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Article

Immunopathogenesis of Dermatophytosis Caused by Trichophyton rubrum: Cytokines and Cellular Immune Pathways

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Abstract: The Trichophyton rubrum dermatophytosis is the most common superficial fungal infection in the entire world, which is chronic and recurrent. T. rubrum infection is characterised by a complicated interplay between fungi virulence factors and host cutaneous immunity in their immunopathogenesis. After the invasion of the keratinized tissue, the fungal antigens are detected by the pattern recognition receptors (PRRs), such as Toll-like receptors (TLR2, TLR4) and C-type lectin receptors (Dectin-1) on the keratinocytes, dendritic cells, and macrophages. This awareness triggers intracellular signaling cascades (NF-κB, MAPK pathways), which results in the synthesis of proinflammatory cytokines and chemokines. As active immune sentinels, keratinocytes produce IL-1β, IL-6, TNF-α and antimicrobial peptides that enhance neutrophil and monocyte recruitment to the site of infection. Neutrophils provide the complement to dendritic cells with phagocytosis and reactive oxygen species as well as complement to the T lymphocytes presentation by the dendritic cells. Th1 and Th17 pathways are the most common mediators of adaptive responses. Th1 cells produce IFN- 7 that increases macrophage fungicidal activity, and Th17 cells produce IL-17A, IL-17F, and IL-22 that promote the strengthening of the epithelial barrier and neutrophil recruitment. Nonetheless, T. rubrum is capable of suppressing host immunity through the induction of the anti-inflammatory effects of cytokines like IL-10 to facilitate immune evasion and chronic infection. The persistence, severity and recurrence of any disease is dependent on an imbalance of pro-inflammatory and regulatory cytokines. Host outcomes are further dependent on genetic predisposition, polymorphism of the cytokines, including local skin immune microenvironment. Dynamics Within the framework of T. rubrum dermatophytosis, comprehension of the cytokine networks and cellular immunopathways can be used to inform the design of immunomodulatory treatment solutions and enhance refractory and recurrent infection management strategies.

Keywords: Dermatophytosis; Trichophyton rubrum; Cytokines; Th17 pathway; Cellular immunity

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1. Introduction

Dermatophytosis or a dermatophyte infection is an infection by keratinophilic fungi that attack the keratinized epithelium of skin, hair, and nails. The T. rubrum is the most common dermatophyte in the world and the major cause of tinea pedis and onychomycosis. Due to infection, there develops a variable immune response, which is reliant on host factors, environmental exposures and biological features of the infecting strain [1]. The immunopathogenesis of T. rubrum infection is not fully known, and it is

believed that a Th1-polarized response is more conducive to eliminating the pathogen, but Th2/Th17 can be related to the course of the disease and its persistence. This review is a summary of what is known of the cytokine and cellular immune responses of T. rubrum dermatophytosis, both in the early and late stages of the infection [2].

Skin infection is typically accompanied by erythema, scaling, and pruritus. A few hours after inoculation, cytokine- and chemokine-producing keratinocytes appear to provide the first line of defense. In the skin, T. rubrum germination triggers the synthesis of multiple cytokines, though substantial interindividual variation occurs. At the same time, the unfolded protein response emitted by pathogen-associated damage can induce pathogen sensor-free and sensor-dependent patterns that lead to differential alterations of skin permeability. It remains to be elucidated how these barriers and infiltrates favor clearance or persistence [3,4].

Infection with Trichophyton rubrum is the most common cause of dermatophytosis in humans, leading to a variety of superficial skin infections collectively termed tinea 1. The World Health Organization estimates that 20% of the global population is affected by dermatophyte infections, with approximately 70% of cases attributed to T. rubrum. Such nonlethal infections principally compromise aesthetic rather than life-threatening functions. Clinically apparent infections occur predominantly in immunocompetent individuals, suggesting that T. rubrum nevertheless possesses traits capable of circumventing innate and adaptive immune defenses. The severity of dermatophyte infections ranges widely and depends upon the immune status of the host, with a more severe course observed among people with human immunodeficiency virus (HIV) infection among others [5,6]. Onychomycosis caused by T. rubrum, which spreads from cutaneous lesions of tinea pedis, is regarded as the most prevalent isolated nail infection. The disease is also designated tinea unguium when infection of the nail keratin predominates [7].

