The Role of the Sebaceous Gland

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Contents

Core Messages

- The sebaceous gland cell is a key player in the pathogenesis of acne.
- Increased sebum excretion and alteration of lipid composition contribute to acne.
- Sex steroids and growth factors play a profound role in the regulation of sebum production.
- Emotional stress induces central and local expression of CRH and other neuropeptides, which trigger inflammation.
- The sebaceous gland cell possesses the enzyme machinery of the PG and LT pathway.
- *P. acnes* may produce proteins, which become active via binding and activation of TLR. The latter stimulate the synthesis of antimicrobial peptides and lipids.

10.1 Introduction

The pathogenesis of acne, the most common skin disorder, which manifests in the pilosebaceous follicle, is attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, inflammatory processes, dysregulation of the hormone microenvironment, interaction with neuropeptides, follicular hyperkeratinisation and the proliferation of *P. acnes*

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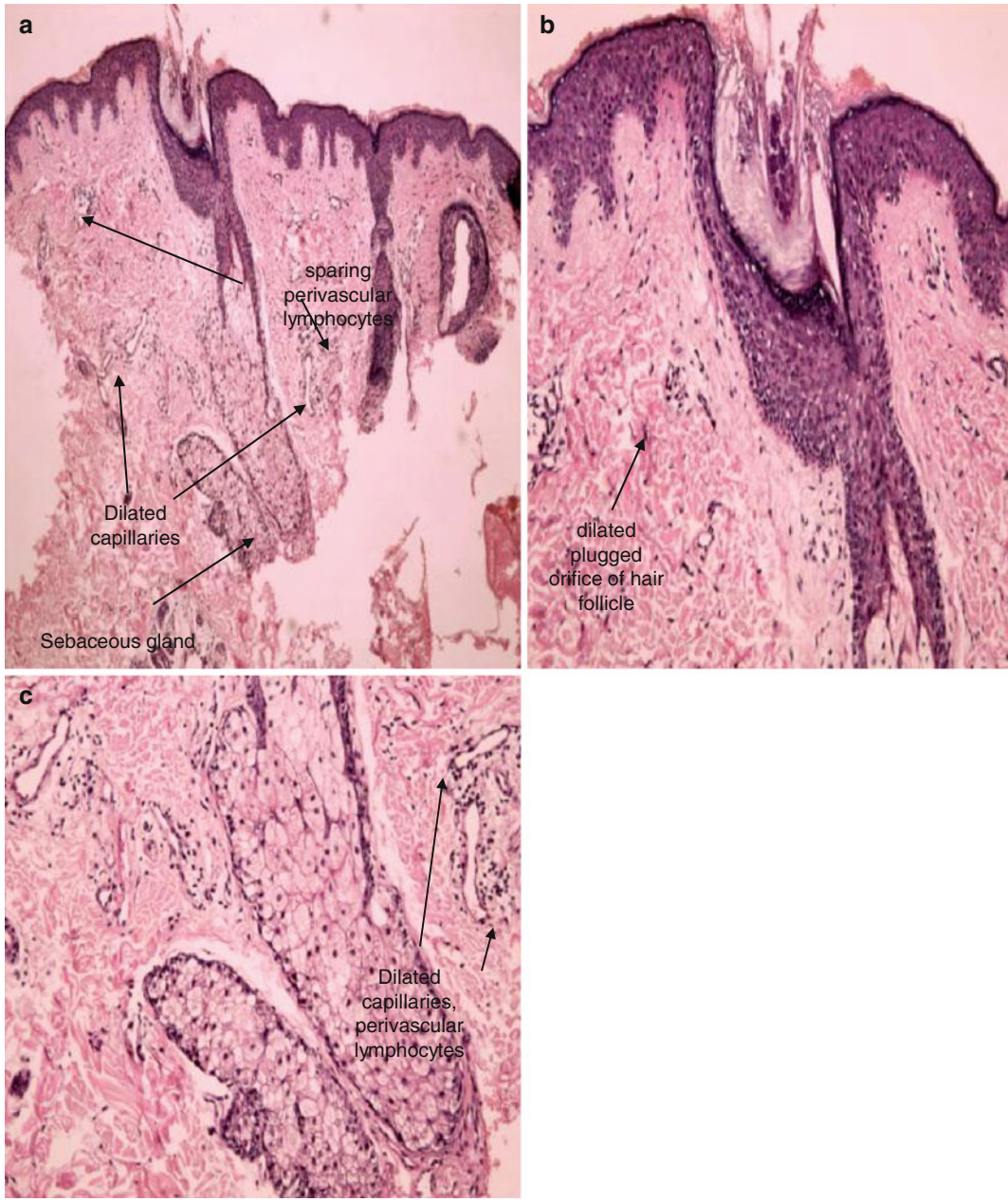

Fig. 10.1 Pilosebaceous unit in the face skin of acne patients. Faintly hypertrophic sebaceous gland. Dilated capillaries and perivascular lymphocytes (**a**, **c**) are early sings of the inflammatory process in acne-involved skin. The dilated plugged orifice of hair follicle is a sign of acne comedone (**b**) (the photos were kindly contributed by Dr. Ruta Ganceviciene)

within the follicle (Fig. 10.1). In particular, the sebaceous gland plays an exquisite role in the initiation of the disease [1].

Sebaceous glands or *holocrine glands* are found over the entire surface of the body except the palms and the soles. They are largest and most concentrated in the face and scalp where they are the sites of origin of acne. The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils including triglycerides

and fatty acid breakdown products, wax esters, squalene, cholesterol esters and cholesterol [2–5]. Sebum lubricates the skin to protect against friction and makes it more impervious to moisture. Furthermore, the sebaceous gland transports antioxidants in and on the skin and exhibits a natural light protective activity. It possesses an innate antibacterial activity and has a pro- and anti-inflammatory function. It can regulate the activity of xenobiotics and is actively involved in the wound healing process [6].

In the last years, acne research has made a remarkable progress in understanding the mechanisms involved in the pathogenesis of the disease by using cell culture models and new molecular techniques. Mammal sebocytes and sebocyte-like cells (human, mouse, hamster and rat) and human sebaceous gland cell lines (SZ95, SEB-1, Seb-E6E7) [7–9] have been used in monolayer cultures as models to study specific functions involved in development, growth and differentiation of sebaceous gland cells. More complex culture systems, including three-dimensional models, are under development.

10.2 Sebum and Acne

Increased sebum excretion, alteration of lipid composition and the oxidant/antioxidant ratio characteristic of the skin surface lipids are major concurrent events associated with the development of acne [6]. If sebum interferes with the process of follicular keratinisation in the pilosebaceous unit, pore blockage may occur, contributing to lesion formation and acne. However, seborrhoea per se is not considered to be the only responsible factor for the development of acne, as demonstrated by the success of treatment with agents with no effect on sebum secretion rate that can inhibit the inflammatory process, such as antibiotics, topical retinoids, azelaic acid and benzoyl peroxide [10]. The composition of the produced lipids is also of great importance. Lower essential fatty acid levels were found in wax esters in twins with acne rather than in twins with no acne [11]. Moreover, low levels of linoleic acid have been observed in skin surface lipids of acne patients [12]. Evidence suggests that diet may be an important source of substrate for the synthesis of sebaceous lipids [13]. This notion is supported also by the observation that sebum contains linoleic acid, an essential fatty acid that cannot be synthesised in vivo and therefore must be obtained from the diet. It has recently been hypothesised that low glycaemic load diets may influence sebum production based on the beneficial endocrine effects of these diets [14].

