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Psoriasis and *Malassezia* Yeasts

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1. Introduction

There is evidence that psoriasis is principally a T cell-mediated skin disease. The interaction between T cells and keratinocytes via cytokines probably plays a very important role in the pathogenic process (Lee & Cooper, 2006). However, little is known about the initial stimulus that leads to the abnormal T-cell activation.

Yeasts of the genus *Malassezia* are now considered synonymous with those previously named *Pityrosporum*, which are members of the normal cutaneous microbiota from humans and other warm-blooded animals. They have also been associated with several skin diseases such as pityriasis versicolor, seborrheic dermatitis and atopic dermatitis (Gupta et al., 2004; Ashbee 2007).

Although streptococcal infection is the commonest and best delineated infective trigger for psoriasis, fungal infections have been noted on occasion to cause an exacerbation of psoriasis or psoriatic arthritis (Fry & Baker, 2007).

The role of *Malassezia* species in psoriasis is still undetermined, but several reports have associated these lipophilic yeasts with the development of skin lesions in psoriasis. Mostly of these studied are treatment studies, showing the efficacy of antifungal drugs, both topical and systemic, in the treatment of the disease (Rosenberg & Belew, 1982; Alford et al., 1986).

Currently, the genus *Malassezia* includes 14 species, which have been identified traditionally based on their morphology and biochemical features (Cafarchia et al., 2011). Since the description of new species a number of studies have evolved to elucidate the role of the different species in the ecology and pathogenicity in a range of dermatoses, in which variable results have been reported from different geographical regions.

2. *Malassezia* yeasts

2.1 Description and natural habitats

The genus *Malassezia* (former *Pityrosporum*) belongs to basidiomycetous yeasts and is classified in the *Malasseziales* (*Ustilaginomycetes, Basidiomycota*) (Boekhout & Gueho, 2003).
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Malassezia yeasts are part of the normal cutaneous commensal flora. However, under the influence of predisposing factors these yeasts are able to cause a number of cutaneous and systemic diseases in humans and different animal species. Unlike many other microorganisms, Malassezia yeasts are rarely found in the environment. Their natural habitat is primarily the skin of most warm-blooded vertebrates (Midgley, 2000).

Malassezia yeasts have an affinity for lipids as substrates and the term ‘lipophilic yeasts’ is frequently used to identify the genus. Due to their dependence on lipids for survival, they are most often found in sebum rich areas of the skin such as scalp, face and the trunk. Less frequently, they may be also found on other areas of the body including arms, legs and genitalia.

Colonization with Malassezia may occur as early as neonatal period and increases after puberty, which is related to the increase in skin surface lipids that results from higher sebaceous gland activity during this period. Their density varies depending on age, body site, geographic area, and the presence of normal or diseased skin (Ashbee, 2006).

2.2 Historical review and taxonomy

The taxonomy of Malassezia has been confused because yeasts are dimorphic, existing in both yeast and mycelial (hyphal) forms, depending on culture conditions.

For many years two taxonomy systems existed. The yeast phase was originally described as Pityrosporum and the mycelial phase as Malassezia, with two species M. furfur and M. pachydermatis, before they were unified in 1986 with both phases included in Malassezia (Cannon, 1986).

On the basis of genome differences, in 1990, the third species M. sympodialis was described (Simmons & Gueho, 1990), and some years later, with the use of new molecular techniques, the genus was taxonomically revised and enlarged with four new species: M. slooffiae, M. globosa, M. obtusa and M. restricta (Gueho et al., 1996). M. pachydermatis is the only non lipid-depended species confirmed to be associated with animals, while remaining species are obligatory lipophilic and found primarily in humans (Guillot & Bond, 1999).

Furthermore, in last few years some new species have been isolated from human (M. dermatis, M. japonica and M. yamotensis) and animal skin (M. nana, M. caprae and M. equina, M. cuniculi) (Sugita et al., 2002; Sugita et al, 2003; Sugita et al, 2004; Hirai et al., 2004; Cabañes et al., 2007; Cabañes et al., 2011). At present, 14 species of Malassezia have been identified.

The different species of Malassezia yeasts that are known so far are shown in Table 1. No doubt that additional new species will be identified from both humans and animals in close future.

