

The Role of Sebaceous Gland Activity and Scalp Microfloral Metabolism in the Etiology of Seborrheic Dermatitis and Dandruff

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Most common scalp flaking disorders show a strong correlation with sebaceous gland (SG) activity. Early SG activity in the neonate results in microfloral colonization and cradle cap. After maternal hormonal control subsides, there is little SG activity until puberty, when the SG turns on under sex hormone control. When the SG activity increases, the present but low *Malassezia* population has a new food source and proliferates, resulting in the scalp itching and flaking common to greater than 50% of adults. Dry scalp flaking, dandruff, and seborrheic dermatitis are chronic scalp manifestations of similar etiology differing only in severity. The common etiology is a convergence of three factors: (1) SG secretions, (2) microfloral metabolism, and (3) individual susceptibility. Dandruff and seborrheic dermatitis (D/SD) are more than superficial stratum corneum disorders, including alteration of the epidermis with hyperproliferation, excess lipids, interdigitation of the corneal envelope, and parakeratosis. The pathogenic role of *Malassezia* in D/SD has recently been elucidated, and is focused on their lipid metabolism. *Malassezia restricta* and *M. globosa* require lipids. They degrade sebum, free fatty acids from triglycerides, consume specific saturated fatty acids, and leave behind the unsaturates. Penetration of the modified sebaceous secretions results in inflammation, irritation, and scalp flaking.

Key words: dandruff/microflora/sebaceous gland/seborrheic dermatitis/sebum
J Investig Dermatol Symp Proc 10:194–197, 2005

Sebaceous Gland (SG) Activity

Human SG are found over the entire skin surface (except the palms of the hands and soles of the feet), but sebum secretion is highest on the scalp, face, chest, and back (Strauss and Pochi, 1968a). Sebum is produced under hormonal control, with SG active at birth under the control of maternal androgens. They quickly reduce in size and sebum production until the onset of puberty. As puberty begins the SG again activate, this time under the control of circulating androgens. The sebum secretion rate increases throughout the teens, remains steady through the 20s and 30s, then lessens with age (Strauss *et al*, 1983; Dawber, 1997). Throughout the active period of sebum secretion, the secretion rate is higher in males than in females. In males, the rate remains higher longer, into the 50s and 60s, but in females, the secretion rate drops quickly after menopause (Strauss and Pochi, 1968b). Common scalp flaking disorders all show a strong temporal correlation with sebaceous activity, following the pattern of early cradle cap, low incidence until puberty, increasing incidence through the teens, second and third decades, then declining (Dawber, 1997; Gupta *et al*, 2003, 2004a, b).

The primary functions of sebum have historically been controversial, but are recently being elucidated. Sebum is

involved in development of epidermal structure and maintenance of the epidermal permeability barrier (Pilgram *et al*, 2001), carrying anti-oxidants to the skin surface (Theile *et al*, 1999), protection from microbial colonization, generation of body odor, and pheromone generation (Kligman, 1963). It has also recently come to light that sebum is directly involved in skin-specific hormonal signaling, epidermal differentiation, and protection of the skin from ultraviolet irradiation (Thiboutot *et al*, 2003; Zouboulis, 2003).

Composition of Human Sebum

When secreted human sebum is a complex mixture of triglycerides, fatty acids, wax esters, sterol esters, cholesterol, cholesterol esters, and squalene (Fig 1) (Strauss *et al*, 1983). As the sebum is secreted, it consists primarily of triglycerides and esters, which are broken down by commensal microbes into diglycerides, monoglycerides, and the constituent free fatty acids. Human sebum contains both saturated and unsaturated fatty acids, with a preponderance of unsaturates. The fatty acid chain lengths of human sebum vary considerably, but are predominantly 16 and 18 carbons (stearic, C18:0, oleic, C18:1 Δ 9, linoleic, C18:2 Δ 9 Δ 12, palmitic, 16:0, sapienic, 16:1 Δ 6, and palmitoleic, C16:1 Δ 9, Fig 1). The role of specific fatty acids of human sebum becomes apparent when we examine the metabolism of *Malassezia*.

