REVIEW

Superficial mycosis and the immune response elements *

Micoses superficiais e os elementos da resposta imune

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Abstract: Superficial mycoses are prevalent worldwide. They are often caused by dermatophytes and restricted to the stratum corneum. The host's immune response against infections caused by dermatophytes basically depends on the host's defense against metabolites of the fungi, virulence of the infecting strain or species and anatomical site of the infection. We will review some of the factors of the host's immune defense that influence the efficacy of the immune response. We will particularly review the role of pattern recognition receptors (PRRs), such as toll-like receptors or lectin receptors (DCSIGN and Dectin 2), which participate in the innate immune response, bringing specificity to the immune response and setting its pattern. The predominance of a cellular or humoral immune response determines the clinical manifestations and the prognosis of the infection, leading to healing or chronicity.
Keywords: Allergy and immunology; Fungi; Inflammation mediators; Integumentary system

Resumo: As micoses superficiais são prevalentes em todo o mundo, geralmente ocasionadas por dermatófitos e restritas à camada córnea. A resposta imunológica do hospedeiro às infecções dos fungos dermatófitos depende basicamente das defesas do hospedeiro a metabólitos do fungo, da virulência da cepa ou da espécie infectante e da localização anatômica da infecção. Serão revistos alguns dos fatores da defesa imunológica do hospedeiro que influenciam na eficácia da resposta imune. Em especial, a participação dos receptores de padrão de reconhecimento (PRRs), tais como os receptores *toll-like* ou os da família lectina (DC-SIGN e dectin-2), que participam da resposta imune inata, conferindo-lhe especificidade e definindo o padrão da resposta imune como um todo. O predomínio celular ou humoral da resposta imune definirá o quadro clínico e o prognóstico da infecção, levando à cura ou cronicidade.
Palavras-chave: Alergia e imunologia; Fungos; Mediadores da inflamação; Tegumento comum

Received on 14.07.2010
Approved by the Editorial Board and accepted for publication on 08.10.2010.
* Work conducted at the Department of Dermatology, Faculty of Medicine, University of Sao Paulo; Medical Mycology Laboratory of the Tropical Medicine Institute of Sao Paulo, USP, IAMSPE, UNICID and Oswaldo Cruz Faculties Foundation - Sao Paulo (SP), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding / *Suporte financeiro:* O presente trabalho foi desenvolvido com bolsas de iniciação científica vinculadas ao programa de pós-graduação em ciências da saúde do Iamspe, das alunas Filomena Amaro Takiguti (CNPQ n. 122819/2008) e Luciana Vasconcellos Benini (CNPQ n. 129074/2009), sob a orientação da Profª.

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INTRODUCTION

Superficial mycoses are common in tropical countries like Brazil. They are usually caused by dermatophytes and restricted to the stratum corneum.[1] The host immune response against infections caused by dermatophytes depends on factors such as the host defenses against metabolites of the fungus, the virulence of the infecting strain or species, the anatomical site of infection and local environmental factors.[1]

The most prevalent dermatophytes are mainly those of the genera - *Trichophyton, Microsporum* and *Epidermophyton,*[2] classified as anthropophilic, zoophilic and geophilic according to their primary habitat.[3,4] The most common infection in the Americas and in parts of Europe is caused by anthropophilic dermatophytes.[5]

The *Trichophyton rubrum,* an anthropophilic dermatophyte, can cause non-inflammatory chronic infections of the skin, which could facilitate its transmission.[4] Transfer of infectious soil organisms to other animals or humans occurs through arthrospores, skin scales or hair, with direct contact not being necessary. [1] Invasion of the skin follows adhesion of fungal cells to keratinocytes.[6]

2. Factors Predisposing to Skin Infections Caused by Dermatophytes

2.1 Factors related to the host

Susceptibility to dermatophytosis is variable.[7] Individual susceptibility factors are still unclear and may be related to variations in the composition of sebum fatty acids, skin surface carbon dioxide tension, presence of moisture or presence of inhibitors for the growth of dermatophytes in sweat or serum, such as transferrin. [8]

It was experimentally observed that the main efferent arm of immune resistance to fungal infection is T lymphocytes, which are not influenced by administration of specific antibodies. Apparently, the kinetics of the immune response in humans would be similar: during infection, there is the development of both delayed hypersensitivity skin reaction to trichophytin and blastogenic response of T lymphocytes with progression to healing,[9] which relates chronicity to incomplete cellular immune responses. [10]

