DOI:10.1111/j.1600-0625.2008.00725.x
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Frontiers in sebaceous gland biology and pathology

Christos C. Zouboulis[1,2], Jens Malte Baron[3]*, Markus Böhm[4]*, Stefan Kippenberger[5]*, Hjalmar Kurzen[6]*, Jörg Reichrath[7]* and Anja Thielitz[8]*

[1]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany;
[2]Laboratory of Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology, Institute of Clinical Pharmacology and Toxicology, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Berlin, Germany;
[3]Department of Dermatology and Allergology, University Hospital RWTH Aachen, Aachen, Germany;
[4]Department of Dermatology, University of Münster, Münster, Germany;
[5]Department of Dermatology and Venerology, University Hospital, University of Frankfurt, Frankfurt, Germany;
[6]Department of Dermatology, Venereology and Allergology, Medical Faculty of Mannheim, Ruprecht-Karls University of Heidelberg, Mannheim, Germany;
[7]Department of Dermatology, The Saarland University Hospital, Homburg, Germany;
[8]Department of Dermatology and Venereology, Otto von Guericke University Magdeburg, Magdeburg, Germany
Correspondence: Prof. Dr. Christos C. Zouboulis, Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany, Tel.: +49 340 5014000, Fax: +49 340 5014025, e-mail: christos.zouboulis@klinikum-dessau.de
**The co-authors have equally contributed to the manuscript.*

Accepted for publication 28 February 2008

Abstract: The development of experimental models for the *in vitro* study of human sebaceous gland turned down the theory of a phylogenetic relict and led to the identification of several, unknown or disregarded functions of this organ. Such functions are the production of foetal vernix caseosa, the influence of three-dimensional organization of the skin surface lipids and the integrity of skin barrier and the influence on follicular differentiation. In addition, the sebaceous gland contributes to the transport of fat-soluble antioxidants from and to the skin surface, the natural photoprotection, the pro- and antiinflammatory skin properties and to the innate antimicrobial activity of the skin. It is mainly responsible for skin's independent endocrine function, the hormonally induced skin ageing process, the steroidogenic function of the skin as well as its thermoregulatory and repelling properties and for selective control of the hormonal and xenobiotical actions of the skin. Interestingly, sebocytes, at least *in vitro*, preserve characteristics of stem-like cells despite their programming for terminal differentiation. This review reports on various sebaceous gland functions, which are currently under investigation, including its role on the hypothalamus–pituitary–adrenal-like axis of the skin, the impact of acetylcholine on sebocyte biology, the activity of ectopeptidases as new targets to regulate sebocyte function, the effects of vitamin D on human sebocytes, the expression of retinoid metabolizing cytochrome P450 enzymes and the possible role of sebum as vehicle of fragrances. These multiple homeostatic functions award the sebaceous gland the role 'brain of the skin' and the most important cutaneous endocrine gland.

Key words: functions – pathology – physiology – sebaceous gland – sebaceous gland cells

Please cite this paper as: Frontiers in sebaceous gland biology and pathology. Experimental Dermatology 2008; 17: 542–551.

The Sebaceous Gland and Its Functions

Sebaceous glands are found in the skin of all mammals except whales and porpoises (1). One of their apparent functions is to excrete sebum, a mixture of relatively neutral lipids most of which are synthesized *de novo* by the glands (2), to coat the fur as a hydrophobic protection against overwetting and for heat insulation (3). In addition, in many species, specialized sebaceous-like structures, such as the preputial glands of rodents, are responsible primarily for the release of pheromones that are used for territorial marking and sexual attraction (4,5). However, the composition of sebum is remarkably species specific (2,6,7), and in humans, these sebaceous gland's functions appear to have limited importance. Although sebum is the major ingredient of human skin surface lipids, the latter were suggested not to form a barrier; sebum had previously been considered not to have antibacterial or antifungal properties *in vivo* (8). On the other hand, increased sebum excretion is a major aetiological factor involved in the development of acne; however, although hormones control sebaceous gland's size and its activity, the acne patient is not considered to be an androgen mismatch (9). In 1963, Albert M. Kligman has suggested in 'Montagna's Advances in Biology of the Skin' that the sebaceous gland is a reminiscence of human development, a 'living fossil with a past but no future' (8).

Despite this pessimistic approach, which made the sebaceous gland an overall limited and less attractive field to work in, a few dedicated researchers have made a silent revolution during the last years by revising entirely the role of the sebaceous gland in human skin (10). The lack of an ideal animal model compatible to human sebaceous glands was recently surmounted by the development of experimental models for the *in vitro* study of human sebaceous gland (11–14). The latter have led to the identification of several, unknown or disregarded functions (Table 1) introducing the major role of this organ in skin homeostasis (10,15). During the last trimenon of the intrauterine life, sebaceous glands produce vernix caseosa (15), a lipid film which protects the embryonic skin from amniotic water. After the birth, sebaceous glands are responsible for the three-dimensional organization of the skin surface lipids, which supports the integrity of the skin barrier (16,17), as well as they influence follicular differentiation (18,19). Sebum, the product of active sebaceous glands, transports fat-soluble antioxidants from and to the skin surface (20) and exhibits a natural photoprotective activity; the sebaceous platelet-activating factor acetyl hydrolase II was found to protect the skin against oxidative stress and, especially, epidermal keratinocytes against ultaviolet B irradiation (21). On the other hand, sebocytes are able to produce protoporphyrin IX under exposure to δ-amino-levulinic acid (22). Sebaceous gland lipids exhibit direct pro- and antiinflammatory properties (12,23–26). Whereas the induction of the 5-lipoxygenase and cycloxygenase-2 pathways in sebocytes leads to the production of pro-inflammatory lipids (24–26), anti-inflammatory lipids can also be produced by activating the liver X receptor pathway (27,28). Moreover, the palmitoleic acid isomer (C16:1Δ6) sapienic acid, a prominent sebum-specific lipid, exhibits innate antimicrobial activity (29), which is upregulated by activation of the Toll-like receptor 2 by commensal gram-positive bacteria (30). On the other hand, antibacterial peptides and proinflammatory cytokines/chemokines are ubiquitarily expressed in normal sebaceous glands (31,32) and can be induced in human sebocytes in the presence of bacteria (33), whereas some of the upregulated antimicrobial peptides, such as cathelicidin, are locally bacteriotoxic (34).

The sebaceous gland confers upon the skin an independent endocrine function (35,36) and plays a major role in the hormonally induced skin ageing process (37,38). It expresses all enzymes required for steroidogenesis being able to produce active steroid hormones using circulating lipids (14,39). Under the stimulation of androgens, sebum has thermoregulatory and repelling properties (40). Androgens and peroxisome proliferators-activated receptor (PPAR) ligands as well as oestrogens and the complex insulin-like growth factor-I/insulin-like growth factor-I receptors modify lipid synthesis (41,42). On the other hand, the levels of squalene, another prominent sebaceous lipid, are decreased by antihistamines *in vitro*, whereas human sebocytes express histamine 1 receptors *in vivo* and

