Skin structure and skin care requirements – From past to future

published in Ästhetische Dermatologie (mdm) 2016 (8), 10-15

For a long time in human cultural development, cosmetics and medicine had been considered as one discipline. About 150 years ago, with the onset of industrialisation, the influence of natural science and the identification, isolation and big scale production of chemicals and ingredients, the separation into individual disciplines became apparent.

Initially it was a matter of skin protection and the treatment of dry skin conditions. Subsequently the focus was on skin moisturisation until the importance of the barrier lipids of the skin was recognized. In trying to treat diseased skin conditions like atopic dermatitis (AD) and psoriasis, also the knowledge on biochemical processes, the role of genetics and the colonization of the skin with microorganisms grew. Since the last decade, there is culminating evidence, that not only the skin microbiome but also the human microbiome in total plays a key role in skin health.

From petrolatum to the NMF

In my opinion, modern cosmetics began in 1872 when Robert Cheseborough started to market a mineral oil derivative called petrolatum under the brand name Vaseline (1). Vaseline actually can be considered as a prototype of skin protectant as it's mode of action is based on forming a film on the skin, which is impermeable to water (and water based irritants) thus increasing the barrier function of skin. As Vaseline was stable to rancidity in contrast to the then used animal fats and marketed to cure (almost) everything. At that time also pharmaceutical formulas were developed, which contained the then popular ingredients like lanolin, Vaseline and paraffin oil. They are still listed in today's pharmacopoeias i.e. Eucerinum anhydricum (Unguentum adeps lanae; a synonym for wool fat and alcohol based ointment, extemporaneous preparation).

Whereas the lipid components for skin moisturizing purposes have been controversially discussed for a long time, things were different for water and other humectants. In 1952 Blank published first studies on skin moisturisation and identified water as a main factor for skin elasticity. Jacobi described the composition of the natural moisturizing factor (NMF) in 1959 (3). Main feature of the NMF is its hygroscopicity, which was postulated to be a relevant in vivo factor in protecting the skin against desiccation.

In 1984, Takahashi developed a process to assess the mechanical properties of isolated stratum corneum (SC) (4). The research group studied the effects of water, glycerine and NMF components. They could correlate the improved plasticizing effect of the treated skin with the water holding capacity of skin. Years later it was found that the NMF components are breakdown products of filaggrin (5) and that the absence of certain NMF components was not the trigger but a result of certain pathologic skin conditions. Based on today's genetic analysis, the NMF components can be considered as biomarkers of certain filaggrin genotypes (7). At this time also glycerine was examined, which actually has proven in vivo skin moisturisation effects, but performed poorly in the in vitro experiments. Glycerine's mode of action consists of stimulating the aquaporine-3 expression. In 1990, Agre identified aquaporines as ubiquitous membrane structures.

In general, humectants serve to maintain the elasticity of skin (protection against mechanical stress), to create ideal conditions for hydrolytic enzymes (proper function of the desquamation process i.e. shedding of the loose cells) and for the stimulation of the aquaporine expression in keratinocytes (supports the barrier function). While the first efficacy measurements were conducted on isolated SC, today's gold standard is the in vivo measurement. Measurements of skin moisturisation, (electrical capacity), skin dryness and barrier function (TEWL) and skin roughness are well established methods to diagnose the skin condition in vivo.

Lipid barrier and skin: ceramides and fatty acids

Main emphasis in the 1950ies was laid on the study of the skin structure (10) and the analysis of its lipid composition (11, 12). Turning

point in understanding the skin barrier was the study of Elias and Friend published in 1975 (13). They used electron microscopy and comprehensively described preparation and analysing methods for skin biopsy (freeze fracture and RuO_4, OsO_4 fixation). They identified "lamellar granules" in the stratum granulosum and suggested lipid-rich regions within the SC. Subsequent to their discoveries, hundreds of additional studies followed which confirmed the lipid rich regions. Three major lipid groups of the SC were identified and their molar ratio confirmed to be 1:1:1: ceramides, cholesterol and free fatty acids.

In 1988, Elias introduced the "brick and mortar" model of the SC (14). Crucial material of the model is the "mortar" which consists of structured lipid bilayers. They were considered to be relevant for the intact barrier of the skin. By correlating different analytical techniques i.e. skin biopsies, assessment of epidermal lipid composition, electron microscopy, x-ray diffraction, visual scoring, in vivo TEWL measurements, and structure-effect relations could be established. In the course of these studies, nine different ceramides have been isolated in human skin. They play a crucial role in the formation of the lipid bilayers of the SC. Their absence can be correlated with diseased skin conditions (15-18).

