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REVIEW ARTICLE

A Comprehensive Pathophysiology of Dandruff and Seborrheic Dermatitis – Towards a More Precise Definition of Scalp Health

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Despite an increasing knowledge of dandruff and seborrheic dermatitis (D/SD), the pathophysiological understanding is still incomplete but suggests a role of *Malassezia* yeasts in triggering inflammatory and hyper-proliferative epidermal responses. The objective of this report is to review published literature from *in vivo* studies of D/SD populations to provide a more complete description of overall scalp health. New biomolecular capabilities establish a depth of pathophysiological understanding not previously achievable with traditional means of investigation. Biomarkers representing inflammation, hyper-proliferation and barrier function are all perturbed by the D/SD condition and robustly respond to therapeutic resolution. These biomarkers can be sampled noninvasively, enabling their use in routine clinical evaluations as either surrogate endpoints or complementary ones to classical signs/symptoms to broaden the etiological learning. *Key words*: *dandruff; seborrheic dermatitis; inflammation; hyper-proliferation; skin barrier; biomarkers; scalp health.*

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Dandruff and seborrheic dermatitis (D/SD) are common afflictions of the human scalp (1) and considered the same basic condition differing only in magnitude (2). Heredity plays only a small role in developing a predisposition for the condition (3). A comprehensive review of the pathophysiological changes in the stratum corneum (SC) in these conditions at the macro (signs and symptoms), micro (physiological structure and function) and biomolecular strata may enable a precise and more complete determination of the condition of the scalp and also the therapeutic responses to treatment leading to restoration of homeostasis. A more complete description of the pathophysiology of the D/SD condition results from combining these 3 informational strata. This combination can lead to a paradigm shift in describing what constitutes a return to "scalp health."

A more comprehensive description of "scalp health" incorporating new biomolecular markers in addition to the existing clinical parameters has several benefits: (*i*) Advances the understanding of the biopathology of the condition; (*ii*) Provides a framework to assess the thoroughness of therapies; (*iii*) Enables the use of other clinical endpoints in addition to the commonly observed signs and symptoms; and (*iv*) Establishes relevant sub-clinical parameters that can supplement clinical observations.

In order to discuss the characteristic structural and biomolecular abnormalities associated with D/SD, it is convenient to categorize them by the following 4 sequential pathophysiological phases (4):

- *Malassezia* ecosystem and interaction with the epidermis;
- Initiation and propagation of inflammation;
- Disruption of proliferation and differentiation processes of the epidermis; and
- Physical and functional skin barrier disruption.

Each pathophysiological phase can then be considered sequentially at the 3 informational strata, progressing from macro to micro perspective, *viz*. Symptoms and signs; Structure and function, and Biomolecular changes, focusing almost exclusively on *in vivo* observations on D/SD populations to assure the relevance to the clinical condition (see supplementary Appendix for Material and Methods; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1382).

The 4 pathophysiological phases and the 3 informational strata can be considered orthogonal views of the total D/SD data. By combining these views, an organizational model emerges (Fig. 1) which allows each independent measure to be categorized by its pathophysiological phase and informational stratum. This categorization facilitates the comparison of measures within a given phase and across the strata or *vice versa*. A more complete model of scalp health emerges, including the circular nature of the pathophysiology, in which decreased barrier integrity increases further susceptibility.

In this review, each informational stratum will be covered sequentially, starting with the macro level observations and finishing at the foundational biomolecular level,

