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Review Article

Malassezia spp. beyond The Mycobiota

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Abstract

Malassezia species are part of the normal mycobiota of skin of animals and humans but they can cause skin and blood stream infections as well. These yeasts are all lipid dependent explained by the absence of fatty acid synthase genes in their genome. At the same time, metabolic reconstruction revealed differences in the metabolism of fungal steroids and degradation of CoA-activated long-chain FAs, arachidonic acid, and butanoate metabolism between *Malassezia* yeasts. In addition, differences in the assimilation of palmitic acid were predicted. Indeed, *M. furfur* was able to metabolize palmitic acid but *M. globosa, M. sympodialis, M. pachydermatis,* and an atypical variant of *M. furfur* were not able to do so. Tools to genetically modify *Malassezia* have become available recently, which will speed up the process to decipher mechanisms underlying growth and pathogenicity of these yeasts. Here, we will provide an overview about the genus *Malassezia* and make an assessments to the new insights in this yeast.

Introduction to the Genus *Malassezia*

The genus *Malassezia* belongs to the phylum Basidiomycota and comprises 14 established species as well as 3 species that were first described in 2016 (Table 1) [1-4]. *Malassezia* yeasts are part of the microbiome of healthy human skin but they have also been associated with dermatological conditions like dandruff (D), Seborrheic Dermatitis (SD), and Pityriasis Versicolor (PV) [5,6]. Moreover, they have been associated, albeit at low incidence, with systemic infections in patients such as neonates that receive intravenous lipid therapy. As such, they are recognized as opportunistic pathogens [7-10]. *Malassezia* is characterized by lipid-dependency due to the lack of cytosolic Fatty Acid Synthase (FAS). This multifunctional enzyme is required for the *de novo* synthesis of Fatty Acids (FAs). It typically produces palmitic acid that serves as a precursor of (very) long-chain FAs [11,12]. Pathogenicity of *Malassezia* has been related to several factors including the ability to produce enzymes such as esterases, lipases, lipoxygenases and proteases. These enzymes enable growth of these yeasts on the host skin and lead to changes in sebum composition. For instance, release of FAs from triglycerides can result in inflammation, irritation, and scaling in susceptible individuals (Figure 1) [13-15]. Genome sequence analysis of *Malassezia* species revealed possible mechanisms to adapt to the host such as to its immune system [1,2,16,17]. Yet, a relation of these mechanisms to the disease process has, in most cases, not been shown. This review presents an update about the *Malassezia* genus and show new data that open new perspectives about the research of this yeast**.**

Malassezia spp: Taxonomy and Epidemiology

Since the first description of *Malassezia* by Eichstedt in 1846 many taxonomic revisions have been made based on phenotypic and molecular tools [18]. Currently, 14 well established *Malassezia* species and 3 new species have been described [3,4,19-26]. They belong to the phylum Basidiomycota, subphylum Ustilaginomycotina, and class Malasseziomycetes. *Malassezia* is closely related with the class Ustilaginomycetes that consists almost exclusively of plant pathogens such as *Ustilago maydis* [27,28]. *Malassezia* yeasts are characterized by their lipophilic and lipid-dependent metabolism [13]. It is the most abundant yeast skin commensal, representing 50%-80% of the total skin fungi. *Malassezia* is most common in areas rich in sebum such as the face and scalp but also occur on skin poor in sebum such as toe web space and hand palms [29,30]. The establishment of *Malassezia* species as normal members of the skin microbiota begins early after birth [31]. Culture-and non-culture-dependent methods showed differences in the distribution of the species [32,33]. Age and gender are associated with changes in *Malassezia* composition of the skin likely due to differences in the activity of sebaceous glands [15,31]. Presence of *Malassezia* increases in males between 15-18 years of age. The increase in abundance on skin of females can occur already at the age of 10-12 years, after which the load of *Malassezia* may decrease [29,31]. *Malassezia* species are also part of the normal microbiota of animal skin [34,35] and can be isolated from very diverse environments including deep hydrothermal vents and stony corals [36]. These findings have led to the reevaluation of this genus and suggest that more species exist in niches that contain lipid sources [2,35,37].

The skin functions in the innate defense against pathogens due to its low water content, acidic pH, its microbiota, and antimicrobial lipids (i.e. free FAs) [38]. Any changes in these conditions or composition may provide pathogens and even commensals an opportunity to cause disease.

The lipid dependency of *Malassezia* on the one hand and the antimicrobial activity of these compounds on the other hand show the successful adaptation of these yeasts to the skin. Its capacity to adapt is also illustrated by its exposure to other residents of the skin such as *Propionibacterium acnes* and *Staphylococcus aureus* [30].