Abbreviations: D/SD, dandruff and seborrheic dermatitis; SG, sebaceous gland

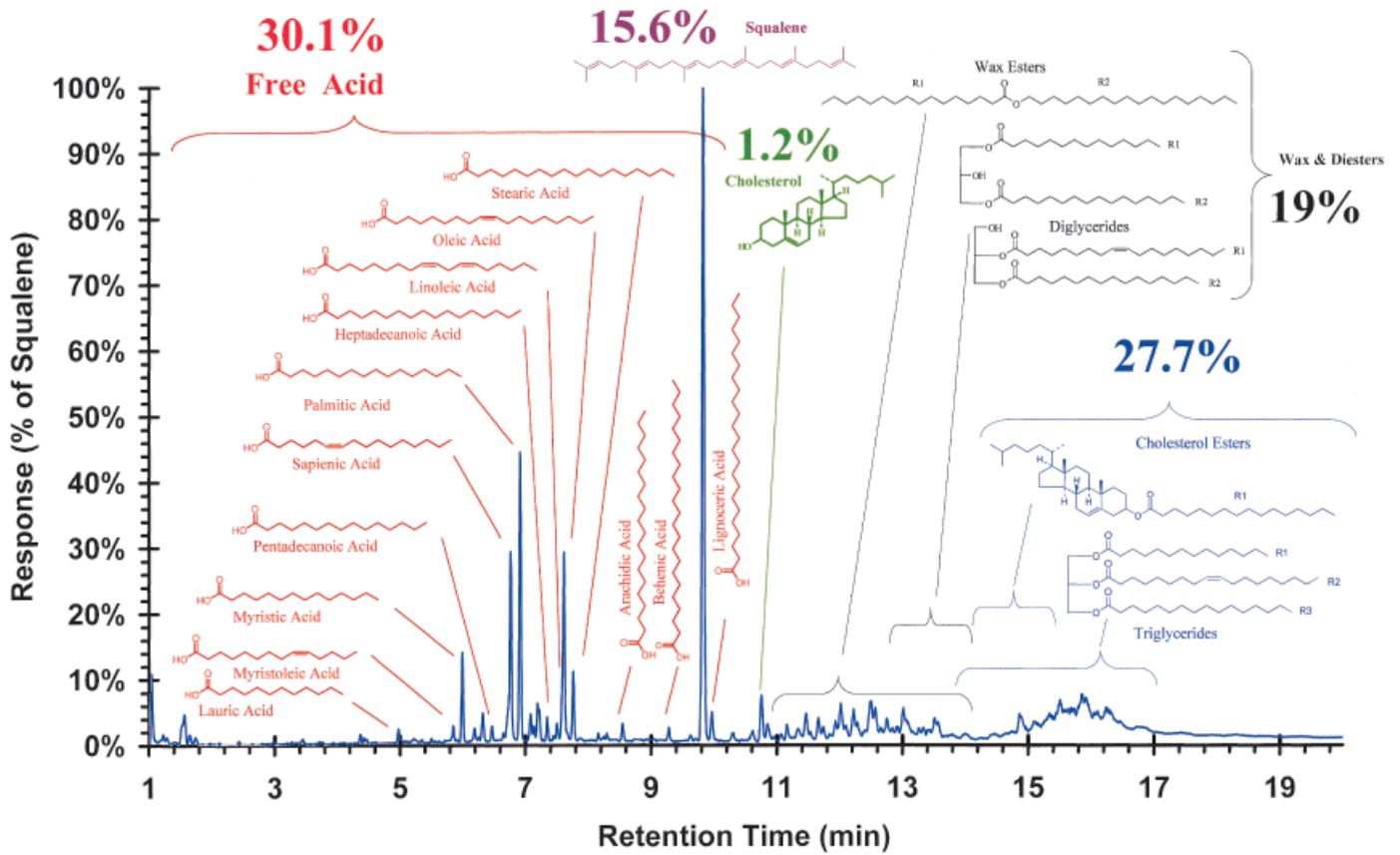


Figure 1
Relative composition of human sebum. Samples of human sebum were collected and analyzed by gas chromatography. Peaks were identified by comparison to known standards. Identifications confirmed by GC-mass spectrometry.