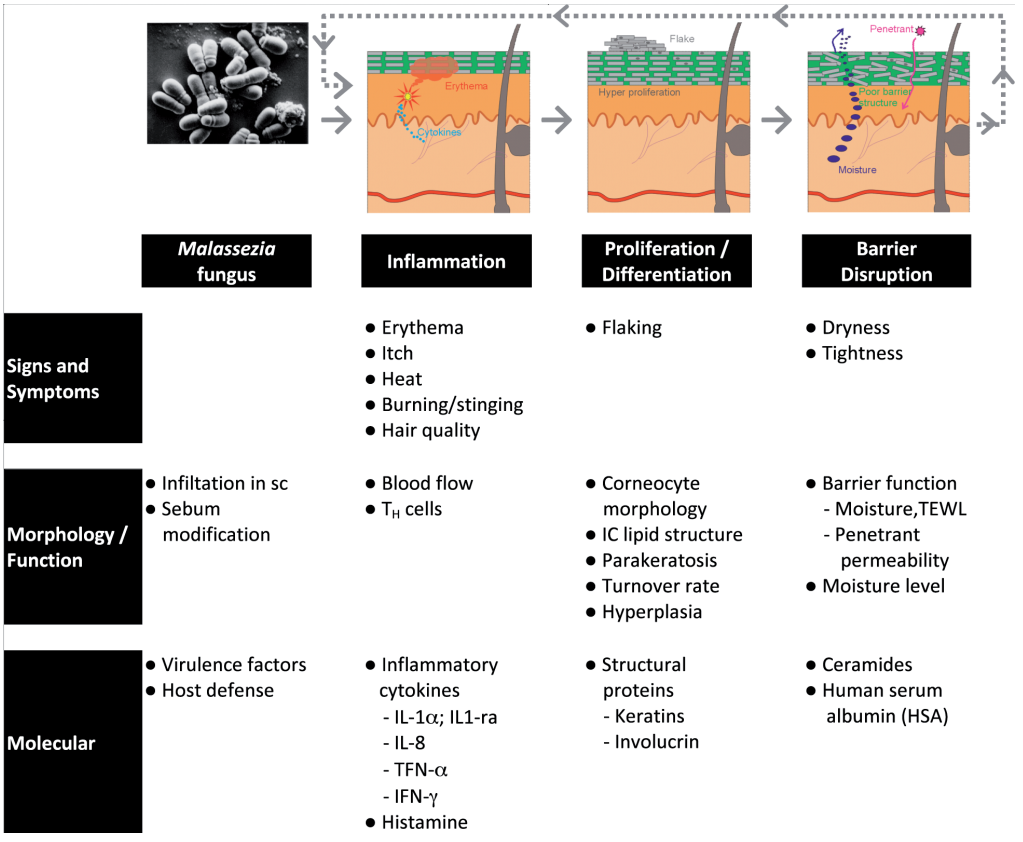

Fig. 1. Chart summarizing the measures of dandruff and seborrheic dermatitis arranged by the pathophysiological phase and informational stratum showing a more complete model for scalp health.

representing an increasing level of depth in analysis from superficial/optical, to fundamental/physiological.

Initially, the focus will be on differences between D/SD and normal populations to enable a comprehensive description of the D/SD condition and its pathophysiological foundations. Finally, the available therapeutic data will be reviewed, allowing a determination of which measurements represent useful clinical parameters to evaluate treatment effectiveness more accurately than possible with traditional approaches.

SIGNS AND SYMPTOMS OF DANDRUFF AND SEBORRHEIC DERMATITIS

The predominant and hallmark signs and symptoms are, respectively, flaking and pruritus, which tend to correlate with each other in intensity (4). The quantification of flakes has generally relied on assessments by expert graders involving various grading schemes within blinded studies, but can also be measured instrumentally (5). Assessment of pruritus is inherently subjective and generally involves subjects' marking of various types of graduated severity scales (6). Erythema can occasionally accompany D and more commonly SD and, like flake assessments, can be assessed by expert graders or optical instruments (7). The symptom of scalp dryness, which can be manifested as the sensation of tightness, originates in impaired stratum corneum barrier function. Skin dryness sign is most frequently evaluated by a range of skin surface electrical property-based instruments or inferred by measurement of the rate of transepidermal water loss (TEWL); assessment of tightness typically relies on subjective self-assessment scores.

Malassezia are commensal scalp yeasts (8) that are generally regarded as an etiological factor in D/SD (9). An empirical piece of support for their pathogenicity is that known therapeutic materials are chemically diverse but have in common the property of potent anti-fungal activity (10). Also, it is generally accepted that effective therapies reduce the *Malassezia* load from the pre-treatment level and that re-colonization of *Malassezia* post-treatment results in reoccurrence of the condition (11–15). A potential etiopathological mechanism (16) involves the lipolytic release of the fatty acid moieties from the parent sebaceous triglycerides by lipase activity originating from secreted *Malassezia* lipases (17); free fatty acids, especially unsaturated ones, can induce the inflammation and hyperproliferation (16) known to be components of D/SD leading to the commonly observed signs and symptoms associated with the conditions.