A recent phylogenic analysis distributed *Malassezia* species in clusters A, B, and C (Table 1) [2]. Cluster A consists of the anthropophilic species *M. furfur* that is associated with mild dermatological conditions such as PV and more severe conditions such as bloodstream infections [7,18,39]. It also includes other anthropophilic species that are less frequently isolated from healthy humans such as *M. japonica, M. yamatoensis,* and *M. obtusa*. These species have been isolated from the skin of Atopic Dermatitis (AD) or SD patients [2,5,31]. Cluster B is represented by *M. globosa* and *M. restricta* that are the most abundant species on healthy human skin and *M. sympodialis* and *M. dermatis* that are slightly less common on healthy individuals. These 4 species have also been associated with dermatological diseases such as D/SD, AD, and PV [5,31]. A subcluster of cluster B encompasses zoophilic species including *M. caprae, M. equina, M. nana,* and *M. pachydermatis*. The latter species is particularly associated with otitis in canines and bloodstream infections in humans [31,34,35]. Cluster C is defined by *M. cuniculi* and *M. slooffiae* that are commonly isolated from animals [26,40]. *M. slooffiae* is also isolated with low frequency from healthy and lesioned human skin.

The demanding nutritional requirements hampered the description and identification of *Malassezia* species. The implementation of complex media such as modified Dixon agar mDA (Table 2) that support *Malassezia* growth was the first step to solve these problems. Notably, *M. pachydermatis* is a less demanding species that can also grow on Sabouraud Agar (SA). This medium contains peptone with traces of lipids such as palmitic acid [2,41].

Table 1: The genus *Malassezia* consists of 14 established species as well as 3 species described for the first time in 2016.

Phylogenetic Cluster [2]	Species	Reference
A	*M. furfur*	[20]
	M. obtusa	
	M. yamatoensis	[23]
	M. japonica	[22]
B	*M. globosa*	[20]
	M. restricta	[20]
	M. sympodialis	[19]
	M. dermatis	[21]
	M. caprae	[25]
	M. equina	
	M. nana	[24]
	M. pachydermatis	[20]
C	*M. slooffiae*	[20]
	M. cuniculi	[26]
Not included	*M. arunalokei sp. Nov*	[4]
Not included	*M. brasiliensis sp. Nov*	[3]
Not included	*M. psittaci sp. Nov*	

Identification of *Malassezia* species is mainly based on morphological characteristics as well as biochemical tests such as utilization of the non-ionic detergents Tween 20, 40, 60, and 80, or Cremophor EL (Tables 2 and 3) and catalase, urease, and β-glucosidase activity (Table 3) [20,41]. Molecular tools, however, are superior to identify *Malassezia* species, preventing a 13.8% misidentification by the other methods [31]. Molecular tools have also been used to study *Malassezia* biodiversity and community structure on the human skin, as well as the epidemiology related to this genus [31,42]. The molecular tools that are used include pulsed field gel electrophoresis of chromosomes [43], PCR-based methods (RAPD, PCR-RFLP, AFLP) [43-46], and DNA sequence based methods of D1/D2 domains of the large subunit rDNA and the Internal Transcribed Spacer (ITS) regions and the Intergenic Spacer (IGS) region [47-50]. For instance, patient material was used for qPCR [51] and Luminex [31] analysis to study the epidemiology of *Malassezia.* Moreover, a Matrix-Assisted Laser Desorption / Ionization–Time of Flight (MALDI-TOF) database was implemented to reliably identify *Malassezia* species by mass spectrometry [52-53].

Dermatological Diseases Associated with *Malassezia*

Malassezia has been traditionally linked with dermatological diseases because of the isolation of these yeasts from infected skin and the reduction of the load of *Malassezia* and the recovery of the lesions with antifungal treatments [54]. Yet, PV is the only skin disease for which a pathogenic role of *Malassezia* is established, being mainly related with *M. globosa,* followed by the isolation of *M. sympodialis* and *M. furfur*. This latter one has been reported as the main species isolated from skin and probable causal agent for PV in Indonesia and recently in Nigeria [6,39,55-56]. Exogenous factors such as humidity, sweat, and heat are associated with the onset of PV [5,6]. This infection is characterized by the presence of hypo- or hyperpigmented macules in the neck, trunk, and arms without inflicting inflammation. The mechanisms of skin color changes are not completely understood. *Malassezia* produces indoles such as malassezin, indirubin, indolo [3,2-b] carbazole [ICZ], and formylindolo [3,2-b] carbazole from tryptophan. These indoles are potent ligands of the Aryl Hydrocarbon Receptor (AhR), which is a ligand dependent transcription factor [13,57]. The activation of the AhR signal transduction pathway by the *Malassezia* indoles leads to apoptosis of melanocytes and the inhibition of tyrosinase that is a key enzyme of melanin synthesis (Figure 1) [5,13]. Recently, the AhR receptor has been related with carcinogenesis, immune regulation, and mediation of ultraviolet radiation damage, illustrating the importance to explore its interaction with *Malassezia* [14,35].

