# Acne and Antimicrobial Lipids

# 23

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## Contents



**Core Messages**

- Currently reported data strongly indicate a central role of sebaceous lipid quality and not quantity on the development of acne and other inflammatory skin diseases.
- Several lipid fractions, especially sebaceous lipid fractions, also express antibacterial activity, possibly protecting the sebaceous gland from major infections.

## 23.1 Introduction

The most obvious function of the sebaceous gland is to excrete sebum [1, 2]. For a long time hyperseborrhea has been considered as a major etiopathogenetic factor for the development of acne. However, current research provides evidence that sebum quantity per se cannot be the only responsible factor, as demonstrated by the success of treatment with agents with no primary effect on sebum excretion rate [3]. Indeed, additional functions of the gland are associated with the development of acne (Table 23.1), with prominent among them alterations in sebaceous lipid fractions.

## 23.2 Sebaceous Glands and Innate Immunity

Keratinocytes and sebocytes, as major components of the pilosebaceous unit, may act as immune-active cells capable of microbial

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

- Production of sebum [4]
- Regulation of cutaneous steroidogenesis [5–9]
- Regulation of local androgen synthesis [6]
- Interaction with neuropeptides [10, 11]
- Synthesis of specific lipids with antimicrobial activity [12]
- Exhibition of pro- and anti-inflammatory properties [9, 13–15]

recognition and abnormal lipid presentation (see Chap. 16). Acting that way, keratinocytes and sebocytes may be activated by *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 immune reactive in the sebaceous gland [16–19]. Human β-defensin-2 (hBD-2) is expressed upon exposure to lipopolysaccharides and *P. acnes* [18] and upregulated by sebum free fatty acids [19]. Stearoyl coenzyme A desaturase (SCD), an enzyme responsible for the biosynthesis of monounsaturated fatty acids, is also expressed by the sebaceous gland [20, 21]. The TLR-2 ligand macrophage-activating lipopeptide-2 stimulates both SCD and its downstream enzyme fatty acid desaturase-2 in SZ95 sebocytes.

## 23.3 Sebum

Sebum is the first demonstrable glandular product of the human body [22]. It is a mixture of relatively nonpolar lipids [22, 23], most of which are synthesized de novo by the sebaceous gland of the mammals to coat the fur as a hydrophobic protection against overwetting and for heat insulation [22, 24]. The composition of sebum is remarkably species specific [4, 22, 25].

## 23.4 Sebaceous Lipids

Human sebaceous glands secrete a lipid mixture containing squalene and wax esters, as well as cholesterol esters, triglycerides, and possibly some free cholesterol [22, 23, 26–28]. Bacterial hydrolases convert some of the triglycerides to free fatty acids on the skin surface [29, 30], however, there is also evidence indicating that sebaceous glands can also synthesize considerable amounts of free fatty acids [15].

## 23.5 Alterations in Acne

It is not long ago that the oxidant/antioxidant ratio of the skin surface lipids [31] and currently alterations of fatty acid composition [32, 33] have been taken into consideration in the etiopathogenesis of acne and other skin diseases (Fig. 23.1). Lower essential fatty acid levels were found in wax esters in twins with acne rather than in twins without acne [34]. The sebaceous ω9-fatty acids sapienate C16:1δ6, palmitate C16:0, and oleate (C18:1) are very effective against Staphylococcus aureus [12, 16, 20, 35]. Lipids at the skin surface, mostly secreted from the sebaceous glands (90 %) and transported through the follicular canal, are part of the innate immunity of the skin and contribute to the antimicrobial skin barrier. On the other hand, dysfunction of the upstream lipidogenic enzymes stearoyl-CoA desaturase and fatty acid desaturase 2 is associated with skin infection and inflammation [20, 21]. However, neither all ω6-fatty acids are comedogenic nor all ω9-fatty acids (Fig. 23.2) inhibit comedogenesis. For example, oleate alters the calcium dynamics in epidermal keratinocytes and induces abnormal follicular keratinization leading to comedogenesis in rabbit skin but to minor irritation in human skin [36]. Overall, free fatty acids were detected to express proinflammatory and anti-inflammatory properties [13, 19, 37, 38].

Altered ratio between saturated and unsaturated fatty acids has been indicated as an important feature to be considered in addition to the altered amount of specific fatty acids such as linoleate (LA; C18:2), an essential ω6-fatty acid that cannot be synthesized in vivo, and therefore must be obtained from the diet [33]. High levels of sebum LA may protect from the development of comedonal acne [39]. On the other hand, low LA levels have been observed in skin surface

