"Sebocytes' makeup" - Novel mechanisms and concepts in the physiology of the human sebaceous glands

**Balázs I. Tóth · Attila Oláh · Attila G. Szöllősi ·
Gabriella Czifra · Tamás Bíró**

Abstract The pilosebaceous unit of the human skin consists of the hair follicle and the sebaceous gland. Within this "mini-organ", the sebaceous gland has been neglected by the researchers of the field for several decades. Actually, it was labeled as a reminiscence of human development ("a living fossil with a past but no future"), and was thought to solely act as a producer of sebum, a lipid-enriched oily substance which protects our skin (and hence the body) against various insults. However, due to emerging research activities of the past two decades, it has now become evident that the sebaceous gland is not only a "passive" cutaneous "relic" to establish the physico-chemical barrier function of the skin against constant environmental challenges, but it rather functions as an "active" neuro-immuno-endocrine cutaneous organ. This review summarizes recent findings of sebaceous gland research by mainly focusing on newly discovered physiological functions, novel regulatory mechanisms, key events in the pathology of the gland, and future directions in both experimental and clinical dermatology.

Keywords Human sebaceous gland · Lipid synthesis · Immuno-endocrine functions · Signal transduction · Acne vulgaris

Preface

The sebaceous gland (glandula sebacea) is a holocrine gland located in the dermis of the skin, where it is primarily associated with hair follicles forming the pilosebaceous unit [111]. Its cells are the sebocytes, and their main, well-known function is the production of sebum (tallow) [147]. Sebaceous glands can be found in the skin of all terrestrial mammals, but the density of the glands in the different regions of the body, as well as the composition of the sebum, exhibit a marked species specificity. The primary isolated sebaceous glands and sebocytes cannot be kept in culture for a long time because of their rapid and excessive differentiation [36, 106]. Taking in account that most of the pathological alterations of the sebaceous gland functions (e. g., acne vulgaris) are exclusively human diseases, the identification of relevant models has been a critical question of human sebaceous gland research. In the last decade, the in vitro animal models, e.g., preputial gland of rodents [103, 153] or sebaceous gland of hamster ear [99], were mainly substituted by human sebaceous gland-derived cell lines, such as the SZ95 [171], Seb-1 [144], and Seb-E6E7 [66]. These models have provided a new insight into human sebaceous gland biology and have broadened our understanding of the molecular mechanisms and regulation of different sebaceous functions [169, 172]. This review summarizes recent findings of sebaceous gland research by mainly focusing on newly discovered functions (e.g., immunological functions) and novel regulatory mechanisms.

Diverse functions of an ancient gland

Development, differentiation, and regeneration

Differentiation of the pilosebaceous unit occurs in the embryonic stage between months 2 and 4 of gestation. During this process, a complex, in many aspects still unresolved, signaling interplay between dermal mesenchy-

B. I. Tóth · A. Oláh · A. G. Szöllősi · G. Czifra · T. Bíró (✉)
Department of Physiology, Medical and Health Science Center,
Research Center for Molecular Medicine, University of Debrecen,
4032 Debrecen, Nagyerdei krt. 98, PO Box 22, Hungary
e-mail: biro@phys.dote.hu

mal cells and the embryonic epidermis induces the formation of the dermal papilla of the hair follicle, which initiates the final differentiation of the pilosebaceous unit. The source of the sebocytes is the basal layer of the epidermis and the progenitor cells are identical to the cells which form the outer root sheath of the hair follicle [26]. During embryonic life, the sebaceous glands may contribute to the formation of vernix caseosa [26, 165].

Recent findings shed a light on the molecular mechanisms of the sebaceous gland differentiation. The differentiation of pilosebaceous stem cells depends on Sox9 signaling since this signal is important for both hair follicle and sebaceous gland differentiation [84]. However, during the following steps, the development of the two structures is regulated differentially. The lineage choice of the progenitors can be regulated by the Wnt target β-catenin; i.e., the presence of β-catenin promotes hair follicle differentiation whereas its inhibition, e.g., by Smad7 overexpression, shifts the process towards the sebaceous linage. The further proliferation of sebocyte precursors is stimulated by Indian Hedgehog signaling [4, 45, 83] while the bone morphogenic protein pathway, similar to Wnt signaling, was reported to inhibit sebaceous differentiation [42].

During embryonic development, a population of unipotent sebaceous stem cells is established which express the B lymphocyte-induced maturation protein 1 (Blimp1) transcription factor [48]. These cells appear to be essential in the renewing of sebocytes (and hence regenerating the mini-organ) in the adult skin; however, stem cells from the bulge region of hair follicle are also capable of forming sebaceous glands [110, 111]. In addition, Blimp1 inhibits the expression of c-myc which suppression is essential in normal sebaceous gland homeostasis; consequently, deletion of Blimp1 results an overexpression of c-myc and causes the hyperplasia of sebaceous glands [48]. Other results show that sebaceous cell lines can differentiate into both sebocytes and keratinocytes, which suggests the presence of bi-potential progenitor stem cells among them [66].

The adult, fully developed sebaceous gland can be divided into three zones which contain cells at different stages of differentiation. The *peripheral zone* is composed of small, mitotically active cells. During their differentiation, these cells move towards the center of the gland, lose their mitotic activity, increase their size, and accumulate lipid droplets, forming the *maturation zone*. In the *central necrosis zone*, the terminally differentiated sebocytes disintegrate and release their content via holocrine secretion [110, 147]. This continuous differentiation program is under the control of various paracrine, endocrine, and neural mediators acting on a wide array of receptors expressed by sebocytes [162]. Some of the newly recognized factors, which influence/regulate the physiological

processes of the sebaceous gland, will be discussed in detail below.