On the other hand, extreme caloric restriction dramatically decreases the sebum excretion rate and these changes can be reversed when a normal diet is resumed [15, 16]. Other studies have demonstrated that increased consumption of dietary fat or carbohydrate increases sebum production and modifications to the type of carbohydrate can also alter sebum composition [17]. Typical Western diet, comprised of milk and hyperglycaemic foods, may have potentiating effects on serum insulin and insulin-like growth factor-I (IGF-I) levels, thereby promoting the development of acne [18].

Another hallmark of sebum in acne patients is the presence of lipoperoxides, mainly due to the peroxidation of squalene and a decrease in the level of vitamin E, the major sebum antioxidant [19]. Both lipoperoxides and monounsaturated fatty acid (MUFAs) are capable of inducing alteration in keratinocyte proliferation and differentiation, whereas peroxides are capable of inducing production of pro-inflammatory cytokines and activation of peroxisome proliferator-activated receptors (PPARs) [14, 19].

The biological function of sebocytes is further regulated by several factors including ligands of receptors expressed in sebocytes, such as androgens and oestrogens, PPAR ligands and neuropeptides, liver-X receptor (LXR) ligands, histamines, retinoids and vitamin D. The ligand–receptor complexes activate pathways involving cell proliferation, differentiation, lipogenesis, hormone metabolism and cytokine and chemokine release [20] (Fig. 10.2).

LXRs which are members of the nuclear receptor superfamily and play a critical role in cholesterol homeostasis and lipid metabolism

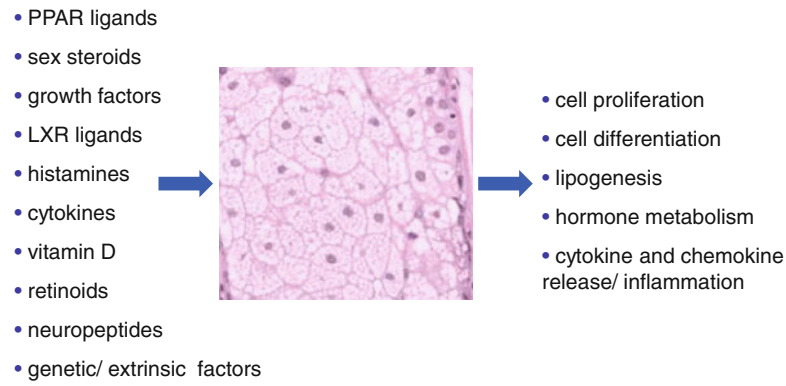

Fig. 10.2 Regulation of the biological function of human sebaceous gland cells. Schematic overview (*PPARs* peroxisome proliferator-activated receptors, *LXR* liver X receptors)

have been documented to regulate lipid synthesis in the immortalised human sebaceous gland cell line SZ95. Treatment of SZ95 sebocytes with LXR ligands such as TO901317 or 22(R)-hydroxycholesterol enhanced accumulation of lipid droplets in the cells which could be explained through induction of the expression of the LXRalpha receptor and known LXR targets, such as fatty acid synthase and sterol regulatory binding protein-1 [21, 22].

On the other hand, sebaceous function can be also significantly modified by histamines and, conversely, antihistamines. Diphenhydramine (DPH), an H-1 receptor antagonist, significantly decreases squalene levels in human sebaceous gland cells as determined by means of high-performance liquid chromatography. These data were further verified by the identification of histamine receptors histamine-1 receptor (H-1 receptor) in human sebaceous glands [23].

Retinoids are also suggested to influence the biological function of sebocytes. Retinoic acid receptors (RAR; isotypes α and γ) and retinoid X receptors (RXR; isotypes α, β, γ) are expressed in human sebocytes [24]. The natural ligands for RAR and RXR are atRA and 9-*cis* retinoic acid. In SZ95 sebocytes 13-*cis* retinoic acid may unfold its action through a marked isomerisation to all-*trans* retinoic acid. All three compounds all-*trans* retinoic acid, 13-*cis* retinoic acid and 9-*cis* retinoic acid exhibit anti-proliferative effects [25] and inhibit sebocyte differentiation and lipid synthesis [26]. RXR agonists stimulate sebocyte differentiation and proliferation. The RXR agonist rexinoid in combination with the specific PPAR agonists, WY 14643, troglitazone and cabaprostacyclin, affects differentiation and growth in cultured primary sebocyte-like rat preputial cells [27].

The enzymatic machinery for the local synthesis and metabolism of 1, 25-dihydroxyvitamin D (3) [1,25(OH)(2)D(3), calcitriol] has been also investigated in human sebocytes. Vitamin D receptor (VDR), vitamin D-25-hydroxylase (25 OHase), 25-hydroxyvitamin D-1alpha-hydroxylase (1 alphaOHase) and 1, 25-dihydroxyvitamin D-24-hydroxylase (24 OHase) are expressed in SZ95 sebocytes in vitro. Furthermore, incubation of SZ95 sebocytes with 1,25(OH)(2)D(3) leads to a dose-dependent modulation of cell proliferation, cell cycle regulation, lipid content and interleukin-6/interleukin-8 secretion in vitro [28]. In hamster auricular sebocytes while EGF and atRA can decrease the intracellular accumulation of triglycerides and free fatty acids in the cells, 1alpha, 25-dihydroxyvitamin D3 decreases the triglyceride level but augments the accumulation of wax esters. No difference has been detected in the level of cholesterol after the above treatments [29].

10.3 Effects of Hormones on Sebocytes

10.3.1 Sex Steroids

Several studies have demonstrated that there is an association between local overproduction of

active androgens and acne. Acne patients produced higher rates of testosterone and 5α-DHT in their skin than healthy individuals [30]. High testosterone levels have been implicated with enhanced sebaceous gland activity in humans [31, 32] and consequently with diseases marked by hyperseborrhea, such as acne vulgaris. However, only a few patients with androgenic disorders exhibit hyperandrogenemia, an observation which indicates the predominance of peripheral tissue events for the occurrence of clinical signs [33].

Enhanced sebaceous gland activity is attributed to the potent androgen 5α-dihydrotestosterone (5α-DHT) [6] as sebaceous gland cells possess all necessary enzymes for conversion of testosterone to 5α-DHT [34]. The isozyme 5α-reductase type I, which catalyses the conversion from testosterone to 5α-DHT in peripheral tissues by a NADPH-dependent reaction, is expressed predominantly in skin. It is present in the cytoplasm and cell membrane compartment in skin cells [35] and particularly in facial sebocytes [34], illustrating the key role of sebaceous gland cells in androgen metabolism.

The effects of testosterone and 5α-DHT are mediated by binding to the nuclear androgen receptor (AR), also expressed in human sebaceous gland cells [36]. AR is a member of the steroid superfamily of ligand-dependent transcription factors. 5α-DHT binds to the AR with greater affinity than testosterone and the 5α-DHT/androgen receptor complex appears to be more stable [37] and, therefore, more effective.