2.3 Biological, cultural and immunological characteristics

The different Malassezia species are distinguished based on their morphology, growth characteristics, enzyme activities, as well as by molecular characteristics.
<table>
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<tr>
<th>Malassezia specijes</th>
<th>First description</th>
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<th>Isolation from animals</th>
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<tr>
<td><em>M. furfur</em></td>
<td>Baillon 1889</td>
<td>Healthy skin</td>
<td>Healthy skin</td>
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<td></td>
<td></td>
<td>Skin diseases: mainly pityriasis versicolor, systemic infections</td>
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<tr>
<td><em>M. pachydermatis</em></td>
<td>(Weidman) Dodge 1925</td>
<td>Systemic infections</td>
<td>Healthy skin: mainly dogs and cats</td>
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<td></td>
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<td>Skin diseases: seborrheic dermatitis and otitis in dogs</td>
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<tr>
<td><em>M. sympodialis</em></td>
<td>Simmons &amp; Guého 1990</td>
<td>Healthy skin</td>
<td>Healthy skin</td>
</tr>
<tr>
<td></td>
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<td>Skin diseases: atopic dermatitis</td>
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<td><em>M. slooffiae</em></td>
<td>Guillot, Midgley &amp; Guého 1996</td>
<td>Healthy skin: external ear canal Skin diseases: pityriasis versicolor</td>
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<tr>
<td><em>M. globosa</em></td>
<td>Midgley, Guého &amp; Guillot 1996</td>
<td>Healthy skin Skin disease: mainly pityriasis versicolor</td>
<td>Healthy skin: otitis in cats</td>
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<td><em>M. obtusa</em></td>
<td>Midgley, Guillot &amp; Guého 1996</td>
<td>Healthy skin Skin diseases: mainly pityriasis versicolor</td>
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<tr>
<td><em>M. restricta</em></td>
<td>Guého, Guillot &amp; Midgley 1996</td>
<td>Healthy skin Skin diseases: mainly pityriasis versicolor</td>
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<td><em>M. dermatis</em></td>
<td>Sugita, Takashima, Nishikawa &amp; Shinoda 2002</td>
<td>Healthy skin Skin diseases: atopic dermatitis</td>
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<td><em>M. japonica</em></td>
<td>Sugita, Takashima, Kodama, Tsuboi &amp; Nishikawa 2003</td>
<td>Healthy skin Skin diseases: atopic dermatitis</td>
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<tr>
<td><em>M. yamatoensis</em></td>
<td>Sugita, Takashima, Tajima, Tsuboi &amp; Nishikawa 2004</td>
<td>Healthy skin Skin diseases: seborrheic dermatitis</td>
<td></td>
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<tr>
<td><em>M. nana</em></td>
<td>Hirai, Kano, Makimura, Yamaguchi &amp; Hasegawa 2004</td>
<td>Skin diseases: cats and cows</td>
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<tr>
<td><em>M. caprae</em></td>
<td>Cabanes &amp; Boekhout 2007</td>
<td>Healthy skin: goats</td>
<td></td>
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<tr>
<td><em>M. equina</em></td>
<td>Cabanes &amp; Boekhout 2007</td>
<td>Healthy skin: horses</td>
<td></td>
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<tr>
<td><em>M. cuniculi</em></td>
<td>Cabanes, Vega &amp; Castella 2011</td>
<td>Healthy skin: rabbits</td>
<td></td>
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</tbody>
</table>

Table 1. *Malassezia* species isolated from humans and animals
The fungus is dimorphic, existing in both saprophytic yeast and a parasitic mycelial form. The yeast form is most commonly associated with normal skin and predominates in culture, although hyphae may be seen with some species (Saadatzadeh et al., 2001).

For direct demonstration of the yeasts, the specimen is collected from the clinical lesions by scraping or tape stripping and a potassium hydroxide mount is prepared. The cells are morphologically variable, occurring in round, oval or cylindrical forms. They show the production of blastoconidia by a process of repetitive monopolar or sympodial budding. Direct microscopy of the pityriasis versicolor scales reveals predominantly hyphae with clusters of yeast cells (spaghetti and meatball appearance), due to the phase transition from yeast to mycelium seen in this disease (Figure 1).

Fig. 1. The typical appearance of the hyphae and spores of *Malassezia* in the scales of pityriasis versicolor

The colonies of *Malassezia* spp. are raised, dull, creamy yellow and have a characteristic brittle texture (Figure 2). The characteristic morphological features of *Malassezia* yeasts include thick, multi-layered cell wall which is surrounded by a lamellar layer which contains lipids (Gueho et al., 1996).

Fig. 2. The colonies of *M. globosa* on modified Dixon agar
*Malassezia* species produce a wide range of enzymes, including lipases, phospholipases and hydrolase. The lipases are essential in providing the lipids required for growth in vitro and in vivo. All species of *Malassezia* with the exception of *M. pachydermatis*, are lipid-dependent due to an inability to synthesize long-chain saturated fatty acids (Nazzaro Porro et al., 1986; Juntachai et al., 2009).