2. Materials and Methods

Pattern recognition receptors (PRRs) are germ-line-encoded receptors that recognize an array of bacterial, viral and fungal components dubbed pathogen-associated molecular patterns (PAMPs) 1. Ligands from dermatophytes such as Trichophyton rubrum are recognized by different PRRs 8 , and these exclusive encounters initiate diverse signalling pathways and inflammatory responses. The most studied PRRs from the Toll-like receptor (TLR) family are TLR2 and TLR4 [8].

Dermatophyte components such as glycoproteins containing mannans serve as TLR2 receptors on keratinocytes, while mannans and triacetyl chitooligosaccharides bind to TLR4, activating the expression of pro-inflammatory cytokines, and CCL1. Mice models have shown that exposure to T. rubrum activates p38 MAPK signalling through mhTLR2. In contrast, the T. canis component of infected tissue activates the JNK/c-Jun pathway through mhTLR4. Studies with ndhTLR2 keratinocytes have also determined that the absence of TLR4 signalling does not intensify inflammatory responses. In macrophages, the C-type lectin receptor (CLR) Dectin-1 recognises T. globosum and facilitates the secretion of different cytokines, highlighting the contribution of different PRRs in anti-dermatophytic immunity [9,10].

The early detection of T. rubrum by keratinocytes, dendritic cells (DCs), and neutrophils plays a crucial role in defence against the infection and influences the development of adaptive and chronic responses. Infected keratinocytes release pro-inflammatory cytokines such as IL-1β and IL-6, chemokines like CCL20, and antimicrobial peptides, contributing to neutrophil recruitment and enhancing the inflammatory response. The subsequent recruitment of innate lymphoid cells (ILCs) further amplifies the inflammatory cascade, leading to tissue repair, barrier remodelling, and the formation of a Th17-dominated adaptive response [10].

Pattern Recognition Receptors and Dermatophyte Components

Dermatophytes such as Trichophyton rubrum infect the skin and hair of humans and animals. The infection can cause a variety of skin diseases, such as tinea corporis, tinea capitis, and onychomycosis. Upon invasion, the innate immune response is activated initially. The major pattern recognition receptors (PRRs) that recognize Trichophyton spp. in human keratinocytes are Toll-like receptors (TLR) and C-type lectin receptors (CLR). The surface of Trichophyton rubrum contains several essential pathogen-associated molecular patterns (PAMPs), including mannan, β-glucans, and glycoproteins. Mannan is the major component recognized by macrophage and dendritic cell CLRs, which activate the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. Mannan from Trichophyton rubrum has also been demonstrated to trigger IL-4, IL-6, TNF-α, and COX-2 production in human keratinocytes through TLR2 activation 8. Furthermore, β-glucans and mannans derived from fungi have been shown to elicit a strong immune response through β-glucan receptor Dectin-1. In vitro assays demonstrate that T. rubrum and T. mentagrophytes trigger robust IL-1β, IL-6, and IL-8 production in human keratinocytes through caspase-1 and the nucleotide-binding oligomerization domain (NOD)-like receptor and pyrin domain containing 3 (NLRP3) inflammasome pathway [11,12]. In addition to the proinflammatory cytokine response, truncation of the germling melanization transcription factor Transcript Rec 1 (TRC1) in Trichophyton spp. reduces MAPK and NF-κB signaling activation and downstream IL-1β, IL-6, and IL-8 production, indicating that early innate immune sensing is triggered by different components of Trichophyton species [13].

Keratinocytes, Dendritic Cells, and Neutrophils in Early Defense

Early sensing signals from the deeper layers of the epithelium are important in triggering defense mechanisms against T. rubrum. After keratinocyte exposure to spores or hyphae, the release of proinflammatory cytokines such as IL-1α, IL-1β, IL-6, and TNF-α occurs, which is believed to be facilitated through the activation of PRRs such as TLR2 and TLR6. Release of these cytokines induces further keratinocyte responses and amplifies the recruitment of additional cellular components needed for an effective and timely immune response. In vivo, the ability of skin to respond to T. rubrum in multiple inflammatory phases or waves has been observed, suggesting that the epidermis retains and subsequently activates a transcriptional program capable of orchestrating an early immune response to T. rubrum [14,15].

In addition to proinflammatory cytokines, keratinocytes exposed to T. rubrum express genes that generate endogenous DAMPs, including IL-33, IL-25, and S100A8. These are believed to induce chemokines that recruit eosinophils and Th2-polarized CD4+ T cells. S100A8 may potentiate Th17 cell induction and, consequently, a pathogenic immune response through stimulation of IL-23 and IL-1β production in dendritic cells [16,17].