One sign/symptom associated with D/SD that has only recently been described is that some properties of

the hair fibers on the scalp can be negatively impacted by the poor scalp skin physiology associated with D/SD (paralleling similar observations for scalp psoriasis). For example, comparison of the hairs from D/SD and normal populations demonstrated D/SD-derived hair to be more narrow, with a more brittle surface and less shine (18, 19). D/SD can also contribute to increased rates of hair loss (4, 20), which may be directly due to the presence of *Malassezia* (20, 21); anti-dandruff shampoos with anti-fungal actives appear to reduce hair loss even in androgenic alopecia populations (22, 23), further supporting a potential involvement of *Malassezia*.

Therapeutic considerations. Therapeutic resolution of the signs and symptoms of D/SD has been the traditional focus of clinical studies. Published studies following traditional measures of resolution (most commonly expert-assessed flake appearance) are summarized in a review (1) that covers efficacy achieved by the common active materials such as zinc pyrithione (ZPT), ketoconazole and other azoles, selenium sulfide and piroctone olamine. Since this data is commonly available and recently reviewed, it will not be reiterated here.

THE IMPACT ON THE STRUCTURE AND FUNCTION OF EPIDERMIS

The outward manifestations of D/SD discussed above are the result of epidermal structural and functional disruption. From a structural point of view, while surface *Malassezia* are present on all individuals, they are seen within the layers of the SC of D/SD sufferers (5, 24, 25). These yeast cells appear to be closely associated with flakes and parakeratotic cells (26). The persistence of these parakeratotic (partially nucleated) cells in the upper SC appears to be a common structural feature of these conditions (25, 27–29); the quantity correlates with flaking severity (4). The parakeratotic cells are likely due to the hyper-proliferative nature of the epidermis in D/SD, which is evident by an increased turnover rate (27) and thicker epidermis (30). The corneocyte envelope structure has also been observed (24) to be irregular and highly invaginated due to the lack of synchronization between proliferation and differentiation in D/SD. These changes are reflected in irregular moisture-holding capacity and protein compositions of superficial skin samplings from dandruff-suffers (31).

In addition to the cellular structure alterations, the epidermal lipids are affected by D/SD. The characteristic lamellar structure formed by ceramides is replaced with a much wider, unstructured lipid material (24, 25); there are also lipid droplets of undetermined origin or composition within the cellular cytoplasm. Typically, the sebaceous lipids are altered: free fatty acids are released by *Malassezia*-derived lipase activity (*in vitro* incubation (17)) and these fatty acids form the basis for generation of lipid peroxides (27), which may represent the primary initiators of inflammation.

At the cellular level, evidence for inflammatory activity includes leukocytic infiltration in D/SD (32). More recently, there has been a more extensive histological cataloging of inflammatory cells, including various MHC+ lymphoid and NK cells (33). Subtle neutrophil infiltration into dandruff lesions has also been reported (34) and neutrophil chemotaxis via anaphylatoxins derived from the dandruff scales. Recent histologic analysis has shown such evidence of mild inflammation (perivascular lymphocytes) in dandruff lesions (30).

These structural variations at the cellular level result in a SC barrier that is functionally impaired. The barrier is no longer as effective as normal skin at reducing moisture vapor transmission (35) nor is it as effective at reducing the penetration of exogenous materials, such as topical application of a solution containing histamine (36). This impaired barrier function leads to acceleration of the condition progression, likely disposing the skin to be less effective at blocking the penetration of the inflammatory initiators originating from *Malassezia* metabolic activity.

Therapeutic considerations. Effective therapeutic D/SD treatments not only alleviate the signs and symptoms of the condition, but result in normalization of the structure and function of the skin as well. For example, the structural abnormalities previously associated with hyperproliferation (parakeratosis, poorly formed corneocyte envelope, *Malassezia* infiltration and lack of epidermal lipid structure) all are significantly improved after use of a shampoo containing potentiated ZPT (24). As expected, function follows structure and, as the structure improves due to treatment, so does the function of the skin. Barrier structural integrity as assessed by corneosurfammetry improves (37) as does a normalization of TEWL (35).