To differentiate among the *Malassezia* species, cultures should be done in special media (Leeming and Notman agar or modified Dixon agar), except for *M. pachydermatis*, the only one that is able to grow in Sabouraud agar (Guillot et al., 1996).

However, difficulties in cultivating *Malassezia* organisms may limit the analyses and bias the observations (Batra et al., 2005). Thus, molecular approaches, particularly analyses of ribosomal genes and internal transcribed regions, have been used for detection, identification, and characterization of *Malassezia* species (Cafarchia et al., 2011).

*Malassezia* has the ability to stimulate the immune system via classical and alternative complement pathways, acting as an adjuvant and elicits both humoral and cellular immune response. In contrast, it is able to resist phagocytic killing by neutrophils and downregulate cytokine responses when co-cultured with peripheral blood mononuclear cells. With the interaction of yeasts with keratinocytes they induce the production of different cytokines, especially IL-6, IL-8 and IL-10 (Asbbee 2006; Blanco & Garcia 2008).

### 2.4 Human disease associated with *Malassezia* yeasts

In recent years, the genus *Malassezia* has come to be considered important in the etiology of various skin and systemic diseases. Both immunocompetent and immunosuppressed patients may be affected by this type of infection. In immunologically competent hosts, *Malassezia* species are implicated in the pathogenesis of variety of skin infections such as pityriasis versicolor, *Malassezia* folliculitis, seborrheic dermatitis, and, rarely, in a range of other dermatological disorders (Midgley 2000; Gupta et al., 2004). In contrast, in immunocompromised patients, including patients with AIDS, immune-haematological, oncological, and solid organ and bone marrow transplant recipients, these yeasts have been associated with catheter-related fungemia, sepsis and a variety of deeply invasive infections (Tragiannidis et al., 2010).

The etiological role of *Malassezia* yeasts in pityriasis versicolor is unquestioned; the organism found in the lesions is predominantly in its mycelial phase (Crespo et al., 1999; Gupta et al., 2001; Prohic & Ozegovic, 2007; Trabelsi et al., 2010).

In the case of the other skin diseases such as seborrheic dermatitis, *Malassezia* folliculitis, confluent and reticulate papillomatosis, atopic dermatitis, and psoriasis, the pathogenic role of *Malassezia* yeasts remains less clear; transition of the yeast cells to their pathogenic hyphal form cannot be clearly demonstrated (Gupta et al., 2004; Ashbee 2007).

With the revision of the taxonomy of *Malassezia*, new questions have been raised about their significance and relative prevalence in various dermatologic disorders.

The diseases where *Malassezia* species have been implicated and the most frequent species isolated are summarized in Table 2.
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3. Psoriasis

3.1 Superantigens

The pathogenesis of psoriasis is quite complex, but there is compelling evidence that T-cell activation and resultant overproduction of proinflammatory cytokines are critical for the development and maintenance of psoriatic lesion (Lee & Cooper, 2006; Tokura et al., 2010).

A variety of different environmental factors are accepted as of importance in provoking new episodes of psoriasis or in modifying preexisting diseases. They include trauma, infections, drugs and psychological stress (Fry & Baker, 2007). However, definite proof that particular autoantigens, antigens or both contribute to the immunopathology of psoriasis is still lacking.

Nevertheless, a number of keratins microbial proteins have been postulated as putative candidates (Jones et al., 2004). Keratin (K) 13 has significant homology with K17, which was previously identified as candidate autoantigen based on the presence of both antibodies and T cells that cross-react with a streptococcus M protein (Gudmundsdottir et al, 1999). Furthermore, K13 is not present in adult skin normally, but is present in fetal skin (van Muijen et al, 1987), and is up-regulated during trauma or inflammation. (Kallioinen et al, 1995). This could potentially provide an explanation for the Koebner phenomenon, where new psoriasis plaques can flare up at or old lesions spread to a site of injury.

Superantigens may exacerbate psoriasis by stimulating T cells to initiate the pathogenic events of psoriasis. Microorganisms such as β-haemolytic streptococci, *Staphylococcus aureus* and *Candida albicans* have been suggested as external triggers that activate large number of T cells and release proinflammatory cytokines, particularly tumour necrosis factor (TNF)-α (Macias et al., 2011). Massive cytokine production could lead to reduced vascular tone, resulting in widespread organ hypoperfusion, acidosis and multiorgan failure.