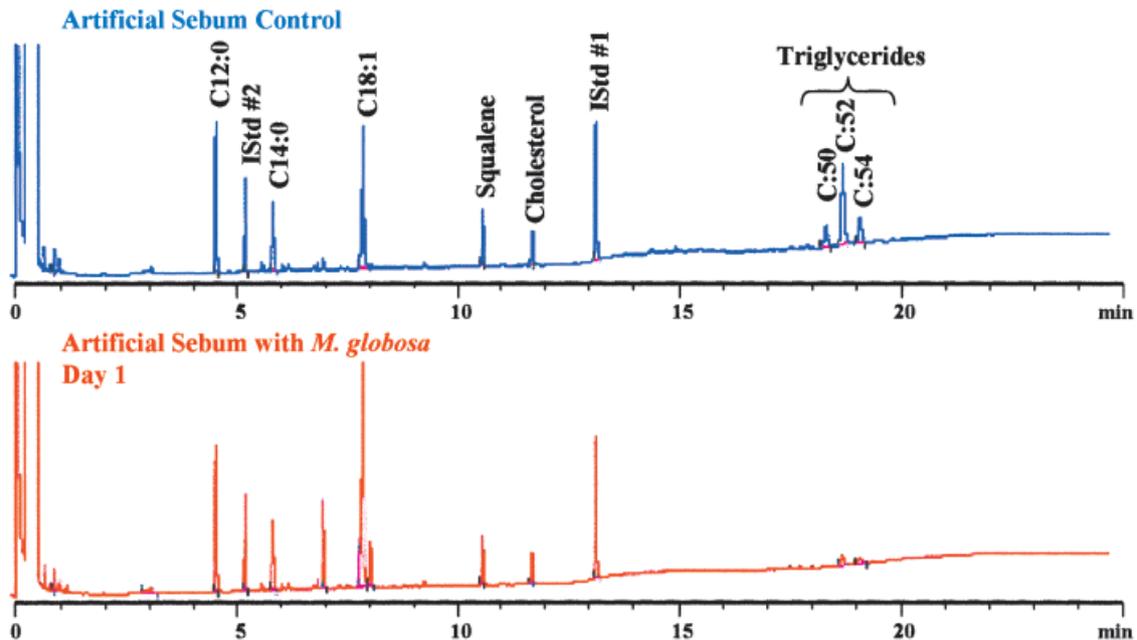


Figure 2
Triglyceride degradation and increased free fatty acids after incubation of artificial sebum by *Malassezia globosa*. Lipid composition analyzed as in Fig. 1, but following incubation of *M. globosa* for 24 hours with defined lipid matrix.

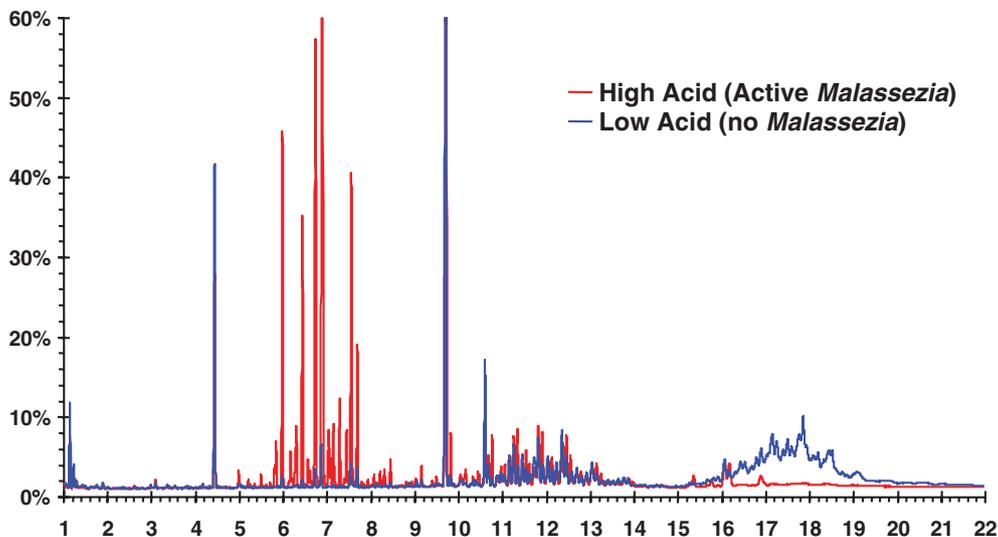


Figure 3
Triglyceride and fatty acid composition of sebum extracted from human scalp. Lipid profile analyzed as in Fig. 1, samples collected from a dandruff sufferer with high *Malassezia* counts before (red, primarily free fatty acids) or after (blue, both triglycerides and free fatty acids) treatment with a commercial antifungal shampoo.

Role of *Malassezia*

Over 100 y ago, Malassez implicated the yeast *Pityrosporum* in the etiology of dandruff (Malassez, 1874). Although there has been much debate regarding whether the yeast is actually a causative agent (Leyden *et al.*, 1976; Shuster, 1984) there is now general agreement (Pierard Franchimont *et al.*, 2000; Gupta and Kohil, 2004).

Early SG activity in the neonate allows initial *Malassezia* colonization and is likely an initiating factor for cradle cap. The *Malassezia* population then drops dramatically, only to re-appear as SG activity increases at the onset of puberty (Gupta and Kohil, 2004). As the SG begins increased activity, the present but low *Malassezia* population has a new food source and proliferates (Gupta *et al.*, 2001; Gupta and Kohil, 2004). *Malassezia*, however, have a very specific taste for individual fatty acids (Gueho *et al.*, 1996, 1998). The *Malassezia* lipases are non-specific and degrade any available triglycerides (Fig 2). The saturated fatty acids are consumed, and the abundant unsaturates are left on the skin (Figs 2 and 3).

