Frontiers in sebaceous gland biology and pathology

Christos C. Zouboulis1,2, Jens Malte Baron3*, Markus Böhm4*, Stefan Kippenberger5*, Hjalmar Kurzen6*, Jörg Reichrath7* and Anja Thielitz8*

1Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany; 2Laboratory of Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology, Institute of Clinical Pharmacology and Toxicology, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Berlin, Germany; 3Department of Dermatology and Allergology, University Hospital RWTH Aachen, Aachen, Germany; 4Department of Dermatology, University of Münster, Münster, Germany; 5Department of Dermatology and Venereology, University Hospital, University of Frankfurt, Frankfurt, Germany; 6Department of Dermatology, Venereology and Allergology, Medical Faculty of Mannheim, Ruprecht-Karls University of Heidelberg, Mannheim, Germany; 7Department of Dermatology, The Saarland University Hospital, Homburg, Germany; 8Department 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 seocytes, 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). Sebaceous, 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 acetylsalicylic acid II was found to protect the skin against oxidative stress and, especially, epidermal keratinocytes against ultraviolet B irradiation (21). On the other hand, sebocytes are able to produce protoporphyrin IX under exposure to δ-aminolevulinic acid (22). Sebaceous gland lipids exhibit direct pro- and antiinflammatory properties (12,23–26). Whereas the induction of the 5-lipoxygenase and cyclooxygenase-2 pathways in sebocytes leads to the production of proinflammatory lipids (24–26), anti-inflammatory lipids can also be produced by activating the liver X receptor pathway (27,28). Moreover, the palmitoleic acid isomer (C16:1ω7cis,ω6trans) 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

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

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

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, M1–M5 AChR. The α5, α7, α10, β4, M2 and M4 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 transmembrane 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 potentiates 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(NO₂)]-thiazolidide and Lys[Z(NO₂)]-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 D₃ [1,25(OH)₂D₃; calcitriol], vitamin D has to be metabolized in the liver to 25-hydroxyvitamin D₃ [25(OH)D₃] and then in the kidney to 1,25(OH)₂D₃. There are two principal enzymes involved in the formation of circulating 1,25(OH)₂D₃ 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)D₃ respectively (89,90). 1,25(OH)₂D₃ 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 monoxygenases (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)₂D₃ (91,92). 1,25(OH)₂D₃ 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)₂D₃ 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)₂D₃ 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
Sebaceous gland physiology and pathology

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 [CYP27B1]) to synthesize the biologically active vitamin D metabolite 1,25-(OH)2D3. 7-DHC, 7-dehydrocholesterol; preD3, previtamin D3; ZD0HD3, 25-hydroxyvitamin D3; 1,25(OH)2D3, 1,25-dihydroxyvitamin D3; 24,25(OH)2D3, 24,25-dihydroxyvitamin D3; 1,24,25(OH)3D3, 1,24,25-trihydroxyvitamin D3; CYP27A1, vitamin D-25-hydroxylase; 25OHzase; CYP27B1, 25-hydroxyvitamin D-1α-hydroxylase, 1αOHase; CYP24A1, 1,25-dihydroxyvitamin D-24-hydroxylase, 24OHzase; Δ7-R, 7-DHC-Δ7-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′-CCAGTCGTGTAAGATGGA-3′, reverse 5′-GTCGTCCATGATGAGA-3′) and 10-fold serial dilutions of cDNA as external standards. Expression levels were determined as ratios between VDR and the reference gene β2-microglobulin (108).

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)2D3 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 anti-inflammatory 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 retinoid 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 play 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) 26Al expression in epithelial cells of the sebaceous gland indicates expression of CYP26Al 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 CYP26Al (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×.

CYP26Al and CYP2S1 (100,101). Current immunohistochemical analysis using a newly developed antibody specific for the detection of CYP26Al revealed strong constitutive expression of the CYP26Al 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 CYP26Al in the epithelium of sebaceous glands may determine how the sebaceous follicle responds to acrogenic 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 repellent 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 androsteneone (102). Other experiments have demonstrated that women are able to trace androsteneone at dilutions up to one to a trillion, particularly during ovulation (103).

To avoid an impulsive overdosage of apocrine 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 relic 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

29 Wille J J, Kydonieus A. Palmitoleic acid isomer (C16:1a6) is the active antimicrobial fatty acid in human skin sebum. Skin Pharmacol Appl Skin Physiol 2003: 16: 176–187.
Zouboulis et al.


67 Slominski A, Wortmann J, Lugter T, Paus R, Solomon S. Corticotropin-releasing hormone and proopiomelanocortin involvement in
Sebaceous gland physiology and pathology