3.1.1 Bacterial superantigens

Streptococcal superantigens appear to play a direct role in the pathogenesis of guttate psoriasis. It is well documented that streptococcal infection can trigger guttate psoriasis or
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exacerbate chronic plaque psoriasis, possibly through the release of bacterial superantigenic toxins, now known as streptococcal pyrogenic exotoxins (Gudjonsson et al., 2003).

The high level of streptococcal throat cultures and sore throats in chronic plaque psoriasis implies that patients with chronic plaque psoriasis are extremely efficient at streptococcal throat carriage. It was purposed that part of the psoriatic genotype protects against death during epidemics of invasive streptococcal infections, but at the expense of increased streptococcal carriage and predisposition to the development of psoriasis (McFadden et al., 2009).

Furthermore, T lymphocytes specific for group A streptococci have been isolated and cloned from the skin of guttate psoriatic patients suggesting a role of these cells in the disease process (Baker et al., 1993; Valdimarsson et al., 1995). These observations indicate that streptococcal infections are major etiological factors for psoriasis in genetically predisposed individuals. However, this does not exclude a role for other microorganisms in the disease.

3.1.2 Fungal superantigens

Fungal organisms have also been suggested as external triggers that release factors which serve as superantigens and stimulate T cells to initiate the pathogenic events of psoriasis (Waldman et al., 2001).

Regarding the prevalence of Candida albicans infections in psoriasis, data are controversial. Some authors found no increase in the prevalence of Candida in intertriginous area of psoriatic patients as compared with healthy individuals (Flytstrom et al., 2003; Leibovici et al., 2008). As ketoconazole appeared to be helpful in the treatment of some inverse psoriasis patients, the authors suggested an anti-inflammatory effect, which may explain some of its beneficial effects irrespective of Candida infection. However, Rebora reported the presence of Candida in the intertriginous areas of psoriatic patients and commented that Candida present in the intertriginous areas disappears when replaced by Gram negative bacteria, but leaves a kobnerising effect (Rebora, 2004).

4. Malassezia and psoriasis

4.1 Historical review

Rivolta made the first association of the lipophilic yeasts and psoriasis in 1873 (Rivolta, 1873). He reported on round double-contoured budding cells in the epidermis of a patient with psoriasis and named them Cryptococcus psoriasis.

The role of Malassezia yeasts in psoriasis is still undetermined, but there are several reports indicating that these microorganisms are able to elicit psoriasiform lesions in both human and animals. Rosenberg reported that, after heavy dense suspensions of Malassezia were applied to the shaved rabbits skin, lesions both grossly and microscopically similar to psoriasis developed. The lesions persisted as long as Malassezia continued to be applied but otherwise resolved within 3 to 4 days (Rosenberg et al., 1980).
The same group claimed to be able to induce lesions that developed following patch testing with sonicates of heat killed *Malassezia* cells on nonlesional skin of patients with psoriasis and biopsy specimens showed features consistent with psoriasis (Lober et al., 1982).

Although a Koebner phenomenon could not be excluded, their hypothesis was that psoriasis was produced by *Malassezia* yeasts through activation of the alternative pathway of complement, and also activated by other microorganisms and endotoxins.

Elewski reported of a patient developing guttate psoriasis in sites of *Malassezia* folliculitis. In this case, pustules transformed into guttate lesions prior and during erythromycin therapy but resolved when ketoconazole was applied (Elewski, 1990). Although this transformation could also be Koebner phenomenon, this case report supported the proposal that psoriasis may be included in *Malassezia*-associated diseases.

The beneficial effect of both oral and topical ketoconazole, followed by reduction of yeasts, indicates that *Malassezia* yeasts may represent another antigenic stimulus in psoriasis (Rosenberg & Belew, 1982). Although this antimycotic drug may act through a direct mode of action, it has also been shown that it can suppress *Malassezia*-induced proliferation of lymphocytes in psoriatic patients and thus reduce the response to the antigenic stimulation in skin lesions (Alford et al., 1986).

More recent studies have indicated that *Malassezia* yeasts cause exacerbation of psoriasis by triggering the release of cytokines, in particular IL-8 through a Toll-like receptor 2-mediated pathway (Baroni et al., 2006). However, convincing evidence of their importance in the pathogenesis of the disease is still lacking.

### 4.2 Isolation to the species level

Since the description of the new species some studies have focused on their distribution in various diseases, and also in psoriasis.