Table 1. Current aspects of sebaceous gland functions

Embryology, development and differentiation
Expression of terminal differentiation-triggering transcription factors, incl. CCAAT/enhancer binding proteins and peroxisome proliferators-activated receptors (24,94)
Partial responsibility for the three-dimensional organization of skin surface lipids and the integrity of the skin barrier (16,17)
Influence on follicular differentiation (18,19,37)
Highly complex acetylcholine receptor expression pattern (70)
Preservation of characteristics of stem-like cells despite their terminal cell differentiation programme (47,48)
Synthetic activity
Production of vernix caseosa (15)
Production of sebum (2)
Histamine 1 receptor expression and inhibition of squalene synthesis by antihistamines (43)
Protection
Natural photoprotective activity against ultaviolet B irradiation (21)
Thermoregulatory and repelling properties (40)
Possible involvement in wound healing (46)
Transportation
Delivery of anti-oxidants from and to the skin surface (20)
Sebum as vehicle of fragrance (103)
Inflammation, immunity
Direct pro- and antiinflammatory properties (12,23–26)
Production of proinflammatory (24–26) and of anti-inflammatory lipids (27,28)
Toll-like receptor 2-induced upregulation of lipogenesis (30)
Lipid-induced innate antimicrobial activity (29)
Presence of antimicrobial protective immunoglobulin A and cytokine/chemokine mRNA in normal sebaceous glands (31,32)
Synthesis of antibacterial peptides and proinflammatory cytokines/chemokines in the presence of bacteria (33) with some of the peptides being bacteriotoxic (34)
Expression of ectopeptidases (74,75)
Endocrine properties
Regulation of the independent endocrine function of the skin (35,36)
Expression of all enzymes required for steroidogenesis from circulating lipids (14)
Regulation of local androgen synthesis (37)
Substantial involvement in the hormonally induced skin ageing process (38,39)
Modification of lipid synthesis by combined androgens and peroxisome proliferator activated receptor ligands, estrogens and the insulin-like growth factor-I/insulin-like growth factor-I complex (41,42)
Expression of vitamin D receptor and vitamin D-matabolizing enzymes (93)
Expression of retinoid metabolizing cytochrome P450 enzymes (45,97)
Selective control of the action of hormones and xenobiotics on the skin (44,45)
Exhibition and affection by a regulatory neuropeptide programme (50,52–63,65,66)

in vitro (43). Sebocytes selectively control the action of hormones and xenobiotics on the skin (44,45), and androgens are also possibly involved in wound healing (46).

Interestingly, sebocytes, despite their programming for terminal differentiation, preserve characteristics of stem-like cells, as they present a remarkable potential of bipotential differentiation. The interactions between β-catenin and Sonic hedgehog promote proliferation of progenitors of the hair lineages, while Indian hedgehog stimulates proliferation of sebocyte precursors (47). Overexpression of Myc stimulated sebocyte differentiation, whereas overexpression of β-catenin stimulates interfollicular epidermal differentiation *in vitro* (48).

Several further sebaceous gland functions being currently under investigation are the scope of this frontiers article.

The hypothalamus–pituitary–adrenal-like axis of the skin

The corticotropin-releasing hormone system

The human sebaceous gland has lately been shown to express and underlie to a complex regulatory neuropeptide programme (49,50), which provides them the role 'brain of the skin' (Fig. 1). Corticotropin-releasing hormone (CRH), the most proximal module of the cutaneous hypothalamus–pituitary–adrenal-like (HPA), its binding protein (CRHBP) and corticotropin receptors (CRH-Rs) act as a central regulatory system of the HPA axis (51). Pro-CRH processing into CRH appears to be similar at the central and peripheral levels, including the skin. Current studies have confirmed the presence of a complete CRH/CRHBP/CRH-R system in human sebaceous glands *in vivo* and SZ95 sebocytes *in vitro* at both mRNA and protein levels

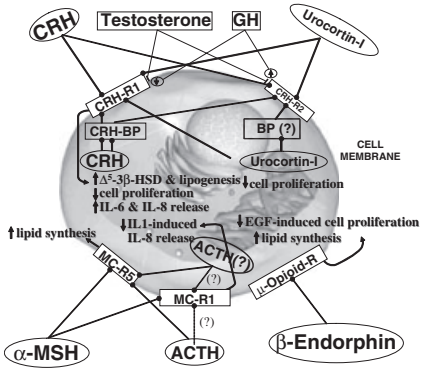

Figure 1. Effects of the neuropeptide and sexual hormone network on human sebocytes *in vivo* and *in vitro* [modified from Ref. (54)]. CRH, corticotrophin-releasing hormone; GH, growth hormone; ACTH, adrenocorticotropin; α-MSH, α-melanocyte-stimulating hormone; BP, binding protein; EGF, epidermal growth factor; MC-R, melanocortin receptor; R, receptor; IL, interleukin; HSD, hydroxysteroid dehydrogenase.

(52–55). CRH is likely to serve as an important autocrine hormone in sebocytes with a homeostatic pro-differentiation activity. It directly inhibits proliferation, induces synthesis of neutral lipids and enhances mRNA expression of Δ5-3β-hydroxysteroid dehydrogenase in human sebocytes *in vitro*. Δ5-3β-hydroxysteroid dehydrogenase is responsible for androgen activation through the conversion of dehydroepiandrosterone to testosterone (37,54). The induction of sebaceous lipids by CRH is CRH-R1-mediated (55). As a feedback mechanism, testosterone antagonizes CRH by down-regulating CRH-R expression in human sebocytes *in vitro* (54). In addition, growth hormone, which also enhances sebaceous lipid synthesis, modifies CRH-R expression by reducing mRNA levels of CRH-R1 and by enhancing CRH-R2 mRNA levels (54). CRH also enhances the release of interleukin (IL)-6 and IL-8 in SZ95 sebocytes *in vitro* by an IL-1β-independent pathway. These *in vitro* data are compatible with the significant increase in CRH expression in acne-involved compared with acne non-involved sebaceous glands (56). These effects are likely to be CRH-selective, as urocortin-I, a recently described member of the family of structurally related CRH-like peptides with a 45% homology with CRH, only exhibited a weak antiproliferative effect on SZ95 sebocytes *in vitro* (55).

These findings implicate a major involvement of CRH in the clinical development of seborrhoea and acne vulgaris, as well as in other skin disorders and diseases associated with alterations in the formation of sebaceous lipids. In addition, they indicate that central or topical 'stress' may, indeed, influence the feedback regulation, thus inducing the development of clinical inflammation in early acne lesions.

The proopiomelanocortin system

The proopiomelanocortin (POMC) system represents currently the best characterized neuromediator system of the sebaceous gland (57) (Fig. 1). Recent studies confirmed and substantially extended earlier work which had provided a first connection between the pituitary and rat preputial gland (7), the latter being a modified sebaceous gland. It is now clear that human sebocytes express functional melanocortin receptors (MC-Rs) and that melanocortin peptides such as α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropin (ACTH) mediate direct effects on these glandular epithelia (58–60). In accordance with the lipogenic effect in the rat preputial gland (7), ACTH and the superpotent MSH analogue [Nle4, D-Phe7]-α-MSH increased squalene synthesis in primary human sebocytes (59). In line with the immunoregulatory actions of α-MSH on other skin cells, the peptide also suppressed in SZ95 sebocytes basal and IL-1β-induced secretion of IL-8 (58), a central proinflammatory mediator in the pathogenesis of neutrophilic inflammation, e. g. in acne vulgaris. Interestingly, human sebocytes express concomitantly MC-1Rs and

MC-5Rs (58–63). It is possible that MC-1R is more involved in immunoregulation (58), while MC-5R is more concerned with sebocyte differentiation and lipogenesis (60,63). Targeted disruption of MC-5R reduces sebum secretion in the mouse (64). On the other hand, sebocytes of acne-involved sebaceous glands express higher levels of MC-1R than sebocytes of healthy glands (65). In addition to melanocortins and their receptors, recent findings also indicate that another representative of the POMC system is operational in the sebaceous gland. β-endorphin suppresses cell proliferation and induces lipid formation in SZ95 sebocytes *in vitro*. These effects appear to be mediated by the μ-opioid receptor which is expressed in human sebocytes *in vivo* and *in vitro* (66).