In contrast to the in vivo observations, in vitro experiments with human sebocytes have shown that testosterone affects proliferation in a dose-dependent manner [9, 38] but not lipid synthesis [39, 40]. This contradiction has led to the assumption that cofactors may be required for the induction of the entire so-called androgenic influence of the sebaceous gland [41]. Current research has indicated that PPARs and their ligands may be the primary candidates [39, 40]. PPARs regulate multiple lipid metabolism genes in mitochondria, peroxisomes and microsomes, all prominent in sebocyte cytoplasm [39, 40].

Indeed, we have previously demonstrated the interaction of testosterone with PPAR ligands in inducing differentiation of human sebaceous gland cells and lipid synthesis [42]. PPARα is the most important PPAR that regulates lipid synthesis and inflammation [41, 43]. In addition, PPAR-α, -δ, -γ1 and -γ2 have been shown to be expressed at mRNA and protein levels in SZ95 sebocytes [39].

Dehydroepiandrosterone (DHEA) has been also shown to regulate sebum production especially in postmenopausal women [44]. Consequently, several researchers have suggested the use of DHEA as an anti-ageing agent [45, 46]. However, in in vitro experiments DHEA has been shown to have no direct effect on the biological activity of human sebocytes. Substitution with DHEA in elderly persons is accompanied by a small increase of testosterone and oestradiol, which may indeed yield an explanation of the clinical change demonstrated [44], suggesting that the action of DHEA may be implemented through indirect pathways.

10.3.2 Growth Factors

Growth hormone (GH) activity is considered to be mainly attributed to IGFs, but GH has also been shown to exhibit direct effects on human skin cells [47]. The increased serum GH levels in acromegaly are associated with enhanced sebum secretion [48], an observation that could be confirmed by GH treatment of human SZ95 sebocytes in vitro [49]. In acne vulgaris, increased sebum production peaks in mid-adolescence at a time that GH and IGF-I reach their highest serum levels [50]. In mini rats, suppression of GH gene expression by an antisense transgene leads to thinner skin with less collagen and increase of subcutaneous adipose tissue and also to small-sized sebaceous glands [51].

Increased serum levels of IGF-I have been observed in adult women and men with acne and the number of total acne lesions, inflammatory lesions, serum levels of dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate (DHEAS), each correlated with serum IGF-I levels in women with acne [52, 53]. A correlation between the mean facial sebum excretion rate

and serum IGF-I levels has been demonstrated in postadolescent acne patients [54]. IGF-I has been localised to the peripheral cells of sebaceous glands in the rat [55], while in human skin the strongest expression of IGF-I protein has been found in maturing sebocytes and suprabasal cells of sebaceous ducts [56]. The expression of IGF-I receptor mRNA is the strongest in basal cells of sebaceous glands and immature sebocytes, whereas IGF-I receptor protein expression was uniform and intense in all regions of the gland [56]. In animal studies, IGF-I has been shown to stimulate sebocyte differentiation in vitro especially in combination with GH [50], while in human keratinocytes it acts as a mitogen [57]. On the other hand, in humans, IGF-I plays a key role in the induction of lipid synthesis in human sebocytes [49, 58]. In SEB-1 sebocytes, IGF-I increases lipogenesis by the induction of *sterol response element-binding protein-1* (SREBP-1) [58] through activation of PI3K/Akt and MAPK/ERK signal transduction pathway [59]. SREBP-1 preferentially regulates genes of fatty acid synthesis [59]. In the hamster ear sebaceous model, androgens rapidly induce the expression of SREBP-1 [60]. In addition, an interaction between the IGF-I and oestradiol signalling pathway has been described in human SZ95 sebocytes, implicating that oestrogens may have an indirect effect on the pathogenesis of acne [49].

Recent data suggest that incubation of human sebaceous gland cells with a hormone mixture consisting of growth factors and sex steroids at age-specific levels may alter the biological activity of the cells by regulating their transcriptome and thus illustrate the importance of the hormone environment for cell function [61]. Human SZ95 sebocytes treated with hormone levels that can be found in 60-year-old women produce less lipids than sebocytes treated with a hormone mixture representing that found in serum of 20-year-old women [61]. Gene expression profiling via cDNA microarray between SZ95 sebocytes under the 20- and 60-year-old hormone mixture detected differentially expressed genes, which are involved in biological processes such as DNA repair and stability, mitochondrial function, oxidative stress, cell cycle and apoptosis, ubiquitin-induced proteolysis and transcriptional regulation. The most significantly altered signalling pathway was that of transforming growth factor-β (TGF-β). A disturbed function of this cascade has been also associated with tumourigenesis, i.e. in pancreatic, prostate, intestine, breast and uterine cancer. Interestingly, genes expressed in signalling pathways operative in age-associated diseases such as Huntington's disease, dentatorubral-pallidoluysian atrophy and amyotrophic lateral sclerosis were also identified. These data demonstrate that hormones interact in a complex fashion, and sebocytes may be affected to a large extent by the changes in their circulating blood levels with age [61].

10.4 Effects of Neuropeptides on Sebocytes

Neuropeptides are a heterogeneous group of biologically active peptides that are present in neurons of both the central and peripheral nervous system. However, human skin and in particular the human sebaceous gland have been shown to express functional receptors for neuropeptides, such as corticotropin-releasing hormone (CRH), melanocortins, β-endorphin, vasoactive intestinal polypeptide, neuropeptide (NP) Y and calcitonin gene-related peptide. These receptors modulate the production of inflammatory cytokines, proliferation, differentiation, lipogenesis and androgen metabolism in human sebocytes [6].

CRH, the most proximal element of the HPA axis, acts as central coordinator for neuroendocrine and behavioural responses to stress. It has been shown that CRH, CRH-BP, CRH-R1 and CRH-R2 are expressed in SZ95 sebocytes at mRNA and protein level, while CRH-R1 is the predominant type (CRH-R1/CRH-R2=2). In addition, CRH significantly induces sebaceous lipids production, IL6- and −8 synthesis and may up-regulate mRNA levels of 3β-hydroxysteroid dehydrogenase/Δ^{5-4} isomerase [62, 63]. In acne-involved skin the complete CRH system is abundant especially in the sebaceous glands, possibly activating pathways which affect immune and inflammatory processes leading to the development and stress-induced exacerbation of acne [64].

Melanocortin (MC) peptides can also directly affect the function of human sebocytes via MC receptors. α-Melanocyte-stimulating hormone (α–MSH) has been demonstrated to act as a modulator of the rat preputial gland, a specialised SG-like structure of rodents [65]. The presence of both MC-1R and MC-5R which bind α–MSH was detected in primary cell cultures of facial human sebocytes. The expression of MC-5R is weaker than that of MC-1R, but it has been shown to be a marker of human sebocyte differentiation, since it is expressed in differentiated, lipid-containing sebocytes only [66, 67]. In acne-involved skin sebocytes and keratinocytes of the ductus seboglandularis showed very intense MC-1R expression in contrast to less intense scattered immunoreactivity in normal skin samples, suggesting that this receptor is involved in the initiation of acne [68]. MC-1R expression has been shown to be up-regulated by pro-inflammatory signals [69, 70]. As pro-inflammatory cytokines are up-regulated in acne lesions [71], sebocytes may respond to these signals with increased MC-1R expression, thereby generating a negative feedback mechanism for α-MSH which exerts direct anti-inflammatory actions, i.e. inhibition of IL-1-mediated IL-8 secretion [66, 68].