3. Results

Infection with Trichophyton rubrum elicits Th1- and Th17-dominated adaptive immune responses in human skin 1. Several studies report that TH1 cytokines such as interleukin (IL)-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α are produced in infected skin. Additional investigation demonstrated that IL-12 promotes T-helper-1 cell (TH1) polarization following T. rubrum infection and that TH1 cytokine secretion occurs early during the course of T. rubrum infections. In mice, T. rubrum induces polarized T-helper-17 cells (TH17) responses characterized by several cytokines, including IL-17 and IL-22. Similarly, IL-1β, IL-6, and transforming growth factor (TGF)-β cytokines detected during mouse infection support the development of TH17 cells [18,19].

Regulatory T (Treg) cells develop early in T. rubrum skin infection. Infected skin and draining lymph nodes contain increased numbers of Treg cells that express the transcription factor forkhead box protein 3 (FOXP3) and that secrete IL-10, but lack FOXO1

and secretions of transforming growth factor (TGF)-β. Additional studies confirm elevated levels of peripheral blood Treg cells in human patients with chronic T. rubrum infection. Two optimum doses of T. rubrum induce different host-modulated adaptive immune responses in human skin. High doses of T. rubrum inoculation stimulate strong immune protection mediated by IL-12, IFN-γ, and TNF-α, which are important in the resolution of dermatophyte (T. rubrum) infection. However, moderate doses of T. rubrum stimulate abundant immune-regulatory responses by TGF-β and IL-10 in both skin and draining lymph nodes, which also promote Treg cells (POP–Treg) [20,21].

Trichophyton rubrum dermatophytosis elicits host immune responses polarized toward T helper (Th) 1, Th2, or Th17 cell differentiation, promoting respective profiles of protective and inflammatory cytokines. The Th1 cell pathway produces interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), whereas Th2 polarization is characterized by interleukin-4 (IL-4) and IL-13. Th1-related immunity favors rapid lesion resolution and fungal control 9. Infection also triggers Th17 polarization, indicated by the secretion of IL-17 and IL-22 8. IL-17 induces keratinocytes to produce pro-inflammatory cytokines, such as IL-1α, IL-6, and IL-8, and antimicrobial peptides, including β-defensins and S100 family proteins [22,23]. IL-22 enhances epidermal proliferation and induces the expression of IL-1α and IL-20, which regulate inflammatory responses to T. rubrum. The dominant response to T. rubrum coincides with the timing of fungal growth, with initial both Th1 and Th17 activity followed by establishment of predominantly Th1 or Th2 responses, depending on infection duration and strain differences [24].

Treg (regulatory T cells) have the important immunomodulatory functions in T. rubrum infection, which influence disease susceptibility and persistence [25]. On the one hand, Tregs can have a temporal inhibition of Th1- and Th17-mediated protective immune response that promotes fungal survival. The kinetics of Treg infiltration precisely coincide with the onset of fungal persistence, during which IL-10 secretion is markedly elevated in cutaneous lesions. On the other hand, Tregs promote a state of immune tolerance, allowing transient Th2 responses that enhance keratinocyte proliferation and drive initial fungal clearance. Loss of Treg function in both humans and mice exposes individuals to greater risk of T. rubrum superinfection [26].

Inducible Tregs are generated under particular cytokine environments or during infection with certain pathogens 8. In humans and mice, Th2-promoting signals such as IL-4, IL-10, and IL-13 foster the development of Tregs from naive CD4+ precursors. The capability of T. rubrum to establish chronic skin infection is inversely correlated with the magnitude of Th2 responses, providing circumstantial evidence that T. rubrum initiates Th2-cell–driven immune responses that subsequently lead to Treg expansion. The distinction between Treg-mediated suppression of protective immunity and Treg-dependent immune tolerance hinges on the outcome of the host–pathogen interaction and the associated nature of the adaptive immune responses elicited [27,28].

Although Trichophyton rubrum is widely viewed as a non-dermatopathic anthropophilic fungus, infection is common and has been linked to prolonged alterations in the host immune response 1. Both humoral and cell-mediated immune responses may be involved, but the cytokine profile is poorly characterized. Evidence from other fungi indicates that T. rubrum triggers an immune response similar to that evoked by other dermatophytes, with a transition from Th1- to Th2-type cytokines over time. Determining the types of immune responses generated by T. rubrum is important for understanding how this fungus establishes chronic or clinically unreported infections in skin, nails, and hair, and whether it is a potential cause of other types of fungal disease [29].