These data emphasize the sebaceous gland as a prominent target organ for POMC peptides. Whether the sebaceous gland is capable of generating POMC peptides autonomously or whether it acts primarily as a target of the classical or 'cutaneous' HPA axis (67) is incompletely understood. POMC RNA as well as α-MSH and ACTH immunoreactivities have been detected in human sebocytes *in situ* (52,68). In light of the presence of POMC-derived peptides in many other cutaneous cell types, the existence of a ''seboglandular'' HPA axis would not be too much surprising.

The impact of acetylcholine on sebocyte biology

Extraneuronal acetylcholine (ACh) has been demonstrated to influence a plethora of cutaneous cell functions in an autocrine, paracrine and endocrine fashion. Through the differentiation specific expression of its different nicotinic (nAChR) and muscarinic receptors (mAChR), ACh induces keratinocyte proliferation and migration, terminal differentiation and barrier formation [reviewed in Ref. (69)]. The functional consequences of the recently characterized highly complex AChR expression pattern in the pilosebaceous unit is only beginning to be understood. In sebaceous glands, the undifferentiated sebocytes produce the α3, α9, α10, β2, β4, M_3-M_5 AChR. The α5, α7, α10, β4, M_2 and M_4 AChR subunits are produced in mature sebocytes (70) (Fig. 2). Sebocyte differentiation, sebum production or sebum composition may be altered by endogenously produced ACh acting in a paracrine manner or exogenously by tobacco-derived nicotine. The production of ACh and AChR by sebocytes, keratinocytes, immune cells and cutaneous nerves is the structural basis for a complex neuroimmuno-endocrinological interplay. The highest concentration of both ACh (Fig. 3), AChR and nicotine can be found at the infundibulum of the pilosebaceous unit suggesting an important role of the cholinergic system in, for example, acne vulgaris (71). AChR composition or the level

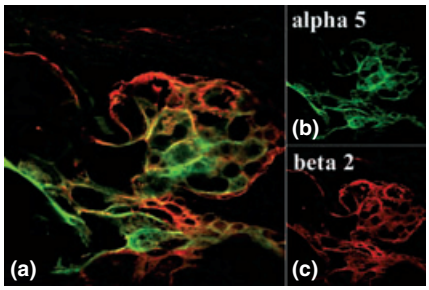

Figure 2. Differential expression of α5 and β2 acetylcholine receptor in a sebaceous gland (a). The α5 subunit is predominantly expressed in the mature sebocytes in the centre of the gland (b), while the β2 subunit (c) shows a stronger expression in the undifferentiated sebocytes at the outer rim. For immunofluorescence analysis, 5 μm cryostat sections of human scalp skin were blocked with 5% non-fat dry milk and 1% bovine serum albumin in Tris-buffered saline. The primary rabbit anti-α5 and -β2 acetylcholine receptor antibodies (Santa Cruz, Heidelberg, Germany) were applied to the specimens for 1 h at room temperature. The following biotin-coupled secondary antibodies were applied for 1 h at room temperature: Cy-2- and Cy-3-coupled preabsorbed goat anti-mouse, anti-rabbit, and anti-guinea-pig antisera and a Cy-3-coupled rabbit anti-goat antiserum (Dianova, Hamburg, Germany). The staining was observed and visualized with a Zeiss Laser Scan Confocal Microscope (LSM 510 UV; Jena, Germany) (70,71). Original magnification 40×.

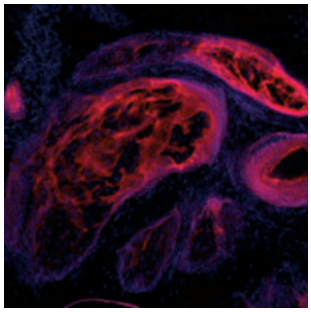

Figure 3. The sebaceous duct and mature sebocytes show a strong acetylcholine production as evidenced by expression of choline-acetyltransferase (ChAT). Immunofluorescence analysis using a primary rabbit polyclonal anti-ChAT antibody (107) was performed as mentioned in the legend of Fig. 2. Original magnification 40×.

of endogenously produced ACh may explain the conflicting results reported for the influence of smoking on the course of acne vulgaris (72,73).

Ectopeptidases as new targets to modulate sebocyte function

In 2002, neutral endopeptidase (CD10), a member of the ectopeptidase family, was shown to be significantly upregulated within sebaceous glands of acne patients but was not detectable in sebaceous glands of healthy subjects (74). Recently, two further ectopeptidases, dipeptidyl peptidase IV (DP IV, CD 26, E.C. 3.4.14.5) and aminopeptidase N

(APN, CD13, E.C. 3.4.11.14) have been shown to be highly expressed in human sebocytes *in vivo* and *in vitro* (75).

The DP IV is a homodimeric type II transmembranic glycoprotein (76) and belongs to the group of postproline dipeptidyl aminopeptidases, which also includes fibroblast activation protein, DP VIII, DP IX and DP II. DP IV is a serine exopeptidase, which catalyses the release of N-terminal dipeptides from oligo- and polypeptides preferentially with proline in the penultimate position. DP IV plays a key role in the catabolism of several neuropeptides, immunopeptides and peptide hormones, such as substance P, VIP, neuropeptide Y, peptide YY or glucagon-like peptide-1 (77). Although receptors for the majority of these neuropeptides are expressed in human sebocytes, among their ligands, only substance P influences sebocyte function [reviewed in Ref. (78)]. APN is a 150 kDa type II membrane metalloprotease, which is predominantly expressed on cells of the myelo-monocytic lineage and catalyses the hydrolysis of neutral amino acids from the N-terminus of oligopeptides (79). This enzyme has been shown to be involved in the degradation of several neuropeptides, angiotensins, cytokines, immunomodulatory peptides and extracellular matrix proteins. The interaction with agonistic antibodies or enzyme inhibitors revealed that beyond their proteolytic activity, both ectopeptidases influence fundamental biological cellular processes such as growth, apoptosis, differentiation, adhesion, motility, invasion, cell–cell interaction, angiogenesis and malignant transformation (79,80). The pharmacological inhibition of DP IV and APN affects growth, cytokine production and typical functions of human peripheral T cells both *in vivo* and *in vitro* (81). Recent investigations revealed that dual targeting of DP IV and APN potentates the effects of single DP IV or APN targeting. This combination represents a novel and efficient strategy for the treatment of autoimmune and inflammatory diseases (84,85). In the skin, DP IV and APN are expressed on human keratinocytes *in vivo* and are upregulated in hyperproliferative skin diseases, e.g. psoriasis (84,85). Inhibitors of DP IV and APN suppress keratinocyte proliferation *in vitro* (86,87) and partially restore keratinocyte differentiation *in vivo* (87).