BIOMOLECULAR CHANGES

Quantification of molecular level data from the epidermis represents a recently developed capability that was enabled by new molecular techniques that have become reliable and reproducible. By comparison of D/SD and normal populations, such data not only provide etiopathological details previously unavailable, noninvasive approaches also greatly facilitate the evaluation of therapeutic benefits of treatments. Initial work within this context focused on inflammatory mediator molecules using traditional punch biopsy samples and immunohistochemistry (33). Using these techniques, elevated levels of the following cytokines were observed from D/SD lesions: IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α and IFN-γ vs. skin from normal volunteers. Also non-lesional skin from D/SD subjects had elevated levels of these cytokines vs. normal skin. These data provided an early indication that D/SD might

be differentiated from the norm at a molecular level (and provided further support that these conditions have an inflammatory component). Subsequent improvements in methodology were developed using non-invasive skin surface sampling methodologies combined with highly sensitive ELISA-based quantification (38). The non-invasive techniques facilitate larger clinical sample sizes thereby enhancing the quality of the data and allowing this approach to become routinely integrated in clinical evaluations. In the first use of this type of methodology on scalp to differentiate D/SD from normal populations, the following inflammatory markers were found to link accurately with the condition and other traditional parameters measured: IL-1ra (ratio to IL-1α), IL-2, IFN-γ, nitric oxide and TNF-α (39).

Extensive clinical populations (using expert flake assessment to identify D/SD) have recently been evaluated (30, 40) for a wide range of molecular level biomarkers comparing D/SD and normal populations. The data from these two studies is re-plotted and represented in Fig. 2. Statistically significant differences were seen for the two populations for all three inflammatory biomarkers investigated: IL-1ra/IL-1α, IL-8 and histamine. Structural biomarkers related to differentiation were also evaluated: the cell envelope protein involucrin showed only small differences between the two populations (but is sensitive to response to treatment, see below) and the keratins 1, 10 and 11 are substantially reduced in the D/SD population indicating incomplete terminal differentiation. Molecular markers of barrier integrity were quantified that completed the etiologic cascade: human serum albumin (HSA) and the epidermal intercellular lipids. Quantification of HSA in the outer SC is a molecular measure of the decreased barrier integrity and function observed for D/SD. Decreases in total ceramides and sphingoid bases were observed for D/SD, supporting similar previous observations (36) and likely part of the reason for the decreased skin barrier function.

Based on the availability of these new non-invasive sampling methods as well as bio-analytical capabilities, other relevant biomarkers of the D/SD condition can be expected to be identified in the future. These may include the induction of endogenous anti-microbial materials such as β-defensins, which have been observed *in vitro* as a result of *Malassezia* exposure (41) and *in vivo* in *Malassezia*-positive psoriasis (42) as well as the expression of *Malassezia*-related inflammatory mediators such as malassezin (43). It is also possible that biomarker quantifications associated with reactive oxygen species (ROS) defense will be identified, as there are indications that oxidative damage accompanies or causes D/SD.

Therapeutic considerations. While these molecular level indications of D/SD increase the understanding of the pathological condition, they can also serve as new measures to evaluate the therapeutic resolution of D/SD. The data summarized from recent publications (30, 40) tracking the above biomarkers before and after treatment with a commercial 1% potentiated ZPT shampoo are re-plotted in Fig. 3. The data and statistical analysis are based on change from baseline; normalization in some cases requires some parameters to decrease while others to increase. Significant reductions in all inflammatory biomarkers quantified (IL-1ra/IL-1α, IL-8 and histamine) were observed, showing a normalization of the skin inflammatory state (relative to the levels of these biomarker molecules observed in normal population, see Fig. 2). Likewise, both differentiation biomarkers were also significantly normalized: involucrin decreased while terminal differentiation products keratins 1, 10 and 11 increased. HSA also significantly decreased, indicative of the barrier function returning to normal and consistent with structure/function level improve-

