Proceedings of the Heinz Maurer-Symposium "Review and Preview in Science for Healthy Skin" June 28th 2014, Jakobsberg, Boppard, Germany*

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Introduction

On June 28, 2014 a scienitfic symposium titled **Review and Preview in Science for Healthy Skin** was held on the occasion of the 10th conferment of the Heinz Maurer Award, the Jury represented by the Chairman, Prof. Wolfgang Gehring to Prof. Johanna Brandner, Laboratory for Cell and Molecular Biology of the Department of Dermatology of the University Hamburg-Eppendorf for her work on "Contribution of tight junction proteins to ion, macromolecule, and water barrier in keratinocytes", published in the Journal of Investigative Dermatology 2013, and to Dr. Peter Arne Gerber, Dermatological Department of the University of Düsseldorf for his publication "EGFR Controls Cutaneous Host Defense and Prevents Inflammation" published in Science Translational Medicine 2013 (**Fig. 1**). The symposium following the conferment of the award provided an overview on past, recent, and future developments in the field of skin research, presented by former Heinz Maurer Award winners.

Since 1996 the Heinz Maurer Award is allocated biannually to researchers who have published outstanding results in dermatology and related fields

Fig. 1 10th Conferment of the Heinz Maurer Award on June 27th 2014. From left to right: Dr. Rüdiger Mittendorff, Chairman of Board of Directors Sebapharma, Boppard, Germany; Prof. Johanna Brandner, Laboratory for Cell and Molecular Biology, Department of Dermatology, University of Hamburg-Eppendorf, Germany; Peter Arne Gerber, Department of Dermatology, University of Düsseldorf, Germany; Thomas Maurer, Chairman of Board of Directors Sebapharma, Boppard, Germany; Prof. Wolfgang Gehring, Director Department of Dermatology, Karlsruhe, Germany; Prof. Otto Braun-Falco, Emeritus Professor and Chairman, Department of Dermatology, Ludwig Maximilians University Munich, Germany.

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concerning **Skin Surface – Modulation of Skin Structure and Function**. The award is divided into two relevant categories: Basic Research and Clinical Research, which are endowed with € 10.000 each.

Dr. med. Heinz Maurer, the owner and founder of Sebapharma GmbH & Co. KG which is located in Boppard, Germany, installed the award two decades ago with the aim to support the continuous progress in understanding the skin's physiological and pathological functions in relation to its interactions with the environment as well as other organ systems. This dedication of the pioneer of skin care adjusted to the physiological skin surface pH of 5.5 mirrors Sebapharma's aim to apply **Science for Healthy Skin** to ensure **Quality through Research.**

The members of the jury for the 10th Heinz Maurer Award are: Prof. Dr. med. O. Braun-Falco – Munich (Honorary Chairman), Prof. Dr. med. Markus Braun-Falco – Munich, Prof. Dr. med. C. Bayerl – Wiesbaden, Prof. Dr. rer. nat. R. Daniels – Tübingen, Prof. Dr. med. W. Gehring – Karlsruhe (Chairman), Prof. Dr. med. M. Kerscher – Hamburg, Dr. rer. nat. A. von Petersenn – Bergisch-Gladbach, Prof. Dr. med. T. Ruzicka – Munich, Prof. Dr. rer. nat. M. Schäfer-Korting – Berlin, Dr. rer. nat. M. Arens-Corell – Boppard.

