Acne and Sebaceous Gland Function

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Abstract: The embryologic development of the human sebaceous gland is closely related to the differentiation of the hair follicle and the epidermis. The number of sebaceous glands remains approximately the same throughout life, whereas their size tends to increase with age. The development and function of the sebaceous gland in the fetal and neonatal periods appear to be regulated by maternal androgens and by endogenous steroid synthesis, as well as by other morphogens. The most apparent function of the glands is to excrete sebum. A strong increase in sebum excretion occurs a few hours after birth; this peaks during the first week and slowly subsides thereafter. A new rise takes place at about age 9 years with adrenarche and continues up to age 17 years, when the adult level is reached. The sebaceous gland is an important formation site of active androgens. Androgens are well known for their effects on sebum excretion, whereas terminal sebocyte differentiation is assisted by peroxisome proliferator-activated receptor ligands. Estrogens, glucocorticoids, and prolactin also influence sebaceous gland function. In addition, stress-sensing cutaneous signals lead to the production and release of corticotropin-releasing hormone from dermal nerves and sebocytes with subsequent dose-dependent regulation of sebaceous nonpolar lipids. Among other lipid fractions, sebaceous glands have been shown to synthesize considerable amounts of free fatty acids without exogenous influence. Sebaceous lipids are responsible for the three-dimensional skin surface lipid organization. Contributing to the integrity of the skin barrier. They also exhibit strong innate antimicrobial activity, transport antioxidants to the skin surface, and express proinflammatory and anti-inflammatory properties.

Sebaceous Gland Development

The human sebaceous gland is a multiacinan, holocrine-secreting tissue present in all areas of the skin except for the palms and soles (and only sparsely on the dorsal surfaces of the hand and foot). Its development is closely related to the differentiation of the hair follicle and the epidermis. By 13–15 weeks of fetal life, the sebaceous gland is clearly distinguishable arising in a cephalocaudal sequence from the hair follicle. Lipid drops are visible at the center of the gland at 17 weeks. The future common excretory duct, around which the acini of the sebaceous gland attach, begins as a solid cord. The cells composing the cord are filled with sebum, and eventually they lose their integrity, rupture, and form a channel that establishes the first pilosebaceous canal. New acini result from buds on the peripheral sebaceous duct wall. The cell organization of the neonatal sebaceous acini consists of undifferentiated, differentiating, and mature sebocytes.

The number of sebaceous glands remains approximately constant throughout life, whereas their size tends to increase with age. Within any one glandular unit, the acini vary in differentiation and maturity. The sebaceous cells of prepupertal and hypogonadal males are qualitatively similar to those of normal adults, even though the glands are smaller. Synthesis and discharge of the lipids contained in sebaceous cells takes more than 1 week. The turnover of sebaceous glands is slower in older than in young adults.

Sebaceous Gland Functions

The most obvious function of the sebaceous gland is to excrete sebum. Additional functions of the gland are associated with the development of acne (Table 1).

Sebum Production

Sebum is a mixture of relatively nonpolar lipids, most of which are synthesized de novo by the sebaceous gland to coat the fur as a hydrophobic protection against overwetting and for heat insulation in mammals. The composition of sebum is remarkably species-specific. Increased sebum excretion is a major factor involved in the pathophysiology of acne.
ACNE AND SEBACEOUS GLAND FUNCTION

Table 1. Sebaceous gland functions, which are possibly involved in the development of acne

- Production of sebum (12)
- Regulation of cutaneous steroidogenesis (13-15)
- Regulation of local androgen synthesis (14)
- Interaction with neuropeptides (16)
- Synthesis of specific lipids with antimicrobial activity (17)
- Expression of pro- and anti-inflammatory properties (13, 18, 19)

mation; sebum is the first demonstrable glandular product of the human body.12 It is major ingredient of vernix caseosa, which progressively coats the fetus during the last trimester of gestation. Development and function in the fetal and neonatal periods appear to be regulated by maternal androgens and by endogenous steroid synthesis, as well as by other “morphogens,” including growth factors, cell adhesion molecules, extracellular matrix proteins, intracellular signaling molecules (β-catenin and LEF-1), other hormones, cytokines, enzymes, and retinoids.4,24