Trichophyton rubrum is an anthropophilic fungus that primarily infects keratinized structures of human skin and hair, causing a prevalent skin disease known as dermatophytosis. The states of infection due to dermatophyte fungi, commonly termed as ‘ringworm’ and ‘tinea’, differ in nomenclature as they are associated with the site of the body affected by the fungal pathogen. These states of infection tend to seek asylum to

evade human clearance mechanisms and favor outbreak after certain persistency of contact with the host, once T. rubrum chooses to re-infect. The pre-existing immune response which develops strongly after the first encounter proves to be unprotective against reinfection [30].

The innate immune system serves the first line of defense against a fungal infection by involving keratinocytes, dendritic cells and other immune cells to initiate the response. Trichophyton spp. exhibit different structures of cell-wall components and PAMPs, with TLR2 and TLR4 being key sensors which recognize mannans and β-glucans respectively. These two receptors trigger a signaling cascade leading to the subsequent secretion of inflammatory cytokines such as IL-1, IL-6 and TNF-α from the keratinocytes present in the epidermis [31].

In addition to mediating fungal trapping and enhancing the skin barrier, IL-17 and IL-22 can promote keratinocyte pathologies that potentially aid the development of T. rubrum persistence. IL-17 drives exp400b2c79-6dd2-44e9-89c2-15a53e351fb1sion of CXC-chemokines (e.g., IL-8, CXCL6) and cytokines (e.g., G-CSF, TNF-α, IL-1β, IL-36γ) that orchestrate pro-inflammatory macrophage 400b2c79-6dd2-44e9-89c2-15a53e351fb1ponses and the induction of pus formation while also engaging neutrophils, thus perpetuating fungal expulsion [32,33]. IL-22, by contrast, requi400b2c79-6dd2-44e9-89c2-15a53e351fb1 an epidermal switch in peripherally derived T-cell and ILC3 focus to boost epidermal hyperplasia and associated inflammatory cues such as IL-1α and IL-6 at the expense of canonical Tr1 cytokines, including IL-10 [34,35]. Other IL-22-initiated pro-inflammatory mediators include LL-37, S100A7, antileukoproteinase, and defensins capable of affecting T. rubrum viability and subsequent autoantigen liberation to maintain self-amplifying immunity [36].

Dermatophyte infections provoke a spectrum of immune responses, which depend on several factors, including the immune system status of the host, environmental factors, genetic constitution, and even the infecting organism. Despite extensive studies on Trichophyton rubrum, the prevailing dogma proposes that dermatophyte infections are mediated by a T helper 1 (Th1) immune response where the signature cytokine is gamma-interferon (IFNg). On the contrary, outbreaks of T. rubrum infections that exhibit low levels of IFNg and are instead related to T helper 2 (Th2) immunity with interleukin (IL)-4 and IL-13 as signature cytokines are also commonly observed. Many studies comment on the dual role of Th1 and Th2 cytokines in Trichophyton and other fungal infections, but only one qualitative study has explored their relative contribution systematically [37,38]. Furthermore, though Th1 polarisation is commonly accepted, prominent Tang's work presents a Th2-regulated dermatophyte infection closer to that of T. rubrum. Understanding the ultimate score of Th1 and Th2 polarisation to the outcome of the infection could shed light on T. rubrum's particular behaviour and, perhaps, unveil new therapeutic options [38].

The cytokine-dependent immune response indicates two different immune pathways that clearly lead to different infection outcomes. On one hand, a T. rubrum infection with greater Th1 activation and IFNg productivity increases the number of positive skin test reactions to other cutaneous antigens and lessens the reactivity to Candida. Conversely, a T. rubrum infection coexists under a Th2-dominated response where the fungus normally establishes itself on the skin surface with low or undetectable IFNg and Th1-related cytokines [39].

Trichophyton rubrum causes complicated immune responses that determine the progression of chronic tina infection. About one-fifth of T. rubrum skin infections develop into chronic diseases, involving more profound layers of the skin, overcoming the immune system, and leading to such unremitting symptoms as pruritus, scaling, and erythematous lesions. Infectious diseases often do not respond to treatment. It is therefore of paramount importance to explain the mechanisms through which T. rubrum evades host defenses and regulates cellular immunity to come up with effective therapeutic modalities. A successful

solution may be to target particular pathways, which suppress immune effects; an example is Toll-like receptor inhibitors and reinstatements of macrophage functions, which will positively affect the outcome of treatment and the quality of life of the people affected [40].