The acid mantle of the skin: new stories about an old coat

▼

Nanna Y. Schürer

The "skin's acid mantle" is an old story, first told by Heuss 1892 and consolidated by Schade and Marchionini 1928. The skin surface pH on the forearm of healthy adult white males was interpreted to range between 5.4 – 5.9 (Braun-Falco and Korting 1986). 1994 Öhman and Vahlquist re-established the stratum corneum (SC) pH gradient in relation to pH-dependent enzyme activity, necessary for SC lipid synthesis, barrier integrity, cohesion and regeneration. Barrier repair is perturbed in an environment with a neutral pH (Mauro et al., 1998), most likely due to impaired activities of acyl-glucosylceramidase and sphingomyelinase, relevant for SC lipid synthesis (Hachem et al., 2003). Furthermore, serine proteases are more active at a neutral compared to an acidic pH. The SC pH gradient reflects the hydrogen ion concentration distributed in form of acidic microdomains (Behne et al., 2002). The skin surface pH has been attributed to byproducts of microbial metabolism, lactic acid from sweat, free fatty acids, progressive desiccation of the SC, and/or generation of cis-urocanic acid from filaggrin. Lambers et al. revealed 2006 a mean skin surface pH value of 4.7 according to a meta-analysis of the literature, confirmed by Segger et al. 2007, measuring the skin surface pH of 222 forearms of healthy adult white 18-69 y.o. males and females. The skin surface acidity varies, according to its anatomical site, environmental and disease relation and is influenced by a number of endogenous and exogenous factors. The negative effects of alkaline detergents on the skin's acid mantle has been well studied (Korting et al., 1995). The positive effects of alpha hydroxyl acids has been linked to cohesion and desquamation (Van Scott 1987). Recent clinical, yet unpublished studies consolidate skin surface pH dependent barrier integrity and regeneration with age and skin pigmentation. Further, via pH-modulation epidermal barrier function improves in aged skin, however does not seem to be influenced in young healthy skin.

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The skin barrier from a lipid perspective: in vitro and in vivo studies

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Joke A. Bouwstra

In the nineties of the last century we studied the lipid organization in the outermost layer of the skin, the stratum corneum of various species, including humans. We showed that the lipids in human stratum corneum adopted two crystalline lipid lamellar phases with repeat distances of around 6 and 13 nm [1]. In subsequent studies we were interested in the relationship between the lipid organization and lipid composition. This was studied using lipid mixtures prepared from ceramides, cholesterol and fatty acids, the three main lipid classes in stratum corneum. These studies revealed that the ceramides and cholesterol are important for the formation of the lipid lamellae, while the fatty acids are important for the formation of the very dense crystalline packing [2]. Crucial is the inclusion of acyl-ceramides, a very special group of ceramide subclasses.

With this knowledge, we started our work on the barrier function of diseased skin. In recent years we mainly focussed on atopic dermatitis (AD). An important feature of AD is a decreased skin barrier function. With the introduction of a mass spectrometer method, not only lipid classes and subclasses, but also lipid chain length distributions can be studied.

We performed a clinical study in which the stratum corneum lipids and their importance for the skin barrier function was examined. AD patients were compared with control subjects. In particular the carbon chain length of the ceramides and FFAs was investigated in relation to the density of the SC lipid organization (examined by infrared spectroscopy) and the transepidermal water loss (TEWL), a marker for the permeability barrier. The most important findings are 1) The chain length of ceramides and free fatty acids is reduced, 2) In lesional skin the reduction in chain length was more pronounced than in non-lesional skin, 3) The reduction in lipid chain length correlated excellent with a less dense lipid organization and a reduced skin barrier function [3] (▶ **Fig. 2**). In additional studies using lipid membrane we showed that changes similar as observed in atopic eczema can account for an increased permeability of compounds. Finally we