Participation of each element of the immune response has been explored and gradually elucidated over time: Langerhans cells (LC) act as antigen presenting cells; mononuclear phagocytes, especially polymorphonuclear neutrophils, lyse dermatophytes both intra and extracellularly via the oxidative pathway; [7] and dermatophyte antigens have shown to be chemotactic to human leukocytes, activating the alternative pathway of the complement.[11]

However, with the exception of clinical cases of inflammatory tinea, neutrophils are not usually seen as part of the inflammatory infiltrate observed in histological sections under the microscope. This indicates that other mechanisms of fungal clearance must be involved in this process.[11]

The mechanism(s) through which lymphocytes affect recovery from the disease are less known. It is believed that the immune system amplifies an endogenous epidermal response to infection, since a high rate of epithelial replacement with peak at the maximal immune response is observed. It is possible that elimination of dermatophytes is also accomplished by this shedding of the stratum corneum. [12]

2.2 Factors related to dermatophytes

Factors related to the fungus also contribute to development of infection. Different dermatophyte species vary in their ability to stimulate an immune response: organisms such as *Trichophyton rubrum* cause chronic or relapsing infections, whereas other fungi induce resistance to reinfection.[3,6] Some dermatophytes produce glycopeptides that are able to reversibly inhibit blastogenesis of T lymphocytes *in vitro,* thus modulating host immunity.[3]

It is important to emphasize that dermatophytes cause infection regardless of the patient's immune status.[13] On rare occasions, individuals that are immunocompromised or not develop infections caused by dermatophytes with invasion of subcutaneous tissue. However, the clinical aspect varies. It is less inflammatory in individuals with impaired function of T lymphocytes.[14]

Dermatophyte infections induce specific humoral and cellular immune response,[15-17] with protective response against dermatophytes being mediated primarily by delayed type hypersensitivity reaction, which is characterized by the action of macrophages as effector cells with increased activity of key cytokines of the Th1 pole (Type 1 T helper lymphocytes), such as IL-12 (interleukin-) and INF-γ (interferon gamma). [15]

Thus, the fungus/host interaction, which includes fungus species, host species, immmune response capacity and response modulation by the parasite, will exert influence on the degree of inflammatory reaction, which will define the clinical presentation and duration of the lesion. [15]

Chronic or relapsing infections with *T. rubrum* in immunocompetent individuals are related to the prevalence of immediate hypersensitivity mediated by IgE (immunoglobulin E) to the fungus, as well as high serum levels of IgE and IgG4 (immunoglobulin G4). [15]

3. Cellular, innate and humoral immunity in der-

matophytosis

There is increasing evidence that both anti-fungal protective and non-protective antibodies (inhibitors/blockers) coexist[18] and that host protection could be conferred by induction of appropriate humoral response,[19] since the production of antibodies by the host is induced by antigens secreted by dermatophytes during the early phase of invasion of the stratum corneum, such as keratinolytic proteases. [6, 20-22]

The role of innate immunity in dermatophytoses remains uncertain. It is known that keratinocytes are the first cellular elements with which dermatophytes come into contact during infection[15] and that they modulate the host immune response.[23] Upon exposure to dermatophytes or their antigens, these keratinocytes produce a wide range of cytokines, which include IL-8 (potent neutrophil chemotactic factor) and the pro-inflammatory cytokine TNF (tumor necrosis factor alpha),[24] which, together, can destroy dermatophytes. The various species of dermatophytes differ in their ability to induce secretion of proinflammatory cytokines in keratinocytes. Zoophilic species, for instance, are more effective in causing a greater degree of inflammation in the host's skin. [25]

Human keratinocytes also secrete antimicrobial peptides such as cathelicidins and defensins with potential antifungal activity.[15] Several authors have shown that human ,-defensin and cathelicidin LL-37 are fungistatic and fungicidal *in vitro* against *T. rubrum* and that their expression is increased *in vivo* in tinea corporis caused by this fungus.[26,27]

As for epidermal dendritic cells (DC), especially LC, they are essential to initiate and modulate adaptive responses of the immune system against dermatophytes.[15] They are usually equipped with receptors for pathogen-associated molecular patterns called pattern recognition receptors (PRRs). These PRRs include Toll-like receptors (TLRs), which have a central role in the activation of DC, and lectin and lectin-like receptors, specialized in recognizing pathogen structures associated with carbohydrates. An important example is DC-SIGN (CD209) [dendritic cell-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing non-integrin], a type II transmembrane protein belonging to the C-type lectin family of the PRRs.[28,29]