"Classical" functions of the sebaceous glands—sebum production: the barrier and beyond

Sebum is mainly composed of neutral lipids, with a relatively high amount of triglycerides, free fatty acids, wax esters, cholesterol, and squalene. Among these, squalene and wax esters are unique and typical components of the sebum [97, 104, 136]. The secreted sebum covers the fur and the surface of the skin, and forms the majority of skin surface lipids. In addition, a much smaller lipid fraction is produced by epidermal keratinocytes, which mostly fill the intercellular spaces between keratinocytes and ensure the skin permeability barrier [93].

In animals, sebum plays important roles in the impregnation of fur and thermal insulation, while in some species the sebaceous glands have specialized to produce pheromones. Since these functions are mostly unrecognizable in humans, it has been a long-standing view that the human sebaceous gland is an evolutional relic [100]. However, the unique composition of the sebaceous lipids plays important roles in the skin barrier function. For instance, waxes can be more resistant to oxidation than other lipids and can improve the water resistance of the surface [93]. Others reported the potential role of squalene and its peroxides in the process of protection against sunburn and UV radiation [88]. It was also found that sebum contains the antioxidant vitamin E [146]. Furthermore, sebaceous lipids are not only a part of the physico-chemical barrier of the skin, but they form a biological barrier as well; indeed, sebum contains various lipids with antimicrobial activity (see below).

Besides the well-documented barrier function, other roles are also ascribed to human sebum. One of them is the supposed role in thermoregulation. Under cold circumstances, sebum can form a water-repellent layer whereas in warmer environments, it is transformed to a more fluidic form. The latter can serve as an emulsifier for eccrine sweat by decreasing its surface tension and thereby helping to keep the sweat on the skin surface which increases the efficacy of evaporation [68, 102]. In addition, sebum may influence not only the eccrine, but also the apocrine sweat functions. This new theory hypothesizes that sebum, produced by axillary sebaceous glands, can serve as vehicle for fragrances, and, as such, it may influence odor and can also play a role in the interpersonal communication [165].

Immunological functions of the sebaceous glands

Recent findings also show that functions of sebocytes may go far beyond the production of sebum and the formation of the passive cutaneous barrier. Via numerous paracrine,

endocrine, and immunological mechanisms, sebaceous glands greatly contribute to the physiological homeostatic function of the skin.

Sebocytes participate in the regulation of immunological functions and inflammatory processes. They are capable of producing different (mostly pro-inflammatory) cytokines and lipid-derived inflammatory mediators. Among cytokines, the expression of interleukin (IL) 1α, IL-1β, IL-6, IL-8/CXCL-8, and tumor necrosis factor-α (TNFα; but not IL-10 and IL-12) was reported in human sebaceous glands and cultured sebocytes [3, 81]. It was also shown that the expression and release of cytokines could be affected by various factors, such as, e.g., inflammatory signals. While the presence of *Propionibacterium acnes* up-regulated the expression of TNFα and IL-8/CXCL-8, bacterial lipopolysaccharide (LPS), treatment elevated the levels of IL-1α as well [81]. Likewise, arachidonic acid (AA) and the Ca^{2+} ionophore A23187 increased the release of IL-6 and IL-8 [3] whereas IL-1β was found to stimulate the release of IL-8 [170]. Interestingly, the activation of the Ca^{2+} permeable transient receptor potential vanilloid-1 (TRPV1) channel did not affect the release of IL-6, but it did decrease that of IL-1β [149]. Various hormones and neuropeptides are also able to influence the cytokine release of sebocytes; these include hypothalamic and pituitary hormones, i.e., corticotropin-releasing hormone (CRH) and α-melanocyte stimulating hormone (αMSH), and the neuropeptide substance P (SP); hence, these mediators may affect the inflammatory processes of these cells (see also below).

As inflammatory signals, certain lipid mediators may also play a crucial role. These substances are derivates of AA produced by the cyclooxygenase (COX) or lipoxygenase (LOX) pathways [37, 139]. The sebocytes express key enzymes of both pathways—i.e., 5-LOX and leukotriene A$_4$-hydrolase (LTA$_4$-hydrolase) of the LOX pathway and COX-1 and 2—and are able to synthesize leukotriene B$_4$ (LTB$_4$) and prostaglandin E$_2$ (PGE$_2$), which production can be enhanced by inflammatory stimuli, for example UV irradiation or AA administration [3, 160].

The above listed wide array of inflammatory mediators produced by the sebaceous gland may act as key players in the pathogenesis of inflammatory syndromes such as, e.g., acne vulgaris. The development of acne requires multiple pathological processes such as comedo-genesis due to the hyperproliferation of keratinocytes, increased lipid synthesis of sebocytes with alterations in the lipid content of the sebum, and the proliferation of pathogenic microorganisms such as *P. acnes*. In parallel, the production of inflammatory mediators (produced both by keratinocytes and sebocytes) is increased which, in turn, attract the "on-site" invasion of (first) CD4+ T lymphocytes then neutrophil granulocytes to infiltrate the affected pilosebaceous unit. Of further importance, novel etiological models emphasize that

acne may develop without the colonization of pathogenic microorganisms, provided that some other factors (e.g., enhanced effect of androgenic hormones, activation of peroxisome proliferator-activated receptors (PPAR), SP-mediated stress response, other hormonal effects, etc.) increase the production of the inflammatory mediators and induce hyperseborrhea [33, 59, 161, 168].