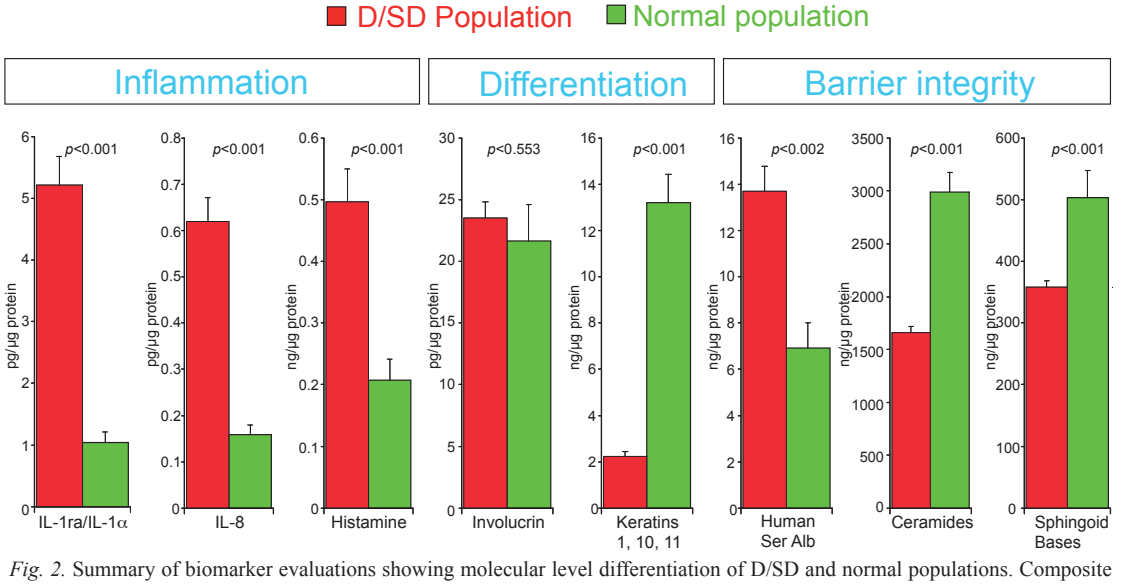

Fig. 2. Summary of biomarker evaluations showing molecular level differentiation of D/SD and normal populations. Composite representation of data (30, 40).

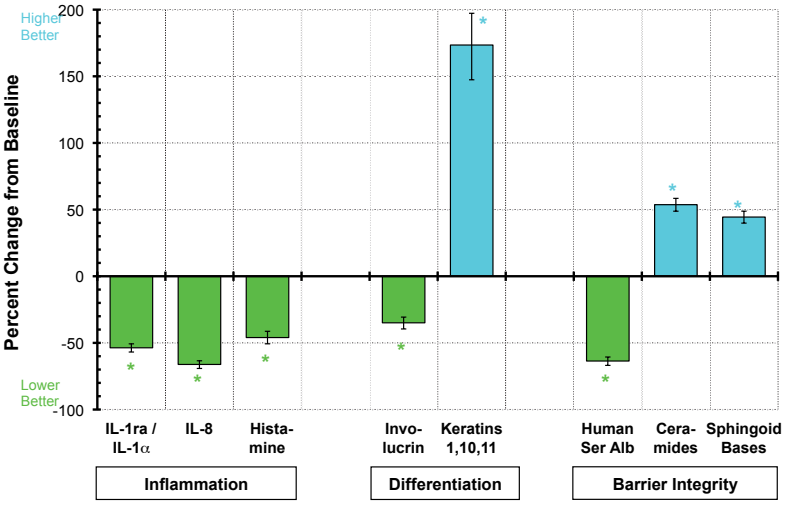

Fig. 3. Summary of biomarker improvements upon D/SD treatment. Composite representation of data from (30, 40).

ments observed (see above). Finally, intercellular lipids responsible for barrier function also increased significantly, consistent with previous observations (37) and supporting barrier function improvement.

Taken together, these molecular biomarker observations provide a further insight into the picture of the pathophysiology of the D/SD condition and offer more detailed evidence of resolution with commercially available treatments. While there is a consistency between resolution of signs and symptoms of D/SD and the normalization of the biomarkers [22,32], we sought to assess the statistical significance of the correlations. The commonly assessed variable of flake reduction as quantified by the adherent scalp flake score (ASFS) (44) was used as the accepted clinical endpoint. This was done (previously unpublished) by evaluating correlations as change from baseline on a person-by-person basis between the two parameters (a rigorous approach). Since this represents a correlation between two independent *in vivo* measures, one depending on an expert grader (ASFS) and the other on an objective molecular technique (biomarker), including normal biological variability, low absolute correlations were expected. These correlations are summarized for selected biomarkers in Table I, general ranges were ± 0.2, indicating the degree of variability expected from these studies. However, these correlations are all highly statistically significant, typically with *p*-values much lower than 0.0001. If these statistical analyses were done as averages by treatment (rather than by person), thereby reducing the person-to-person variability, correlation coefficients between individual biomarkers and flake reduction are substantially higher (often in the 0.7 range, data not shown). This analysis demonstrates the significant correlation between individual biomarkers and the reduction in flakes as the key symptom and current routine measure of the scalp condition. This both shows the relevance of the biomarkers to the overall pathophysiological definition of the D/SD condition and also establishes them as relevant surrogate measures for the classical clinical flake appearance reduction endpoint.