The study of the role of PRRs in immune response to fungi could explain the chronicity of some infections. Several molecules have been described, including Dectin-2, a C-type lectin-like receptor expressed in most differentiated DC, such as LC, which is able to recognize and bind to *M. canis* and *T. rubrum* hyphae, determining the secretion of proinflammatory cytokines such as TNFα.[28] In contrast to this immunostimulatory effect, phagocytosis of *T. rubrum* conidia by macrophages induces secretion of IL-10, a cytokine with anti-inflammatory properties, while other factors related to protective immunity [such as human leukocyte antigen class II (MHC-II), CD54 and CD80 lymphocytes (costimulatory molecules), nitric oxide and IL-12] are suppressed. [30]

In addition to keratinocytes and DC, neutrophils are important cellular elements in innate immunity to dermatophytes, accumulating early - soon after the adherence of conidia to corneocytes - during germination. Neutrophils are believed to be, together with macrophages, the final effector cells in elimination of dermatophytosis, via Th1-dependent inflammatory response (Figure 1).[15]

Several studies suggest that the immunosuppressive properties of the mannans are responsible for the chronicity of dermatophytosis by *T. rubrum* in humans.[15] One of them emphasizes that phagocytosis of *T. rubrum* conidia by macrophages is inhibited by the mannans of the fungal wall and by their exo-antigen.[25]

Mannans derived from dermatophytes can inhibit DC-SIGN-dependent cell adesion to ICAM-3 of wild-type T cells, which raises the hypothesis that dermatophyte mannans could also avoid initial interactions between DC and wild-type T cells, thus blocking antigen presentation and activation of T cells, favoring the development of invasive or disseminated infections caused by dermatophytes.[31]

The expression of DC-SIGN is IL-4 dependent and is detected in both DC and subtypes of macrophages *in vivo*.[32] DC-SIGN recognizes carbohydrates with mannose and Ca^{2+}-dependent oligosaccharides on the surface of various pathogens such as *Candida albicans, Aspergillus fumigatus* and *Chrysosporium tropicum*.[32] Although the function of this receptor in immune response to fungi has not yet been extensively studied, it is believed that DC-SIGN mediates fungal capture, internalizing antigens through endocytosis,[32] as well as intercellular adhesion, recognizing endogenous molecules such as ICAM-2 on the surface of endothelial cells and ICAM-3 on the surface of wild-type T-cells.[32]

In fact, some characteristics of the immunomodulation practiced by dermatophytes seem to depend not only on factors produced by them in the course of infection but also on how they are detected by the host.[15] Alike Zymosan, which is derived from the yeast cell wall and considered an inducer of proinflammatory cytokines, which was recently identified as an inducer of DC regulating immunological tolerance via TLR-2 and Dectin-1 and a mediator of IL-10 release. [33]

Virulence factors of dermatophytes contribute to modulation of the host immune response and can be expressed throughout the whole infectious process.[34,35] Among these factors are cell wall glycoprote-