Malassezia is considered to play an important role in D/SD that is a common abnormal skin conditions characterized by flaking and itch. Their incidence ranges between 1-3% in the general population, while patients with Acquired Immunodeficiency Syndrome (AIDS) show an incidence of 30-83% [58]. Costs of treatment of these diseases are considerable but the socioeconomic impact is even higher [59]. *M. globosa* and *M. restricta* are the most frequent species isolated from scalp of individuals with D/SD [60]. *M. furfur* as well as *M. slooffiae* have been reported but differences in the species isolated in these patients could be associated with geographical variations [32,61]. *Malassezia* releases lipases, phospholipases C, and acid sphingomyelinases that hydrolyze lipid sources like triglycerides

to obtain FAs for growth. The unsaturated FAs resulting from the enzymatic action can give rise to irritation and are assumed to exacerbate the disease in susceptible individuals [15,59]. However, *M. globosa* and *M. restricta* were shown to metabolize the unsaturated oleic acid [62], suggesting that unsaturated FAs are not the etiological factors in D/SD [62]. Notably, *M. globosa* and *M. restricta* lack $\Delta^{3,2}$-enoyl CoA isomerase (EC 5.3.3.8) that is involved in catalyzing an important step in catabolism of unsaturated FAs. Possibly, *Malassezia* contains a $\Delta^{3,2}$-enoyl-CoA isomerase that is structurally distinct from that of other fungi or it uses an alternative biochemical route to degrade unsaturated FAs [62,63]. It should also be noted that *M. globosa* lacks a $\Delta 9$-desaturase (EC 1.14.19.2) gene. This suggests that it is not capable to synthesize unsaturated FAs, and therefore, has to import it from its environment [63]. Additional studies should further clarify the role of the unsaturated FAs in the etiology of DS.

AD is a chronic and inflammatory skin disease. It is characterized by severely itchy, red, and dry skin that also may include steps of

remission and deterioration [5,63]. The prevalence has increased to 15-30% in children and 2-10% in adults [64]. Pathogenesis is multifactorial and related with a disturbed skin barrier and with genetic and environmental factors such as life style, stress, allergens, and the skin microbiome. *M. sympodialis* is frequently isolated from AD patients; however *M. globosa* and *M. furfur* have been reported as the main species in Japanese people [6]. Anti-*Malassezia* IgE antibodies have been detected in these patients but not in healthy individuals. Currently 13 allergens are characterized, 3 from *M. furfur* and 10 from *M. sympodialis* [5,60].

Malassezia folliculitis is an inflammatory papulopustular eruption that occurs on the back or front of the upper trunk [5]. Triglyceride hydrolysis by the yeast leads to an inflammatory reaction in the hair follicles [14]. The diagnosis can be misleading due to similarity with other forms of folliculitis caused by bacteria. The increase of folliculitis in the clinical practice underlines the need for a right diagnosis [5,18,31]. Other dermatological diseases such as psoriasis,

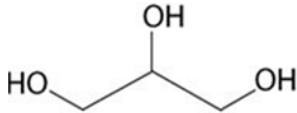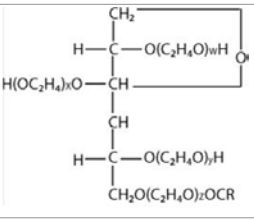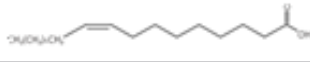**Table 2:** Composition of the culture media used for isolation and identification of *Malassezia* species [41]
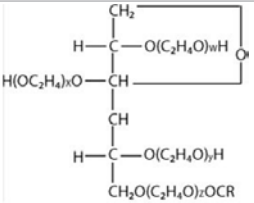
Medium* or test**	Composition	Additional description	Structural formula
Modified Dixon agar mDA* [41]	3.6% malt extract		
	2.0% desiccated oxbile	Bile composition (water 92 g/dl, bile salts 6 g/dl, bilirubin 0.3 g/dl, cholesterol 0.3 to 0.9 g/dl, FA 0.3 to 1.2 g/dl, lecithin 0.3 g/dl and 200 meq/l inorganic salts [93]. Lecithins: phospholipids, glycolipids or triglyceride. Glycerophospholipids as phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and phosphatidic acid [97].	
	1.2% agar		
	0.6% peptone		
	0.2% glycerol		[98]
	1.0% Tween 40		[99]**
	0.2 % Oleicacid		[99]**
Utilization of Tween 20, 40, 60, 80, or Cremophor EL**	Tween 20 (Polyoxyethylene (20) sorbitanmonolaurate) Tween 40 (Polyoxyethylenesorbitanmonopalmitate) Tween 60 (Polyoxyethylene (20) sorbitanmonostearate) Tween 80 (Polyoxyethylene (20) sorbitanmonooleate)		[100]**
	Cremophor EL (CrELor castor oil)		[101]