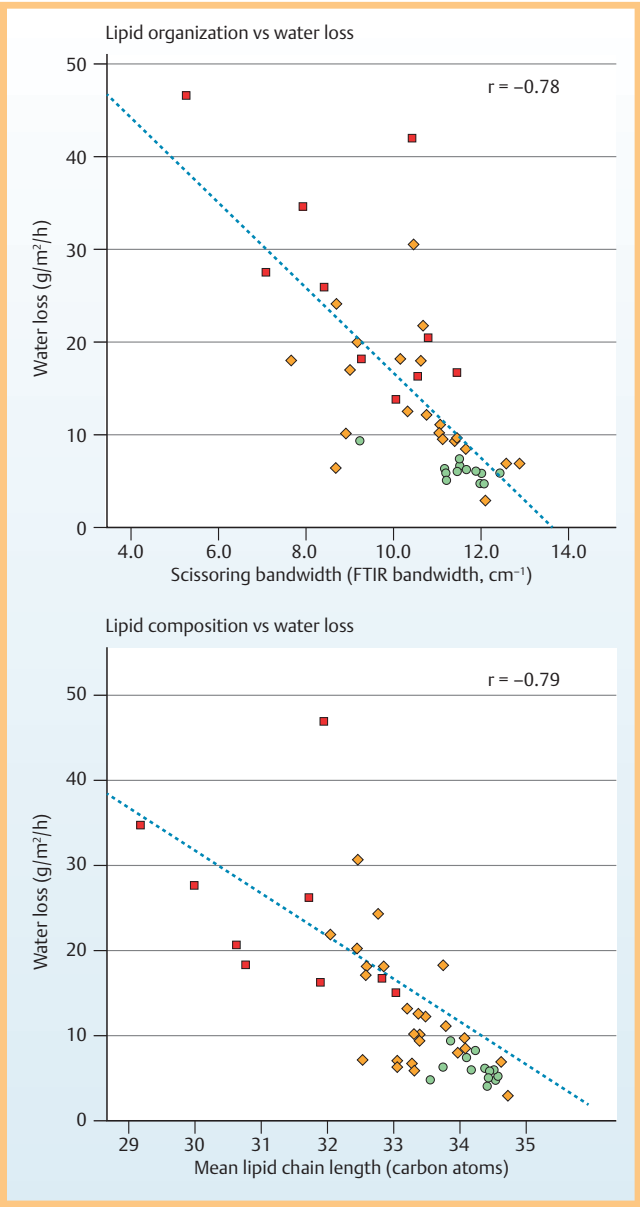

Fig. 2 The scissoring bandwidth, which is a measure for the lipid organization (higher value a more orthrhorhombic packing) and the mean lipid chain length of ceramides and fatty acids correlate excellently with the skin barrier function as measured by water loss [3].

noticed that using human skin equivalents inflammation may induced changes in the lipid composition.

The outcome of our studies provides insights into the role of the SC lipid chain length and shows that the lipids play a role in the impaired skin barrier of AD patients. These results may provide opportunities for studies on skin barrier repair by topical treatments and show evidence that normalisation of the lipid synthesis may enhance normalisation of the skin barrier function.

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Melanocyte Stem Cells in the Hair Follicle

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Mayumi Ito

Melanocyte stem cells (McSCs) intimately interact with epithelial stem cells (EpSCs) in the hair follicle region called the bulge/sHG niche. While EpSCs produce the hair follicle, McSCs produce melanocytes to provide pigment for the hair. At the onset of hair follicle regeneration, McSCs undergo proliferation and differentiation, which ultimately leads to the formation of pigmented hair. However, the mechanisms behind this coordinated stem cell behavior have not been elucidated. Here, we identified Wnt signaling as a key pathway that couples the behavior of the two stem cell populations. Using genetic mouse models that specifically target EpSCs, we show that Wnt activation in EpSC not only dictates hair follicle formation but also regulates McSC proliferation during hair regeneration (▶ **Fig. 3**). To understand the mechanisms underlying this effect, we performed microarray analyses and identified that EpSCs express endothelins upon Wnt pathway activation, which is known to be a potent mitogenic signal for melanocytes. Endothelins function as ligands that activate endothelin receptor B signaling in adjacent McSCs thereby promoting their proliferation. Our data demonstrate a mechanism by which EpSCs and McSCs interact during hair follicle regeneration. These results provide insight into the understanding of how complex organs can be regenerated through the collaboration of heterotypic stem cell populations.

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Fig. 3 β-catenin stabilization in epithelial stem cells directs expansion and localization of melanocytes.