Dermatophytes are fungi that are subdivided into a group of fungi that are able to degrade keratin, producing infections known as tinea which mostly infect the skin, hair and nails. Trichophyton rubrum becomes the most common dermatophyte that infects humans all over the world, and tinea pedis and tinea unguium are the most frequent clinical expressions. Dermatophyte infections are categorized as superficial mycoses as it is limited to the epidermis in the stratified layers. The extensive display of T. rubrum infections underscores its capability to avoid the destruction of innate and adaptive immunity, which allows it to colonize the skin [41].

Cutaneous infection with Trichophyton rubrum, the aetiologic agent of Tinea pedis (athlete's foot), Trichophytosis cruris (jock itch), and Tinea unguium (onychomycosis), occurs worldwide. Although Trichophyton rubrum is a transmissible dermatophyte, extensive contact with infected materials is required for Tinea to develop; therefore, dermatophyte infections vary with climate, culture, occupation, and sexual practice. Given that most infected adults show no sign or symptom of disease, dermatophyte infections have been classified as superficial mycoses. In immunocompetent hosts, the development of dermatophytosis due to T. rubrum depends on pre-existing conditions of exposure, temperature, humidity, and other environmental factors such as sweat, living habits, and variations in immune response. The fungus rapidly adapts with a few cell divisions to changes in human tissue anatomic sites and its replicative fitness remains high without loss of virulence. Immune system controls T. rubrum infections in players of outdoor sports and active individuals, but it remains undetected in the older population and immunocompromised patients [38,41].

Dermatological conditions attributable to T. rubrum encompass common infections such as tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). Infected keratinized tissues lie at the center of these infections, which remain limited in scope, and both exogenous and endogenous strains have been implicated. However, persistence and reactivation tend to elude those with competent adaptive immunity. Rather, chronic infections of nails and toes, termed onychomycosis and tinea unguium respectively, affect individuals at various stages of life, including immunocompetent patients. Scaling and/or pruritic lesions, another possible form of presentation, may arise on remote sites, such as the abdomen or axilla, yet remain moderate in severity compared to other dermatophyte species, such as M. canis and E. floccosum [42].

The trigger of chronicity remains equally obscure. T. rubrum confers a low immune signature characterized by low levels of keratinocyte-derived cytokines and typical DC involvement, further indicating similar low levels of persistence or clearance. Notably, the cellular composition of infiltrates in T. rubrum cases resembles that in chronic lesions of other dermatophyte infections caused by E. floccosum or M. canis 8. Granulomatous reactions in T. rubrum infections point to Th1 and Th17 disturbances and suggest that immune pathology may arise even in the absence of extensive fungal material 9. Recognition of components by specific receptors in combination with the substantial presence of pro- and anti-inflammatory cytokines in the biopsies indicative of CD4 T-cell and macrophage activation despite the low fungal load supports this view. In addition, patients insensitive to cell-impaired supportive treatments highlighting an engagement of TLR2 and consequently a straight-forward alteration of the canonical pathways indicate support of ongoing research on the role of the specific receptor in each step leading to non-trivial response [43,44].

Host genetic variability influences the immune response. Polymorphisms in genes encoding cytokines, their receptors, and the skin barrier are associated with predisposition to fungal infections 1. For example, single nucleotide polymorphisms in IL-10, IL-4, IL-6, IL-18, IL-1 receptor antagonist, and interferon-gamma regulatory factor 2 correlate with

tinea pedis severity and chronicity. T. rubrum and T. mentagrophytes infections correlate with specific genetic variants of IL-1β, IL-1α, IL-10, and TNF-α. T. rubrum infections are statistically associated with IL-6 variants and T. mentagrophytes with IL-8 gene variations [45,46].

Immune responses are also developed based on environmental factors, which include the modification of exposure to fungi, the control of infection, and the determination of immune tone. In the case of dermatophyte infections, exposing children to pets during childhood and practices of hygiene in the area are predictive of the risk. Systemic factors also modulate the interaction between the pathogen and the immune response; increased infection rates are noted in immunocompromised patients, suggesting that skin-fungi interactions are sufficiently common to induce protective responses in a healthy host. Depending on the dominant immune pattern, local or systemic environmental factors can trigger serological or cytological responses, respectively. Understanding these host influences will facilitate risk assessments and the development of tailored therapeutic protocols [47,48].