The strong expression of DP IV and APN on the surface of human SZ95 sebocytes *in vitro* suggests that sebocytes could be effectively targeted by peptidase inhibitors. In SZ95 sebocytes, single or combined application of the DP IV inhibitors Lys[Z(NO_2)]-thiazolidide and Lys[Z(NO_2)]-pyrrolidide and the APN inhibitors actinonin and bestatin suppressed proliferation, enhanced terminal differentiation and slightly decreased total neutral lipid production. Especially the combination of DP IV and APN inhibitors affected proliferation in a comparable magnitude with high doses of isotretinoin ($>10^{-6}$ M). The combination also shows a faster onset of action compared to the retinoid (74).

Furthermore, IL-1 receptor antagonist, an antiinflammatory and differentiation-restoring cytokine, is significantly upregulated in SZ95 sebocytes in the presence of DP IV and APN inhibitors (74). It is, therefore, evident that ectopeptidases directly affect human sebocytes in addition to the indirect effects exerted via immune cells. The mechanism by which their inhibitors mediate their effects on sebocytes remains to be established.

These data provide evidence for a functional role of ectopeptidases in the sebaceous gland apparatus and for inhibitors of these ectopeptidases, used alone or in combination, as a completely new substance group strongly affecting sebocyte functions with a possible therapeutic role in early stages of acne pathogenesis.

Vitamin D and human sebocytes

Humans and most vertebrates have to absorb vitamin D from the diet or to synthesize it in the skin by the action of sunlight, to develop and to maintain a healthy mineralized skeleton (88). To generate the circulating, biologically active vitamin D metabolite 1,25-dihydroxyvitamin D_3 [1,25($OH)_2D_3$; calcitriol], vitamin D has to be metabolized in the liver to 25-hydroxyvitamin D_3 [25($OH)D_3$] and then in the kidney to 1,25($OH)_2D_3$. There are two principal enzymes involved in the formation of circulating 1,25($OH)_2D_3$ from vitamin D, the hepatic microsomal or mitochondrial vitamin D 25-hydroxylase [cytochrome P (CYP)27A1, 25OHase] and the renal mitochondrial enzyme 1α-hydroxylase (CYP27B1, 1αOHase) for vitamin D and 25($OH)D_3$ respectively (89,90). 1,25($OH)_2D_3$ is metabolized in target cells at least in part by 24OHase (CYP24A1), resulting in a specific C-24 oxidation pathway to yield the biliary excretory product calcitroic acid (Fig. 4). CYP27A1, CYP27B1 and CYP24 belong to a class of proteins known as cytochrome P450 mixed function monooxidases (89,90). In recent years, it has been shown that epidermal keratinocytes (Fig. 4) and other cell types including Langerhans cells, dermal dendritic cells, macrophages, melanocytes, prostate, lung and colon cancer cells, contain the enzymatic machinery needed to produce 1,25($OH)_2D_3$ (91,92). 1,25($OH)_2D_3$ exerts its effects via binding to a specific nuclear vitamin D receptor (VDR), a ligand-dependent transcription factor that belongs to the superfamily of steroid/thyroid hormone/retinoid nuclear receptors and that recognizes specific DNA sequences named vitamin D response elements. 1,25($OH)_2D_3$ interacts with VDR in intestine and bone to maintain calcium homeostasis. However, the VDR is also present in a wide variety of other tissues. 1,25($OH)_2D_3$ interacts with VDR in these cell types that are not related to calcium or bone metabolism to regulate a multitude of important cellular functions and physiological effects, that include regulation of cell growth and that may include

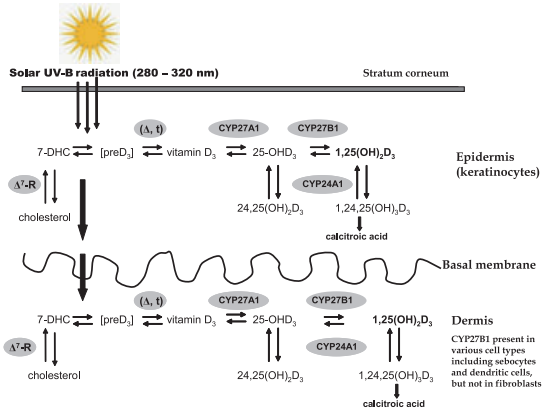

Figure 4. Synthesis and metabolism of vitamin D metabolites in human skin. Note that sebocytes and various other cell types present in epidermal or dermal compartments possess the enzymatic machinery [cytochrome P450 (CYP)27B1] to synthesize the biologically active vitamin D metabolite 1,25-dihydroxyvitamin D_3. 7-DHC, 7-dehydrocholesterol; preD_3, previtamin D_3; 25OHD_3, 25-hydroxyvitamin D_3; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; 24,25$(OH)_2D_3$, 24,25-dihydroxyvitamin D_3; 1,24,25$(OH)_3D_3$, 1,24,25-trihydroxyvitamin D_3; CYP27A1, vitamin D-25-hydroxylase, 25OHase; CYP27B1, 25-hydroxyvitamin D-1α-hydroxylase, 1αOHase; CYP24A1, 1,25-dihydroxyvitamin D-24-hydroxylase, 24OHase; Δ^7-R, 7-DHC-Δ^7-reductase.

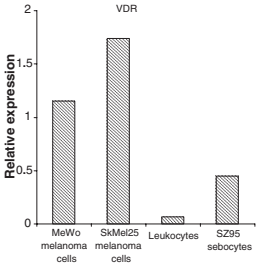

Figure 5. The nuclear receptor for 1,25-dihydroxyvitamin D (vitamin D receptor, VDR) is expressed in human sebocytes, identifying human sebocytes as target cells for biologically active vitamin D analogues. VDR mRNA was detected in cultured human SZ95 sebocytes, human melanoma cells (MeWo, SkMel25), and human leucocytes using a Roche real-time PCR (LightCycler; Mannheim, Germany; 50 cycles), gene specific primers (forward 5′-CCAGTTCGTGTGAATGATGG-3′, reverse 5′-GTCGTCCATGGTGAAGGA-3′) and 10-fold serial dilutions of cDNA as external standards. Expression levels were determined as ratios between VDR and the reference gene β_2-microglobulin (108). The figure presents duplicate data.

protection against cancer and other diseases (88). The knowledge about these new important physiological functions of vitamin D metabolites is growing rapidly.

Over the past decade, considerable progress has been made in our understanding of the molecular events regulating sebocyte differentiation. Several transcription factors, including CCAAT/enhancer binding proteins and PPAR, have been identified, which act cooperatively and sequentially to trigger their terminal differentiation programme (24,93). The hypothesis whether key components of the vitamin D endocrine system are also present in human sebocytes and whether vitamin D analogues target human sebocytes regulating their proliferation *in vitro* has recently been tested (94). Expression of VDR (Fig. 5), CYP27A1, CYP27B1 and CYP24A1 mRNA was detected, indicating that human sebocytes are able to both synthesize and metabolize the biologically active vitamin D metabolite 1,25$(OH)_2D_3$. Additionally, splicing variants of CYP27B1 were found and further analyzed. Incubation of SZ95 sebocytes with 1,25$(OH)_2D_3$ resulted in a dose-dependent suppression of cell proliferation, modulation of cell cycle regulation and of apoptosis. Expression of VDR and CYP24A1 was upregulated in SZ95 sebocytes along with vitamin D analogue treatment. Although several other splicing variants of CYP27B1 were detected, these findings indicate that the full length product represents the major CYP27B1 gene product in human sebocytes.

It is likely, therefore, that the vitamin D endocrine system is of high importance for regulation of sebocyte function and physiology, including sebum production. Acne or other skin disorders that involve disturbances of sebaceous gland physiology may represent potential targets for therapy with vitamin D analogues or for pharmacological modulation of 1,25$(OH)_2D_3$ synthesis/metabolism.