Langerhans cells as skin immune sentinels – shaping immune responses during inflammation

Günther Weindl

Dendritic cells (DC) are professional antigen presenting cells and provide a link between the innate and adaptive immune system. Several human DC subsets within the skin delineate a complex network of dermal DC and Langerhans cells (LC), a highly specialized population localized in the epidermis (**Fig. 4**). At present, the distinctive functions of human subsets are mainly derived from genetically modified mice, despite various physiological differences, including origin and distribution of murine DC, compared to human counterparts [1]. During steady state immune surveillance, LC and dermal DC act as sentinels against commensals and invading pathogens depending on the expression and functionality of specific pattern recognition receptors. Under pathological skin conditions, inflammatory cytokines, secreted by surrounding keratinocytes and dermal fibroblasts, modulate the activation and maturation of DC populations. However, considering the diverse functional properties of LC and dermal DC, their specific contribution in the induction, regulation or aggra-

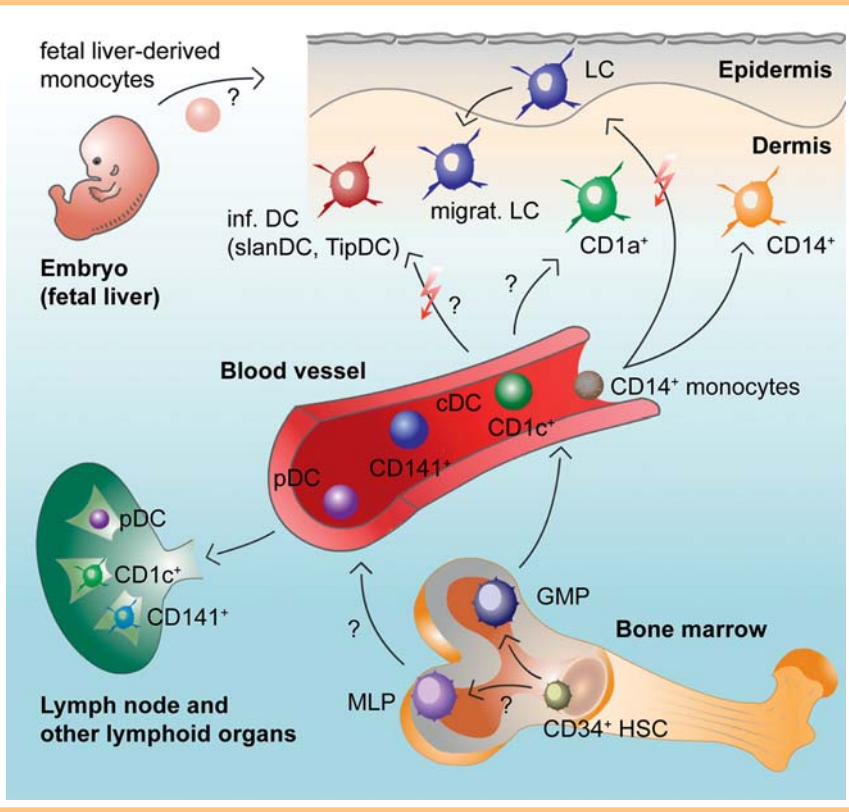

Fig. 4 Origin and organization of human dendritic cell subsets. This simplified illustration summarizes the current model of the developmental pathways of human dendritic cell (DC) subsets. Adult Langerhans cells (LC) derive predominantly from embryonic fetal liver monocytes. Under inflammatory conditions $CD14^+$ monocytes are involved in the short-term repopulation of the epidermis with LC. Question marks indicate unknown identity or speculative relationships. Red lightning signs indicate important pathways during inflammation. cDC, conventional DC; GMP, granulocyte macrophage progenitors; HSC, hematopoietic stem cells; inf. DC, inflammatory DC; migrat. LC, migratory LC; MLP, mixed lymphoid progenitors; pDC, plasmacytoid DCs; slanDC, 6-sulfo LacNAc expressing DC; TipDC, TNF-α and iNOS-producing DC (figure kindly prepared by André Said).

vation of inflammatory skin disorders, such as psoriasis vulgaris, is still poorly understood [2]. Strong evidence exists that highly reactive Th1, Th17 and Th22 cells play an important role in the development of inflammatory and hyperproliferative tissues within the psoriatic plaques, indicating activation of T cells by DC. In fact, recent studies suggest that dermal DC and LC are a main source of IL-23 [3,4], which is essential for the expansion and survival of IL-17-producing Th17 cells [5]. Although recent work provides insight into the immunoregulatory role of distinct DC subsets in inflammatory environments, further studies will be required to understand the molecular mechanisms balancing innate and adaptive immune responses in human skin.