A significant increase in sebum excretion occurs a few hours after birth and peaks during the first week.25,26 Maternal and neonatal sebum excretion rates directly correlate.26 This correlation is lost in the following weeks and is independent from breast-feeding. At this time, the sebum level per unit skin surface is in the same range as in young adults,25 and the sequence of sebaceous transformation seems identical to that in postnatal life. These events suggest an important role of the maternal hormonal environment on the neonatal sebaceous gland and indicates that androgenetic stimulus for sebum secretion occurs before birth through the placenta.25,26 Sebum excretion then slowly subsides. A new rise occurs at about age 9 years,27 with adrenarche and continues up to age 17 years, when the adult level is reached.28 It has been suggested that the endocrine environment of the neonate correlates with and may influence sebaceous gland development in puberty.26

Regulation of Cutaneous Steroidogenesis and Local Androgen Synthesis

The skin, and especially the sebaceous gland, is important sites of formation of active androgens.13,14 All enzymes required for transformation of cholesterol to steroids and adrenal precursors [dehydroepiandrosterone (DHEA) sulfate and DHEA] are localized in the skin.13,15 Hydroxysteroid dehydrogenases (HSD), which activate and inactivate androgens,14 are present after 16 weeks of fetal life.29,30 DHEA sulfate is transformed not only systemically,31 but also locally to DHEA by the widely distributed steroid sulfatase.32 DHEA is metabolized to androstenedione and testosterone by 3β-hydroxysteroid dehydrogenase-Δ5-4 isomerase and 17β-HSD, which have been localized to the sebaceous gland.14,33 The intracellular conversion of testosterone to 5α-dihydrotestosterone (DHT), the most potent androgen in tissue, takes place by 5α-reductase. Two types of 5α-reductase have been isolated from human tissues.34 The type I isozyme is the predominant type expressed in human skin and can be localized in sebaceous glands, sweat glands, and in the epidermis,35 whereas its highest activity is found in the sebaceous gland with a maximum in sebaceous glands of facial skin and scalp.36,37 Conversion of adrenal precursors to tissue active androgens is involved in the full development of the sebaceous glands during intrauterine life and adrenarche, whereas gonadal androgens overtake in puberty.4

Hormonal Control of the Sebaceous Gland

Both clinical observation and experimental evidence confirm the importance of hormones in the pathophysiology of acne. Hormones are most well known for their effects on sebum excretion. It has also been suggested that hormones may play a role in the follicular hyperkeratinization seen in follicles affected by acne.38,39 From a therapeutic standpoint, the importance of the role of hormones in acne is supported by the clinical efficacy of hormonal therapy in women with acne. Three components of sebocyte function—differentiation, proliferation, and lipid synthesis—are controlled by complex endocrinologic mechanisms. Despite the hormonal control of sebaceous gland size and activity, the acne patient is not considered to be an androgen mismatch.23

Androgens regulate the sebaceous gland function through binding to nuclear androgen receptors (ARs).14 ARs have been detected by immunohistochemistry in sebaceous glands, eccrine glands, and the mesenchymal cells of the hair follicle; the highest AR density in human skin has been demonstrated in the sebaceous gland.40-42 AR distribution in human skin is consistent with known androgen targets, and its role is obvious in acne.43 In sebaceous glands, AR was identified in basal and differentiating sebocytes, indicating that androgens are involved in the regulation of cell proliferation and lipogenesis.31,42