Cannabinoid receptors which mediate the psychopharmacological action of marijuana have been not only localised in the central and peripheral nervous system but also in human skin. Cannabinoid receptors (CR) 1 and 2 are expressed in human sebaceous glands [72], whereas the CB2 and other prototypic endocannabinoids are present in SZ95 sebocytes and may induce in a dose-dependent manner lipid production and cell death. These actions are selectively mediated by CB2-coupled signalling involving the MAPK pathway [73].

Other neuropeptides such as substance P or vasointestinal peptide may also be involved in the pathogenesis of acne vulgaris. Substance P, which can be elicited by stress, may promote the development of cytoplasmic organelles in sebaceous cells, stimulate sebaceous germinative cells and induce significant increases in the area of sebaceous glands. It also increases the size of individual sebaceous cells and the number of sebum vacuoles for each differentiated sebaceous cell, all of which suggest that substance P promotes both the proliferation and the differentiation of sebaceous glands. Substance P induces the expression of neutral endopeptidase, a potent neuropeptide-degrading enzyme, in sebaceous germinative cells and of E-selectin by perisebaceous venules. Facial skin from acne patients is characterised by rich innervation, by increased numbers of substance P-containing nerves and mast cells and by strong expression of neutral endopeptidase in sebaceous glands and E-selectin in venules around sebaceous glands, compared with normal skin [74]. Recently, ectopeptidases dipeptidyl peptidase IV (DP IV or CD 26) and aminopeptidase N (APN or CD13), which have been shown to be involved in the degradation of several NPs, especially SP, have been found to be highly expressed in human sebocytes in vivo and in vitro. Further studies have shown unexpectedly that inhibitors of DP IV and APN can suppress proliferation and slightly decrease neutral lipids, but can also enhance terminal differentiation in SZ95 sebocytes. This suggests that ectopeptidases may be new targets to modulate certain sebocyte functions and that ectopeptidase inhibitors may have potential therapeutic roles in acne pathogenesis [75].

A central integrator of nociception, the transient receptor potential vanilloid-1 (TRPV1), is expressed in human skin, in sebaceous glands in situ and in SZ95 sebocytes in vitro. It has been documented that the prototypic TRPV1 agonist, capsaicin, selectively inhibits basal and arachidonic acid-induced lipid synthesis in a dose-, time- and extracellular calcium-dependent and a TRPV1-specific manner. Low-dose capsaicin stimulates cellular proliferation via TRPV1, whereas higher concentrations inhibit sebocyte growth and induce cell death independent of TRPV1 [76]. These findings suggest the strong involvement of neurogenic factors and sebocytes in the disease process of acne.

10.5 Inflammation, Sebocytes and Acne

Inflammation is being regarded as a key component of the pathogenesis of acne [77]. In the last few years, there has been a debate as to whether hyperkeratinisation of the follicular duct precedes

the influx of inflammatory cells or vice versa. Recent studies support the latter hypothesis by demonstrating that an increase in IL-1 activity occurs before the hyperproliferation around uninvolved follicles and this triggers the activation of the keratinocytes [71, 78]. Expression profiling of acne-involved and uninvolved skin from acne patients and from subjects without acne via cDNA microarrays has given us a better insight into the etiological factors giving rise to acne [79]. In inflammatory acne lesions, the majority of the regulated genes, which showed to be up-regulated, are involved in inflammatory processes. These include matrix metalloproteinases, β-defensin 4, IL-8 and granulysin. No differences were noted between normal skin from acne patients and that from patients without acne in the array analysis. NF-κB, a transcription factor critical for up-regulation of many proinflammatory cytokine genes, has been shown to be activated in acne lesions [80]. NF-κB-regulated cytokine mRNA gene levels of TNF-α, IL-1β, IL-8 and IL-10 are significantly up-regulated in acne-involved skin compared to uninvolved normal adjacent skin. Elevated expression of the chemokine IL-8 is able to attract circulating cells into the tissue. Indeed, in lesional skin of acne, there is a marked increase in the presence of polymorphonuclear leucocytes (PMNs), as compared to the uninvolved skin whereas lymphocytes are prominently visible in inflammatory acne lesions as compared to normal controls [80]. Another transcription factor involved in inflammation, AP-1, has been shown to be activated in inflammatory acne lesions in vivo as well. Levels of the pro-inflammatory cytokine interleukin-1 were also up-regulated perifollicularly in uninvolved skin from acne patients. This cytokine may be responsible for the cutaneous inflammation and the resulting keratinocyte proliferation and may play a profound role in the transformation of a normal follicle into an acne lesion [71].

Inflammation is further characterised by action of active lipid mediators, such as leucotrienes (LT), prostaglandins (PG) and 15-hydroxyeicosatetraenoic acids. These molecules are synthesised from arachidonic acid (AA) or linolenic acid by the enzymes lipoxygenase (LOX) and cyclooxygenase (COX), respectively. Both COX isozymes, COX-1 and COX-2, are expressed in human sebocytes in vitro, in particular COX-2 expression is selectively up-regulated in acne-involved sebaceous glands in vivo [43]. In hamster sebocytes the expression of COX-2 has been also documented [81], while the 15-desoxy-$\Delta 12^{,14}$-PGJ_2 (15d-PGJ_2) has been shown to induce the lipid synthesis in the cells [82]. Activation of the platelet-activating factor signalling pathway (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) which consists of a group of phosphocholines with various biological effects, including modulation of keratinocyte function and skin inflammation, can regulate the expression of inflammatory mediators, e.g. COX-2 and PGE_2, as well as IL-8 in SZ95 sebocytes [83]. Transgenic keratin 5 promoter-driven overexpression of COX-2 in the basal compartment of the epidermis of the mouse and increased PGE_2 levels have been documented to cause sebaceous gland hyperplasia and overshooting sebum production pointing to a role of COX-2-mediated PGE_2 synthesis in this process [84]. Activation of PPARγ by UVB irradiation and the potent lipid-soluble oxidant tert-butylhydroperoxide (TBH) induces COX-2 expression in SZ95 sebocytes and this finding indicates a PPARγ COX-2-mediated pathway regulating sebocyte proliferation and/or lipogenesis [85].

LT are potent pro-inflammatory mediators and neutrophil attractants produced from arachidonic acid by the enzyme 5-lipoxygenase (5-LOX). Human sebocytes express all necessary enzymes for a functional LT pathway. The enzymes 5-LOX and LTA_4 hydrolase are expressed in SZ95 sebocytes at protein and mRNA level. These enzymes are essential for the formation of LTB_4. On the other hand, 15-LOX expression shows a weak expression in SZ95 sebocytes, indicating that sebocytes do not play a significant role in the biosynthesis of the anti-inflammatory 15-HETE. Treatment of SZ95 sebocytes with AA stimulates 5-LOX expression and induces LTB_4 synthesis [43]. In addition, AA induces the expression of the IL6 and IL8 cytokines. 5-LOX and LTA_4 hydrolase show a stronger expression in acne lesions than in normal skin and in uninvolved

skin of acne patients [43]. The involvement of 5-LOX in the pathogenesis of acne has led to new therapeutic strategies to deal with the disease [86].

