Chapter 23
Acne and Lipid Pathways

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Core Messages

- Hyperseborrhea has been considered as a major etiopathogenetic factor of acne.
- Changes in sebaceous gland activity not only correlate with seborrhea but also with alterations in sebum fatty acid composition.
- Sebum lipid fractions with proinflammatory properties are associated in the process of the development of acne lesions.
- The oxidant/antioxidant ratio of the skin surface lipids and alterations of lipid composition are the main players in the induction of acne inflammation.
- Nutrition may influence the development of seborrhea, the fractions of sebum lipids, and acne.

Abstract Hyperseborrhea has been considered as a major etiopathogenetic factor of acne. However, changes in sebaceous gland activity not only correlate with seborrhea but also with alterations in sebum fatty acid composition. Current findings

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indicate that sebum lipid fractions with proinflammatory properties and inflammatory tissue cascades are associated in the process of the development of acne lesions. The oxidant/antioxidant ratio of the skin surface lipids and alterations of lipid composition are the main players in the induction of acne inflammation. Nutrition may influence the development of seborrhea, the fractions of sebum lipids, and acne. Acne is an inflammatory disease probably triggered, among others, by proinflammatory sebum lipid fractions.

Abbreviations

5-LOX	5-lipoxygenase
COX-2	Cyclooxygenase-2
CRH	Corticotropin-releasing hormone
FADS	Fatty acid desaturase
FoxO1	Forkhead box transcription factor O1
IL	Interleukin
K	Keratin
P. acnes	*Propionibacterium acnes*
PPAR	Peroxisome proliferator-activated receptor
mTORC1	Mammalian target of rapamycin complex 1
SCD	Stearoyl-CoA desaturase
TLR	Toll-like receptor

Introduction: Inflammation in Acne

Induction of inflammatory signalling in the pilosebaceous unit is a major component in the process of the initiation of acne lesions (Zouboulis 2001, 2004a; Zouboulis et al. 2005). Among the 211 upregulated and the 18 downregulated genes in lesional skin of acne patients—compared to normal human skin—a significant proportion is involved in pathways that regulate inflammation (Trivedi et al. 2006a). Scarce inflammatory infiltrates around the ductus seboglandularis, and later on perifollicular infiltration and enhanced cytokine expression at the mRNA and protein levels are closely associated with comedone formation (Jeremy et al. 2003); comedones do not develop in a later stage leading to "inflammatory comedones," as previously reported (Chiba et al. 2000). NF-κB, a transcription factor critical for upregulation of several proinflammatory cytokine genes, has been shown to be activated in acne lesions (Kang et al. 2005). Interestingly, interleukin (IL)-1α is strongly expressed in comedones (Chiba et al. 2000; Anttila 1992; Ingham et al. 1992). It induces hyperproliferation, assessed by the enhanced expression of the hyperproliferative markers keratin (K) 6 and K16 (Hughes et al. 1996) and disturbs terminal differentiation of infundibular keratinocytes, which is related to increased filaggrin expression (Kurokawa et al. 1988), leading to hyperkeratinization in the follicular infundibulum detected in vivo and ex vivo (Guy et al. 1996). IL-1α activates basal keratinocytes by autocrine production inducing K16 expression in suprabasal cells in the active state.

Sebaceous Glands and Innate Immunity

Follicular keratinocytes and sebocytes, the major components of the pilosebaceous unit, may act as symbiotically or immune responding cells capable of microbia recognition and abnormal lipid presentation (Koreck et al. 2003). Innate immunity molecules, such as toll-like receptor (TLR)2, TLR4, CD1d, and CD14, are expressed in human keratinocytes (Song et al. 2002) and SZ95 sebocytes (Koreck et al. 2003; Oeff et al. 2006). Acting that way, keratinocytes and sebocytes may be activated by *Propionibacterium acnes* (*P. acnes*) and recognize altered lipid content in sebum, followed by the production of proinflammatory cytokines. In addition, antimicrobial peptides, such as defensin-1, defensin-2, and cathelicidin, are expressed and are active in the sebaceous gland (Chronnell et al. 2001; Nagy et al. 2006; Nakatsuji et al. 2010; Chen et al. 2011). Human β-defensin-2 is expressed upon exposure to lipopolysaccharides and *P. acnes* (Nagy et al. 2006) and upregulated by sebum free fatty acids (Nakatsuji et al. 2010).