Expression of retinoid metabolizing CYP enzymes in the epithelia of the sebaceous gland

In addition to their effect on growth and differentiation, retinoids exert antiinflammatory actions and suppress sebum production in sebaceous glands (95,96). *In vitro*, retinoids significantly reduce sebocyte proliferation (11,13,45). All-*trans* retinoic acid is thought to be the major 'natural ligand' of all three nuclear retinoic acid receptors. In human skin, the primary metabolite of all-*trans* retinoic acid is 4-hydroxy all-*trans* retinoic acid, which is further metabolized to 4-oxo all-*trans* retinoic acid (97,98). 4-oxo-metabolites of retinoic acid have long been thought to be inert catabolic end-products until recent studies indicated that these substances display strong and isomer-specific transcriptional regulatory activity in different cell types of the human skin (97,99). Microarray and proteomic analyses identified a number of novel genes/gene products that are influenced by retinoid treatment, including genes for enzymes catalysing biotransformation of retinoids, corticosteroids and antioxidants and structural and transport proteins known to be essential for homeostasis. Several metabolic pathways are involved in transformation of retinoic acid especially CYP enzymes such as

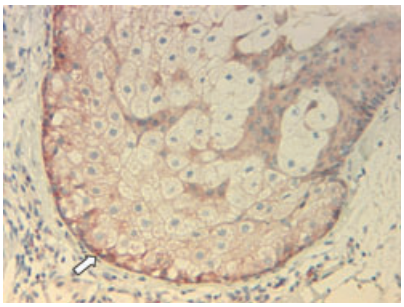

Figure 6. Immunohistochemistry of cytochrome P450 (CYP) 26AI expression in epithelial cells of the sebaceous gland indicates expression of CYP26AI in undifferentiated outermost sebocytes (→). Paraffin-embedded skin specimen from normal human skin was cut into 4 μm sections, mounted on superfrost slides, deparaffinized and rehydrated. To unmask antigens, the specimens were pretreated with citrate buffer pH 6.0, rinsed in distilled water, and placed in washing buffer (DCS, Hamburg, Germany). Specimens were incubated for 30 min with the peptide primary antibody against the N-terminus of CYP26AI (Alpha Diagnostic, San Antonio, TX, USA) and rinsed in washing buffer for 10 min. Binding of the antibodies was visualized by the DCS Detection Line HRP/AEC (DCS) as specified by the manufacturer. Finally, specimens were counterstained with haematoxylin and mounted with coverslips. Examination and photodocumentation were performed using a Leica inverse photomicroscope (DMIL; Wetzlar, Germany) (97,101). Original magnification 100×.

CYP26AI and CYP2S1 (100,101). Current immunohistochemical analysis using a newly developed antibody specific for the detection of CYP26AI revealed strong constitutive expression of the CYP26AI protein in epithelial cells of the sebaceous gland (Fig. 6) in a pattern similar to that seen in basal keratinocytes (101). Although untreated and retinoic acid-stimulated SZ95 sebocytes reveal no expression of CYP26 mRNA (45), the expression of CYP26AI in the epithelium of sebaceous glands may determine how the sebaceous follicle responds to acnegenic stimuli as well as exogenous or endogenous retinoids.

'Smells like…' – sebum as vehicle of fragrance?

By the time puberty arrives, the human skin has been ravaged by the sebaceous gland, which triggered by hormones, becomes active and exudes excess sebum over the skin giving it an oily pustular appearance. Because of this negative effect on human appearance, the sebaceous gland and sebum as their product have been considered as a phylogenetic relict or a kind of living skin fossil (8). Bearing in mind that most of us suffer at some time of life from acne vulgaris, why has evolution not eradicated the sebaceous gland to provide us with a perfect skin? This question is corroborated by the 'perfect' skin of small children and babies with almost quiescent sebum glands. This assumption seems doubtful as evolution never maintains an organ or structure without function, and as discussed above current research has entirely changed our understanding of sebaceous gland role celebrating this organ as the 'brain of the skin' (Table 1).

For the cosmetic industry properties of sebum, such as the skin barrier role (16,17), the transportation of fat-soluble antioxidants from and to the skin surface (20), the natural photoprotective activity against ultraviolet B irradiation (21) and the thermoregulatory and repelling activity (38) are of major importance. On the other hand, another question has currently arisen: could sebum function as an odour carrier steering our behaviour to find the perfect mate?

The knowledge that fat is an effective carrier of volatile flavours is old as probably the pharaohs of ancient Egypt used ambrosial oils and ointments. In the middle ages in Europe, a method was evolved to extract flavours from flowers by distillation. Etheric oils embedded in fat, the so called *concrete*, preserved the ambrosial flavours for long periods of time. From the animal kingdom, we know that volatile compounds are often used as sexual attractors, particularly during mating seasons. Of particular interest in this context are the glandular secretions of the musk deer and the beaver (castoreum, 'Bibergeil'). Interestingly, these particular scents have also been used by humans over the years; however in almost homeopathic dilutions as the undiluted smell of musk for example is simply overbearing. In the 19th century, the captains of tea clippers refused to carry musk glands as cargo from the Himalayas because they were afraid that the musk would spoil the flavour of the tea (102). Dosage is what matters!

Apocrine glands of the human axilla release androgenic metabolites, e.g. androstene, which are transformed by microorganisms giving rise to a characteristic odour (103); freshly released apocrine secretions have no smell – at least to our conscious mind. Behavioural experiments have supported the effect of volatile odours on human behaviour: women who had a free choice of a chair in a waiting room preferred that which was treated with androstenone (102). Other experiments have demonstrated that women are able to trace androstenone at dilutions up to one to a trillion, particularly during ovulation (103).

To avoid an impulsive overdosage of apocrinic odours, it is possible that the sebum derived from the sebaceous glands may retard the odours providing a continuous release. This assumption is backed by the observation that apocrine and sebaceous glands are located in intimate spatial proximity. The role of pheromones in human behaviour, aside from an artificial experimental setting, remains an enigma. The fact that man harbours a receptor which is specialized for pheromones, the vomeronasal organ that projects into the limbic brain bypassing cortical brain areas, shows that odour provides important environmental information (104). From animal experiments, it is known that

in maize the individual odour is connected with immunological parameters (105). Particularly, information about the configuration of major histocompatibility (MHC) genes, which play an important role in the recognition of pathogens, was conveyed by odour (106). A high recombination with different MHC alleles increases the fitness of an organism against pathogens. In this respect, similar MHC alleles repel and *vice versa* different MHC alleles attract each other like magnets (107). In this concert of odours, sebum may function as a finely tuned dosage unit that provides putative sexual partners with information about the status of the immune system, building the basis for a well-equipped offspring.

Conclusion

Miracles do not happen often, but it looks as if this is the case with the change in our current understanding of sebaceous gland functions. From a phylogenetic relict or a kind of living skin fossil, the sebaceous gland turned to be considered the 'brain of the skin' and the most important cutaneous endocrine gland. The exact determination of sebaceous gland functions not only improved our knowledge of skin physiology but also revolutionized the understanding of sebaceous gland diseases and their treatment, among them of the most common skin disease acne vulgaris (108).

References

1 Montagna W. Comparative aspects of sebaceous glands. In: Montagna W, Ellis R A, Silver A F, eds. Advances in Biology of Skin. Vol IV. The Sebaceous Glands. Oxford: Pergamon Press, 1963: 32–45.