Terminal differentiation of cultured preputial rat cells in vitro, which exhibit sebocyte-like differentiation, has been shown to require the presence of not only DHT, but also of peroxisome proliferator-activated receptor (PPAR) ligands.44 PPARs are present in human sebocytes45 and regulate multiple lipid metabolic genes in mitochondria, peroxisomes, and microsomes.46 All of these organelles are prominent in the cytoplasm of human sebocytes.14,46,47

Estrogens exhibit an inhibitory effect on excessive sebaceous gland activity in vivo.9,13,48,49 This down-regulatory effect possibly can be explained by inhibition of gonadotropin secretion or by enhancement of testosterone binding to its binding globulin.2

In patients with adrenal insufficiency, sebum secre-
tion is decreased as it is decreased after substitution with glucocorticoids. A possible mechanism of glucocorticoid action could be through the resulting decrease in adrenal androgens.\textsuperscript{50,51}

A clinical indication of the influence of prolactin on sebaceous glands is the seborrhea seen in hyperprolactinemic women. The effect of prolactin is mediated indirectly through increased production of adrenal androgens.\textsuperscript{52} Neither prolactin synthesis nor prolactin receptors have been identified on human sebaceous glands.

**Interaction With Neuropeptides**

There is increasing evidence that the cutaneous nervous system modulates physiologic and pathophysiologic effects in the skin. To effectively deal with cell-damaging signals, the skin has a highly organized corticotropin-releasing hormone (CRH)/propiomelanocortin (POMC) system.\textsuperscript{53} Activation of this pathway by stress-sensing cutaneous signals, mainly proinflammatory cytokines, leads to the production and release of CRH from dermal nerves and several skin cells, including sebocytes.\textsuperscript{16} CRH stimulates its receptors on skin cells in paracrine and autocrine manners. In sebocytes, CRH leads to a dose-dependent regulation of nonpolar lipids and of the expression of 3β-hydroxysteroid dehydrogenase-\(Δ^\Delta\)\textsuperscript{5,4} isomerase.\textsuperscript{18} The expression of CRH receptors in human sebocytes can be regulated by several hormones, mainly testosterone, estrogens, and growth hormone. CRH enhances the production and secretion of the POMC peptide \(α\)-melanocyte–stimulating hormone which reduces interleukin (IL)-8 synthesis in IL-1β-challenged sebocytes in vitro.\textsuperscript{19} Adrenocorticotropic hormone activates the steroidogenic acute regulatory protein and thus the melanocortin receptors, thereby inducing the production and secretion of cortisol,\textsuperscript{24} a powerful natural anti-inflammatory factor that counteracts the effect of stress signals and buffers tissue damage. Dermal nerves around the sebaceous glands of acne patients express the neuropeptide substance P, whereas undifferentiated sebocytes at the acinar periphery respond by producing the substance P inactivator neutral endopeptidase.\textsuperscript{55,56}

**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.\textsuperscript{3,20,27} It is known that bacterial hydrolases convert some of the triglycerides to free fatty acids on the skin surface;\textsuperscript{57,58} however, there is also evidence indicating that sebaceous glands can also synthesize considerable amounts of free fatty acids.\textsuperscript{18} The lipid secretion rates correlate well with low levels of gonadal and adrenal androgens.\textsuperscript{59} Although the composition of epidermal lipids in young children is typically not sebaceous,\textsuperscript{12} consisting largely of cholesterol esters and free cholesterol, androgen stimulation of the glands at adrenarche (age 7–10 years) seem to cause an increase in lipid synthesis and changes in lipid composition toward the adult pattern.\textsuperscript{60} A number of studies have confirmed changes in the lipid composition of sebum associated with age or with sebaceous gland activity.\textsuperscript{20,27,61,62} In addition, the effect of androgens on sebaceous cell proliferation and differentiation is dependent on the origin of the sebaceous glands; for example, facial sebaceous glands are more sensitive to androgens.\textsuperscript{63}