Fatty Acid / Sphingosine	Non-hydroxy fatty acid [N]	α-hydroxy fatty acid [A]	Ersterfied ω-hydroxy fatty acid [EO]
Dihydrosphingosine [DS]	CER [NDS]	CER [ADS]	CER [EODS]
Sphingosine [S]	CER [NS] (Cer 2)	CER [AS] (Cer 5)	CER [EOS] (Cer 1)
Phytosphingosine [P]	CER [NP] (Cer 3)	CER [AP] (Cer 6)	CER [EOP] (Cer 9)
6-Hydroxy Sphingosine [H]	CER [NH] (Cer 8)	CER [AH] (Cer 7)	CER [EOH] (Cer 4)

Figure: Nomenclature of Ceramides

With stratification of the epidermis several molecular and enzymatic changes take place (19-21). Precursors of barrier lipids are formed in the Golgi apparatus of living cells and then differentiated in the lamellar granules. There the lipids either are excreted together with a lot of different enzymes or already hydrolysed in situ.

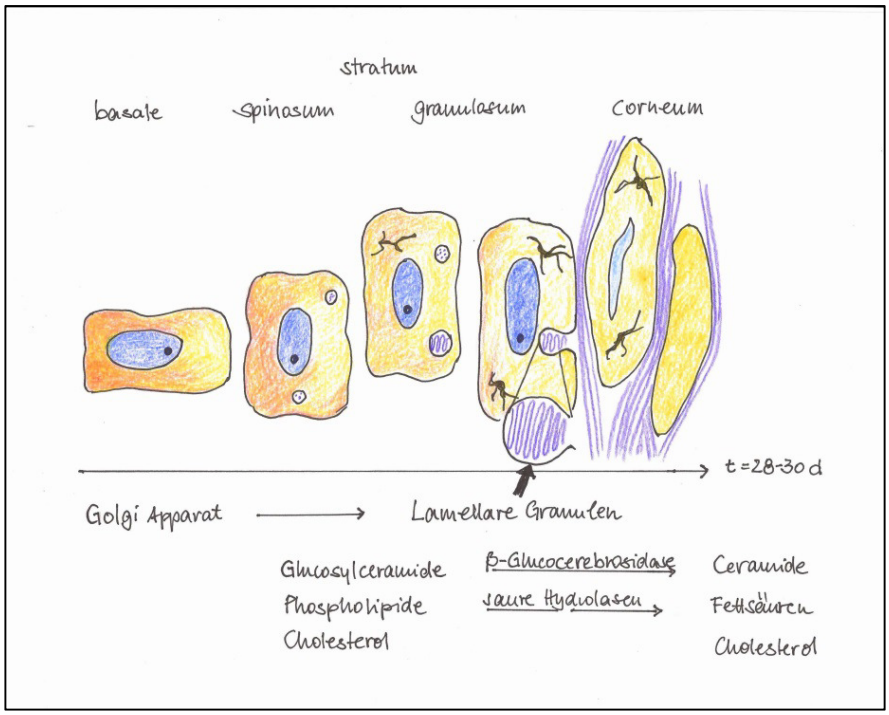

Figure: Differentiation of the epidermis and excretion of lipids

Taking together all the results, ceramides should be the top candidates to cure diseased skin: the topical supplementation of ceramides is assumed to be an effective therapy for psoriasis and atopic dermatitis (AD) and should be preferred to the administration of cortisone. However, a therapy with ceramides alone does not prove to be superior to a steroid treatment (22). Nevertheless, ceramides are used in cosmetics as effective skin care substances. There are other compounds in the lipid barrier meriting a closer look, e.g. fatty acids. The epidermis is a very active site of lipid synthesis and most of the fatty acids can be synthesized by keratinocytes de novo. Here the stratum granulosum seems to be the most active area (23).

Fatty acids play a key role in (skin) health and particularly essential fatty acids (EFA), which cannot be synthesized by the body itself, but have to be supplemented by nutrition. They regulate membrane

functions, are relevant for the cholesterol metabolism, act as ß-blockers, diuretics, and have anti-hypertensive and anti-arteriosclerotic effects (24). Furthermore, linoleic acid is the acyl-component of ceramide 1, and the administration of evening primrose oil (high content of γ-linolenic acid) proved to be particularly beneficial for the treatment of AD in children.