Cytokines are present in normal sebaceous glands, and they are affected by many factors. IL-1α, tumour necrosis factor (TNF)-α, IL-6 and IL-8 are released into supernatant in unstressed sebocyte culture [43]. In a stressed environment, the amounts of released cytokines increase significantly. AA and calcium ionophore enhance the level of IL-6 and IL-8, but that of IL-1β and TNF-α is not affected [10, 43].

Psoriasin, a member of the S100 gene family, was shown to be highly expressed in the epidermis and the ductus seboglandularis of acne-involved skin in contrast to uninvolved control [87]. Psoriasin has been suggested to be involved in the pathogenesis of several inflammatory skin diseases, and its levels increase in response to inflammatory stress. Retinoic acid (RA) and inflammatory agents have been also implicated in the up-regulation of psoriasin [88, 89].

10.6 *Propionibacterium acnes* Effects on Sebocytes

Propionibacterium acnes (*P. acnes*) is a gram-positive anaerobic bacterium which among with other non-pathogenic microorganisms such as coagulase negative staphylococci and diphtheroid rods resides in pilosebaceous follicles as a member of the resident bacterial flora. The mechanism by which *P. acnes* contributes to the pathogenesis of acne is debated. While in several studies it could be shown that *P. acnes* numbers are higher in acne patients than in healthy individuals, other studies found no difference between the numbers of *P. acnes* in affected and non-affected follicles. Nevertheless, an abnormal colonisation by *P. acnes* has been implicated in the occurrence of acne via the induction of inflammatory mediators. The bacteria stimulate the production of pro-inflammatory cytokines, including interleukin-1β, -8 and −12 and tumour necrosis factor-α. It is known that *P. acnes-induced* cytokine production is mediated by Toll-like receptor 2 [90–93]. The pilosebaceous unit is an immunocompetent organ. Keratinocytes and sebocytes may act as immune cells capable of pathogen recognition and abnormal lipid presentation. Both cell types can be activated by *P. acnes* via Toll-like receptors (TLR) and CD14 and CD1 molecules [90]. The expression of TLR2, TLR4, TLR6 and CD14 has been already documented in SZ95 sebocytes [94, 95]. Recent evidence has indicated that human sebaceous glands may contribute to the skin immune defence by releasing antimicrobial peptides (AMPs). For example, human β-defensins (hBDs) are expressed in human pilosebaceous units and their expression is up-regulated in acne lesions [96]. Cathelicidin and hBD-2 are detected in cultured human sebocytes, the predominant cells residing in the sebaceous gland, and their expression levels are up-regulated in the presence of *P. acnes* [93, 97]. Each *P. acnes* strain has been shown to influence sebocyte viability and differentiation differentially which raises the possibility that certain *P. acnes* strains may be responsible for opportunistic infections worsening acne lesions [93, 97, 98]. A description of phylogenetically distinct *P. acnes* clusters has been already undertaken [99].

The MUFA, mainly palmitic acid (C16:1) and oleic acid (C18:1), both of which are bactericidal against gram-positive organisms [94], are produced by the sebaceous gland, as is sapienic acid, an important antimicrobial lipid. Stearoyl coenzyme A desaturase (SCD) 1, an enzyme responsible for the biosynthesis of MUFA, is also expressed by the sebaceous gland [100]. The TLR-2 ligand macrophage-activating lipopeptide-2 stimulates both SCD and fatty acid desaturase-2 mRNA expression in SZ95 sebocytes [94]. Lauric acid (LA) (C12:0), one of the sebum free fatty acids (FFAs), has strong antimicrobial activity in vitro against skin bacteria, including *P. acnes*. Topical application or intradermal injection of LA in vivo shows remarkable therapeutic effectiveness against *P. acnes*-induced inflammation and significant reduction in the number of bacteria [101]. Furthermore, LA, palmitic acid (PA; 16:0) and oleic acid (OA; C18:1, *cis*-9), which are the typical FFAs found in human sebum, enhanced the hBD-2 expression and

antimicrobial activity of human sebocytes against *P. acnes* [102], indicating that sebum FFAs are involved in the disinfecting activity of the human skin both through their direct antimicrobial characteristics and by inducing AMP in human sebocytes to enhance their innate immune defence ability.

The treatment of cultured sebocytes with *P. acnes* and lipopolysaccharides (LPS) significantly up-regulates the expression of proinflammatory cytokines [93]. There is a difference in the cytokine production curve over time after treatment between *P. acnes* and LPS. While LPS stimulates CXCL8, TNF-α and IL-1α, *P. acnes* stimulates CXCL8 and TNF-α only. *P. acnes* has no effect on IL-1α. Furthermore, viable *P. acnes* and not heat-killed organisms can stimulate the release of cytokines such as IL-1b, GM-CSF and IL-8 [103, 104].

Conclusions

Together, all these current research results have allowed us to elucidate a part of the mechanisms involved in the pathogenesis of one of the most common skin disorders, acne, and critically revisit conventional concepts of its pathogenesis. In addition, it has helped us to the determination of new targets for future drug development. The sebaceous gland cell is a key player in the initiation of the disease, and sebocyte culture models have become so far very useful tools to provide new chances for further research.

References

1. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinol. 2011;3(1):41–9.
2. Downing DT, Stewart ME, Wertz PW, Colton SW, Abraham W, Strauss JS. Skin lipids: an update. J Invest Dermatol. 1987;88(3 Suppl):2s–6.
3. Nikkari T, Schreibman PH, Ahrens Jr EH. In vivo studies of sterol and squalene secretion by human skin. J Lipid Res. 1974;15(6):563–73.
4. Ramasastry P, Downing DT, Pochi PE, Strauss JS. Chemical composition of human skin surface lipids from birth to puberty. J Invest Dermatol. 1970;54(2):139–44.
5. Thody AJ, Shuster S. Control and function of sebaceous glands. Physiol Rev. 1989;69(2):383–416.
6. Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol. 2004;22(5):360–6.
7. Lo Celso C, Berta MA, Braun KM, Frye M, Lyle S, Zouboulis CC, Watt FM. Characterization of bipotential epidermal progenitors derived from human sebaceous gland: contrasting roles of c-Myc and beta-catenin. Stem Cells. 2008;26(5):1241–52.
8. Thiboutot D, Jabara S, McAllister JM, Sivarajah A, Gilliland K, Cong Z, Clawson G. 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(6):905–14.
9. Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterization of an immortalized human sebaceous gland cell line (SZ95). J Invest Dermatol. 1999;113(6):1011–20.
10. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, Chen W, Nagy I, Picardo M, Suh DH, Ganceviciene R, Schagen S, Tsatsou F, Zouboulis CC. New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol. 2009;18(10):821–32.
11. Stewart ME. Sebaceous gland lipids. Semin Dermatol. 1992;11(2):100–5.
12. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. J Am Acad Dermatol. 1986;14(2 Pt 1):221–5.
13. Rasmussen JE. Diet and acne. Int J Dermatol. 1977;16(6):488–92.
14. Smith RN, Braue A, Varigos GA, Mann NJ. The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides. J Dermatol Sci. 2008;50(1):41–52.
15. Downing DT, Strauss JS, Pochi PE. Changes in skin surface lipid composition induced by severe caloric restriction in man. Am J Clin Nutr. 1972;25(4):365–7.
16. Pochi PE, Downing DT, Strauss JS. Sebaceous gland response in man to prolonged total caloric deprivation. J Invest Dermatol. 1970;55(5):303–9.
17. Macdonald I. Changes in the fatty acid composition of sebum associated with high carbohydrate diets. Nature. 1964;203:1067–8.
18. Melnik BC, Schmitz G. Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris. Exp Dermatol. 2009;18(10):833–41.
19. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. J Invest Dermatol. 2006;126(11):2430–7.
20. Zouboulis CC, Schagen S, Alestas T. The sebocyte culture: a model to study the pathophysiology of the sebaceous gland in sebostasis, seborrhoea and acne. Arch Dermatol Res. 2008;300(8):397–413.
21. Hong I, Lee MH, Na TY, Zouboulis CC, Lee MO. LXRalpha enhances lipid synthesis in SZ95 sebocytes. J Invest Dermatol. 2008;128(5):1266–72.