The identification of *Malassezia* yeasts to a species level is of no diagnostic value in skin diseases, as the same species form an integral part of normal cutaneous microflora in humans. However, it is of great importance to determine which species are implicated in certain skin disease and whether there is variation in the distribution of the yeasts with clinical data, body site, origin of the population, etc.

The results of the *in vitro* susceptibility studies have shown variations in susceptibility of the seven *Malassezia* species to ketoconazole, variconazole, itraconazole, and terbinafine. Strains of *M. furfur, M. globosa, and M. obtusa* were more tolerant to terbinafine than other species, while *M. sympodialis* was found to be highly susceptible (Gupta et al., 2000). Therefore, correct identification of *Malassezia* species is required for the selection of appropriate antifungal therapy.

Some authors have stated that *M. globosa* predominate (Prohic, 2003; Zomorodian et al., 2008) whilst others have found *M. restricta* (Amaya et al., 2007) or *M. sympodialis* (Hernandez et al., 2003) to be the most common species in scalp lesions of psoriasis.

The higher detection rate of *Malassezia* species was observed using molecular determination method than by conventional culture methods. These variations may be attributed to the
different sampling technique and inadequate determination of the relative proportion of species on the skin, or the consent ability of the fungus to grow in each specified medium that have impact on the range of species recovered. Geographical and racial factors were also suspected as playing a part in the results yielded by conventional culture systems (Sandstrom Falk et al., 2005).

4.3 Immune response to Malassezia yeasts

Psoriasis is also known to have a strong genetic component. Therefore, several studies have examined the immune responses of psoriasis patients to Malassezia. It has been shown that these individuals have immunologic responses to both Malassezia yeasts and to proteins derived from them. T cells reactive to the various morphological variants of yeasts have been isolated from lesional skin, but they were not specific for the disease (Baker et al., 1997). Furthermore, antibodies to proteins from Malassezia have been reported in patients with psoriasis, but not healthy subjects (Squiquera et al., 1994; Liang et al., 2003). These antibodies were subsequently shown to recognize the N-acetylglucosamine terminals of glycoproteins present in Malassezia (Mathow et al., 1996). However, both of these proteins are recognized by sera from patients with atopic dermatitis (Lintu et al., 1997; Nissen et al., 1998), and so they are not specific markers for psoriasis.

Kanda et al. found that Malassezia yeasts induce Th-1 and Th2-related cytokine, chemokine and prostaglandin E2 production in peripheral blood mononuclear cells from patients with psoriasis vulgaris (Kanda et al., 2002).

Furthermore, Malassezia can invade cultured human keratinocytes, modulate proinflammatory and immunomodulatory cytokine synthesis, and affect the expression of cutaneous proteins (Baroni et al., 2001). A study done by same authors added to the evidence of its role in the hyperproliferation seen in psoriasis. Using western blot analysis they found that Malassezia can induce the overproduction of molecules involved in cell migration and hyperproliferation, thereby favoring the exacerbation of psoriasis. (Baroni et al., 2004).

Malassezia species differ in their ability to induce cytokine production by human keratinocytes, which is reflected in the different inflammatory responses in Malassezia-associated dermatoses, resulting in varied clinical and pathological manifestations.

A study examining the chemotaxis of neutrophils from psoriatic patients and controls demonstrated the presence of Malassezia-derived soluble components with chemo-attractant properties for polymorphonuclear leukocytes of psoriatic patients (Bunse & Mahrle, 1996).

Psoriatic lesions often develop at sites of trauma (the Koebner phenomenon) (Mohla & Brodell, 1999), and the increased chemotactic response of neutrophils to Malassezia was suggested to play a role in this event.

Kesavan et al. have shown that Malassezia yeasts significantly reduce the production of pro-inflammatory cytokines what is related to the presence of lipid-rich microfibrilar layer
surrounding yeast cells (Kesavan et al., 1998) High quantity of lipid may prevent the yeast cell from inducing inflammation what is in consistent with their commensal status. Further study by the same group demonstrated that extraction of cell wall lipids reversed their capacity to reduce the level of pro-inflammatory cytokines (Kesavan et al., 2000). In psoriasis, however, these yeasts fail to possess lipid layer due to abnormalities in enzymes involved in lipid formation in stratum corneum of patients with psoriasis.

5. Conclusion
The role that Malassezia plays in psoriasis is, as yet, undetermined. Although it may contribute to the inflammation associated with the disease, via complement activation and neutrophil recruitment, convincing evidence that it is of prime importance in the pathogenesis of the disease is still lacking.

6. References
Psoriasis and Malassezia Yeasts


Psoriasis and Malassezia Yeasts


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

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