNF, they promote lymphoid neogenesis, which is of great clinical importance in view of the exacerbation of inflammatory processes that it promotes.

Even considering that TNF and LT are not necessary in adaptive immunity, various studies have analyzed this effect, i.e. on immunity that involves a response to a foreign antigen, which should be processed by dendritic cells, macrophages, B cells or antigen presenting cells, to exposure to T and B cells, triggering cell and humoral immunological responses to the antigen. [18,19]

It has been established that TNF is able to direct the differentiation of monocytes into dendritic cells instead of macrophages and to induce the production of a series of chemokines that facilitate the migration of dendritic cells and the initiation of immune response during dendritic cell maturation. In the response of the T cells to the antigens, TNFR2 binds functionally to CD28 and plays a critical role in IL-2 induction and in the survival of T lymphocytes. [20]

Furthermore, TNF is able to stimulate the proliferation of T cells, but may also be able to promote their apoptosis and the end of immune response through the death of these cells. It is also possible that TNF may increase the chemotaxis of T cells to the site of the lesion, with the mediation of CXCL-10 through regulation of the adhesion molecules in the endothelial cells. [21]

In autoimmune processes, TNF may sequester autoreactive T cell precursors in the thymus or even render circulating T cells anergic. This finding suggests that TNF may exert both an immunosuppressive and an immunostimulating role depending on the individual's genetic composition, the time of the disease and the levels of circulating TNF. [22]

In psoriasis, TNF is synthesized in macrophages, keratinocytes and in intraepidermal Langerhans cells, and is distributed throughout the epidermis, preferentially close to the blood vessels in the upper dermis. In injured skin, TNFR1 predominates in the keratinocytes, intraepidermal Langerhans cells and in the blood vessel walls, whereas TNFR2 is expressed to a greater extent in the dermal blood vessels and in the perivascular infiltrating cells. [14]

All this evidence resulted in the development of biological therapy to block the effect of TNF and its receptors, reducing the inflammatory process in diseases such as psoriasis, rheumatoid arthritis and Crohn's disease. Nevertheless, following the introduction of these drugs, a recrudescence of latent tuberculosis occurred, causing investigators to also analyze the action of TNF in tuberculosis. [23,24]

TNFR1, essential in the formation of the granuloma of *M. tuberculosis*, binds predominantly to the soluble form, whereas TNFR2 binds to the transmembrane form, playing a modest role in combating bacterial infections. TNF-α regulates molecular adhesion expression in endothelial cells by stimulating the migration of macrophages in addition to playing an important role in the apoptosis of cells infected by these bacteria. [11] This knowledge becomes relevant when we analyze the greater risk of reactivating latent tuberculosis in individuals exposed to treatments with an anti-TNF effect.

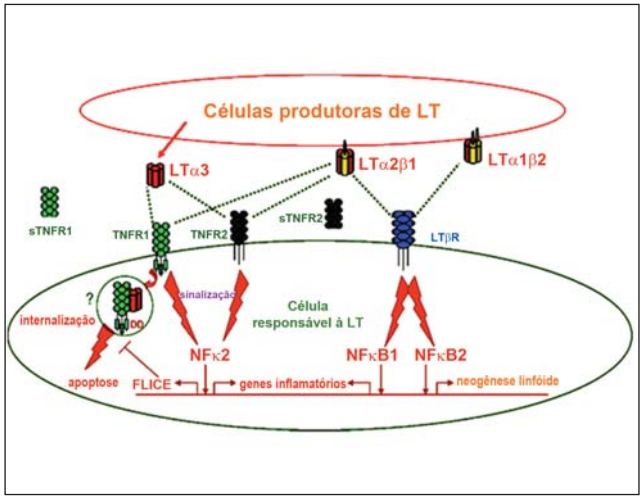

Figure 5: The biology of lymphotoxin production, receptor interaction and signaling in normal skin

Adapted source: Tracey et al., 2008 [14]
Note: The stimulation of LT-producing cells results in the expression of LTα3, LTα1β2 or LTα2β1. These ligands may bind to TNFR1 and TNFR2 or LTαR, initiating apoptosis and NF-κB synthesis and triggering the inflammatory process or lymphoid neogenesis. FLICE activity may inhibit the inflammatory and apoptotic processes

Psoriasis and comorbidities

Clinical evidence confirms that psoriasis is not a disease whose manifestations are confined exclusively to the skin. The genetic association between psoriasis and other diseases such as Crohn's disease and type II diabetes (CDKAL1) has also been reported recently, based first of all on epidemiological studies that showed a high frequency of psoriasis patients with these

diseases and later through a better understanding of the immunological processes involved. [25,26]

The similarity between the immunological factors held responsible for the process of forming the atheromatous plaque and those involved in the onset and progression of chronic inflammatory diseases such as psoriasis permitted an association to be established with the incidence of cardiovascular diseases. In support of these findings, patients with severe psoriasis present a high frequency of psoriatic arthritis, cardiovascular disease, hypertension, obesity, diabetes and an increased risk of acute myocardial infarction. [24, 26-36]

Gisondi et al. studied a group of patients with psoriasis and identified a greater prevalence of metabolic syndrome in these patients compared to a control group. Cohen et al. studied 340 patients with psoriasis and 6,643 controls and identified an association between this disease and acute myocardial infarction, diabetes, hypertension, obesity and dyslipidemia, particularly in males of 35 to 50 years of age, suggesting the presence of metabolic syndrome in these patients. An evaluation of 16,851 patients with psoriasis detected an increase in total cholesterol and triglyceride levels associated with a reduction in serum HDL levels compared to controls. [37,38]

Endorsing these findings, more than 20 gene loci have been detected that interfere with an individual's susceptibility to psoriasis. These are related to the metabolic syndrome, type II diabetes, familial hyperlipidemia and cardiovascular disease. [39-42]

CONCLUSION

Accurate information on the immunological mechanisms of the onset of psoriasis, characterizing the role of each cytokine involved in triggering inflammation, enabled this condition to be recognized as a systemic disease. This new picture stimulated the development of studies and led to improvements in diagnosis of the condition by taking other medical specialties into consideration, leading also to the development of new drugs to control this disease. By acting to block crucial steps in the progression of inflammation, these treatments prevent disease progression and attenuate the symptoms resulting from its chronicity, rendering these therapeutic options extremely promising in severe cases and in those resistant to conventional therapies. It is the dermatologist's duty to have an in-depth knowledge of the immunopathogenesis of psoriasis, which will facilitate the comprehension of new and current discoveries on its triggers, progression and control. ❑

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How to cite this article/*Como citar este artigo*: Lima EA, Lima MA. Reviewing concepts in the immunopathogenesis of psoriasis. An Bras Dermatol. 2011;86(6):1151-8.