22. Russell LE, Harrison WJ, Bahta AW, Zouboulis CC, Burrin JM, Philpott MP. Characterization of liver X receptor expression and function in human skin and the pilosebaceous unit. Exp Dermatol. 2007;16(10):844–52.
23. Pelle E, McCarthy J, Seltmann H, Huang X, Mammone T, Zouboulis CC, Maes D. Identification of histamine receptors and reduction of squalene levels by an antihistamine in sebocytes. J Invest Dermatol. 2008;128(5):1280–5.
24. Reichrath J, Mittmann M, Kamradt J, Muller SM. Expression of retinoid-X receptors (−alpha,-beta,-gamma) and retinoic acid receptors (−alpha,-beta,-gamma) in normal human skin: an immunohistological evaluation. Histochem J. 1997;29(2):127–33.
25. Tsukada M, Schroder M, Roos TC, Chandraratna RA, Reichert U, Merk HF, Orfanos CE, Zouboulis CC. 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(2):321–7.
26. Zouboulis CC, Korge B, Akamatsu H, Xia LQ, Schiller S, Gollnick H, Orfanos CE. Effects of 13-cis-retinoic acid, all-trans-retinoic acid, and acitretin on the proliferation, lipid synthesis and keratin expression of cultured human sebocytes in vitro. J Invest Dermatol. 1991;96(5):792–7.
27. Kim MJ, Deplewski D, Ciletti N, Michel S, Reichert U, Rosenfield RL. Limited cooperation between peroxisome proliferator-activated receptors and retinoid X receptor agonists in sebocyte growth and development. Mol Genet Metab. 2001;74(3):362–9.
28. Kramer C, Seltmann H, Seifert M, Tilgen W, Zouboulis CC, Reichrath J. Characterization of the vitamin D endocrine system in human sebocytes in vitro. J Steroid Biochem Mol Biol. 2009;113(1–2):9–16.
29. Sato T, Imai N, Akimoto N, Sakiguchi T, Kitamura K, Ito A. Epidermal growth factor and 1alpha,25-dihydroxyvitamin D3 suppress lipogenesis in hamster sebaceous gland cells in vitro. J Invest Dermatol. 2001;117(4):965–70.
30. Sansone G, Reisner RM. Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal human skin–a possible pathogenic factor in acne. J Invest Dermatol. 1971;56(5):366–72.
31. Giltay EJ, Gooren LJ. Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. J Clin Endocrinol Metab. 2000;85(8):2913–21.
32. Pochi PE, Strauss JS. Sebaceous gland response in man to the administration of testosterone, delta-4-androstenedione, and dehydroisoandrosterone. J Invest Dermatol. 1969;52(1):32–6.
33. Orfanos CE, Adler YD, Zouboulis CC. The SAHA syndrome. Horm Res. 2000;54(5–6):251–8.
34. Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. J Invest Dermatol. 2001;116(5):793–800.
35. Chen W, Zouboulis CC, Fritsch M, Kodelja V, Orfanos CE. Heterogeneity and quantitative differences of type 1 5 alpha-reductase expression in cultured skin epithelial cells. Dermatology. 1998;196(1):51–2.
36. Fimmel S, Saborowski A, Orfanos CE, Zouboulis CC. Development of efficient transient transfection systems for introducing antisense oligonucleotides into human epithelial skin cells. Horm Res. 2000;54(5–6):306–11.
37. Anderson KM, Liao S. Selective retention of dihydrotestosterone by prostatic nuclei. Nature. 1968;219(151):277–9.
38. Akamatsu H, Zouboulis CC, Orfanos CE. Control of human sebocyte proliferation in vitro by testosterone and 5-alpha-dihydrotestosterone is dependent on the localization of the sebaceous glands. J Invest Dermatol. 1992;99(4):509–11.
39. Chen W, Yang CC, Sheu HM, Seltmann H, Zouboulis CC. Expression of peroxisome proliferator-activated receptor and CCAAT/enhancer binding protein transcription factors in cultured human sebocytes. J Invest Dermatol. 2003;121(3):441–7.
40. Rosenfield RL, Deplewski D, Kentsis A, Ciletti N. Mechanisms of androgen induction of sebocyte differentiation. Dermatology. 1998;196(1):43–6.
41. Zouboulis CC, Eady A, Philpott M, Goldsmith LA, Orfanos C, Cunliffe WC, Rosenfield R. What is the pathogenesis of acne? Exp Dermatol. 2005;14(2):143–52.
42. Makrantonaki E, Zouboulis CC. Testosterone metabolism to 5alpha-dihydrotestosterone and synthesis of sebaceous lipids is regulated by the peroxisome proliferator-activated receptor ligand linoleic acid in human sebocytes. Br J Dermatol. 2007;156(3):428–32.
43. Alestas T, Ganceviciene R, Fimmel S, Muller-Decker K, Zouboulis CC. Enzymes involved in the biosynthesis of leukotriene B(4) and prostaglandin E(2) are active in sebaceous glands. J Mol Med. 2006;84(1):75–87.
44. Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Faucounau V, Girard L, Hervy MP, Latour F, Leaud MC, Mokrane A, Pitti-Ferrandi H, Trivalle C, de Lacharriere O, Nouveau S, Rakoto-Arison B, Souberbielle JC, Raison J, Le Bouc Y, Raynaud A, Girerd X, Forette F. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. Proc Natl Acad Sci U S A. 2000;97(8):4279–84.
45. Minghetti P, Cilurzo F, Casiraghi A, Montanari L, Santoro A. Development of patches for the controlled release of dehydroepiandrosterone. Drug Dev Ind Pharm. 2001;27(7):711–7.
46. Shin MH, Rhie GE, Park CH, Kim KH, Cho KH, Eun HC, Chung JH. Modulation of collagen metabolism by the topical application of dehydroepiandrosterone to human skin. J Invest Dermatol. 2005;124(2):315–23.
47. Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. Endocr Rev. 2000;21(4):363–92.
48. Burton JL, Libman LJ, Cunliffe WJ, Wilkinson R, Hall R, Shuster S. Sebum excretion in acromegaly. Br Med J. 1972;1(5797):406–8.