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In Vitro Skin Models – Chances and Limitations

▼
Sarah Küchler

The development and characterization of *in vitro* skin models gained increasing interest during the past 25 years. As for today, several types of skin models exist such as epidermal models (stratum corneum and viable epidermis) or full thickness skin models (stratum corneum, viable epidermis and dermal equivalent) [1,2]. Some of them such as the EpiDermFT (MatTek, Ashland, MA) and EpiSkin (SkinEthic, Lyon, France) are commercially available. Nevertheless, in-house generated skin models undergo substantial progress [3 – 5] and offer the advantage to design specific skin models which meet the individual research interests.

Reconstructed skin models (**Fig. 5**) nicely mimic the anatomy and physiology of human skin [5] and can be employed for a variety of applications. Some of the commercially available skin models have been validated for acute skin irritation and skin corrosion testing aiming for a reduction of animal studies in this field [6]. Additionally, reconstructed skin models are interesting test systems for fundamental studies of (patho)physiological aspects. For instance, a gene knock down induced by RNA interference allows to inhibit the function of a gene of interest and, hence, allows to mimic a specific disease pattern *in vitro* [3]. For instance, we successfully established filaggrin deficient skin models and use these to investigate fundamental processes in filaggrin deficient skin. Further skin disease models such as skin tumor models or inflammatory skin models [4] are of high interest not only for the academic field but also for pharmaceutical and cosmetic companies due to growing political and social pressure in terms of the replacement and reduction of animal studies.

Aside from various advantages, we have to keep in mind that we are still dealing with models which cannot fully mimic the processes and homeostasis of native human skin. Major limitations are the reduced skin barrier function [7], the lack of immunocompetent cells as well as the limited cultivation period due to the lack of self-renewal and/or desquamation. These aspects require further research efforts. Nevertheless, *in vitro* skin model possess high potential for multiple applications such as toxicity testing, pharmacological studies *in vitro* as well as basic research studies. To fine tune the existing models intensified research efforts are required to overcome the drawbacks and to develop even more realistic models.

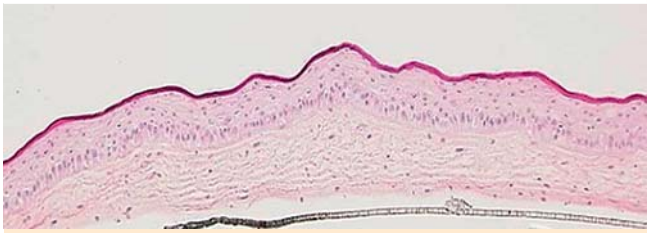

Fig. 5 H&E staining of a reconstructed skin model resembling nicely the physiological structures of native human skin.

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YosipovITCH Journey from Skin to Brain

▼
Gil Yosipovitch

Chronic pruritus has a significant impact on the quality of life of millions of patients. It is exacerbated at night time and causes sleep abnormalities. The underlying mechanisms responsible for nocturnal pruritus are yet unclear. One possible explanation may be related to the circadian rhythms of skin temperature and trans-epidermal water loss (TEWL). We were the first to show that the TEWL, skin temperature and skin surface pH have time circadian rhythms and are elevated at night time. These findings led to my Heinz Maurer Award. In the current talk I will cover some of the work I have performed in 3 continents on mechanisms of itch and scratch extending from the stratum corneum up to the brain the final common pathway of itch. Special emphasis will be focussed on the effect of changes in pH and skin barrier function on itch (**Fig. 6**), areas that the late Dr Maurer had major interest. These topics have recently emerged to be of sig-

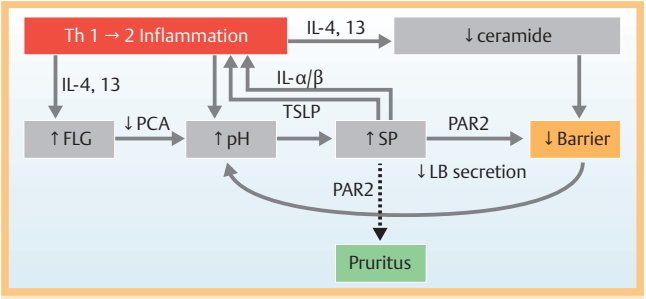

Fig. 6 Mechanisms of itch induction by ↑ pH in atopic eczema and impaired barrier.

nificant relevance to itch in inflammatory skin diseases and dry skin.

