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EDITORIAL

Dermatophytes and Dermatophytoses: A Thematic Overview of State of the Art, and the Directions for Future Research and Developments

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Fungal pathogens predominant on the hair, skin, and nail ('dermatophytes') cause most common mycotic diseases ('dermatophytoses') worldwide. Although fatal rarely, dermatophytoses manifest as significant causes of hair and nail loss, inflammation, pustules, itching, and scaling. *Mycopathologia* continues to maintain a dual focus on both dermatophytes and dermatophytoses. The balanced coverage of the clinical and laboratory developments had been reinvigorated by periodic special issues. A 2008 special issue covered 14 relevant topics that generated over 1600 citations so far [1]. The present special issue builds upon the previous coverage after a gap of 8 years. Twenty-one invited articles contributed by 60 experts all over the word focus on four major themes including pathogen–host genetics, clinical prevalence, presentation, therapy and laboratory diagnosis, and host–pathogen interactions.

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de Hoog, Graser, and colleagues describe a taxonomic reappraisal of dermatophytes in the first article of this special issue [2]. Notably, 13 new combinations are proposed based on the internal transcribed spacer (ITS) regions 1 and 2 of ribosomal DNA (rDNA) and partial LSU, the ribosomal 60S protein, and fragments of β-tubulin and translation elongation factor 3. The affected taxa are the geophilic and zoophilic *Microsporum* species. Seven phylogenetic clades were identified and the nomenclature summarized. All anthropophilic *Trichophyton*, as well as *Epidermophyton*, are within the derived clades. This most comprehensive overview of the family Arthrodermataceae is likely to become the sole source for authentic information of pathogenic dermatophytes. This seminal work is also likely to guide future taxonomic and phylogenetic studies [2]. Genetic manipulations of pathogenic fungi are essential tools to get a deeper insight into pathogenic mechanisms, and finding a better cure eventually. These experimental approaches took a while to become available for the dermatophytes as they exhibit high frequency of non-homologous recombination. Alshahni and Yamada map the recent progress in the transformation and manipulations of gene expressions among various dermatophyte species [3]. An inventory of dominant selectable markers, an inducible promoter, and marker recycling system is provided to highlight both the challenge and progress being made with the molecular toolbox. The authors include a brief description of the whole genome sequences and transcriptomes of dermatophytes and their potential to enhance the selection and experimental targeting of genes and genomes of dermatophytes [3]. Metin and Heitman describe the extant evidence for sexual reproduction in the dermatophytes [4]. A detailed insight into the organization of the two mating loci in different phylogenetic clade is presented. The authors also include comparative schematics on the organization of the MAT locus in different pathogenic fungi. The concluding comments address the observed sexual reproduction in geophilic and zoophilic species and its absence in anthropophilic species [4]. It has been known for almost thirty years that there is a significant genetic and physiological variation among the clinical isolates of dermatophytes. Mochizuki, Takeda and Anzawa detail the tools for the molecular epidemiology of dermatophytes so as to highlight the inter- and intraspecies differentiations among various pathogens [5]. Their overview details some investigations on the application of mitochondrial DNA analysis, random amplification of polymorphic DNA (RAPD), sequencing of the ITS or non-transcribed spacer (NTS) regions of rDNA, and microsatellite analysis for genotyping. Some host- and pathogen-specific attributes of dermatophytes have already been discovered. Nevertheless, the more refined discriminatory power of the whole genome comparisons will likely lead to more discoveries of the strain variations [5]. All human populations are exposed to dermatophytes, but dermatophytoses are more prevalent in certain communities and ethnic groups. Does host genetics plays a role in susceptibility to dermatophytes? This intriguing question is the central theme of the article by Abdel-Rahman [6]. The theme is summarized in schematic that goes to highlight the genetic evidence of association and causal relationships. Some genetic loci and their putative roles are summarized succinctly. The author concludes by highlighting the need for future genetic studies so as to define the host genes critical in susceptibility and resistance to dermatophytoses [6].

Zhan and Liu cover the rise and fall of various dermatophytes as prominent pathogens globally [7]. Their analysis stretching back to the beginning of the twentieth century focuses on the socioeconomic conditions, life style changes, and the introductions of new drugs as the major drivers of these changes. Hay's rich clinical and research experience with Tinea capitis provides an excellent coverage of the topic with initial comments on great advances made in the understanding of host–pathogen interactions [8]. His expert review covers epidemiology, clinical varieties, conditions, differential diagnosis, management, and community control. Also highlighted is the introduction of more sensitive molecular diagnostic tests in routine clinical practice. In concluding comments, Prof. Hay highlights the recent discovery of CARD9 deficiency as a risk factor and the opportunity for the future development of a vaccine [8]. Asz-Sigall and colleagues provide an overview of dermatophyte nail infections termed onychomycosis or *Tinea unguium* [9]. This clinical condition has assumed great significance given increased incidences of *T. rubrum* infections of the nails and the therapeutic challenges. The epidemiology, etiology, clinical features, diagnosis, various treatment options, and the criteria for cure are covered with most appropriate literature citations [9]. The appearance of the typical dermatophyte lesion on the skin might be mimicked by other, non-fungal etiologies. Libon and colleagues highlight the clinical and histopathological appearances of dermatophyte infections of hair and skin with a special focus on the intertriginous regions [10]. The lucid description is enhanced with many illustrative photographs from the affected patients. Equally importantly, these experts go on to cover the differential diagnostic features and methods for the relevant skin lesions [10]. Pin presents a comprehensive overview of the clinical presentations of dermatophytoses in animals [11]. Several illustrative photographs accompany the expert commentary. Additionally, the clinical presentations of non-dermatophytic dermatoses mimicking dermatophytoses are also compared and contrasted. Gupta's unique perspective on the antifungal drugs against dermatophytes includes a progress report since the publication of a similar article in an earlier special issue of *Mycopathologia* [12, 13]. In collaborations with colleagues, Dr. Gupta describes the main treatment modalities in use against various forms of 'Tinea.' Although focused on studies from Europe and North America, the pros and cons of various drugs and dosages are covered in sufficient detail with citations of relevant publications. The authors also provide insight as to how new formulations of existing drugs as well as drug delivery innovations are invigorating the treatment options despite a lack of new classes of antifungal drugs against dermatophytes [13]. As the pharmaceutical choices for dermatophytoses are perceived to be limited, the natural products are being still evaluated for their direct efficacy and as the source for new drugs. Lopes and colleagues review published evidence of anti-dermatophytic properties in various classes of plant-derived compounds and their active chemical constituents [14]. They highlight the need for more standardization of test methods and ex vivo–in vivo testing.