Table I. *Statistical correlation assessment (parametric) between selected biomarker and flaking changes from baseline on an individual basis*

Biomarker (log_{10} ratio Baseline:Treatment)	Observations *n*	Pearson correlation coefficient (r)	*p*-value
IL-1ra: IL-1α	1,960	0.2814	<0.0001
IL-8	1,966	0.2290	<0.0001
Histamine	1,237	0.1038	=0.0003
Involucrin	1,964	0.2223	<0.0001
Keratins	1,966	–0.2675	<0.0001
Serum albumin	1,965	0.2563	<0.0001

DISCUSSION

Definition of a comprehensive pathophysiological description of dandruff and seborrheic dermatitis

The signs and symptoms of the D/SD conditions are well established mainly through traditional (macro) assessment of the scalp skin condition. The description of the scalp condition at the structural and molecular level is now enabled by new molecular measurement capabilities. The pathophysiological model that is emerging (Fig. 1) is based on the established etiological phases of *Malassezia* metabolism initiating the inflammatory cascade, resulting in scalp skin hyper-proliferation and incomplete corneocyte differentiation that yields an impaired SC barrier.

Measures at the structure/function level, such as epidermal morphology, *Malassezia* infiltration and instrumental assessments related to moisture content have supported the basic etiology sequence discussed above. These measures have enabled a deeper understanding of the pathophysiology of these conditions by demonstrating that the superficial signs and symptoms are the result of an irregular epidermal construction and resultant dis-organization in the onset of D/SD. These observations, in turn, have led to probing specific molecular mechanisms in the skin, which established the inflammatory nature of the condition, the poor synchronization of proliferation and differentiation and the relatively ineffective barrier function.

Rather than describing a healthy scalp as simply being free from signs and symptoms of a condition, these new parameters enable both a more complete pathophysiological description of D/SD as well as establishing more specific criteria for assessing whether the condition has been effectively treated.

Additionally, these new D/SD measures support the inclusion of D/SD in the broad group of inflammatory dermatoses, including psoriasis, atopic dermatitis and acne. These conditions have different triggering events, but share the pathophysiology of inflammation, proliferation and skin barrier impairment. Other inflammatory dermatoses have been studied in more detail (45) than D/SD; and the biomarker data reviewed here are especially useful for demonstrating the commonalities of pathophysiology with these well-established conditions (49).

Relevance of biomarkers as surrogate clinical measures

The benefits of developing a molecular, biomarker-based quantification capability is likely to extend beyond a more thorough understanding of a disease condition and include the potential to use biomarkers as relevant efficacy measures (46). If the biomarkers reflect disease mechanisms underlying the clinical pathophysiology, as they appear to in the case of D/SD, they can be useful tools as measures earlier in the onset of the condition, and/or as surrogate endpoints for clinical efficacy of treatments. The FDA recognizes this advantage of biomarker tools and encourages the use of biomarkers in a recent white paper "Innovation or Stagnation?" (47). An example of the use of biomarker analysis in dermatology exists for atopic dermatitis (AD) (48). Surface quantification of IL-18 was found to correlate with the severity of the condition and appeared to be due to *Staphylococcus aureus* colonization. This is an example demonstrating both benefits of this biomarker for AD: generation of new pathophysiological information and the establishment of a new clinical measurement endpoint.

A number of biomarkers have been found to be significantly correlated to the key D/SD symptom of flaking (see Table I), even when evaluated on the basis of individuals analyzed. All of these biomarkers have a specific rationale within the known etiology of the condition, enabling a greater, more detailed understanding of the pathophysiology of D/SD. These biomarkers can also be used as surrogate clinical endpoints for the detailed assessment of D/SD treatment success, thus complementing the traditional measures that are mainly focused on visible signs/symptoms.

Future directions

The new capabilities of measuring the state of the scalp skin physiology with biomolecular markers facilitate a greater understanding of pathophysiology of the D/SD condition. New non-invasive measures will continue to be developed in the future that can shed more light on interactions between *Malassezia* and the epidermis. There is still much to learn, for example, why does D/SD of the scalp require a physical covering of hair? Another critical question is why a commensal organism such as *Malassezia* triggers D/SD in some but not others.

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