Table 3: Physiological characteristics of *Malassezia* species.

| Species | Cell morphology | Utilization of tween | | | | Cremophor EL | β- glucosidase activity | Catalase reaction | Growth in mDA | Growth in SA | Growth[d] | |
		20	40	60	80						At 37ºC	At 40ºC
M. furfur	Globose, ellipsoidal, cylindrical	+	+	+	+	+	+	+	+	-	+	+
M. sympodialis	Ellipsoidal	- w	+	+	+	- (w)	+	+	+	-	+	+
M. globosa	Globose	-[b]	-	-	-	-	-	+	+	-	-(w)	-
M. restricta	Ellipsoidal, globose	-	-[c]	-[c]	-	-	-	-	+	-	v	-
M. obtusa	Ellipsoidal,cylindrical	-	-[c]	-[c]	-	-	+	+	+	-	+	-
M. slooffiae	Ellipsoidal,cylindrical	+	+	+	w	-	-	+	+	-	+	+
M. dermatis	Ellipsoidal, globose	+	+	+	+ (w)	-	-	-	+	-	+	-
M. japonica	Globose,ellipsoidal	-[b]	-[b]	+	+	w	+	+	+	-	+	-
M. nana	Ellipsoidal	- [b]	+	+	+	-	+	+	+	-	+	+
M. yamatoensis	Ellipsoidal	+	+	+	+	- (w)	-	+	+	-	+	+
M. equina	Ellipsoidal	w[b]	+	+	+	-	-	+	+	-	w	
M. caprae	Globose,ellipsoidal	-[b](+)	+[a]	+[b]	+[b](-)	-	(+),-	+	+	-	-,(w)	-
M. cuniculi	Globose	-	-	-	-	- (w)	-	+	+	-	+	+
M. pachydermatis	Ellipsoidal	+[a]	+[a]	+	+	+[b]	(+), -	(+), w, (-)	+	+	+	+
M. arunalokei sp. nov	Ovoid, globose	-[b]	-[b]	-[b]	v	(-)[b]	-	-	+	NI	+	-
M. brasiliensis sp. nov	Ovoidal, ellipsoidal	+	+	+	+	+	-	+	+	-	+	+
M. psittaci sp. nov	Globose, ovoidal	+	+	+	+	+	-	-	+	-	-	-

Data are from references [3,4,20] SA: Sabouraud Agar, mDA: modified Dixon Agar, NI: not included in the description. Growth is indicated with: +: positive; -: negative; v: variable; w: weak; ( ): indicate rare deviations

[a]Growth may be inhibited near the well where the substrate is placed.

[b]Growth may occur at some distance from the well where the substrate is placed

[c]Opaque zone may occur.

[d]*Malassezia* species have a very narrow optimum growth temperature range (32°C-34°C) and do not survive very long below 28°C on regular culture media [41].

onycomycosis and confluent and reticulated papillomatosis have also been associated with *Malassezia*. However, a causal relationship is still purely hypothetical because it is based on colonization of affected areas with the yeast [5,18,31].

Malassezia can be considered an opportunistic yeast and emergent pathogen. Bloodstream infections caused by *M. furfur* and *M. pachydermatis* have been reported since 1980 [8,9,65]. Fungemia is associated with the use of intravenous lipid feeds and affects critically ill low-birth-weight infants and immunocompromised children and adults [66,67]. Colonization and pathogenicity of this yeast are related with adherence properties, possibly mediated by the lipid layer that is found at the outer surface of *Malassezia* cells. This layer has also been reported to allow immune system evasion, suppression of cytokine release, and reduction of phagocytic uptake and killing [13,68].

Physiology and Biochemistry

The principal metabolic trait of *Malassezia* that has pressed the adaptation mechanism to the human and animal host is its lipid dependence. Research has therefore especially focused on lipid metabolism to understand the mechanisms of *Malassezia* to sustain growth and maintain commensalism and pathogenicity [2]. The importance of lipids is also illustrated by the "capsule" formed by these molecules at the outer part of the *Malassezia* cell wall (Figure 1). This capsule is assumed to play a major role in commensalism

and pathogenicity. Carbohydrate metabolism strategies may also be linked to the adaptation of the host. For instance, comparative genomics indicated that a large set of genes involved in carbohydrate metabolism such as glycosyl hydrolases are missing in the *Malassezia* genomes [2].