49. Makrantonaki E, Vogel K, Fimmel S, Oeff M, Seltmann H, Zouboulis CC. Interplay of IGF-I and 17beta-estradiol at age-specific levels in human sebocytes and fibroblasts in vitro. Exp Gerontol. 2008;43(10):939–46.
50. Deplewski D, Rosenfield RL. Growth hormone and insulin-like growth factors have different effects on sebaceous cell growth and differentiation. Endocrinology. 1999;140(9):4089–94.
51. Ikawa A, Ishii Y, Suzuki K, Yasoshima A, Suzuki N, Nakayama H, Takahashi S, Doi K. Age-related changes in the dorsal skin histology in Mini and Wistar rats. Histol Histopathol. 2002;17(2):419–26.
52. Aizawa H, Niimura M. Elevated serum insulin-like growth factor-1 (IGF-1) levels in women with post-adolescent acne. J Dermatol. 1995;22(4):249–52.
53. Cappel M, Mauger D, Thiboutot D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. Arch Dermatol. 2005;141(3):333–8.
54. Vora S, Ovhal A, Jerajani H, Nair N, Chakrabortty A. Correlation of facial sebum to serum insulin-like growth factor-1 in patients with acne. Br J Dermatol. 2008;159(4):990–1.
55. Hansson HA, Nilsson A, Isgaard J, Billig H, Isaksson O, Skottner A, Andersson IK, Rozell B. Immunohistochemical localization of insulin-like growth factor I in the adult rat. Histochemistry. 1988;89(4):403–10.
56. Rudman SM, Philpott MP, Thomas GA, Kealey T. The role of IGF-I in human skin and its appendages: morphogen as well as mitogen? J Invest Dermatol. 1997;109(6):770–7.
57. Tavakkol A, Varani J, Elder JT, Zouboulis CC. Maintenance of human skin in organ culture: role for insulin-like growth factor-1 receptor and epidermal growth factor receptor. Arch Dermatol Res. 1999;291(12):643–51.
58. Smith TM, Cong Z, Gilliland KL, Clawson GA, Thiboutot DM. Insulin-like growth factor-1 induces lipid production in human SEB-1 sebocytes via sterol response element-binding protein-1. J Invest Dermatol. 2006;126(6):1226–32.
59. Smith TM, Gilliland K, Clawson GA, Thiboutot D. IGF-1 induces SREBP-1 expression and lipogenesis in SEB-1 sebocytes via activation of the phosphoinositide 3-kinase/Akt pathway. J Invest Dermatol. 2008;128(5):1286–93.
60. Rosignoli C, Nicolas JC, Jomard A, Michel S. Involvement of the SREBP pathway in the mode of action of androgens in sebaceous glands in vivo. Exp Dermatol. 2003;12(4):480–9.
61. Makrantonaki E, Adjaye J, Herwig R, Brink TC, Groth D, Hultschig C, Lehrach H, Zouboulis CC. Age-specific hormonal decline is accompanied by transcriptional changes in human sebocytes in vitro. Aging Cell. 2006;5(4):331–44.
62. Krause K, Schnitger A, Fimmel S, Glass E, Zouboulis CC. Corticotropin-releasing hormone skin signaling is receptor-mediated and is predominant in the sebaceous glands. Horm Metab Res. 2007;39(2):166–70.
63. Zouboulis CC, Seltmann H, Hiroi N, Chen W, Young M, Oeff M, Scherbaum WA, Orfanos CE, McCann SM, Bornstein SR. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. Proc Natl Acad Sci U S A. 2002;99(10):7148–53.
64. Ganceviciene R, Graziene V, Fimmel S, Zouboulis CC. Involvement of the corticotropin-releasing hormone system in the pathogenesis of acne vulgaris. Br J Dermatol. 2009;160(2):345–52.
65. Thody AJ, Cooper MF, Bowden PE, Meddis D, Shuster S. Effect of alpha-melanocyte-stimulating hormone and testosterone on cutaneous and modified sebaceous glands in the rat. J Endocrinol. 1976;71(3):279–88.
66. Bohm M, Schiller M, Stander S, Seltmann H, Li Z, Brzoska T, Metze D, Schioth HB, Skottner A, Seiffert K, Zouboulis CC, Luger TA. Evidence for expression of melanocortin-1 receptor in human sebocytes in vitro and in situ. J Invest Dermatol. 2002;118(3):533–9.
67. Zhang L, Li WH, Anthonavage M, Eisinger M. Melanocortin-5 receptor: a marker of human sebocyte differentiation. Peptides. 2006;27(2):413–20.
68. Ganceviciene R, Graziene V, Bohm M, Zouboulis CC. Increased in situ expression of melanocortin-1 receptor in sebaceous glands of lesional skin of patients with acne vulgaris. Exp Dermatol. 2007;16(7):547–52.
69. Bhardwaj R, Becher E, Mahnke K, Hartmeyer M, Schwarz T, Scholzen T, Luger TA. Evidence for the differential expression of the functional alpha-melanocyte-stimulating hormone receptor MC-1 on human monocytes. J Immunol. 1997;158(7):3378–84.
70. Hartmeyer M, Scholzen T, Becher E, Bhardwaj RS, Schwarz T, Luger TA. Human dermal microvascular endothelial cells express the melanocortin receptor type 1 and produce increased levels of IL-8 upon stimulation with alpha-melanocyte-stimulating hormone. J Immunol. 1997;159(4):1930–7.
71. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003;121(1):20–7.
72. Stander S, Schmelz M, Metze D, Luger T, Rukwied R. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. J Dermatol Sci. 2005;38(3):177–88.
73. Dobrosi N, Toth BI, Nagy G, Dozsa A, Geczy T, Nagy L, Zouboulis CC, Paus R, Kovacs L, Biro T. Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. FASEB J. 2008;22(10):3685–95.
74. Toyoda M, Nakamura M, Morohashi M. Neuropeptides and sebaceous glands. Eur J Dermatol. 2002;12(5):422–7.
75. Thielitz A, Reinhold D, Vetter R, Bank U, Helmuth M, Hartig R, Wrenger S, Wiswedel I, Lendeckel U, Kahne T, Neubert K, Faust J, Zouboulis CC, Ansorge S, Gollnick H. Inhibitors of dipeptidyl peptidase