Sebum and Acne

The most obvious function of the sebaceous gland is to excrete sebum (Zouboulis 2004a). Sebum is a mixture of relatively nonpolar lipids, most of which are synthesized de novo by the sebaceous glands (Nikkari 1974). The composition of sebum is remarkably species- and age-specific (Nikkari 1974; Ramasastry et al. 1970; Picardo et al. 2009; Pappas 2009a). Human sebaceous glands secrete a lipid mixture containing squalene and wax esters, as well as cholesterol esters, triglycerides, and possibly some free cholesterol and fatty acids.

For a long time, hyperseborrhea has been considered as a major etiopathogenetic factor for acne. However, emerging data on alterations of sebum composition in acne patients (Picardo et al. 2009; Makrantonaki et al. 2011; Pappas et al. 2009) indicate that sebum composition may be more important for the development of acne lesions than the secreted amount. Indeed, bacterial hydrolases convert some of the triglycerides to free fatty acids on the skin surface (Nicolaides and Wells 1957). On the other hand, there is also evidence that sebaceous glands can also synthesize considerable amounts of free fatty acids (Zouboulis 2001).

Indeed, the oxidant/antioxidant ratio of the skin surface lipids (Stewart et al. 1986) has been taken into consideration in the etiopathogenesis of acne and other skin diseases. Oxygen and micro-organisms transform “native” sebum, with lysis of triglycerides into fatty acids being their most pronounced activity on the skin (Patel and Noble 1992; Saint-Léger 2003). The quantities of lipid peroxide, IL-1α, and NF-κB were found significantly higher in the content of comedones than those in the stratum corneum (Tochio et al. 2009). Certain components of this complex mixture of molecules present in the sebum are clearly cytotoxic or irritant, provoking reactive follicular hyperkeratosis and comedone formation—the first step to acne. Particular attention has been focused on peroxidation of squalene, a sebaceous

gland-specific lipid, e.g., by ultraviolet radiation, which led to comedogenesis on the rabbit ear skin (Chiba et al. 2000). Squalene peroxide has been shown to induce an inflammatory response in HaCaT keratinocytes through lipoxygenase activation and increase in the proinflammatory cytokine IL-6 production (Ottaviani et al. 2006). Inflammation of acne-involved sebaceous glands is also associated with lipoxygenase activation and intracellular IL-6 increase (Alestas et al. 2006). Therefore, lipoxygenase activity products may contribute to an implementation of the inflammatory reaction with a concomitant anti-inflammatory feedback response of noninvolved cells of the pilosebaceous unit, as demonstrated by the concomitant increase of peroxisome proliferator-activated receptor (PPAR)α mRNA and protein levels. The clinical relevance of these findings were corroborated by the antiacne activity of zileuton, a 5-lipoxygenase (5-LOX) inhibitor (Zouboulis 2009; Zouboulis et al. 2010).