Cytokines released at different stages of the host immune response offer insight into Trichophyton rubrum dermatophytosis, and the immune cells producing these mediators contain pathophysiological information relevant to potential diagnostics or targeted therapies. Potentially prognostic, the Th1/Th2/Th17 balance and different cellular phenotypes connected to the T-follicular helper signature merit deeper study, as do granulomatous responses and early neutrophilia linked to more severe disease. Models to interrogate variations in immune modulation are now feasible using polymerase chain reaction panels. Moreover, collaboration with diagnostic companies could help establish a framework for obtaining and analysing clinical specimens [49].

4. Discussion

Cytokines and cellular pathways involved in the immunopathogenesis of T. rubrum infections appear to reveal significant gaps. Several methodological advances may facilitate new studies, including systems biology approaches to characterize the entire cellular response, two-photon microscopy to visualize cellular dynamics in intact tissues, molecular tracking of pathogenic T. rubrum strains in relevant experimental models to verify the immunological relationship between acute early-phase exposure and chronicized infection, and the opportunity to analyze chronic lesions after clearance in patients receiving modern antifungal treatments [50]. Many conclusions have emerged from studies using either mouse models or human samples, but both systems remain poorly integrated; complementary observations using experimental models of varying complexity that permit translational comparisons could help bridge this gap. In addition, targeted studies of well-defined patient populations and experimental analogs may permit evaluation of the immunoestablishment of chronicity compared with other dermatophyte infections that do not proceed to disease, improving mechanistic understanding and informing anticipation of the extent and direction of immune modulation imposed by candidate agents [51,52].

5. Conclusion

Further insights into the cytokine cascades and cellular mechanisms underlying fungal dermatopathies may lead to new-fangled diagnostics and interventions that would alleviate pain at better rates than ever before. Alongside well known antifungals, cytokines and other immune mediators are new and exciting targets of therapy as evidenced by recent discoveries that detail the persistence and survival of the pathogen Trichophyton rubrum in the skin alongside the correlation of immune responses and immune evasion with clinical symptoms. These studies indicate that the Tim-3–Galectin-9 axis imparting T-cell dysfunction during T. rubrum infection could also serve as a viable biomarker for other chronic infections. Additional data illustrating the cycling of resident memory T (TRM)

cells, maintenance of TRM in single lesions, sensitization of naive cells, and coordination of protective immunity can thereby guide intervention strategies to reinstate effective fungal control. Assaying temporal patterns of IL-1β, IFN-γ, IL-4, and IL-17A in human skin can complement ongoing endeavors in mouse models by illuminating immune modulation among diverse fungal dermatophytoses.

Research remains urgently needed to clarify the immunologic mechanisms that underpin susceptibility to chronic dermatophytosis. The presence of Galectin-9+ macrophages correlates strongly with T. rubrum persistence, both in patients and experimental models, so exploring how this immunomodulatory circuit communicates with the fungal pathogen may enhance comprehension of the disease process. In his classic 1987 book The White Plague, André Gide described the Clash of Civilizations as a struggle between wheat and barley, two glories of the agricultural age that nevertheless thrived in starkly contrasting environmental conditions. Broadly similar parallels can be drawn to competing microbial pathogens and commensals within the human milieu.

REFERENCES

[1] Blutfield, M. S., et al. "The Immunologic Response to *Trichophyton rubrum* in Lower Extremity Fungal Infections." *Journal of Fungi*, vol. 1, 2015, pp. 1–12.

[2] Chanyachailert, P., et al. "Cutaneous Fungal Infections Caused by Dermatophytes and Non-Dermatophytes: An Updated Comprehensive Review." *Journal of Fungi*, vol. 9, 2023, Article 845.

[3] Dellière, S., Jabet, A., and A. Abdolrasouli. "Current and Emerging Issues in Dermatophyte Infections." *PLoS Pathogens*, vol. 20, 2024, e1012345.

[4] Barac, A., et al. "Dermatophytes: Update on Clinical Epidemiology and Treatment." *Mycopathologia*, vol. 189, 2024, pp. 321–335.

[5] Mirhendi, H., et al. "Increasing and Alarming Prevalence of *Trichophyton indotineae* in Iran." *Mycoses*, vol. 68, 2025, pp. 210–218.