Inflammatory skin conditions in atopic dermatitis (AD) and psoriasis

Inflammatory skin diseases such as AD and psoriasis are of high social relevance. They mainly affect people in the western world with an adult prevalence rate of 3% and 2% respectively. Furthermore, over the last century the number of AD cases has doubled or even tripled. To find an effective treatment would significantly enhance the quality of life for many people. Up to now, just the pruritus that frequently accompanies AD can be treated by administration of cortisone. Recent studies report on the development of antibodies that possibly reduce pruritus (26). Insufficient treatment efficacy can be explained with the fact that the triggering mechanisms have not yet been identified. Moreover, barrier disorders seem to be only one symptom out of many which in turn influence the disease. Today it is a fact that besides barrier lipids other key players are involved in AD. Prostaglandin E_2 and leukotriene B_4 levels for instance are increased and interleukin-1α level is decreased in eczematous skin (27). Besides inflammatory mediators, also immune modulating substances are involved. They are internally as well as externally triggered.

Psoriasis and AD are similar in so far, that they are complex inherited diseases involving genes that encode immune components and structural proteins that regulate differentiation of epidermal cells (28, 29). Recent studies show, that these inflammatory skin conditions also correlate with a higher incidence of other diseases: AD with asthma, allergies and psoriasis with metabolic diseases (diabetes), arteriosclerosis, rheumatoid arthritis as well as psychologic disorders. It is discussed that these (metabolic) disorders are the actual underlying disease and the skin lesions are some kind of early symptom preceding the onset (28). Whereas there is an effective therapeutic agent for psoriasis such as cyclosporine A, there is none for AD. Staphylococcus aureus colonization of atopic skin leads to further complications.

The skin biotope and potential future research areas

Recent studies published under the heading ‘human microbiome’ show, that human bodies serve as a huge habitat for microorganisms of all kinds (31). Epidemiological studies on the human gut microbiome indicate that the genetic and metabolic diversity there is at highest. Comparison of faecal samples obtained from people from third world rural areas with those from US metropolitan areas showed significant differences in the phylogenetic composition of the faecal microbiota. The faecal microbiota obtained from US adults was the least diverse (34). There is culminating evidence that our life-style, especially the nutrition habits, has significant impact on the gut microbiome, and consequently is relevant to our health. Recent findings suggest that the higher incidence of allergies, asthma and some autoimmune diseases in western population are related to the gut microbiome (35, 36).

Even though the skin microbiome is not as diverse as the gut microbiome, an abundance of microorganisms (viruses, bacteria and fungi) and mites cover the surface of the skin and reside deep in the hair and glands. Exogenous and endogenous factors contribute to the colonization of the skin such as:

- Host physiology: Sex, age, site
- Host genotype: Susceptibility genes such as filaggrin
- Environment: Climate, geographical location
- Lifestyle: Occupation, hygiene
- Immune system: Previous exposures, inflammation
- Pathobiology: Underlying conditions such as diabetes

Our skin is populated by more than 1 billion bacteria / cm^2, which are fundamental for skin physiology. Staph. epidermidis is one of the dominant bacteria found on the skin. It produces several antimicrobial proteins (AMP) and proteases that can limit biofilm formation of pathogenic species (37). Especially the ratio of Staph. aureus / Staph. epidermidis correlates with the severity of AD (22, 32, 38). These findings taken together pinpoint AD as an acquired disease.

Therefore it is anticipated that future studies concentrate on the individual microbiome composition of diseased individuals. With the skin microbiome serving as the first barrier of our skin, also our skin cleaning and caring routines will be questioned in future. Especially the use

of preservatives in skin care preparations. As the gut microbiome also plays a fundamental role in our immune system, we will pay more attention to the kind and quality of food we eat. Actually that is not new: we already know that healthy beautiful skin comes from within.

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Dr. Ghita Lanzendörfer-Yu

Extended version:
Ghita Lanzendörfer-Yu, Skin Structure and Requirements on Skin Care – From Past to Future, Lecture on 4th International Symposium on Corneotherapy, May 6-8, 2016, Cologne, Proceedings 12-24