Stearoyl-CoA desaturase (SCD) and fatty acid desaturase (FADS)-2 are enzymes responsible for the biosynthesis of monounsaturated fatty acids in human sebocytes. In a feedback mode, their expression is downregulated by their products and upregulated by the unspecific Gram+bacterial antigen and TLR-2 ligand macrophage-activating lipopeptide-2 (MALP-2; Georgel et al. 2005; Zouboulis et al. 2011). Interestingly, while *P. acnes* is unable to induce IL-1α expression in the pilosebaceous unit (Ingham et al. 1998; Seltmann et al. 2000), oleate (C18:1)—through keratinocyte toxicity—causes increased IL-1α mRNA levels. Therefore, alterations of saturated and unsaturated fatty acid composition in sebum have currently been taken into consideration as initiators of follicular inflammation and regulators of innate symbiotic and immunity response (Makrantonaki et al. 2011; Ottaviani et al. 2006). Among the sebum lipids, the ones produced by the sebaceous glands are of great importance for the development of acne. Lower essential fatty acid levels were found in wax esters in twins with acne than in twins without acne (Stewart 1992). Several free fatty acids were detected to express proinflammatory and anti-inflammatory properties (Nakatsuji et al. 2010; Alestas et al. 2006; Wróbel et al. 2003; Makrantonaki and Zouboulis 2007). For example, high levels of linoleate (C18:2), an essential ω6-fatty acid (Stewart et al. 1986), may protect from the development of comedonal acne (Nicolaides et al. 1972) and its topical application reduces microcomedones and inhibits steroid 5α-reductase activity (Letawe et al. 1998; Namazi 2004). On the other hand, low linoleate levels have been observed in skin surface lipids of acne patients (Downing et al. 1986). However, neither all ω6-fatty acids are comedogenic, not all ω9-fatty acids inhibit comedogenesis (Fig. 23.1). For example, oleate alters the calcium dynamics in epidermal keratinocytes and induces abnormal follicular keratinization leading to comedogenesis in rabbit skin (Choi et al. 1997; Katsuta et al. 2005) but to minor irritation in human skin (Boelsma et al. 1996). SZ95 sebocytes in vitro were currently shown to produce the same amount of lipids after incubation with linoleate and palmitate (16:0). However, their effects on sebocyte inflammatory signaling were strikingly different (Seltmann et al. 2013).

On the other hand, fatty acids exhibit strong antimicrobial activity. The sebaceous ω9-fatty acids sapienate (C16:1δ6), palmitate (C16:0), and oleate (C18:1) are very effective against *Staphylococcus aureus* (Chen et al. 2011; Georgel et al.

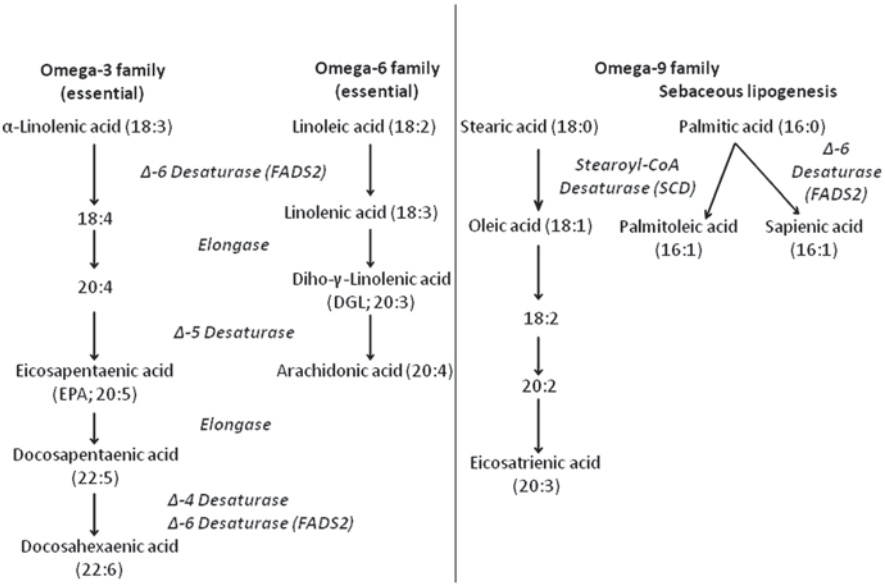

Fig. 23.1 Sebaceous lipogenesis is dependent on the fatty acids available. While unsaturated ω3 and ω6 fatty acids are essential, ω9 can be synthetized by the sebaceous glands. The saturated/unsaturated fatty acid ratio defines inflammatory triggering and can initiate comedogenesis

2005; Wille and Kydonieus 2003; Drake et al. 2008). Moreover, dysfunction of the upstream lipidogenic enzymes SCD and FADS-2 is associated with skin infection and inflammation (Georgel et al. 2005; Seltmann et al. 2000). Lipids at the skin surface, mostly secreted from the sebaceous glands (90%) and transported through the follicular canal, are part of the symbiotic and innate immunity of the skin and contribute to the antimicrobial skin barrier.