Sebocytes of the sebaceous glands can be considered as not only "producers" of potential pathogenic factors but these cells are also part of the innate immune system. As we mentioned above, sebum contains lipids with antimicrobial activity. These lipids are especially effective against Gram-positive bacteria, such as *Staphylococcus aureus* (including methacillin-resistant strains), *Streptococcus salivarius*, *Fusobacterium nucleatum*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *P. acnes* [32, 154]. Chemically, these antimicrobial lipids can be both saturated (e.g., lauric acid, C$_{12:0}$) and unsaturated (e.g., sapienic acid, C$_{16:1\Delta6}$) fatty acids. Importantly, saturated fatty acids with shorter chain length form monomers in aqueous solutions with higher probability. Since the antimicrobial activity of these lipids is attributed chiefly to the monomer forms, the differences seen in their chemical natures suggest that shorter lipids exhibit greater antimicrobial activities than long-chain fatty acids. Furthermore, antimicrobial fatty acids, such as, e.g., the monounsaturated fatty acid (MUFA) sapienic acid, may be synthesized by sebocytes in the form of triglyceride esters and then can be liberated by bacterial triglyceride hydrolysis or by epidermal acid lipase [32]. The antimicrobial role of MUFAs was further supported by the flake homozygote mouse model. These mice exhibit an impaired stearoylcoenzyme A desaturase 1 enzyme function and hence are unable to produce the MUFAs palmitoleate (C$_{16:1}$) and oleate (C$_{18:1}$). Consequently, these animals show signs of severe dermatitis, and are more vulnerable to Gram-positive bacterial infections [39].

Finally, it should be emphasized that, similar to the release of pro-inflammatory immune mediators, sebocytes can also secrete certain peptides/proteins such as, e.g., antimicrobial peptides. Indeed, it was shown on SZ95 sebocytes that these cells express functional cathelicidin [63], β-defensins [81], and histone H4 [62], and that the expression of these peptides can be induced by bacterial stimuli. In addition, sebocytes also express Toll-like receptors [81, 86, 87, 162] further supporting the concept that sebaceous glands are indeed indisputable players in innate immunity.

Extended hormonal control of the sebaceous gland

Our concept about the skin has been dramatically revised in the past 20 years. The function of our largest organ is no

more restricted for the physico-chemical barrier, thermo-regulatory and sensory mechanisms; rather, the skin is introduced as a complex endocrine organ of the human body since it is a source as well as a target of a plethora of (neuro)endocrine hormones and autocrine/paracrine mediators [116, 127, 129, 163]. As an integral part of the human skin, the pilosebaceous unit and its sebocytes also play an active role in these endocrine functions [12, 21].

Effects of steroid hormones

It has been known for a long time that the sebum production of sebaceous glands is stimulated by androgens [100, 147] (Table 1). The presence of androgen receptors was found both in situ on human sebaceous glands [22, 95] and in vitro on human sebocytes [35]. Moreover, testosterone and 5α-dihydrotestosterone (5α-DHT) was shown to increase proliferation of sebocytes in vitro [35, 171]. Using primary isolated sebocytes, it was also reported that the location of the sebaceous gland influences the effect of androgens; namely, these hormones were more effective in increasing the proliferation of facial sebocytes than on non-facial ones [1, 164]. Intriguingly, androgen hormones alone failed to modulate lipid synthesis of cultured sebocytes [35, 171]. However, in the presence of certain co-activators such as, e.g., linoleic acid which stimulates PPARs [107, 108], androgens may exert lipogenic actions.

Of great importance, sebocytes seem to be much more than simple "passive targets" of the effects of androgens. Recent evidence suggests that they are also capable of metabolizing and synthesizing androgen hormones and hence play a central role in cutaneous androgen homeostasis [19, 167]. These cells express members of the P450 side-chain cleavage system which converts cholesterol to pregnenolone [144]. Sebocytes also express the androgen metabolizing enzymes 3β-hydroxysteroid dehydrogenase/Δ5-4-isomerase, 17β-hydroxysteroid dehydrogenase, 5α-reductase-1, and 3β-hydroxysteroid dehydrogenase. Intriguingly, sebocytes are reportedly able to synthesize testosterone and also to convert testosterone into the more effective 5α-DHT which process, like lipid synthesis, was promoted by a simultaneous activation of PPARs [73]. Furthermore, these cells can inactivate testosterone by converting it to androstenedione and further to 5α-androstenedione [35, 113].

In contrast to the actions of androgens, estrogens were originally described to suppress the lipid production of the sebaceous gland [26, 44]. However, recent reports have provided conflicting data; namely, although expressions of estrogen receptors α and β and progesterone receptor were shown on sebaceous glands [95], the female sexual steroids 17β-estradiol and progesterone were found to influence neither proliferation nor lipid synthesis of SZ95 sebocytes in vitro [72].