2 Nikkari T. Comparative chemistry of sebum. J Invest Dermatol 1974: **62**: 257–267.

3 Pochi P. The sebaceous gland. In: Maibach H I, Boisits E K, eds. Neonatal Skin Structure and Function. New York: Marcel Dekker, 1982: 67–80.

4 Mykytowycz R, Goodrich B S. Skin glands as organs of communication in mammals. J Invest Dermatol 1974: **62**: 124–131.

5 Ebling F J G, Cunliffe W J. Disorders of the sebaceous glands. In: Champion R H, Burton J L, Ebling F J G, eds. Textbook of Dermatology, 5th edn. London: Blackwell, 1992: 1699–1744.

6 Wheatley V R. Sebum: its chemistry and biochemistry. Am Perfumer 1956: **68**: 37–47.

7 Thody A J, Shuster S. Control and function of sebaceous glands. Physiol Rev 1989: **69**: 383–416.

8 Kligman A M. The uses of sebum? In: Montagna W, Ellis R A, Silver A F, eds. Advances in Biology of Skin. Vol IV. The Sebaceous Glands. Oxford: Pergamon Press, 1963: 110–112.

9 Cunliffe W J. Acne. London: Martin Dunitz, 1989.

10 Zouboulis C C. Sebaceous gland in human skin – the fantastic future of a skin appendage. J Invest Dermatol 2003: **120**: xiv–xv.

11 Xia L, Zouboulis C, Detmar M, Mayer-da-Silva A, Stadler R, Orfanos C E. Isolation of human sebaceous glands and cultivation of sebaceous gland-derived cells as an in-vitro model. J Invest Dermatol 1989: **93**: 315–321.

12 Zouboulis C C, Xia L, Akamatsu H *et al.* The human sebocyte culture model provides new insights into development and management of seborrhoea and acne. Dermatology 1998: **196**: 21–31.

13 Zouboulis C C, Seltmann H, Neitzel H, Orfanos C E. Establishment and characterization of an immortalized human sebaceous gland cell line (SZ95). J Invest Dermatol 1999: **113**: 1011–1020.

14 Thiboutot D, Jabara S, McAllister J *et al.* Human skin is a steroidogenic tissue: Steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). J Invest Dermatol 2003: **120**: 905–914.

15 Zouboulis C C, Fimmel S, Ortmann J, Turnbull J R, Boschnakow A. Sebaceous glands. In: Hoath S B, Maibach H I, eds. Neonatal Skin – Structure and Function, 2nd edn. New York Basel: Marcel Dekker, 2003: 59–88.

16 Pilgram G S, van der Meulen J, Gooris G S, Koerten H K, Bouwstra J A. The influence of two azones and sebaceous lipids on the lateral organization of lipids isolated from human stratum corneum. Biochim Biophys Acta 2001: **1511**: 244–254.

17 Fluhr J W, Mao-Qiang M, Brown B E *et al.* Glycerol regulates stratum corneum hydration in sebaceous gland deficient (asebia) mice. J Invest Dermatol 2003: **120**: 728–737.

18 Selleri S, Seltmann H, Gariboldi S *et al.* Doxorubicin-induced alopecia is associated with sebaceous gland differentiation. J Invest Dermatol 2006: **126**: 711–720.

19 Winiarska A, Mandt N, Kamp H *et al.* Effect of 5alpha-dihydrotestosterone and testosterone on apoptosis in human dermal papilla cells. Skin Pharmacol Physiol 2006: **19**: 311–321.

20 Thiele J J, Weber S U, Packer L. Sebaceous gland secretion is a major physiologic route of vitamin E delivery to skin. J Invest Dermatol 1999: **113**: 1006–1010.

21 Marques M, Pei Y, Southall M D *et al.* Identification of platelet-activating factor acetylhydrolase II in human skin. J Invest Dermatol 2002: **119**: 913–919.

22 Kosaka S, Kawana S, Zouboulis C C, Hasan T, Ortel B. Targeting of sebocytes by aminolevulinic acid-dependent photosensitization. Photochem Photobiol 2006: **82**: 453–457.

23 Wróbel A, Seltmann H, Fimmel S *et al.* Differentiation and apoptosis in human immortalized sebocytes. J Invest Dermatol 2003: **120**: 175–181.

24 Alestas T, Ganceviciene R, Fimmel S, Müller-Decker K, Zouboulis C C. Enzymes involved in the biosynthesis of leukotriene B_4 and prostaglandin E_2 are active in sebaceous glands. J Mol Med 2006: **84**: 75–87.

25 Zhang Q, Seltmann H, Zouboulis C C, Travers J B. Activation of platelet-activating factor receptor in SZ95 sebocytes results in inflammatory cytokine and prostaglandin E_2 production. Exp Dermatol 2006: **15**: 769–774.

26 Zhang Q, Seltmann H, Zouboulis C C, Konger R L. Involvement of PPAR-gamma in oxidative stress-mediated prostaglandin E_2 production in SZ95 human sebaceous gland cells. J Invest Dermatol 2006: **126**: 42–48.

27 Russell L E, Harrison W J, Bahta A W, Zouboulis C C, Burrin J M, Philpott M P. Characterization of liver X receptor expression and function in human skin and the pilosebaceous unit. Exp Dermatol 2007: **16**: 844–852.

28 Hong I, Lee M-H, Na T-Y, Zouboulis C C, Lee M O. LXRα enhances lipid synthesis in SZ95 sebocytes. J Invest Dermatol (Epub ahead of print, 2007, Oct 25).

29 Wille J J, Kydonieus A. Palmitoleic acid isomer (C16:1Δ6) is the active antimicrobial fatty acid in human skin sebum. Skin Pharmacol Appl Skin Physiol 2003: **16**: 176–187.

30 Georgel P, Crozat K, Lauth X *et al.* A TLR2-responsive lipid effector pathway protects mammals against Gram-positive bacterial skin infections. Infect Immun 2005: **73**: 4512–4521.

31 Gebhart W, Metze D, Jurecka W, Schmidt J B. Immunglobulin A in Talgdrüsen. Wien Klin Wochenschr 1986: **98**: 683–689.

32 Boehm K D, Yun J K, Strohl K P, Elmets C A. Messenger RNAs for the multifunctional cytokines interleukin-1 alpha, interleukin-1 beta and tumor necrosis factor-alpha are present in adnexal tissues and in dermis of normal human skin. Exp Dermatol 1995: **4**: 335–341.

33 Nagy I, Pivarcsi A, Kis K *et al. Propionibacterium acnes* and lipopolysaccharide induce the expression of antibacterial peptides and proinflammatory cytokines/chemokines in human sebocytes. Microbes Infect 2006: **8**: 2195–2205.

34 Lee D-Y, Yamasaki K, Zouboulis C C, Park G T, Yang J-M, Gallo R L. Sebocytes express functional cathelicidin antimicrobial peptides and can act to kill *Propionibacterium acnes*. J Invest Dermatol (Epub ahead of print, 2008, Jan 17).

35 Zouboulis C C. The human skin as a hormone target and an endocrine gland. Hormones 2004: **3**: 9–26.

36 Zouboulis C C, Chen W, Thornton M J, Qin K, Rosenfield R L. Sexual hormones in human skin. Horm Metab Res 2007: **39**: 85–95.

37 Fritsch M, Orfanos C E, Zouboulis C C. Sebocytes are the key regulators of androgen homeostasis in human skin. J Invest Dermatol 2001: **116**: 793–800.