PPAR and Acne

Certain lipid mediators, which are able to interfere with sebocyte differentiation and lipogenesis, have been shown to activate and/or be ligands of PPAR (Makrantonaki et al. 2011; Ottaviani et al. 2006; Alestas et al. 2006; Chen et al. 2003; Zhang et al. 2006). Importantly, lipid peroxidation products are also capable of inducing PPAR activation and production of proinflammatory cytokines. In particular, PPARα seems to be related to β-oxidation of fatty acids and lipid catabolism, whereas PPARγ activation has been linked to lipogenesis (Ferré 2004). Eicosanoid metabolites originated from the arachidonic acid cascade, namely leukotriene B_4 and 15-HETE, have been shown to be ligands of PPARα and PPARγ, respectively (reviewed in Zouboulis et al. 2005; Alestas et al. 2006). Interestingly, the enzymes involved in their formation, including 5-LOX, have been implicated in inflam-

matory skin diseases characterized by keratinocyte hyperproliferation (Ottaviani et al. 2006) and have been found to be expressed at higher extent in acne-involved skin in comparison to the skin of healthy subjects (Alestas et al. 2006). Activation of 5-LOX results, among other effects, in induced IL-6 and IL-8 expression in human sebocytes, whereas enhanced expression of IL-6 and IL-8 has also been found in acne-affected skin (Alestas et al. 2006). Systemic treatment of acne patients with the 5-LOX inhibitor Zileuton reduces the inflammatory lesion count and the synthesis of sebum lipids, in particular, of those with proinflammatory potential (Zouboulis 2009) through an inflammation-preventive mechanism (Zouboulis et al. 2010). 5-LOX inhibitors may also downregulate the inflammatory activity of lymphocytes and macrophages resulting in cumulative beneficial effects (Jeremy et al. 2003).

Prostaglandins are further proinflammatory mediators thought to be involved in acne lesion development (Zhang et al. 2006). Mice with increased cyclooxygenase-2 (COX-2) expression and prostaglandins E2 levels showed sebaceous gland hyperplasia and enhanced sebum production (Neufang et al. 2001) suggesting an important role for COX-2 signaling pathway in sebocyte biology. Expression and activation of COX-2 has been shown in in vitro models to be PPARγ-mediated. General oxidative stressors, including lipid oxidizing agents, activate PPARγ and induce lipogenesis in sebocytes (Trivedi et al. 2006a, b; Zhang et al. 2006; Ottaviani et al. 2010). All these findings allow the hypothesis that sebocyte proliferation and/or lipogenesis as well as inflammatory reaction may be regulated by PPARγ-mediated pathways.

Neuropeptides

Corticotropin-releasing hormone (CRH), the most proximal element of the hypophysis-pituitary-adrenal axis, acts as a central coordinator for neuroendocrine and behavioral responses to stress. CRH, CRH-binding protein, CRH-receptor 1, and CRH-receptor 2 are expressed in SZ95 sebocytes at mRNA and protein level, whereas CRH-receptor 1 is the predominant type (Zouboulis et al. 2002). In addition, CRH significantly upregulates mRNA levels of 3β-hydroxysteroid dehydrogenase/Δ^{5-4} isomerase and induces sebaceous lipogenesis and IL-6 and IL-8 synthesis (Zouboulis et al. 2002; Krause et al. 2007). In acne-involved skin, the complete CRH system is abundant, especially in the sebaceous glands, possibly activating lipid pathways, which affect immune and inflammatory processes leading to the development and stress-induced exacerbation of acne (Ganceviciene et al. 2009).