Among their several functions,\textsuperscript{64} sebaceous lipids are responsible for the three-dimensional organization of skin surface lipids and the integrity of the skin barrier.\textsuperscript{65,66} The sebocyte lipid sapienate (C16:1Δ6)\textsuperscript{67} exhibits strong innate antimicrobial activity.\textsuperscript{17} Sebum transports antioxidants to the skin surface,\textsuperscript{68} and sebaceous lipids and other products were detected to express proinflammatory and anti-inflammatory properties.\textsuperscript{13,18,19,55}

**Alterations in Acne**

Although high levels of sebum linoleate in young children may protect them from comedonal acne,\textsuperscript{69} high levels of DHEA immediately after birth and up to 6 months postnatally as well as at adrenarche may be responsible for acne infantum and prepubertal acne (Fig 1). These types of acne often present not only with comedonal acne, but also later with inflammatory lesions, because DHEA exhibits a proinflammatory activity opposing the anti-inflammatory action of glucocorticoids.\textsuperscript{70} Acne neonatorum, which is present at birth or appears 2–4 weeks after birth, is not uncommon, with a prevalence of approximately 20% in newborns.\textsuperscript{71} It usually presents with mostly mild facial lesions, is self-limited, and has a male predominance (4.5–5:1).\textsuperscript{12} Histologic findings from newborns with acne neonatorum demonstrate hyperplasic sebaceous glands with keratin-plugged orifices.\textsuperscript{71}

Acne in childhood has been suggested to be strongly associated with the development of severe acne during adolescence.\textsuperscript{26,71} On the other hand, high sebum production rates are a predisposing factor associated with the formation of primary acne lesions in adolescence.\textsuperscript{67} DHEA also may be responsible for acne tarda in females, which presents with inflammatory lesions of the lower part of the face (Fig 2).\textsuperscript{43}

**Inflammation and Acne Vulgaris**

It is widely accepted that inflammation in acne vulgaris may be induced mainly by an immunologic reaction to extracellular products of \(P.\) acnes.\textsuperscript{72} However, it is by no means clear that either bacteria or bacterial products initiate follicular inflammation. Ingham et al\textsuperscript{73} investigated the presence of proinflammatory cytokines in 108
open acne comedones from 18 untreated acne patients. Bioactive IL-1α-like material was demonstrated in 76% of open comedones; in 58%, levels exceeded 100 pg/mg. Most of the open comedones (97%) also contained microorganisms, but there was no significant correlation between levels of any cytokine (in particular, IL-1α) and the numbers of microorganisms.

Additional results have shown that the sebaceous gland expresses a number of different cytokines at steady state, without the influence of any external factors. Zouboulis et al\textsuperscript{47} stressed sebocytes in vitro by maintaining them in serum-free medium and detected IL-1α expression at the mRNA and protein levels. Antilla et al\textsuperscript{47} showed that IL-1 is present in normal sebaceous glands, and Boehm et al\textsuperscript{75} used in situ hybridization techniques to demonstrate that messenger RNA (mRNA) for IL-1α, IL-1β, and tumor necrosis factor-α are present at multiple sites in normal skin, including the sebaceous glands. Thus, whereas the presence of bacteria, most notably \textit{P. acnes}, may stimulate up-regulation of cytokine expression in sebaceous glands and in monocytes,\textsuperscript{32,76} inflammatory cells are also present around the sebaceous duct, and substance P is expressed in the nerve endings at the vicinity of healthy-looking glands of acne patients in the absence of bacteria or their agents.\textsuperscript{55,77}