IV and aminopeptidase N target major pathogenetic steps in acne initiation. J Invest Dermatol. 2007;127(5):1042–51.
76. Toth BI, Geczy T, Griger Z, Dozsa A, Seltmann H, Kovacs L, Nagy L, Zouboulis CC, Paus R, Biro T. Transient receptor potential vanilloid-1 signaling as a regulator of human sebocyte biology. J Invest Dermatol. 2009;129(2):329–39.
77. Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? Dermatology. 2001;203(4):277–9.
78. Freedberg IM, Tomic-Canic M, Komine M, Blumenberg M. Keratins and the keratinocyte activation cycle. J Invest Dermatol. 2001;116(5):633–40.
79. Trivedi NR, Gilliland KL, Zhao W, Liu W, Thiboutot DM. Gene array expression profiling in acne lesions reveals marked upregulation of genes involved in inflammation and matrix remodeling. J Invest Dermatol. 2006;126(5):1071–9.
80. Kang S, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. Am J Pathol. 2005;166(6):1691–9.
81. Ito A, Sakiguchi T, Kitamura K, Akamatsu H, Horio T. Establishment of a tissue culture system for hamster sebaceous gland cells. Dermatology. 1998;197(3):238–44.
82. Iwata C, Akimoto N, Sato T, Morokuma Y, Ito A. Augmentation of lipogenesis by 15-deoxy-Delta12,14-prostaglandin J2 in hamster sebaceous glands: identification of cytochrome P-450-mediated 15-deoxy-Delta12,14-prostaglandin J2 production. J Invest Dermatol. 2005;125(5):865–72.
83. Zhang Q, Seltmann H, Zouboulis CC, Travers JB. Activation of platelet-activating factor receptor in SZ95 sebocytes results in inflammatory cytokine and prostaglandin E2 production. Exp Dermatol. 2006;15(10):769–74.
84. Neufang G, Furstenberger G, Heidt M, Marks F, Muller-Decker K. Abnormal differentiation of epidermis in transgenic mice constitutively expressing cyclooxygenase-2 in skin. Proc Natl Acad Sci U S A. 2001;98(13):7629–34.
85. Zhang Q, Seltmann H, Zouboulis CC, Konger RL. Involvement of PPARgamma in oxidative stress-mediated prostaglandin E(2) production in SZ95 human sebaceous gland cells. J Invest Dermatol. 2006;126(1):42–8.
86. Zouboulis CC, Seltmann H, Alestas T. Zileuton prevents the activation of the leukotriene pathway and reduces sebaceous lipogenesis. Exp Dermatol. 2010;19(2):148–50.
87. Ganceviciene R, Fimmel S, Glass E, Zouboulis CC. Psoriasin and follicular hyperkeratinization in acne comedones. Dermatology. 2006;213(3):270–2.
88. Tavakkol A, Zouboulis CC, Duell EA, Voorhees JJ. A retinoic acid-inducible skin-specific gene (RIS-1/psoriasin): molecular cloning and analysis of gene expression in human skin in vivo and cultured skin cells in vitro. Mol Biol Rep. 1994;20(2):75–83.
89. Zouboulis CC, Voorhees JJ, Orfanos CE, Tavakkol A. Topical all-trans retinoic acid (RA) induces an early, coordinated increase in RA-inducible skin-specific gene/psoriasin and cellular RA-binding protein II mRNA levels which precedes skin erythema. Arch Dermatol Res. 1996;288(11):664–9.
90. Kim J. Review of the innate immune response in acne vulgaris: activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses. Dermatology. 2005;211(3):193–8.
91. Kim J, Ochoa MT, Krutzik SR, Takeuchi O, Uematsu S, Legaspi AJ, Brightbill HD, Holland D, Cunliffe WJ, Akira S, Sieling PA, Godowski PJ, Modlin RL. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol. 2002;169(3):1535–41.
92. Koreck A, Pivarcsi A, Dobozy A, Kemeny L. The role of innate immunity in the pathogenesis of acne. Dermatology. 2003;206(2):96–105.
93. Nagy I, Pivarcsi A, Kis K, Koreck A, Bodai L, McDowell A, Seltmann H, Patrick S, Zouboulis CC, Kemeny L. Propionibacterium acnes and lipopolysaccharide induce the expression of antimicrobial peptides and proinflammatory cytokines/chemokines in human sebocytes. Microbes Infect. 2006;8(8):2195–205.
94. Georgel P, Crozat K, Lauth X, Makrantonaki E, Seltmann H, Sovath S, Hoebe K, Du X, Rutschmann S, Jiang Z, Bigby T, Nizet V, Zouboulis CC, Beutler B. A toll-like receptor 2-responsive lipid effector pathway protects mammals against skin infections with gram-positive bacteria. Infect Immun. 2005;73(8):4512–21.
95. Oeff MK, Seltmann H, Hiroi N, Nastos A, Makrantonaki E, Bornstein SR, Zouboulis CC. Differential regulation of Toll-like receptor and CD14 pathways by retinoids and corticosteroids in human sebocytes. Dermatology. 2006;213(3):266.
96. Chronnell CM, Ghali LR, Ali RS, Quinn AG, Holland DB, Bull JJ, Cunliffe WJ, McKay IA, Philpott MP, Muller-Rover S. Human beta defensin-1 and −2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. J Invest Dermatol. 2001;117(5):1120–5.
97. Lee DY, Yamasaki K, Rudsil J, Zouboulis CC, Park GT, Yang JM, Gallo RL. Sebocytes express functional cathelicidin antimicrobial peptides and can act to kill propionibacterium acnes. J Invest Dermatol. 2008;128(7):1863–6.
98. Graham GM, Farrar MD, Cruse-Sawyer JE, Holland KT, Ingham E. Proinflammatory cytokine production by human keratinocytes stimulated with Propionibacterium acnes and P. acnes GroEL. Br J Dermatol. 2004;150(3):421–8.
99. McDowell A, Valanne S, Ramage G, Tunney MM, Glenn JV, McLorinan GC, Bhatia A, Maisonneuve JF, Lodes M, Persing DH, Patrick S. Propionibacterium acnes types I and II represent phylogenetically distinct groups. J Clin Microbiol. 2005;43(1):326–34.

100. Harrison WJ, Bull JJ, Seltmann H, Zouboulis CC, Philpott MP. Expression of lipogenic factors galectin-12, resistin, SREBP-1, and SCD in human sebaceous glands and cultured sebocytes. J Invest Dermatol. 2007;127(6):1309–17.
101. Nakatsuji T, Kao MC, Fang JY, Zouboulis CC, Zhang L, Gallo RL, Huang CM. Antimicrobial property of lauric acid against Propionibacterium acnes: its therapeutic potential for inflammatory acne vulgaris. J Invest Dermatol. 2009;129(10):2480–8.
102. Nakatsuji T, Kao MC, Zhang L, Zouboulis CC, Gallo RL, Huang CM. Sebum free fatty acids enhance the innate immune defense of human sebocytes by upregulating beta-defensin-2 expression. J Invest Dermatol. 2010;130(4):985–94.
103. Nagy I, Pivarcsi A, Koreck A, Szell M, Urban E, Kemeny L. Distinct strains of Propionibacterium acnes induce selective human beta-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. J Invest Dermatol. 2005;124(5):931–8.
104. Schaller M, Loewenstein M, Borelli C, Jacob K, Vogeser M, Burgdorf WH, Plewig G. Induction of a chemoattractive proinflammatory cytokine response after stimulation of keratinocytes with Propionibacterium acnes and coproporphyrin III. Br J Dermatol. 2005;153(1):66–71.