Recently, novel molecular methods have overcome the difficulties presented by culture of *Malassezia*, and the specific *Malassezia* species present on human scalp have been elucidated (Gupta *et al.*, 2000; Gaitanis *et al.*, 2002; Gemmer *et al.*, 2002; Sugita and Nishikawa, 2003; Sugita *et al.*, 2003). *Malassezia* nomenclature has evolved over the last century, but the genus now consists of 10 distinct species: *M. globosa*, *M. restricta*, *M. furfur*, *M. sympodialis*, *M. slooffiae*, *M. obtusa*, *M. nana*, *M. dermatis*, *M. japonica*, and the sole non-lipid-dependent species, *M. pachydermatis*. All except *M. pachydermatis* can be found on human skin, but the most common species on human scalp are *M. restricta* and *M. globosa* (Gemmer *et al.*, 2002). Further molecular investigation will undoubtedly produce more distinct genetic entities, but detailed biochemical and physiological experiments will be needed to define the actual species.

Etiologic Mechanism of Dandruff and Seborrheic Dermatitis (D/SD)

D/SD are chronic clinical scalp conditions affecting greater than 50% of the population, the primary symptom of which

is visibly excessive scalp scaling. Seborrheic dermatitis is a more severe disorder which can include increased desquamation of facial areas other than the scalp and visible inflammation. Although dandruff is not a life-threatening disease, its presence can lead to loss of self-esteem and a negative social image (Hay and Graham-Brown, 1997).

D/SD are characterized by itching and visible dry or oily flakes, induced by excess turnover of scalp cells (Dawber, 1997). D/SD are more than just superficial disorders of the stratum corneum, including alteration of the epidermis with hyperproliferation, excess intercellular and intracellular lipids, interdigitation of the corneal envelope, and parakeratosis (McOsker and Hannon, 1967; Warner *et al.*, 2001).

Although *Malassezia* are not numerically correlated to D/SD, recent evidence strongly supports their causal role (Gupta and Kohil, 2004). This evidence includes the effectiveness of multiple chemical entities whose sole common mechanism of action is antifungal activity, as well as the very distinct numerical correlation of reduction in severity with reduction of *Malassezia* numbers (Shuster, 1984). Combination of several recent lines of investigation points out a novel mechanism for the etiology of D/SD. *M. restricta* and *M. globosa* require lipids as food source (Guillot and Gueho, 1995; Gueho *et al.*, 1996; Guillot *et al.*, 1996), and are perfectly adapted for life on the human scalp. The *Malassezia* degrade sebum, freeing multiple fatty acids from triglycerides (Fig 2). They consume the very specific saturated fatty acids necessary for their proliferation, leaving behind the unsaturated fatty acids (Fig 3). Experimentally, it can be shown that the changes in sebum composition over time are a direct result of *Malassezia* metabolism. Table I illustrates the effect of removing scalp microflora with an antimicrobial shampoo (removal of microorganisms verified by molecular analysis, data not shown). The sebum composition changes back to near normal levels of triglycerides and free fatty acids.

Individual Susceptibility

Penetration of the modified sebaceous secretions into the stratum corneum breaks down the skin barrier function, re-

Table I. Relative composition of human sebum

	As secreted (%)	Post <i>Malassezia</i> exposure (%)	Post anti-fungal treatment (%)
Triglycerides	> 35	18	32
Free fatty acids	< 13	32	16
Wax esters	25	23	25
Squalene	15	15	15
Cholesterol	3	3	3
Cholesterol esters	4	4	4
Others	~ 5	~ 5	~ 5

sulting in inflammation, irritation, and the resultant scalp flaking. Recent data shows that the penetration and inflammatory response to the fatty acids are different between dandruff and non-dandruff sufferers.¹

Additionally, immunodeficiency, such as AIDS, allows excess *Malassezia* proliferation, resulting in severe D/SD. Physical factors, nutritional disorders, drugs, and neurotransmitter abnormalities are additional aggravating factors.

Conclusion

The common etiology of D/SD is therefore a convergence of three factors: (1) SG secretions, which provide the substrate for *Malassezia* growth; (2) *Malassezia* metabolism of the sebaceous secretions, releasing irritating unsaturated fatty acids; and (3) individual susceptibility to the penetration of the fatty acids and the resultant inflammation.

The authors would like to thank Christina Gemmer, Yvonne DeAngelis, and Meredith Leland for their expertise in handling, growing, and detecting *Malassezia*; Shane Whitaker and Joe Kaczvinsky for their analytic expertise; and Aditya Gupta and Teun Boekhout for their expertise in *Malassezia* clinical implications and phylogeny/physiology, respectively.

DOI: 10.1111/j.1087-0024.2005.10104.x

Manuscript received September 20, 2004; accepted for publication October 21, 2004

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