Less data were reported about the sebaceous effects of corticosteroid hormones. The presence of the enzymatic apparatus needed for the production of corticosteroids as well as the corticosteroids (such as, e.g., cortisol) themselves were extensively documented in the skin [52, 121, 122, 131–135]. These facts postulate that the sebaceous gland may also be a target of the locally produced corticosteroids. Early observations suggested that prednisolon failed to induce sebum synthesis but glucocorticoids might have a permissive effect on the sebaceous gland activity [101]. Topically administered glucocorticoids were found to decrease human sebum production [65]. In addition, corticosteroids were shown to be able to stimulate proliferation [172] and inhibit lipid synthesis of cultured sebocytes [18] which findings suggested that corticosteroids may exert a differentiation-inhibiting effect.

Finally, another steroid hormone, the active vitamin D₃ metabolite calcitriol deserves mentioning. The 1,25-dihydroxy vitamin D₃ is produced locally by the keratinocytes of the skin and can regulate the differentiation of several cutaneous cell types [5, 6, 46]. Importantly, SZ95 sebocytes express the 1α, 24, and 25-hydroxylases and vitamin D receptor. Furthermore, calcitriol was shown to influence the lipid content, regulate proliferation, reduce the IL-6 and IL-8 release, and up-regulate cathelicidin antimicrobial peptide expression on SZ95 sebocytes [57, 63]. Hence, calcitriol may also function as a key regulator of sebocyte biology.

Effects of growth hormones and growth factors

Sebaceous gland functions are also under the control of growth-promoting hormones and growth factors (Table 1). The "oily skin" is a characteristic for acromegaly (a syndrome that develops as a result of overproduction of growth hormone, GH) and, moreover, the identification of GH receptors in the sebaceous gland in situ [67, 85] suggested the potential role of GH, mRNA of which was identified also in human skin [123], in sebaceous gland functions. Indeed, in a rat preputial sebocyte model, GH accelerated the differentiation of sebocytes in vitro but did not significantly influence proliferation. In contrast, insulin-like growth factor-I (IGF-I), which was shown to mediate several physiological actions of GH in various tissues, had a minor effect on differentiation but it markedly increased the proliferation of sebocytes. Intriguingly, the "universal growth hormone" insulin was found to stimulate both proliferation and differentiation, and it augmented the effects of GH, IGF-I, and 5α-DHT [25]. In human sebaceous cell lines, both GH and IGF-I were able to enhance lipid synthesis, IGF-I being the more effective one [72]. Of further importance, the effect of IGF-I was found to be mediated by the PI-3-kinase/Akt/sterol response element-binding protein-1 (SREBP1) pathway [137, 138].

Table 1 Mediators and agents influencing the functions of sebocytes

Agents	Potential targets	Possible effects
Bacterial stimuli (e.g., presence of *P. acnes*, LPS)	Toll-like receptor-2, 4, and 6 (TLR-2, TLR-4, TLR-6) [81, 86, 87]	β-defensins↑, cathelicidin↑, tumor necrosis factor-α (TNFα)↑, interleukin-8 (IL-8)↑, IL-1α↑ [62, 63, 81]
AA	Unknown (protein kinases?, peroxisome proliferator-activated receptors—PPARs?)	IL-6↑, IL-8↑, leukotriene B₄ (LTB₄)↑, lipid synthesis↑, apoptosis↑, differentiation↑ [3, 149, 156]
Linoleic acid	PPARs [20, 107, 108, 151]	Lipid synthesis↑, differentiation↑, conversion of testosterone to 5-α-dihidritestosterone (5-α-DHT)↑ [20, 107, 108]
Testosterone, 5α-DHT	Testosterone (androgen) receptor [22, 35, 95] (modification: 3β-hydroxysteroid dehydrogenase/Δ5-4-isomerase, 17β-hydroxysteroid dehydrogenase, 5α-reductase-1 and 3β-hydroxysteroid dehydrogenase) [73]	Proliferation↑ [35, 171] in the presence of cofactors (e.g., PPAR agonists): lipid synthesis↑, differentiation↑ [107, 108]
Estrogens	Estrogen receptor-α and β [95]	Questionable (sebogenesis↓?) [26, 44]
Progesterone	Progesterone receptor [95]	?
(Gluco)corticosteroids	Glucocorticoid receptor (?)	Permissive effect [101], proliferation↑, lipid synthesis↓ [18, 172]
Calcitriol (vitamin D₃)	Vitamin D receptor (VDR) (modification: 1α, 24- and 25-hydroxylases) [57]	IL-6↓, IL-8↓, cathelicidin↑ in rapidly proliferating cultures (with serum): proliferation↓, cell cycle arrest in slowly proliferating cultures (without serum): proliferation↑, lipid synthesis↓ [57, 63]
Growth hormone (GH)	Growth hormone receptor (GHR) [67, 85]	Differentiation↑, no effect on proliferation [25]
Insulin-like growth factor-I (IGF-I)	IGF-I receptor (?)→phosphoinositol-3-kinase/Akt (PI3K/Akt)→sterol response element-binding protein-1 (SREBP1) [136, 137]	Proliferation↑, minor effect on differentiation [25] lipid synthesis↑ [72]
Insulin	Insulin receptor	Proliferation↑, differentiation↑, supportive role in the effect of 5α-DHT, GH, and IGF-I [25]
Epidermal growth factor (EGF)	EGF receptor (EGFR) [82]	Differentiation↓, proliferation↑ [44]
Fibroblast growth factor-7 (FGF7)	Fibroblast growth factor receptor-2b (FGFR2b) [41, 78]	Acne formation↑ FGFR2b knockout mice show sebaceous gland atrophy [41, 78]
IL-1β	Not described on sebocytes	IL-8↑ [170]
β-endorphin	μ opioid receptor [12]	Lipid synthesis↑, proliferation↓, differentiation↑ [12]
Corticotropin-releasing hormone (CRH)	CRH receptor-1, 2 (CRHR1, CRHR2) [125, 170]	Lipid synthesis↑, 3β-hydroxysteroid dehydrogenase/Δ5–4 isomerase expression↑, differentiation↑, proliferation↓, IL-6↑, IL-8↑ [58, 170]
α-melanocyte-stimulating hormone (melanocortin, αMSH)	Melanocortin receptor-1, 5 (MC-1R, MC-5R) [13, 140, 145, 158, 159]	IL-8↓, differentiation↑, lipid synthesis↑ [12, 13, 158, 159]
Adrenocorticotropic hormone (corticotropin, ACTH)	Melanocortin receptor-2 (MC-2R) [43]	Differentiation↑, lipid synthesis↑ [158]
Substance P (SP)	Not described on sebocytes	IL-1↑, IL-6↑, TNF-α↑, PPARγ↑, lipid synthesis↑, Sebaceous gland size↑, differentiation↑ [64, 150]
Endocannabinoids (anadamide—AEA, 2-arachidonoyl glycerol—2-AG)	Cannabinoid receptor 2 (CB2)→mitogen-activated protein kinase (MAPK)→PPAR [31]	Lipid synthesis↑, apoptosis↑, differentiation↑ [31]
Capsaicin	Transient receptor potential vanilloid 1 (TRPV1)→PPARs↓ and retinoid-X receptors (RXRs)↓ extracellular Ca²⁺ dependent [149]	Lipid synthesis↓, differentiation↓, IL-1β↓, proliferation↑ (TRPV1 specific), necrosis↑ (large dose, TRPV1 independent) [149]