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Pathogenesis of chronic hand eczema

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Sonja Molin

Pathogenesis of chronic hand eczema depends on exogenous factors such as chronic irritant damage or contact allergy and on endogenous factors such as atopic diathesis (▶ **Fig. 7**). In many patients, however, factors triggering the eczema cannot be clearly identified, or potential triggers cannot explain the clinical presentation. Recent findings indicate that chronic hand eczema develops as a consequence of an impaired epidermal barrier. Impairment of the natural barrier by genetic defects and/or repeated contact to water or other irritants results in the failure of the skin's repair mechanisms, thereby promoting the penetration of allergens and eczematisation. We have analysed the barrier function in hand eczema with different approaches: genomic analysis of promising candidate genes as well as proteomic profiling of palmar skin. These studies led to the identification of a characteristic expression profile of epidermal barrier components in chronic hand eczema.

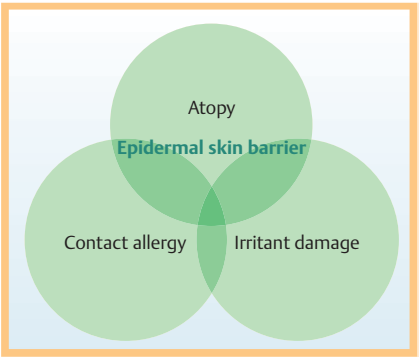

Fig. 7 Multifactorial pathogenesis of chronic hand eczema.

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Maintenance of cutaneous homeostasis – from signaling pathways to novel skin-specific genes

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Peter Arne Gerber

Barrier function, infection and inflammation are three major processes that affect cutaneous homeostasis. Recent clinical observations and systematic *in vitro* and *in vivo* analysis have contributed to our understanding of how cutaneous homeostasis is controlled on the molecular and cellular level. Strikingly, cancer patients that are treated with targeted drugs directed against the Epidermal Growth Factor Receptor (EGFR) and, to a certain extent, also against its down-stream kinases (RAF, MEK) frequently develop severe skin inflammation (rashes) that are often accompanied by bacterial superinfections and progressive skin dryness (▶ **Fig. 8**). These cutaneous adverse effects do represent a serious threat to patient compliance and may lead to dose reduction or even cessation of the targeted anti-tumor therapy. Despite their clinical relevance the pathomechanisms of EGFR-inhibitor (EGFRI)-associated cutaneous adverse effects have remained largely elusive. Down this line we have recently demonstrated that EGFRI induce the expression of pro-inflammatory mediators (cytokines and chemokines) in epidermal keratinocytes, while the production of antimicrobial peptides or defensines and skin barrier genes is impaired. Correspondingly, EGFRI-treated keratinocytes facilitate lymphocyte recruitment, but show a significantly reduced cytotoxic activity against *Staphylococcus aureus*. Mice lacking epidermal EGFR show a skin phenotype that resembles EGFRI-treated patients, which is accompanied by chemokine-driven skin inflammation, hair follicle degeneration, decreased host defense and deficient skin barrier function as well as early lethality. Hence, our findings demonstrate that epidermal EGFR signaling is a key regulator of cutaneous homeostasis [1].

Whereas the EGFR is an established skin marker that controls cutaneous homeostasis in multifarious ways, it is obvious that this receptor is not the only regulator involved in this process. In fact, genes that show a high organ-specific expression are likely to exert important functions for this respective organ or tissue. Interestingly, a recent genome-wide comparative gene-expression analysis of virtually all human organs or tissues reveals that the EGFR is amongst the top 150 skin-associated genes (SAG; rank 144) [2]. This study also identified a list of the "top 100 human skin genes". Whereas the majority of these genes represent established skin markers (the top skin-specific gene is the antimicrobial peptide *dermcidin*, DCD), we have also identified a subset of novel, so far uncharacterized skin-markers. Analyses of the regulation of these SAGs in common skin-diseases suggest that