38 Makrantonaki E, Adjaye J, Herwig R *et al.* Age-specific hormonal decline is accompanied by transcriptional changes in human sebocytes *in vitro*. Aging Cell 2006: **5**: 331–344.

39 Makrantonaki E, Zouboulis C C. The skin as a mirror of the aging process in the human organism – state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). Exp Gerontol 2007: **42**: 879–886.

40 Rhein L D, Zatz J L, Motwani M R. Sebum: physical-chemical properties, macromolecular structure, and effects of ingredients. In: Webster G F, Rawlings A V, eds. Acne and its Therapy. New York, London: Informa Healthcare, 2007: 203–222.

41 Makrantonaki E, Zouboulis C C. Testosterone metabolism to 5α-dihydrotestosterone and synthesis of sebaceous lipids is regulated by the peroxisome proliferators-activated receptor ligand linoleic acid in human sebocytes. Brit J Dermatol 2007: **156**: 428–432.

42 Zouboulis C C, Chen W, Alestas T, Makrantonaki E, Seltmann H, Müller-Decker K. Sexual hormones utilize complex mechanisms to modulate sebocyte differentiation. Exp Dermatol 2005: **14**: 156.

43 Pelle E, McCarthy J, Seltmann H *et al.* Identification of histamine receptors and reduction of squalene levels by an antihistamine in sebocytes. J Invest Dermatol (Epub ahead of print, 2007, Nov 15).

44 Akamatsu H, Zouboulis C C, Orfanos C E. Control of human sebocyte proliferation in vitro by testosterone and 5-alpha-dihydrotestosterone is dependent on the localization of sebaceous glands. J Invest Dermatol 1992: **99**: 509–511.

45 Tsukada M, Schröder M, Roos T C *et al.* 13-*cis* retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-trans retinoic acid and binding to retinoid acid receptors. J Invest Dermatol 2000: **115**: 321–327.

46 Fimmel S, Zouboulis C C. Influence of physiological androgen levels on wound healing and immune status in men. Aging Male 2005: **8**: 166–174.

47 Niemann C, Unden A B, Lyle S, Zouboulis C C, Toftgård R, Watt F M. Indian hedgehog and β-catenin signaling: Role in the sebaceous lineage of normal and neoplastic mammalian epidermis. Proc Natl Acad Sci U S A 2003: **100** (Suppl. 1): 11873–11880.

48 Lo Celso C, Braun K M, Frye M, Berta M, Zouboulis C C, Watt F M. Characterisation of bipotential epidermal progenitors for sebaceous gland and interfollicular epidermis: contrasting roles of c-Myc and β-catenin. Stem Cells (Epub ahead of print, 2008, Feb 28).

49 Ziegler C G, Krug A W, Zouboulis C C, Bornstein S R. Corticotropin releasing hormone and it's function in the skin. Horm Metab Res 2007: **39**: 106–109.

50 Zouboulis C C, Böhm M. Neuroendocrine regulation of sebocytes – a pathogenetic link between stress and acne. Exp Dermatol 2004: **13** (Suppl. 4): 31–35.

51 Slominski A T, Botchkarev V, Choudhry M *et al.* Cutaneous expression of CRH and CRH-R. Is there a 'skin stress response system?' Ann NY Acad Sci 1999: **885**: 287–311.

52 Kono M, Nagata H, Umemura S, Kawana S, Yoshiyuki R. In situ expression of corticotropin-releasing hormone (CRH) and proopiomelanocortin (POMC) genes in human skin. FASEB J 2001: **15**: 2297–2299.

53 Wollina U, Abdel-Naser M B, Ganceviciene R, Zouboulis C C. Receptors of eccrine, apocrine and holocrine skin glands. Dermatol Clin 2007: **25**: 577–588.

54 Zouboulis C C, Seltmann H, Hiroi N *et al.* Corticotropin releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. Proc Natl Acad Sci U S A 2002: **99**: 7148–7153.

55 Krause K, Schnitger A, Fimmel S, Glass E, Zouboulis C C. Corticotropin-releasing hormone skin signalling is receptor-mediated and is predominant in the sebaceous glands. Horm Metab Res 2007: **39**: 166–170.

56 Ganceviciene R, Marciukaitiene I, Graziene V, Rimkevicius A, Zouboulis C C. New accents in the pathogenesis of acne vulgaris. Acta Medica Lituanica 2006: **13**: 83–87.

57 Böhm M, Luger T A. Neurobiology of sebaceous glands. In: Granstein R D, Luger T A, eds. Neuroimmunology of the Skin. Basic Science to Clinical Relevance. Heidelberg: Springer, in press.

58 Böhm M, Schiller M, Stander S *et al.* Evidence for expression of melanocortin-1 receptor in human sebocytes in vitro and in situ. J Invest Dermatol 2002: **118**: 533–539.

59 Zhang L, Anthonavage M, Huang Q, Li W H, Eisinger M. Proopiomelanocortin peptides and sebogenesis. Ann N Y Acad Sci 2003: **994**: 154–161.

60 Zhang L, Li W-H, Anthonavage M, Eisinger M. Melanocortin-5 receptor: a marker of human sebocyte differentiation. Peptides 2006: **27**: 413–420.

61 Thiboutot D, Sivarajah A, Gilliland K, Cong Z, Clawson G. The melanocortin 5 receptor is expressed in human sebaceous glands and rat preputial cells. J Invest Dermatol 2001: **115**: 614–619.

62 Hatta N, Dixon C, Ray A J *et al.* Expression, candidate gene, and population studies of the melanocortin 5 receptor. J Invest Dermatol 2001: **116**: 564–570.

63 Jeong S K, Hwang S W, Choi S Y *et al.* Intracellular calcium mobilization is mediated by melanocortin receptors in SZ95 sebocytes. J Invest Dermatol 2007: **127**: S72 (abstract).

64 Chen W, Kelly M A, Opitz-Araya X, Thomas R E, Low M J, Cone R D. Exocrine gland dysfunction in MC5-R-deficient mice: evidence for coordinated regulation of exocrine gland function by melanocortin peptides. Cell 1997: **91**: 789–798.

65 Ganceviciene R, Graziene V, Böhm M, Zouboulis C C. Increased in situ expression of melanocortin-1 receptor in sebaceous glands of lesional skin of patients with acne vulgaris. Exp Dermatol 2007: **16**: 547–552.

66 Böhm M, Li Z, Ottaviani M *et al.* Beta-endorphin modulates lipogenesis in human sebocytes. J Invest Dermatol 2004: **123**: A10 (abstract).