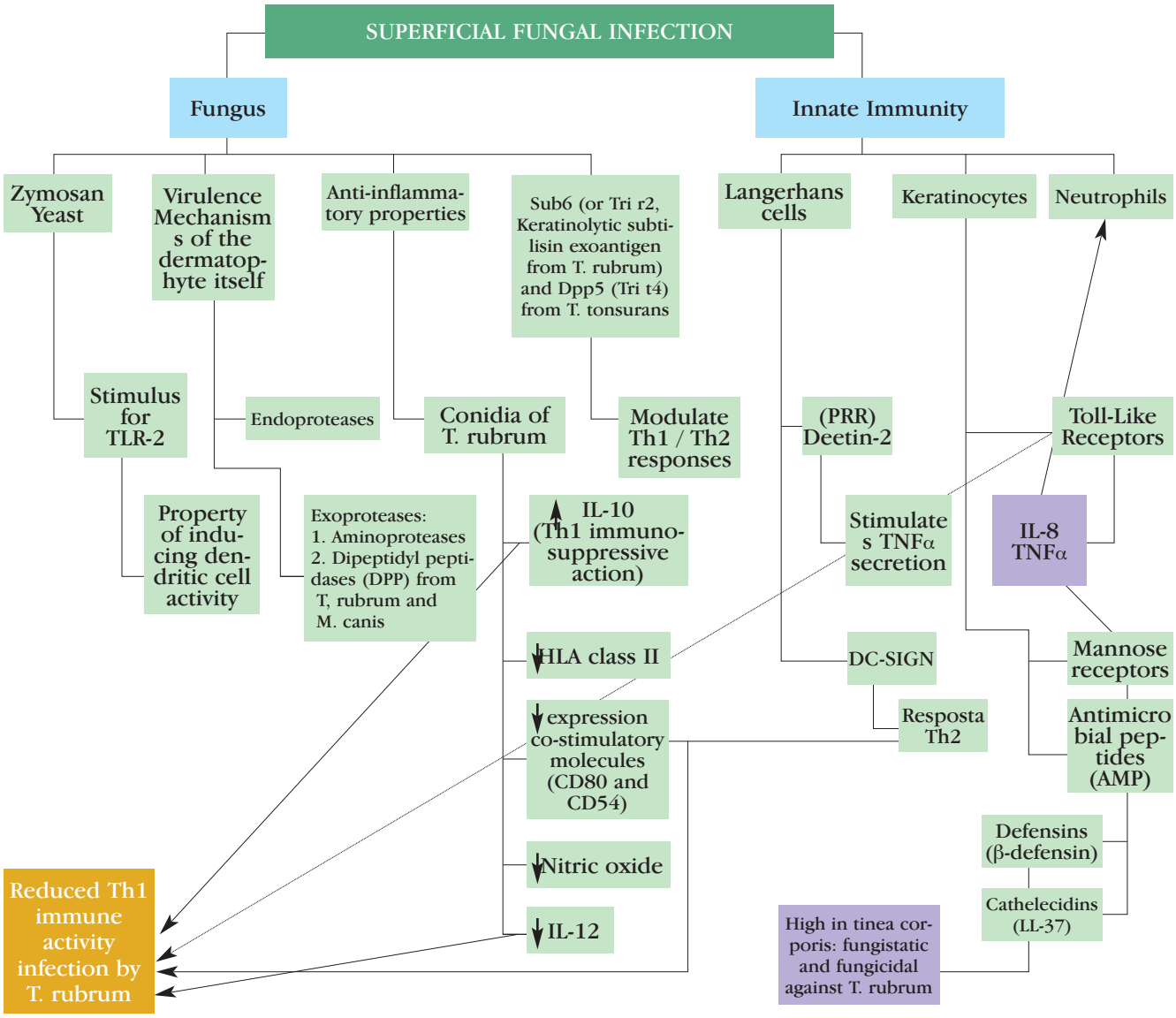

Figure 1: Innate immunity and possible actions in superficial fungal infections. The increased secretion of IL-10 (immunosuppressing action on Th1 activity) determined by T. rubrum conidia and decreased secretion of IL-12 (necessary for Th1 stimulus), both inherent to the action of the pathogen on the host, create an environment conducive to DC-SIGN expression by macrophages, which contributes to chronicity of the infection. We speculate that the expression of Toll-like receptors is also reduced in this context

ins, endoproteases and exoproteases (the latter isolated from *T. rubrum* and *M. canis).*[15]

4. **Toll-like receptors**

TLRs have been observed in several skin cells, including keratinocytes and LC residing in the epidermis and other cells of the immune system (resident or non-resident in the dermis), such as macrophages, T and B cells, mast cells, endothelial cells in the microvasculature and stromal cells (fibroblasts and adipocytes). [36] Since the epidermis is the primary site of dermatophyte infection, we focused on the study of TLR expression by keratinocytes and LC.

TLRs comprise a family of cell surface receptors and constitute key elements in innate or natural immune response, allowing control of the infection until the body orchestrates an antigen-specific immune response (acquired immunity).[37] Although TLRs belong to the innate immune system, they present specificity of response and participate in controlling the activation of the acquired immune response.[37]

Currently, at least 13 different TLR(s) are known, [38] which recognize a wide variety of exogenous and endogenous antigens. The nature of the offending antigen and the TLR to which it binds will determine a specific repertoire of cytokines that is produced by antigen-presenting cells and polarize the acquired immune responses into Th1 or Th2 patterns (type 2 T-helper lymphocytes). [37]

Human keratinocytes express TLRs from 1 to

10.[39] Several studies have proved that these receptors are functional and participate in immune responses.[38,39] *In vitro* studies found that the supernatant from keratinocytes stimulated via TLR3 may stimulate immature DC derived from monocytes toward cell differentiation and, consequently, production of TNFα and type I IFNγ (type I interferon gamma), developing Th1 cell responses from wild-type T cells.[40] This indicates that keratinocytes can direct Th1-type adaptive immune responses.