The presence of epidermal growth factor (EGF) receptor was also identified on human sebocytes [82]. In animal models, EGF increased the number of cells in the sebaceous glands [74] whereas in human in vitro systems, it apparently inhibited sebaceous differentiation [44]. This latter finding was further supported by the observation that the most frequent side effects of the EGF receptor inhibitor monoclonal antibody cetuximab, used in cancer therapy, are the acneiform eruptions [148]. Besides EGF, recent results suggest the role of fibroblast growth factor receptor-2b (FGFR2b)-coupled signaling in the control of sebaceous functions and development of acne [41, 78].

Neuroendocrine regulators

In the last decade, a large number of endocrine mediators and neurotransmitters were reported to have significant influence on sebaceous gland biology (Table 1). Indeed, the skin expresses ligands and receptors for a broad range of neurohormones of the hypothalamic−pituitary axis [116, 127, 129, 163]. Various cell types of mouse and human skin express CRH receptors (CRHR1 and CRHR2) [105, 118, 119]. Likewise, these receptors were also detected in the human sebaceous gland [125]. Intriguingly, the skin is also able to produce the ligands of CRHRs: the expression of both CRH and urocortin was demonstrated in various cutaneous cell types, including those of the sebaceous gland [55, 120, 126]. Likewise, on cultured SZ95 sebocytes, both CRHR1 and CRHR2 as well as CRH were described [170] and the "autocrine" CRH, by acting on its receptors, was implicated to increase lipid synthesis and androgenic hormone production (by elevating the expression of 3β-hydroxysteroid dehydrogenase/Δ5-4 isomerase) [170]. Furthermore, CRH stimulated IL-6 and IL-8 release without affecting IL-1α and IL-1β release and, like urocortin, inhibited the proliferation of the SZ95 cells [58].

Of further importance, CRH also regulates the cleavage of proopiomelanocortin (POMC), whose presence was also reported in several cell types of mouse and human skin [118, 124], including sebocytes [56, 75]. Similar to the pituitary gland, the human skin is also able to process POMC to shorter POMC-derived peptides [155]. These peptides, such as α- and β-MSH (melanocortin), adrenocorticotropic hormone (corticotropin, ACTH), and β-endorphin were demonstrated in sebocytes, and the presence of the prohormone convertase enzymes responsible for enzymatic cleavage of POMC was also documented [55, 75, 124]. Furthermore, the cutaneous expression of their receptors—melanocortin receptor types 1 and 2 (ACTH receptor) and type 5 (MC-1R, MC-2R, and MC-5R, respectively), and μ opioid receptor—were also described [13, 43, 140, 145, 158, 162].

Similar to CRH, POMC-derived peptides were also found to be active on sebocytes. MC-5R-coupled signaling was shown to play a stimulatory role in secretion of mouse exocrine glands, including sebaceous glands [17]. POMC-derived peptides, such as MSH and ACTH, stimulated differentiation of human sebocytes which effect was correlated with an increased expression of MC-5R [158]. Melanocortin and its analogues were suggested to decrease IL-8 secretion and induce lipid synthesis via MC-1R on non-differentiated sebocytes, and via MC-5R on differentiated cells [12, 13, 159]. Pilot results also indicated that β-endorphin (most probably via acting on μ opioid receptors) exerts a differentiation-promoting effect; namely, it increased lipid synthesis and decreases proliferation of cultured sebocytes [12].

These intriguing data unambiguously argue for the presence of a functional hypothalamic−pituitary axis in the skin which may, therefore, play a key role in the regulation of cutaneous stress responses (reviewed in [128, 130]). However, the system may have distinct effects on different cutaneous cell types involving, e.g., both anti- and pro-inflammatory mechanisms [117]. For examples, in sebocytes, an increased expression of CRH, CRHRs, and CRH-binding protein was found in acne-prone skin compared to non-affected skin samples [38].