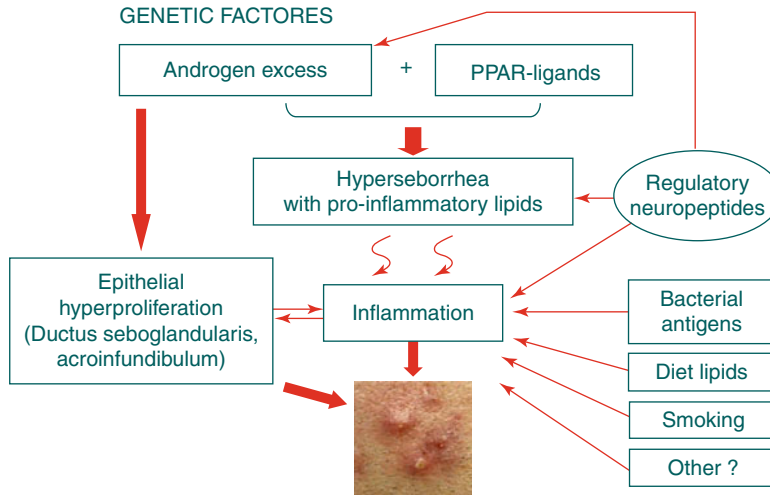


**Fig. 23.1** Modern aspects of acne pathogenesis. Androgens, PPAR ligands, regulating neuropeptides, and environmental factors lead to hyperseborrhea, to epithelial hyperproliferation into the ductus seboglandularis and the acroinfundibulum, and to expression of proinflammatory chemokines/cytokines, which promote the development of comedones and inflammatory acne lesions (by Zouboulis et al. [2])

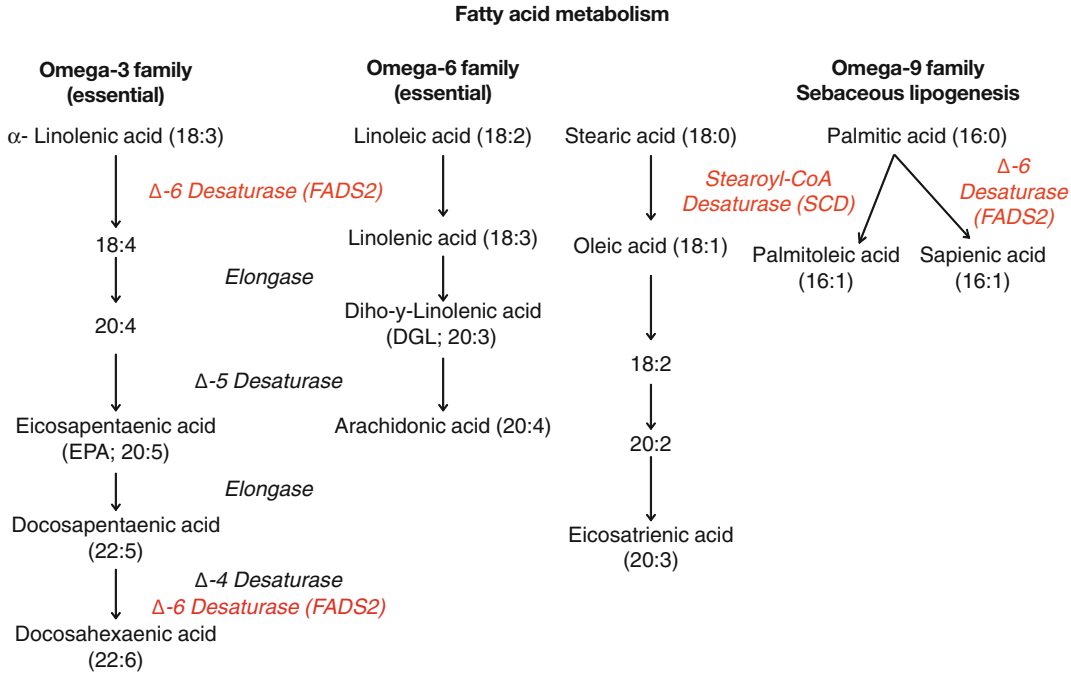


**Fig. 23.2** Fatty acid metabolism and sebaceous lipogenesis

lipids of acne patients [40]. Its topical application reduces microcomedones and inhibits steroid 5α-reductase activity [41, 42].

Particular attention has been focused on peroxidation of squalene, another sebaceous gland-specific lipid, e.g., by UV radiation, which led to comedogenesis on the rabbit ear skin [43]. Moreover, squalene peroxide seems able to induce an inflammatory response beyond cytotoxicity and comedone formation [33]. Oxygen and microorganisms transform "native" sebum with lysis of triglycerides to fatty acids being the most pronounced activity [7, 44]. 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. As discussed above, IL-1α levels are a hallmark of comedogenesis [45, 46] and, while *P. acnes* is unable to induce IL-1α expression in the pilosebaceous unit [47, 48], oleate—through keratinocyte toxicity—causes increased IL-1α mRNA levels. 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, indicating that the accumulation of a certain amount of lipid peroxide in the content of comedones may play an important role in the progression of comedogenesis [25] and the inflammatory changes detected in these apparently non-inflammatory lesions [2, 15]. In any case, scarce inflammatory infiltrates around the ductus seboglandularis and later on perifollicular infiltration are closely associated with comedone formation [2, 15, 49] and does not develop in a later stage leading to "inflammatory comedones," as previously reported [43].

## 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 [1]. Interestingly, currently reported data strongly indicate a central role of sebaceous lipid quality and not quantity on the development of acne and other inflammatory skin diseases. Moreover, several lipid fractions, especially sebaceous lipid fractions, also express antibacterial activity, possibly protecting the sebaceous gland from major infections.

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