Dermatophytes are not only the most common fungal infections, but they are most likely to be diagnosed both by the physicians and by the laboratorians by direct microscopy. Pihet and Le Govic focus on the reappraisal of the direct examination and culture for dermatophyte diagnostics [15]. The authors cover the techniques in details, evaluate merits and shortcomings as well as recent improvements, and end with the focus on the demonstrated sensitivity of molecular methods. The availability of commercial DNA kits is likely to promote wider acceptance of non-culture-based tests although the culture remains relevant to confirm atypical pathogens [15]. L'Ollivier and Ranque share extensive experiences with MALDI–TOF dermatophyte identifications [16]. Many helpful tips for the sample preparations, analysis, and reference spectra library vividly illustrate their rich expertise. The promise of this approach is weighed against the evidence from ten published studies that report 13.5–100% accuracy in the identification of dermatophytes. The authors emphasize the need to expand the commercial reference spectra libraries of uncommon and rare species so as to make MALDI–TOF as the gold standard for identification of dermatophytes [16]. As stated earlier, the diagnosis of dermatophytoses is unique among fungal infections as it could be performed both by the laboratory and by the physician often right at the time of the patient visit. In the USA, the federal laboratory regulations exempt this process from rigorous oversight by treating it as a unique 'provider performed microscopy' (PPM). Some new developments indicate that direct microscopy might not be the best diagnostic approach for the dermatophytoses. Verrier and Monod present a strong case for the primacy of PCR and real-time PCR as diagnostic tools for dermatophytoses of hair, skin, and nail [17]. The advantages are many—higher sensitivity and specificity, more accuracy, and ability to find fungal elements independently of prior treatment history. A few challenges remain including the feasibility, affordability, and a lack uniformity among the preparative methods used for DNA extraction. The authors present comprehensive literature overview and alternate scenarios for the selection of traditional and molecular methods [17]. Hayette and Sacheli deviate from the obvious to provide an excellent overview of new pathogenic species of *Microsporum* and *Trichophyton* [18]. Next, they summarize recent clinical reports on rare pathogens of this group. Lastly, they highlight the unusual clinical manifestations of the common pathogens included among dermatophytes. These details are interspersed with relevant references to any documented transfers of the etiologic agents from animals or soil to humans [18].

Dermatophytes must reprogram their cellular processes to sense and adapt to the host surfaces. Martinez-Rossi and colleagues highlight the fungal transcription factors, proteins, and enzymes involved in this multifactorial process [19]. The adaptations are made in the face of specific host factors elucidated in response to the infection. The challenges posed by unique pH of the host surfaces and the optimal expression of fungal keratinases at such a pH are covered in great detail. The authors make frequent reference to the available whole genome sequences of many dermatophytes, which also provides a roadmap for future investigations aimed at understanding the pathogenesis of dermatophytes [19]. Cambier and colleagues start their overview of published animal models by providing a context for the continuing need for the experimental studies [20]. Next, they do a critical review of published mouse, guinea pig, and rat models. The overview is organized into separates studies on pathogenesis, host response, or efficacy of antifungal treatments. The authors conclude by providing a critique of approaches adopted so far and a possible solution to establishing a workable model in nude mice [20]. Yoshikawa and colleagues detail *T. rubrum* interactions with mouse J774 macrophage-like cells [21]. The authors found *T. rubrum*-induced cell death and release of IL-1β. They also profiled proteomic changes in the macrophages following fungal interactions. The specific observations in this tractable cell line strongly indicate its relevance as an ex vivo model [21]. Heinen and colleagues focus on the emerging role of Th17 pathway in immunity against dermatophytoses [22]. The available direct evidence from animal studies and indirect evidence from receptors and APCs are summarized in informative schematics. The exciting possibility of finding an innate mechanism for Th17 pathway involvement in dermatophytoses is emphasized [22]. Yoshikawa and De Almeida revisit the role of innate immunity against dermatophytosis by focusing on the phagocytic cells including neutrophil extracellular traps (NETs) [23]. The authors cover recent studies on the host pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) involved against dermatophytes. Also covered is the role of inherited CARD9 deficiency as a risk factor for dermatophytoses. Although still in its infancy, insights into how dermatophytes avoid neutrophils, and the induction of NETs would further promote our understanding of innate immune responses against this group of fungal pathogens [23].

We are confident that this sweeping overview of the dermatophytes and dermatophytoses served to convince you the reader about the satisfactory pace of progress made during the last decade. However, as always, more scientific progress leads to additional unanswered questions. We would welcome insight into how many species of dermatophytes there really are, how dermatophytes evolved as pathogens, how do these pathogens maintain and reinvigorate their pathogenic potential, where to find untapped chemical moieties to develop new drugs, and finally, is culture-independent diagnostic testing likely to replace direct microscopy and culture? It is our earnest hope to cover these and other interesting developments in the next special issue in 2028!

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