Biology of sebocytes may additionally be influenced by other paracrine mediators, neurotransmitters, and neuropeptides. Besides stimulating the release of pro-inflammatory cytokines (see above) [64], the sensory neuron-derived SP was found to accelerate differentiation and proliferation of sebaceous glands [150]. On SZ95 sebocytes, on which the presence of H1 histamine receptor was identified, anti-histamines were shown to decrease squalene synthesis [94]. Different muscarinic and nicotinic cholinergic receptor subunits were also found on non-differentiated and differentiated cells of sebaceous gland [60]. It is tempting to hypothesize, therefore, that the activation of these receptors by neural and paracrine acetylcholine or by nicotine from cigarette smoke may play a role in the pathogenesis of acne [165]. A few independent studies and observations furthermore suggest a potential influence of somatostatin, nerve growth factor, calcitonin gene-related peptide, neuropeptide-Y, and serotonin on sebocytes functions [12].

Hence, the plethora of these neuroendocrine agents and their receptors expressed on sebocytes may form a causative link between psycho-emotional stress and the development of acne [166].

Lipid mediators to control sebaceous lipid production

Besides the above wide array of regulatory mechanisms, the biology of sebaceous glands is strongly controlled by paracrine and autocrine lipid mediators. For example, AA

and linoleic acid were shown to induce terminal differentiation of sebocytes and induce lipid synthesis in cultured sebocytes [20, 156]. Therefore, besides the classical lipid-target nuclear receptors, in the sections below we introduce a few novel signaling pathways mediating or modifying the effects of these crucial lipid mediators (Table 1).

"Classical lipid targets"—role of nuclear receptors

PPARs, which belong to the thyroid-hormone receptor-like subfamily of nuclear receptors, are localized in the nucleus and form heterodimers with retinoid-X receptors (RXRs) [80]. PPARs play a central role in the regulation of lipid homeostasis of various tissues. Namely, PPARs can be activated by a wide array of lipid mediators, such as, e.g., fatty acids [27, 152], and PPARγ became well-known as central regulator of adipocyte differentiation [40, 54, 61, 112].

Similar to adipocytes, sebocytes also exhibit an intensive lipid metabolism which is reportedly under the control of PPARs. Sebocytes express all three PPAR isoforms, PPARα, PPARγ, and PPARδ; among them, PPARγ seems to be the dominant form whereas the expression of PPARδ is low. Of great importance, the natural PPAR ligand linoleic acid (similar to synthetic agonists) was shown to increase the lipid production and differentiation of sebocytes [20, 108, 151]. The differentiation-promoting AA can also stimulate PPARs; likewise, the AA-derivative LTB$_4$ was shown to act as a potent activator of PPARα [28]. Furthermore, PPARs take part in the regulation of other cellular processes of sebocytes. Namely, PPARγ was found to be involved in the control of PGE$_2$ production [160] whereas the effects of androgens to modulate sebaceous functions are also mediated by PPARs [107, 108]. Recently, the vitamin D$_3$ was reported to increase the PPARα expression of SZ95 cell line [115].

Recently, the presence of liver-X receptor (LXR) was also identified on human sebocytes [109]. Similar to PPARs, the LXR has a critical role in cholesterol homeostasis and lipid metabolism. Activation of LXRα on SZ95 sebocytes decreased proliferation, increased lipid synthesis, and induced the expression of LXR target genes, such as fatty acid synthase and sterol regulatory-binding protein-1. Furthermore, stimulation of LXRα down-regulated the expression of COX-2 and inducible nitric oxide synthase, induced by LPS treatment. Finally, similar to as reported on adipocytes, LXR activation increased the expression of PPARs on SZ95 sebocytes as well [47, 109].

Role of the endocannabinoid system and related TRP channels

Research efforts of the last two decades have unambiguously confirmed that the human body is able to produce various molecules which exhibit similar biological effects to those agents which can be found in the "infamous" plant Cannabis sativa. These substances are the endogenous cannabinoids, among which the best known ones are the N-arachidonoyl ethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG) [71, 77]. Endocannabinoids may target various receptor structures, which include the G-protein-coupled "classical" CB1 and CB2 cannabinoid receptors; the "novel", also G-protein-coupled GPR55, GPR119, and GPR18; as well as the "ionotropic" cannabinoid receptors, which are certain members of the transient receptor potential (TRP) ion channel superfamily, namely TRPV1, TRPV2, TRPV4, TRPA1, and TRPM8 [2, 14, 24, 49, 50, 71, 76]. Furthermore, certain endocannabinoids may also influence additional signal transduction systems by modulating the activity of other receptors, e.g., ionotropic glutamate receptors, nicotinic acetylcholine receptors, serotonin receptors, μ opioid receptors, and different PPARs [15, 24, 91, 96, 98]. Of further importance, endocannabinoid synthesizing (N-acyl-phosphatidylethanolamine-specific phospholipase D and diacylglycerol lipases [DAGLα and β]) and degrading enzymes (fatty acid amide hydrolase and monoacylglycerol lipase) as well as anandamide/endocannabinoid membrane transporters were also described [23, 29, 34]. Therefore, the endocannabinoids, their receptors, and the enzymes involved in the endocannabinoid metabolism are collectively referred to as the endocannabinoid system (ECS), one of the most complex signaling systems of the human body. Indeed, ECS regulates various biological processes of the human body such as, e.g., food intake, energy balance, body mass, memory, immunological, and vascular responses, bone metabolism, endocrine homeostasis, etc. [70, 71, 92].