67 Slominski A, Wortman J, Luger T, Paus R, Solomon S. Corticotropin releasing hormone and proopiomelanocortin involvement in

the cutaneous response to stress. Physiol Rev 2000: **80**: 979–1020.
68 Kim H S, Cho D H, Kim H J, Lee J Y, Cho B K, Park H J. Immunoreactivity of corticotropin-releasing hormone, adrenocorticotropin and α-melanocyte-stimulating hormone in alopecia areata. Exp Dermatol 2006: **15**: 515–522.
69 Grando S A, Pittelkow M R, Schallreuter K U. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance. J Invest Dermatol 2006: **126**: 1948–1965.
70 Kurzen H, Berger H, Jäger C *et al.* Phenotypical and molecular profiling of the extraneuronal cholinergic system of the skin. J Invest Dermatol 2004: **123**: 937–949.
71 Hana A, Booken D, Henrich C *et al.* Functional significance of non-neuronal acetylcholine in skin epithelia. Life Sci 2007: **80**: 2214–2220.
72 Schafer T, Nienhaus A, Vieluf D, Berger J, Ring J. Epidemiology of acne in the general population: the risk of smoking. Br J Dermatol 2001: **145**: 100–104.
73 Klaz I, Kochba I, Shohat T, Zarka S, Brenner S. Severe acne vulgaris and tobacco smoking in young men. J Invest Dermatol 2006: **126**: 1749–1752.
74 Toyoda M, Nakamura M, Makino T, Kagoura M, Morohashi M. Sebaceous glands in acne patients express high levels of neutral endopeptidase. Exp Dermatol 2002: **11**: 241–247.
75 Thielitz A, Reinhold D, Vetter R *et al.* Inhibitors of dipeptidyl peptidase IV (DP IV, CD26) and aminopeptidase N (APN, CD13) target major pathogenetic steps in acne initiation. J Invest Dermatol 2007: **127**: 1042–1051.
76 Fleischer B. CD26: a surface protease involved in T-cell activation. Immunol Today 1994: **15**: 180–184.
77 Ansorge S, Reinhold D. Immune peptides related to dipeptidyl aminopeptidase IV/CD26. In: Kastin A J, ed. Handbook of Biologically Active Peptides. Amsterdam: Academic Press Elsevier, 2006: 567–572.
78 Zouboulis C C. Acne vulgaris and rosacea. In: Granstein R D, Luger T A, eds. Neuroimmunology of the Skin. Basic Science to Clinical Relevance. Heidelberg: Springer, in press.
79 Riemann D, Kehlen A, Langner J. CD13 – not just a marker in leukemia typing. Immunol Today 1999: **20**: 83–88.
80 De Meester I, Korom S, Van Damme J, Scharpe S. CD26, let it cut or cut it down. Immunol Today 1999: **20**: 367–375.
81 Reinhold D, Kähne T, Steinbrecher A *et al.* The role of dipeptidyl peptidase IV (DP IV) enzymatic activity in T cell activation and autoimmunity. Biol Chem 2002: **383**: 1133–1138.
82 Hunyadi J, Simon M Jr, Kenderessy A S, Dobozy A. Expression of monocyte/macrophage markers (CD13, CD14, CD68) on human keratinocytes in healthy and diseased skin. J Dermatol 1993: **20**: 341–345.
83 Novelli M, Savoia P, Fierro M T, Verrone A, Quaglino P, Bernengo M G. Keratinocytes express dipeptidyl-peptidase IV (CD26) in benign and malignant skin diseases. Br J Dermatol 1996: **134**: 1052–1056.
84 Reinhold D, Vetter R W, Mnich K *et al.* Dipeptidyl peptidase IV (DP IV, CD26) is involved in regulation of DNA synthesis in human keratinocytes. FEBS Lett 1998: **428**: 100–104.
85 Thielitz A, Bukowska A, Wolke C *et al.* Identification of extra- and intracellular alanyl aminopeptidases as new targets to modulate keratinocyte growth and differentiation. Biochem Biophys Res Commun 2004: **321**: 795–801.
86 Holick M F. Evolution and function of vitamin D. Recent Results Cancer Res 2003: **164**: 3–28.
87 Nebert D W, Gonzalez F J. P450 genes: structure, evolution, and regulation. Ann Rev Biochem 1987: **56**: 945–993.
88 Henry H L. Vitamin D hydroxylase. J Cell Biochem 1992: **49**: 4–9.
89 Lehmann B, Querings K, Reichrath J. Vitamin D and skin: new aspects for dermatology. Exp Dermatol 2004: **13**(s4): 11–15.
90 Reichrath J, Rafi L, Rech M *et al.* Analysis of the vitamin D system in cutaneous squamous cell carcinomas (SCC). J Cut Pathol 2004: **31**: 224–231.
91 Chen W, Yang C-C, Sheu H-M, Seltmann H, Zouboulis C C. Expression of peroxisome proliferator-activated receptor and CCAAT/enhancer binding protein transcription factors in cultured human sebocytes. J Invest Dermatol 2003: **121**: 441–447.
92 Reichrath J, Schuler C, Seifert M, Zouboulis C C, Tilgen W. The vitamin D endocrine system in human sebocytes. Exp Dermatol 2006: **15**: 643 (abstract).
93 Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. Drugs 2003: **63**: 1579–1596.
94 Zouboulis C C. Isotretinoin revisited – pluripotent effects on human sebaceous gland cells. J Invest Dermatol 2006: **126**: 2154–2156.
95 Baron J M, Heise R, Blaner W *et al.* Retinoic acid and its 4-oxo metabolites are functionally active in human skin cells in vitro. J Invest Dermatol 2005: **125**: 143–153.
96 Duell E A, Åstrom A, Griffiths C E, Chambon P, Voorhees J J. Human skin levels of retinoic acid and cytochrome P-450-derived 4-hydroxyretinoic acid after topical application of retinoic acid in vivo compared to concentrations required to stimulate retinoic acid receptor-mediated transcription in vitro. J Clin Invest 1992: **4**: 1269–1274.
97 Sorg O, Antille C, Kaya G, Saurat J H. Retinoids in cosmeceuticals. Dermatol Ther 2006: **9**: 289–296.
98 Smith G, Wolf C R, Deeni Y Y *et al.* Cutaneous expression of cytochrome P450 CYP2S1: individuality in regulation by therapeutic agents for psoriasis and other skin diseases. Lancet 2003: **361**: 1336–1343.
99 Heise R, Mey J, Neis M *et al.* Skin retinoid concentrations are modulated by CYP26AI expression restricted to basal keratinocytes in normal human skin and differentiated 3D-skin models. J Invest Dermatol 2006: **126**: 2473–2480.
100 Emsley J. Parfum, Portwein, PVC…Chemie im Alltag, 1st edn. Weinheim: Wiley-VCH, 2003.
101 Gower D B, Nixon A, Jackman P J A, Mallet A I. Transformation of steroids by axillary coryneform bacteria. Int J Cosmetic Sci 1986: **8**: 149–158.
102 Brennan P A, Zufall F. Pheromonal communication in vertebrates. Nature 2006: **444**: 308–315.
103 Kimoto H, Haga S, Sato K, Touhara K. Sex-specific peptides from exocrine glands stimulate mouse vomeronasal sensory neurons. Nature 2005: **437**: 898–901.
104 Penn D J, Oberzaucher E, Grammer K *et al.* Individual and gender fingerprints in human body odour. J Roy Soc Interface 2007: **4**: 331–340.
105 Penn D, Potts W K. Untrained mice discriminate MHC-determined odors. Physiol Behav 1998: **64**: 235–243.
106 Zouboulis C C, Eady A, Philpott M *et al.* What is the pathogenesis of acne? Exp Dermatol 2005: **14**: 143–152.
107 Klapproth H, Reinheimer T, Metzen J *et al.* Non-neuronal acetylcholine, a signalling molecule synthezised by surface cells of rat and man. Naunyn-Schmiedeberg's Arch Pharmacol 1997: **355**: 515–523.
108 Seifert M, Rech M, Meineke V, Tilgen W, Reichrath J. Differential biological effects of 1,25-dihydroxyVitamin D3 on melanoma cell lines in vitro. J Steroid Biochem Mol Biol 2004: **90**: 375–379.