**Proinflammatory Cytokines and Comedone Development**

Guy et al\textsuperscript{78} assessed the action of IL-1 in the human pilosebaceous infundibulum isolated by microdissection and maintained in keratinocyte serum-free culture for 7 days. The addition of 1 ng/mL IL-1α resulted in hypercornification of the infundibulum similar to that seen in comedones. The dependence of this effect on a specific action of IL-1α was confirmed in an additional experiment demonstrating that the IL-1α effect could be nullified by the administration 1000 ng/mL of IL-1 receptor antagonist. They further demonstrated that spontaneous hypercornification of the infundibulum (which occurred in about 20% of isolated pilosebaceous units) could also be blocked by the IL-1α receptor antagonist. These results are compatible with the data of Zouboulis et al\textsuperscript{47}, Boehm et al\textsuperscript{75}, Jeremy et al\textsuperscript{77} and Ingham et al\textsuperscript{73} and provide evidence for the involvement of endogenous inflammatory processes in the initiation of acne. In addition, they offer logical support to the current concept of anti-inflammatory treatment of acne\textsuperscript{18,79,80} (Fig 3).

Therefore, acne vulgaris is a genuine inflammatory disease, and evidence exists indicating that appropriate anti-inflammatory therapy has the potential to effectively treat this condition. Future compounds targeting acne vulgaris should be able to reduce proinflammatory lipids in sebum, down-regulate proinflammatory signals in the pilosebaceous unit, and inhibit LTB\textsubscript{4}-induced accumulation of inflammatory cells and PPAR regulation, as well as significantly reduce sebum production.

**Retinoids, the Sebaceous Gland and Acne**

Isotretinoin is the most effective compound in reducing sebaceous gland size by decreasing proliferation of
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tors must be taken into account for establishing the

efficacy of Zileuton, an oral 5-lipoxygenase inhibitor
in inflammatory acne. Significant reduction is seen in (A) the
number of inflammatory lesions, (B) the acne severity index, and
(C) the total sebum lipid levels after 12 weeks of treatment. The
mean values ± standard error are presented. Values are compared
with baseline. (Modified with permission.)

Figure 3: Efficacy of Zileuton, an oral 5-lipoxygenase inhibitor in inflammatory acne. Significant reduction is seen in (A) the number of inflammatory lesions, (B) the acne severity index, and (C) the total sebum lipid levels after 12 weeks of treatment. The mean values ± standard error are presented. Values are compared with baseline. (Modified with permission.)

...or activating nuclear retinoid receptors, the high antisebotropic activity of isotretinoin is particularly surprising because it exhibits low binding affinities for both cellular retinoic acid-binding proteins I and II as well as for nuclear retinoid receptors, retinoic acid receptors (RAR) and retinoid X receptors. Tsukada et al. have partially elucidated this apparent contradiction by showing that isotretinoin undergoes signiﬁcant and selective isomerization to tretinoin in cultured sebocytes. Intracellular tretinoin acts then via RAR to exert its antiproliferative effect on these cells. Therefore, isotretinoin acts probably as a prodrug that becomes active in the sebaceous glands after isomerization to tretinoin.

Oral isotretinoin has revolutionized the treatment of severe acne. It is the only drug available that affects all four pathogenic factors of the disease. A 6- to 12-month course of isotretinoin 0.5–1 mg/kg/day in most cases with severe acne, to reach a ≥150 mg/kg total cumulative dose is recommended. Individual risk factors must be taken into account for establishing the exact dosage. As a rule, after 2 to 4 weeks of treatment, a 50% reduction of the pustules can be expected. A 6-month treatment course is sufficient for the majority of the patients but a continuation of low-dose treatment (0.2–0.5 mg/kg/day) may optimize the therapeutic outcome. Improvement continues during the post-treatment period. Relapses may occur after a single 6-month course. Relapses necessitating re-treatment occur significantly more frequently under low-doses among patients with severe acne. A 22 to 30% relapse rate was noted in patients followed for 10 years after having received isotretinoin 1 mg/kg/day (or cumulative dose ≥120 mg/kg), as compared to 39 to 82% with lower dose schedules. In female patients, contraception is required and has to be enforced by the physician, because of the strong teratogenicity of isotretinoin. Isotretinoin can be well combined with a contraceptive pill which includes a hormonal anti-androgen.

References