Intriguingly, functional ECS has lately been identified in the skin as well, and was implicated in key regulatory processes affecting cutaneous biology [7]. Several human skin cell compartments such as, e.g., epidermal and hair follicle keratinocytes and sebaceous gland-derived sebocytes were shown to produce prototypic endocannabinoids, and express metabotropic and ionotropic cannabinoid receptors and metabolic enzymes [9–11, 16, 31, 51, 53, 69, 142, 143, 149]. Furthermore, stimulation of CB1 by anandamide (which can be produced by the hair follicles themselves) inhibited in vitro hair shaft elongation and induced apoptosis-driven premature catagen regression of the hair follicle [143].

With respect to sebaceous gland biology, it is also of great importance that anandamide and 2-AG are produced by human sebaceous gland-derived SZ95 sebocytes which predominantly express CB2 (Table 1). Both endocannabinoids stimulated lipid production via CB2-coupled signaling involving the MAPK pathway and the up-regulation of PPARs. Since cells with "silenced" CB2 exhibited signif-

icantly suppressed basal lipid production, these results collectively suggest that human sebocytes utilize an autocrine/paracrine, endogenously (and most probably constitutively) active, CB2-mediated ECS for positively regulating lipid production [31] (Fig. 1).

Sebocytes also express "ionotropic" cannabinoid receptors. Among these, the "capsaicin-receptor" TRPV1—which was shown to be activated by anandamide on various cells types including, e.g., sensory neurons [30, 173]—was identified both in situ on human sebaceous glands [11, 141] and in vitro on cultured SZ95 sebocytes [149]. However, in contrast to previous findings, anandamide does not seem to activate TRPV1 on sebocytes. Actually, TRPV1-coupled signaling evoked opposite effects

to those induced by anandamide since the stimulation of TRPV1 by capsaicin inhibited both basal and AA-induced lipid synthesis in an extracellular calcium-dependent manner [149]. Moreover, in parallel to the inhibition of sebum production, capsaicin treatment down-regulated the expressions of PPAR and related RXR isoforms in SZ95 sebocytes [149]. These results collectively argue for that TRPV1 signaling (in contrast to the action of the sebaceous ECS) inhibits terminal differentiation of sebocytes.

Intriguingly, preliminary findings suggest the possible involvement of other TRP channels in sebaceous gland biology. Besides TRPV1, the presence of TRPV2, TRPV3, and TRPV4 was also identified on SZ95 sebocytes [89, 90]. Moreover, certain plant derived and synthetic
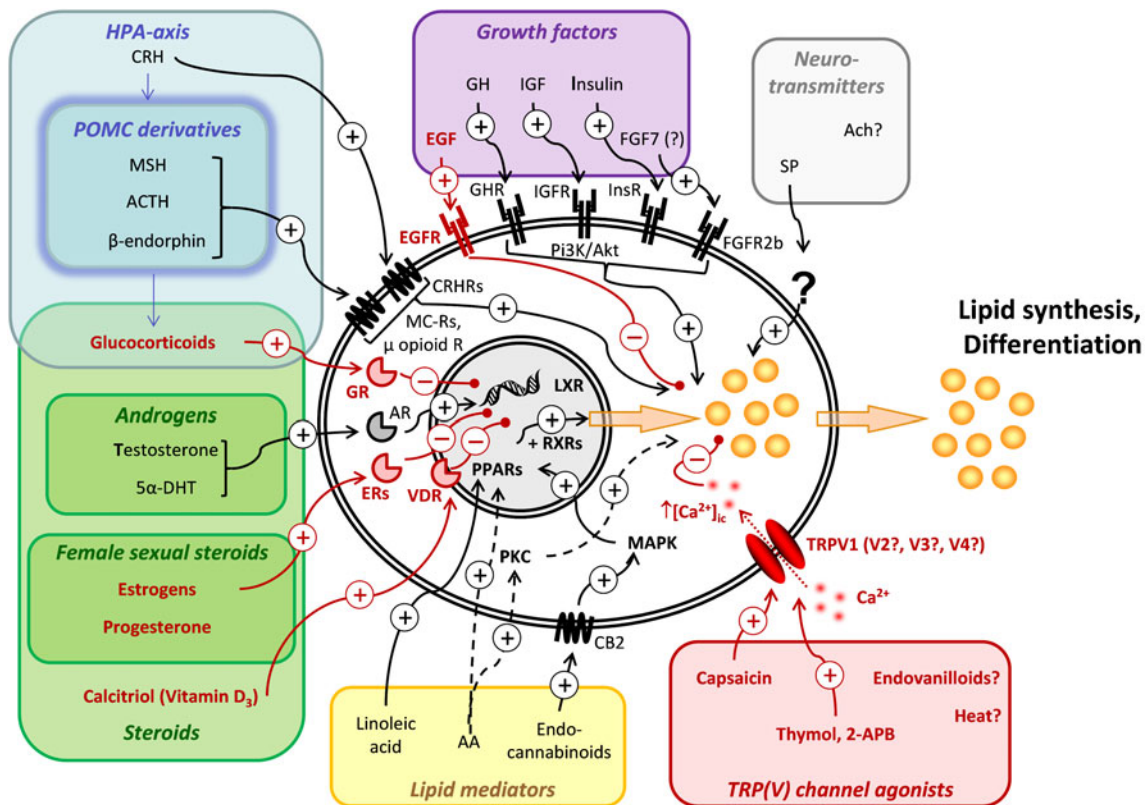