Lipid metabolism

The 14 *Malassezia* genomes lack the genes encoding the cytosolic fatty acid synthase complex (FAS), which explains why these yeasts cannot synthesize palmitate *de novo* [1,2]. To overcome this, *Malassezia* should obtain FA sources from the culture medium or directly from itshost. Human sebum is a complex mixture of triglycerides, FAs, wax esters, sterol esters, cholesterol, cholesterol esters, and squalene [15,59]. These sources are exploited by *Malassezia* by secreting lipases and phospholipases to release FAs. Other secreted hydrolases such as aspartyl proteases, and acid sphingomyelinases support the exploitation of other components of the human skin [2,16,17]. After FA uptake and concomitant activation to coenzyme A derivatives by acyl-CoA synthetases, *Malassezia* metabolizes or modifies FAs. They are used in the synthesis of lipids to build up cell membranes [69], to synthesize triglycerides and / or sterol esters, or they can be degraded via the β-oxidation pathway [13,62] (Figure 2). Intracellular FAs are activated to acyl-CoA derivatives by Faa1, Faa2, Faa3, Faa4, and Fat1. These acyl-CoA synthetases can have different localization and substrate specificity [70]. The elongation steps up
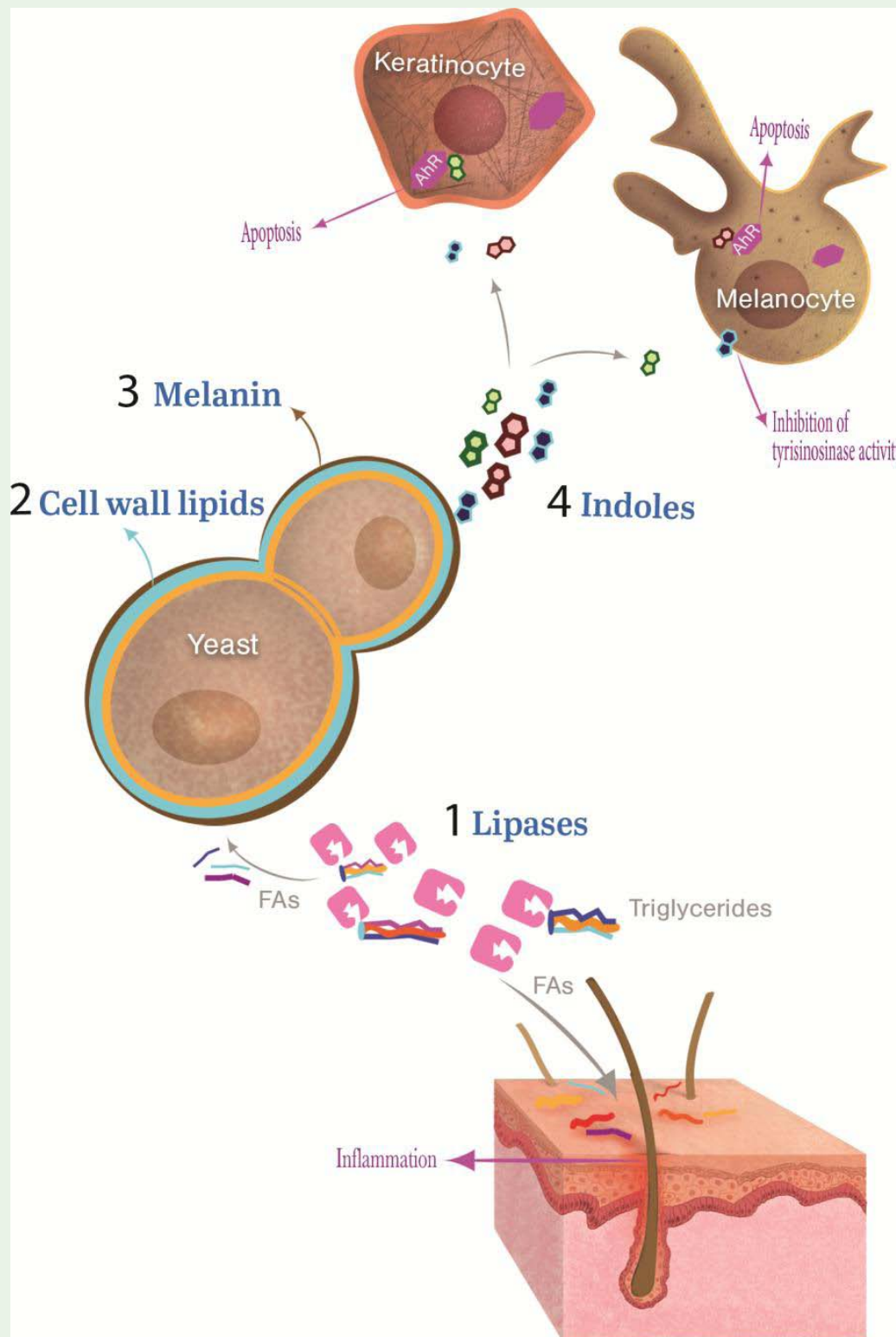
Figure 1: Molecules of *Malassezia* interacting with the host: 1. *Malassezia* obtains Fatty Acids (FAs) from the host by lipase activity. 2. These FAs are used, in part, to form the lipid layer at the outer part of the cell wall. 3. L-DOPA is required to form melanin in the cell wall and is also suggested to induce a dimorphic switch during infection. 4. Indoles such as malassezin and indirubin are potent ligands of the Aryl Hydrocarbon Receptor (AhR), leading to the apoptosis of melanocytes and the inhibition of tyrosinase, a key enzyme of melanin synthesis in melanocytes. Inflammation is amongst others proposed to be due to action of unsaturated fatty acids on keratinocytes. Adapted from [14,35].