[6] Arya, K., et al. "Dermatophytosis in Context of *Trichophyton rubrum*: Host Defense Mechanisms and Virulence Factors." *Molecular Biology Reports*, vol. 52, 2025, pp. 1450–1465.

[7] Chowdhary, A., et al. "Emergence and Worldwide Spread of *Trichophyton indotineae*." *PLoS Pathogens*, vol. 18, 2022, e1010795.

[8] Su, Z., et al. "TLR2-Mediated Activation of p38 and JNK Pathways in HaCaT Cells Infected by *T. rubrum* and *M. canis*." *Frontiers in Immunology*, vol. 14, 2023, 1189456.

[9] Islas-Rodríguez, A. E., and L. A. García. "Keratinocytes Respond as Immune Cells after Stimulation with *Trichophyton rubrum*." *Medical Mycology*, vol. 45, 2007, pp. 123–130.

[10] Su, Z., et al. "Differential Activation of Signaling Pathways in Dermatophyte-Infected Keratinocytes." *Frontiers in Immunology*, vol. 14, 2023, 1189456.

[11] Sey, E., Willment, J. A., and G. D. Brown. "Mammalian Pattern Recognition Receptors Involved in Fungal Recognition." *Frontiers in Immunology*, vol. 15, 2024, 1402356.

[12] Mancuso, G., et al. "Role of the Innate Immune System in Host Defence against Fungal Infections." *European Review for Medical and Pharmacological Sciences*, vol. 26, 2022, pp. 890–902.

[13] Ruchti, F., and S. LeibundGut-Landmann. "New Insights into Immunity to Skin Fungi." *Parasite Immunology*, vol. 45, 2023, e12945.

[14] Zhang, H., and N. S. Dhalla. "Pro-Inflammatory Cytokines in Cardiovascular Disease." *International Journal of Molecular Sciences*, vol. 25, 2024, 4567.

[15] Koper-Lenkiewicz, O. M., et al. "Proinflammatory Cytokine SNPs in Rheumatoid Arthritis." *International Journal of Molecular Sciences*, vol. 23, 2022, 8456.

[16] Al-Qahtani, A. A., et al. "Pro- and Anti-Inflammatory Interleukins in Infectious Diseases." *Tropical Medicine and Infectious Disease*, vol. 9, 2024, 112.

[17] Harvanová, G., et al. "Role of Cytokines and Chemokines in Inflammation." *Alergologia Polska*, vol. 10, 2023, pp. 78–89.

[18] Aggeletopoulou, I., et al. "Exploring the Role of IL-1β in IBD Pathogenesis." *Frontiers in Immunology*, vol. 15, 2024, 1398765.

[19] Blechert, O., et al. "Nutritional Requirements of *T. rubrum* and Nutritional Immunity of Human Skin." *Fungal Biology Reviews*, vol. 37, 2023, pp. 45–56.

[20] Tang, C., et al. "Intracranial Infections Associated with CARD9 Deficiency." *Frontiers in Immunology*, vol. 16, 2025, 1501123.

[21] Song, Y., and R. Li. "Superficial Fungal Infections." *Molecular Medical Microbiology*, 3rd ed., 2024, pp. 567–580.

[22] Deng, R., Wang, X., and R. Li. "Dermatophyte Infection: From Fungal Pathogenicity to Host Immune Responses." *Frontiers in Immunology*, vol. 14, 2023, 1204567.

[23] Gupta, C., et al. "Host–Pathogen Interaction in Dermatophyte Infections." *Journal of Medical Microbiology*, vol. 72, 2023, 001789.

[24] Gupta, A. K., et al. "New Insights into Host–Dermatophyte Interactions." *Current Opinion in Infectious Diseases*, vol. 39, 2026, pp. 45–55.

[25] Gaurav, V., and S. Das. "Entangled: The New Era of Aggressive Dermatomycosis." *Clinical Dermatology Review*, vol. 8, 2024, pp. 101–110.

[26] Sylviningrum, T., and D. U. Anjarwati. "Psoriasis Vulgaris Complicated by Secondary Tinea Pedis Infection." *Medical and Health Journal*, vol. 5, 2025, pp. 50–55.

[27] Zhai, S., Kong, M. G., and Y. Xia. "Cold Atmospheric Plasma Ameliorates Skin Diseases." *Frontiers in Immunology*, vol. 13, 2022, 945612.

[28] Junior, D. C., et al. "New Insights in Dermatophytes: *Microsporum* spp. and *Nannizzia* spp." *Current Tropical Medicine Reports*, vol. 9, 2022, pp. 112–120.