Fig. 1 Control of sebocyte differentiation. Sebaceous lipid synthesis can be stimulated (*black letters and arrows*) and inhibited (*red letters and arrows*) by various mediators/agents and related signaling pathways. These agents activate several surface membrane receptors involving both G-protein-coupled ones and receptor tyrosine kinases, as well as certain nuclear receptors. In the differentiation processes, expression and/or activation of certain "lipid genes" (e.g., PPAR transcription factors) play pivotal roles. These genes can either be activated directly (e.g., by certain lipid mediators) or indirectly via intracellular signaling pathways (e.g., MAPK system). Intriguingly, elevation of intracellular calcium concentration in sebocytes by the stimulation of TRPV1 (and most probably other TRPV channels) appears to inhibit the lipogenic actions of the above mediators. These novel mechanisms may be exploited in the clinical management of sebaceous gland diseases with altered sebum production (e.g., acne vulgaris and dry skin conditions). *Abbreviations*: *HPA* hypothalamic–

pituitary–adrenal cortex, *CRH* corticotropin-releasing hormone, *POMC* proopiomelanocortin, *MSH* melanocyte stimulating hormone, melanocortin, *ACTH* adrenocorticotropic hormone, corticotropin, *5α-DHT* 5α-dihydrotestosterone, *EGF* epidermal growth factor, *EGFR* EGF receptor, *GH* growth hormone, *GHR* GH receptor, *IGF* insulin-like growth factor, *IGFR* IGF receptor, *InsR* insulin receptor, *FGF7* fibroblast growth factor-7, *FGFR2b* FGF receptor-2b, *SP* substance P, *Ach* acetylcholine, *Pi3K* phosphoinositol-3-kinase, *CRHRs* CRH receptors, *MC-Rs* melanocortin receptors, *GR* glucocorticoid receptor, *AR* androgen receptor, *ERs* estrogen receptors, *VDR* vitamin D receptor, *PPARs* peroxisome proliferator-activated receptors, *LXR* liver-X receptor, *RXRs* retinoid-X receptors, *PKC* protein kinase C, *MAPK* mitogen-activated protein kinase, $[Ca^{2+}]_{ic}$ intracellular Ca^{2+} concentration, *TRPV1* transient receptor potential vanilloid 1, *CB2* cannabinoid receptor subtype 2, *AA* arachidonic acid, *2-APB* 2-aminoethoxydiphenyl borate

activators of these channels (e.g., thymol, eugenol, 2-aminoethoxydiphenyl borate) were able to induce transient elevation of the intracellular calcium concentration ($[Ca^{2+}]_{ic}$) and suppressed sebum production induced by AA treatment (similar to the action of TRPV1 stimulation). At present, it is unclear how specific these effects are as dramatic increases in calcium concentration will likely affect proliferation and differentiation of sebocytes, similar to other human skin cells [79, 157]. Indeed, previous reports suggest that the differentiation of sebocytes could be stimulated by the decrease of the extracellular Ca^{2+} concentration [114]. Taken together, it can be postulated that the elevation of $[Ca^{2+}]_{ic}$ by TRPV activation may inhibit differentiation and the closely related lipid production in human sebaceous gland cells (Fig. 1).

Concluding remarks—"Bite the dog that bit you": lipids that target sebaceous diseases

The above, most recently discovered regulatory mechanisms introduce novel therapeutic strategies to manage certain sebaceous gland disorders. A group of these disorders can be characterized by hyperactivity of the sebaceous glands, and associated with overproduction of sebum and inflammatory processes. In other diseases, conversely, the hypofunction of the gland may lead to the development of such conditions as dry skin and associated syndromes. In some rare cases, the hyperproliferation of sebaceous gland may result in sebaceous tumor formation.

Among these disorders, doubtless, acne vulgaris has the highest prevalence. Classical strategies in treatment of acne involves antibiotic treatment, oral contraceptives, and isotretinoin (13(cis)-retinoic acid). Targeting the presented novel regulatory mechanisms may broaden the therapeutic arsenal with anti-androgens, 5-α-reductase inhibitors, LOX, and/or COX inhibitors, and insulin-sensitizing agents acting on PPARs [59].

In addition, recent findings focus the attention on the influence of novel lipid-signaling mechanisms. Among these, the targeted manipulation of the sebaceous ECS may be an effective strategy. For example, in acne and other inflammatory sebaceous gland diseases characterized by sebaceous hyperfunction, the inhibition of CB2-mediated signaling may be of therapeutic value. Alternatively, inhibition of endocannabinoid synthesizing or stimulation of degrading enzymes (thereby "suppressing the sebaceous endocannabinoid tone") may also be beneficial. Conversely, in diseases associated with dry skin conditions or sebaceous hyperproliferation, the activation of endocannabinoid signaling or "augmenting the ECS tone" may be preferable [7]. Furthermore, activators of certain TRPV channels may also have the desired sebostatic

effect in acne [8]. Since transdermal penetration of most of these molecules is well established, it can be envisaged these agents could be efficiently applied topically to the skin in the form of a cream.

Taken together, future clinical studies are now warranted to explore the real therapeutic potential of these intriguing (mostly pre-clinical) data.

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