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Table 4: Number of predicted *Malassezia* genes encoding lipolytic and proteolytic enzymes (Adapted from [2]).

Protein families	*Malassezia* species and number of gene copies (predicted secreted proteins)												
	MP	MSL	MJ	MO	MF	ME	MG	MC	MN	MR	MS	MD	MY
PF03583.9 **Secretory lipase**	13	13	11	10	8-9	8	6-8	5-8	7	4	4-13	4	11
PF01764.20 **Lipase (class 3)**	6	7	8	10	5-6	12	5-8	8-9	7	6-7	6-12	6	4
PF0057.19 **Metallo proteases**	6	6	5	6	6	5-6	6	6	6	6	6	6	6
PF00026.18 **Aspartyl protease**	9	13	13	9	9-8	8	18-22	5-7	8	14	5-7	5	7
Acid sphingomyelinase	4	4	4	4	4	4	4	4	4	4	4	4	4
PF04185.9 **Phosphoesterase family** (Including phospholipase C enzymes EC:3.1.4.3, and acid phosphatases EC:3.1.3.2)	5	4	4	3	1	4	6	5-4	4	7	4-5	4	0

MP: *M. pachydermatis*; MSL: *M. slooffiae*; MJ: *M. japonica*; MO: *M. obtusa*; MF: *M. furfur*; ME: *M. equina*; MG: *M. globosa*; MC: *M cuniculi*; MN: *M. nana*; MR: *M. restricta*; MS: *M. sympodialis*; MD: *M. dermatis*; MY: *M. yamatoensis*

to C26 occurs in the Endoplasmic Reticulum (ER) by subsequent addition of 2 carbons from malonyl-CoA by the elongases ELO1, ELO2, and ELO3 [70,71]. Desaturation that involves the introduction of double bonds into acyl chains also occurs in the ER. For instance, palmitic acid and stearic acid are converted by the Δ9-desaturase OLE1 to their corresponding mono-unsaturated FAs palmitoleic acid (C16:1) and oleic acid (C18:1) [70-72]. Degradation of FAs via β-oxidation occurs in the peroxisomes and mitochondria involving 4 steps. The first step is the oxidation of acyl-CoA to trans-2-enoyl-CoA catalyzed by the acyl-CoA oxidase. Trans-2-enoyl-CoA is converted to 3-ketoacyl-CoA with 3R-hydroxyacyl-CoA as an intermediate. Thiolase cleaves 3-ketoacyl-CoA in the final step of the β-oxidation to acetyl-CoA and a C2-reduced acyl-CoA. Two additional steps are required for β-oxidation of unsaturated FAs. These steps are catalyzed by the enzymes $\Delta^{3,2}$-enoyl -CoA isomerase and 2,4 Dienoyl-CoA reductase [12,72-73].