Activation of different TLRs results in several patterns of immune response.[41] Activation of TLR 3, 4, 5 and 9 in keratinocytes results in production of TNF , IL-8, chemokine CCL2 of monocytes and basophils and macrophage inflammatory protein-3 (CCL20). However, activation of TLR3 and 5 results in increased production of CCL27, promoting the recruitment of memory T cells specifically to the skin. Selective activation of TLR3 and 9 determines the production of CXCL9 and CXCL10, which are important for activation of memory T cells and induction of production of type-I IFN (IFN /). These data demonstrate, in human keratinocytes, that functional TLRs may be important in the induction of different defense responses against various pathogens invading the skin.[38]

There are several studies on the expression and function of TLRs in human LC. [38.39] Comparative studies showed that LC-type DC express the messenger RNA (mRNA) of TLRs 1 to 10 in a way similar to monocyte-derived DC.[42] However, LC-type DC are more responsive to TLR2 ligands (peptidoglycan) and TLR7/8 ligands (R-848 - resiquimod), determining the production of the cytokines IL-8, IL-12 and TNF and the chemokines CCL3 and CCL4. [42] It was also observed that stimulation of LC via TLR3 increased the production of INFγ, suggesting that LC could initiate a direct antiviral activity through stimulation of TLR3. Thus, it is believed that human LC express functional TLRs, which are more active to stimulation with TLR2, 3, 7 and 8 ligands.[38]

In vitro studies with other fungi or yeast, such as *C. albicans,* have shown that TLR2 recognizes the glycopeptide phospholipmannan on the surface of the cell wall of the micro-organism and TLR4 recognizes the polysaccharide mannan, also on the fungal cell wall.[43,44] That is, the expression of TLR2 and TLR4 in keratinocytes is important for the host defense against *C. albicans.* [45]

Studies conducted in *Paracoccidiodies brasiliensis, A. fumigatus and Cryptococcus neoformans* suggest the involvement of TLRs in the recognition of these pathogens. [44,46-49] In paracoccidioidomycosis, possible regulation of DC in susceptible mice was observed, promoting IL-10 production and contributing to the increased susceptibility mediated by the expression of TLR2.[50]

A possible mechanism of susceptibility was considered after an experimental comparison of the expression of DC in mice susceptible and in mice resistant to *P. brasiliensis.* There is reduced production o IL-10, IL-12 and TNF-α in mice resistant to fungal infection, whereas there would be increased production of TNF-α, IL-12, CD80 and CD54 in susceptible mice, as well as increased phagocytosis. Activation of TLR2 would be responsible for the production of IL10 and its increased production would contribute to increase susceptibility to infection. [50]

There are still no published studies regarding the expression of TLRs in infections caused by dermatophytes *in vivo.*

It is suggested that *T. rubrum* has the ability to suppress the expression of TLR receptors in keratinocytes and LC necessary for stimulation of Th1-type cell response. Consequently, there would be marked expression of DC-SIGN in macrophages of the epidermis and dermis, which occurs in Th2-type responses, which are inadequate to fight fungal infection. This would allow a chronic and extensive infection caused by this dermatophyte to set in.

5. Final Thoughts

Although a reasonable number of *in vitro* or experimental studies is found in the literature, little is known about the immune response *in vivo* or the expression and role of TLRs, DC-SIGN, Dectin-2 and other molecules in skin infection caused by dermatophytes.

So far, what is more accepted is that superficial mycosis, with more or less clinical expression of inflammation, as well as its prognosis towards healing or chronicity, depends on cellular or humoral predominance in innate or acquired immune response.

Despite the fact that more and more is known and recognized about the immunological role of the skin, the histopathological and ultrastructural patterns of inflammatory response, in innate or acquired immunity of the skin, have not yet been accurately evaluated so that it is possible to define the role and involvement of immunocompetent cells resident in human epidermis when faced with the need to overcome superficial mycosis. ❑

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How to cite this article/*Como citar este artigo*: Criado PR, Oliveira CB, Dantas KC, Takiguti FA, Benini LV, Vasconcellos C. Superficial mycosis and the immune response elements. An Bras Dermatol. 2011;86(4):726-31.