Diet

Evidence suggests that diet may influence acne (Rasmussen 1997; Pappas 2009b; Liakou et al. 2013; Smith et al. 2007), whereas it is also an important source of substrate for the synthesis of sebaceous lipids (Rasmussen 1997). This notion is

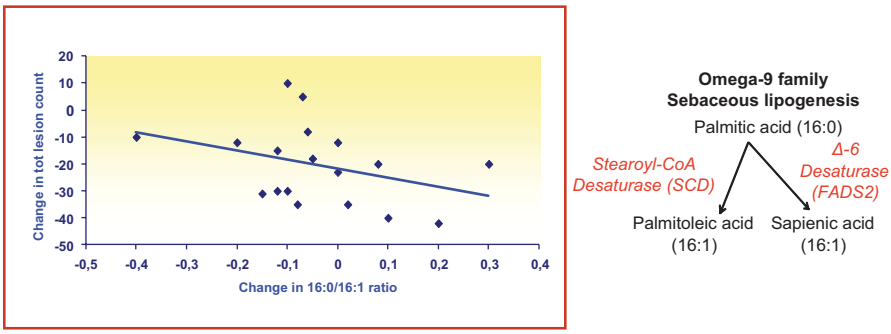

Fig. 23.2 Skin surface lipid composition under a 12-week acne diet. Decrease in the enzymatic desaturation of fatty acids correlates with the clinical improvement in acne

supported also by the observation that sebum contains essential fatty acids, such as linoleate and oleate. 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 (Pochi et al. 1970; Downing et al. 1972). 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 (Macdonald 1964). Typical western diet, comprised of milk and hyperglycaemic foods, may have potentiating effects on serum insulin and insulin-like growth factor-1 levels, thereby promoting the development of acne (Melnik and Schmitz 2009). In contrast, a low-glycemic-load diet for 12 weeks in acne patients reduced parallelly the acne lesion count and increased the C16:0/C16:1 fatty acid ratio (Smith et al. 2007, 2008) suggesting an increased enzymatic desaturation of fatty acids in the sebaceous glands of patients with acne (Fig. 23.2).

The nutritional cell status is primarily sensed by the forkhead box transcription factor O1 (FoxO1) and the serine/threonine kinase mammalian target of rapamycin complex 1 (mTORC1) (Wang et al. 2011). FoxO1 attenuates androgen signaling, interacts with regulatory proteins important for sebaceous lipogenesis, regulates the activity of innate and adaptive immunity, antagonizes oxidative stress, and most importantly functions as a rheostat of mTORC1, the master regulator of cell growth, proliferation, and metabolic homoeostasis. Thus, FoxO1 links nutrient availability to mTORC1-driven processes in the skin: increased protein and lipid synthesis, cell proliferation, cell differentiation including hyperproliferation of acroinfundibular keratinocytes, sebaceous gland hyperplasia, and increased sebaceous lipogenesis (Melnik and Zouboulis 2013). Deeper insights into the molecular interplay of FoxO1/mTORC1-mediated nutrient signaling are thus of critical importance to understand the impact of western diet on the promotion of epidemic acne.

Table 23.1 Sebaceous gland functions, which are possibly involved in the development of acne

Production of sebum (Zouboulis et al. 2003)
Regulation of cutaneous steroidogenesis (Thiboutot et al. 2003; Zouboulis 2004b; Chen et al. 2010; Samson et al. 2010; Slominski et al. 2013)
Regulation of local androgen synthesis (Fritsch et al. 2001)
Interaction with neuropeptides (Zouboulis et al. 2002)
Synthesis of specific lipids with antimicrobial activity (Wille and Kydonieus 2003)
Exhibition of pro- and anti-inflammatory properties (Zouboulis 2001; Zouboulis 2004a; Böhm et al. 2002)

Conclusions

Increased sebum excretion, alteration of lipid composition and the oxidant/antioxidant ratio of the skin surface lipids are major concurrent events associated with the development of acne (Zouboulis 2004a; Table 23.1). Current evidence indicates that sebum composition (lipid quality), and not quantity, plays a central role in the development of acne. This concept is supported by the mode of action of new antiacne compounds, such as the 5-LOX inhibitor Zileuton, which reduces acne lesions by inhibiting proinflammatory lipids (Zouboulis 2009; Zouboulis et al. 2010), and the current evidence of the effect of diet on acne (Melnik and Schmitz 2009). Moreover, old data on in vivo and in vitro modulation of sebaceous lipid composition by isotretinoin, the most potent antiacne drug, can be approached from this new perspective (Stewart et al. 1984; Strauss et al. 1987; Melnik et al. 1988; Zouboulis et al. 1991).

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