Physiological assessments indicated that *Malassezia* could use both saturated and unsaturated FAs [74-76]. Yet, recent *in silico* and *in vitro* analyses of lipid metabolism in *M. globosa* and *M. restricta* showed that *M. globosa* has an intact β-oxidation pathway but lacks $\Delta^{3,2}$-enoyl-CoA isomerase to degrade unsaturated FAs such as oleic acid. Nevertheless, both strains remove oleic acid when growing at high density in chemically defined medium with low amounts of oleic acid. This did not support the hypothesis that this FA has a role in D/SD [62]. However, the conclusions may not be correct. The media that were used also contained polysorbates such as Tween 20, 40, 60 and 80, which may have been used as lipid source. In addition, Dixon medium was used during pre-growth, which might result in accumulation of various FAs in yeast cells present in this medium. This accumulation may be used to support growth of *Malassezia* on defined medium. At the same time, oleic acid would be converted. As a result, this fungistatic FA if present in high amounts would be detoxified.
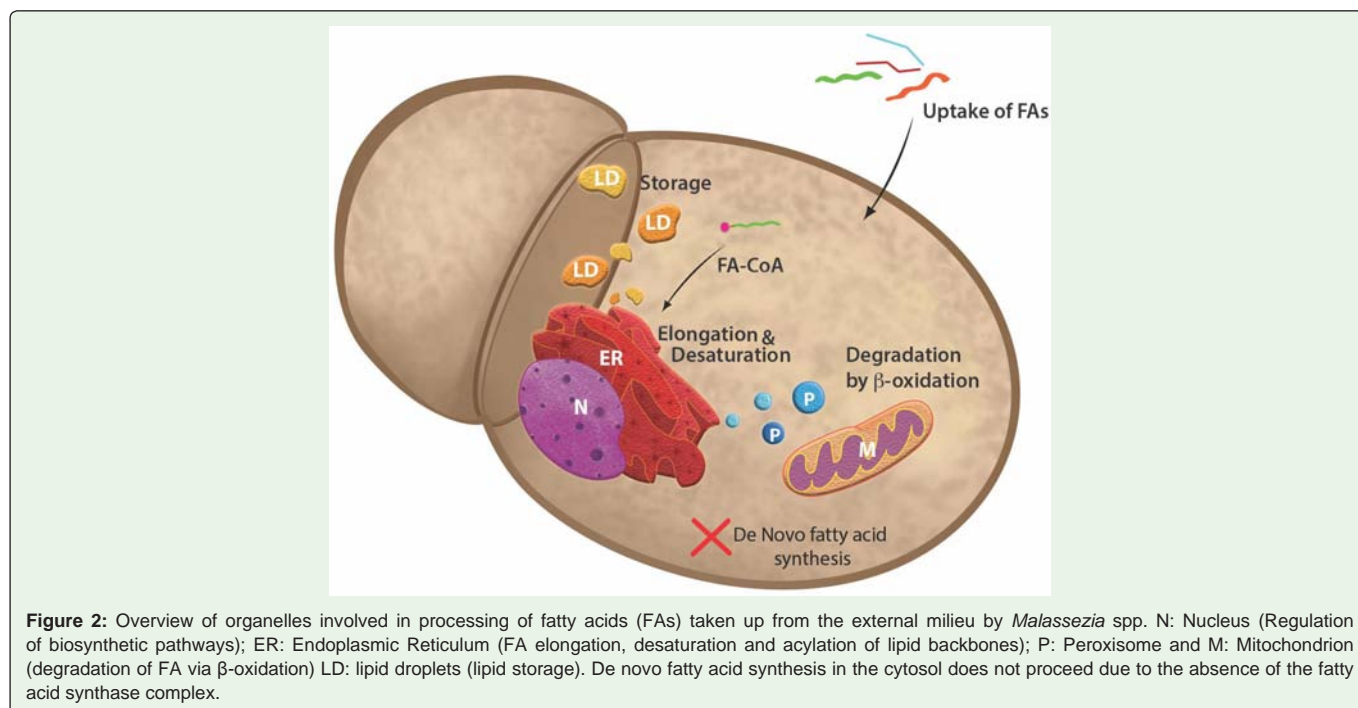

Figure 2: Overview of organelles involved in processing of fatty acids (FAs) taken up from the external milieu by *Malassezia* spp. N: Nucleus (Regulation of biosynthetic pathways); ER: Endoplasmic Reticulum (FA elongation, desaturation and acylation of lipid backbones); P: Peroxisome and M: Mitochondrion (degradation of FA via β-oxidation) LD: lipid droplets (lipid storage). De novo fatty acid synthesis in the cytosol does not proceed due to the absence of the fatty acid synthase complex.

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Lipid-synthesis pathways of *Malassezia* species were reconstructed *in silico* revealing high similarity between these routes [77]. However, differences were observed in the production of fungal steroids in *M. furfur* and in the degradation of the fatty acids in the atypical variant of *M. furfur* and *M. sympodialis*. The results obtained via these metabolic reconstructions also predicted defects in the assimilation of palmitic acid in *M. globosa, M. sympodialis, M. pachydermatis,* and the atypical isolate of *M. furfur*, but not in *M. furfur*. These predictions were validated by physiological characterization in chemically defined media, providing new clues about the metabolic versatility of *Malassezia* [77].

Cell wall and dimorphism

The *Malassezia* cell wall is a very thick multilayered structure. It consist of ~70% sugars, ~10% protein, and 15-20% lipids [78]. The sugars consist of chitin/chitosan, β-(1,3)-glucans, β-(1,6)-glucans, galactofuran and mannan structures [79-81]. The cell wall protects the cells against environmental stresses like high osmolarity and mediates adherence to the host surface [65,82]. Moreover, it allows evasion of phagocytosis and down regulation of the inflammatory immune response [83-86]. Notably, the cell wall of *Malassezia* is covered with a lipid layer thus shielding cell wall components of *Malassezia* that induce an inflammatory response [83,84]. Lipid encapsulated yeast cause a low production of the pro inflammatory cytokines, IL-6, TNF-α, IL-8 and IL-1α and a high production of the anti-inflammatory cytokine IL-10 by keratinocytes and Peripheral Blood Mononuclear Cells (PBMCs). Removing the lipid capsule of the cell wall results in increased levels of IL-6, IL-8, and IL-1α, while IL-10 levels decrease [87].