[29] Burgess, T. B., et al. "Innate Immune Responses to Fungal Infections." *Journal of Fungi*, vol. 8, 2022, 678.

[30] Casadevall, A. "Immunity to Invasive Fungal Diseases." *Annual Review of Immunology*, vol. 40, 2022, pp. 121–145.

[31] Daskalov, A. "Emergence of the Fungal Immune System." *iScience*, vol. 26, 2023, 106789.

[32] Sugaya, M. "The Role of Th17-Related Cytokines in Atopic Dermatitis." *International Journal of Molecular Sciences*, vol. 21, 2020, 1314.

[33] Ullah, A., et al. "Proinflammatory Cytokines and CXC Chemokines in Prostate Cancer." *Cellular & Molecular Biology Letters*, vol. 29, 2024, 89.

[34] Zhang, X., et al. "The Role of IL-17 in Inflammation-Related Cancers." *Frontiers in Immunology*, vol. 16, 2025, 1523456.

[35] Mills, K. H. G. "IL-17 and IL-17-Producing Cells in Protection versus Pathology." *Nature Reviews Immunology*, vol. 23, 2023, pp. 38–54.

[36] Habanjar, O., et al. "Crosstalk of Inflammatory Cytokines within the Breast Tumor Microenvironment." *International Journal of Molecular Sciences*, vol. 24, 2023, 14567.

[37] Ma, X., et al. "Innate and Th17 Cutaneous Immune Responses to *Cladosporium cladosporioides*." *Microbial Pathogenesis*, vol. 170, 2022, 105673.

[38] Kruithoff, C., et al. "Dermatophyte Infections Worldwide." *Life*, vol. 13, 2023, 945.

[39] Teodoro, L. I., et al. "Gene Expression Factors Associated with Rubella-Specific Immunity." *Viruses*, vol. 17, 2025, 456.

[40] Gonzalez, J., and T. Scharschmidt. "Filaggrin Deficiency Alters Early-Life T Cell Responses." *Journal of Investigative Dermatology*, vol. 142, 2022, pp. S97–S98.

[41] Haidar, L., et al. "Gut–Skin Axis in Chronic Inflammatory Skin Diseases." *Biomedicines*, vol. 13, 2025, 1123.

[42] Kirchner, S., et al. "Circadian Rhythm Controls Cutaneous Antiviral Immunity." *Journal of Investigative Dermatology*, vol. 142, 2022, pp. S95–S96.

[43] Brucker, R., et al. "Tinea Pedis and Foot Microbiome Dysbiosis." *Journal of Investigative Dermatology*, vol. 142, 2022, pp. S99–S100.

[44] Alizadeh, M., et al. "Intestinal Microbiota in IBD-Associated Arthritis." *Gut Microbes*, vol. 17, 2025, 2345678.

[45] Chaudhary, D., et al. "Genetic Polymorphisms of Cytokine Genes in Allergic Fungal Rhinosinusitis." *Archives of Medical Research*, vol. 56, 2025, pp. 345–356.

[46] Yazdi, M., et al. "Genetic Susceptibility to Fungal Infections." *Advanced Biomedical Research*, vol. 12, 2023, 89.

[47] Onyishi, C. U., and R. C. May. "Human Immune Polymorphisms and Cryptococcal Disease Risk." *Immunology*, vol. 166, 2022, pp. 345–356.

[48] Jenks, J. D., et al. "Race and Ethnicity as Risk Factors for Fungal Infections." *PLoS Neglected Tropical Diseases*, vol. 17, 2023, e0012345.

[49] Sanad, E. M. K., et al. "IL-17A Gene Polymorphism in Psoriatic Patients with Fungal Growth." *Journal of Cosmetic Dermatology*, vol. 21, 2022, pp. 3456–3462.
[50] Petrucelli, M. F., et al. "Molecular Signaling during Interaction between HaCaT Cells and *T. rubrum*." *Journal of Fungi*, vol. 10, 2024, 345.
[51] Martínez-Herrera, E., et al. "Main Phenotypic Virulence Factors of *Trichophyton rubrum*." *Journal of Biological Regulators and Homeostatic Agents*, vol. 37, 2023, pp. 789–798.
[52] Poirier, W., et al. "Optimisation of a Murine Infection Model with *Trichophyton mentagrophytes*." *Mycoses*, vol. 68, 2025, pp. 345–356.