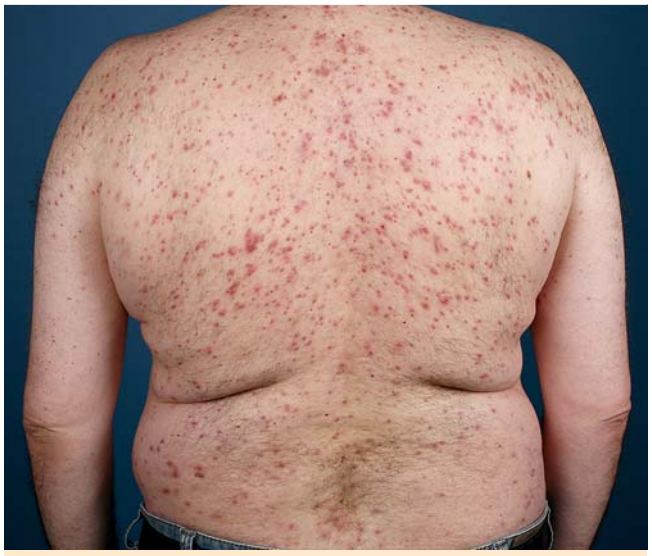

Fig. 8 EGFR-inhibtor-associated papulo-pustular rash.

Fig. 9 Soot and pigment spot occurrence (adjusted for age, skin sensitivity, sunburns, use of sunbeds, smoking, heating with fossil fuels). *Vierkötter et al.* Airborne particle exposure and extrinsic skin aging. J Invest Dermatol 2010 Dec; 130 (12): 2719 – 2726.

selected candidates may serve as biomarkers or drug targets in the future. Interestingly, a subsequent comparative analysis of the top human SAGs (hSAGs) and murine SAGs (mSAGs) revealed a total of only 30.2 percent identity between the two lists. These results illustrate the diversity between the molecular make up of skin of human and mouse and grants a probable explanation, why results generated in murine *in vivo* models often fail to translate into the human [3].

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The effect of airborne pollutants on the skin in the Chinese population

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Recently we could show that exposure to outdoor air pollution from traffic and industry is associated with an increased risk for skin aging in German women (**Fig. 9**). In 2012/2013 we conducted two cross-sectional studies in China, one in Pingding near Peking and one in Taizhou near Shanghai, in order to assess the association between air pollutants from different sources (indoor and outdoor) and skin aging manifestation in Chinese. In Pingding we assessed more than 400 rural housewives in the age range from 30 to 80 years who have high indoor air pollution exposure from cooking and heating with fossil fuels. In Taizhou we recruited more than 1000 Chinese men and women also in the age range from 30 to 80 years. In the latter population we aimed to investigate the influence of indoor air pollution as well as outdoor air pollution. Skin aging was evaluated by a validated skin aging score, the SCINEXA™. Indoor air pollution exposure, sun exposure, smoking and other confounders were assessed by validated questionnaires. We obtained outdoor air pollution data from the Taizhou Environmental Bureau and we will assign air pollution data to each subject using land-use regression models. We investigated the association between indoor air pollution and skin aging manifestation in both populations by using adjusted linear and logistic regression analyses. The analysis showed that indoor air pollution by cooking was significantly associated with an increased appearance of wrinkles on the face. In the population of rural housewives from Pingding more pronounced nasolabialfolds could be observed. In the Taizhou study population more pronounced nasolabialfolds, wrinkles on the forehead, crow's feets, wrinkles on upper lip, laxity and fine wrinkles on back of hands could be seen. Previously, in German women, we observed a significant increase in the nasolabialfold depth with an increase in outdoor air pollution, but also a pronounced increase of pigment spots on face, which we did not observe in our Chinese populations. The present studies thus corroborate our previous finding that air pollution is associated with skin aging and extend it by showing that (i) indoor air pollution might be another risk factor for skin aging and that (ii) ethnic differences might influence the clinical manifestation of pollution-driven skin aging.

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Conflict of Interest

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Wolfgang Gehring is chairman of Sebapharma's Scientific Advisory Board.