The capacity of *Malassezia* to switch from the yeast to a filamentous form may contribute to the establishment of disease as described for the dimorphic fungus *Candida albicans* [29,30]. *M. globosa* hyphae were shown in PV skin lesions and in primary cultures of these samples. High CO_2 conditions and medium supplemented with glycine, cholesterol, and cholesterol esters induced hyphal growth in *in vitro* cultures of *M. furfur* and *M. sympodialis* [13,39].

Metabolites

Malassezia metabolites can impact pathophysiology and exacerbate skin conditions. Products resulting from lipase activity are such a class of metabolites. Genome analysis showed that phospholipases and lipases are the most expanded lipolytic families in *Malassezia* in comparison with other fungi (Table 4). Expression of lipases has been shown *in vivo*. *LIP1* from *M. globosa* was detected by RT-PCR in samples from human scalp [88]. This finding was corroborated by quantitative real-time PCR of 4 lipase genes in samples from individuals without *Malassezia* lesion, and patients with SD that were either (SD+HIV) or not (SD) infected with human immunodeficiency virus. The 4 genes were expressed in all samples but 3 of them (*Mgl0797, Mgl0798*, and *Mflip1*) were up-regulated in SD and SD+HIV suggesting a role of the encoded lipases in the establishment of disease [89]. Polyketide Synthases (PKSs) genes are also present in *Malassezia* species. PKSs are mechanistically and structurally related to FA synthases and have been related with the biosynthesis of unique lipids or glycolipid conjugates in *Mycobacterium turberculosis* [90,91].

Pigments such as melanin are described as fungal pathogenicity factors [92]. A phenoloxidase was identified in *M. furfur* suggesting that L-DOPA melanin can be produced by this fungus as observed inthe opportunistic fungal pathogen *Cryptococcus neoformans.* Indeed, production of L-DOPA melanin was recently shown in *Malassezia.* Interestingly, L-DOPA is also associated with yeast to hypha transition [93,94]. It remains to be determined if the same source of L-DOPA that is used for pigment production in skin is also used by *Malassezia* spp and required for pathogenesis. Tryptophan derived indole pigments have been particularly described in *M. furfur*. Malassezin is produced *in vitro* when *M. furfur* is grown in the presence of the amino acid tryptophan in a selective medium. It is a potent ligand of AhR and implicated in the pathogenesis of the hypopigmented forms of PV because of the capacity to inhibit melanin synthesis [13,35]. Other pigments such as pityriacitrin, pityrialactone, pityriarubins have been proposed to be involved in the inhibition of the respiratory burst in neutrophils or to filter UVA, UVB and UVC [13,86].

A New Genetic Tool

New insights in the pathophysiology of *Malassezia* spp for instance through analysis of genome sequencing and metabolic reconstruction need to be confirmed by genetic tools. *Agrobacterium tumefaciens*-Mediated Transformation (AMT) was implemented to transform *M. furfur* and *M. sympodialis* although with a low efficiency of transformation. Particularly in *M. furfur*, targeted gene replacements were also achieved via homologous recombination, enabling deletion of the ADE2 gene for purine biosynthesis and of the LAC2 gene predicted to be involved in melanin biosynthesis [95]. Recently, this transformation technique was improved and it showed to be highly efficient in introducing a binary T-DNA vector with the hygromycin B phosphotransferase (*hpt*) selection marker and the green fluorescent protein gene (*gfp*) in *Malassezia furfur* and *M. pachydermatis* [96].These new advances will speed up molecular research and allow important advances in the knowledge of this genus. Further analyses can clarify the role of this yeast in disease development and give us clues about the sexual reproduction that might provide genetic variation in this genus.

Conclusions

In this review we described the current status of research and description of the *Malassezia* genus as well as new advances in this field. The interest in *Malassezia* has increased in recent years because this species has been recognized as an unusual and important component of the human microbiota with a particular lipid metabolism and processes to adaptation. The implementation of new bioinformatics approaches combined with genetic tools and culturing in defined media will allow us to unravel the details of lipid metabolism deeper and the relation with underlying pathophysiology. In addition, such research might provide in the future new ways to control the afflictions caused by these yeasts and the implementation of new identification and diagnostic tool that allow a better and fast identification of *Malassezia* species.

Acknowledgements

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Citation: Celis AM, Wösten HAB, Triana S, Restrepo S and de Cock H. *Malassezia* spp. beyond The Mycobiota. SM Dermatolog J. 2017; 3(3): 1019.

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