

Controversies in Experimental Dermatology

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What is the pathogenesis of acne?

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Abstract: For a long time, the mantra of acne pathogenesis debates has been that acne vulgaris lesions develop when (supposedly largely androgen-mediated) increased sebum production, ductal hypercornification, and propionibacteria come together with local inflammatory process in the unlucky affected individual. And yet, the exact sequence, precise interdependence, and choreography of pathogenic events in acne, especially the 'match that lights the fire' have remained surprisingly unclear, despite the venerable tradition of acne research over the past century.

However, exciting recent progress in this – conceptually long somewhat stagnant, yet clinically, psychologically, and socioeconomically highly relevant – everyday battlefield of skin pathology encourages one to critically revisit conventional concepts of acne pathogenesis. Also, this provides a good opportunity for defining more sharply key open questions and intriguing acne characteristics whose underlying biological basis has far too long remained uninvestigated, and to emphasize promising new acne research avenues off-the-beaten-track – in the hope of promoting the corresponding development of innovative strategies for acne management.

Prelude

Dear Sir,

I have to confess that I much hated Peter, John, William and Albert, respectively, from Boston, Iowa-City, Leeds and Philadelphia. The latter described me as 'a bewitching lady, pursued with more passion than intelligence' (1).

Since centuries, I have dedicated my long life to revenge. Afflicted by various skin disgraces, my face is, by itself, a textbook of Dermatology. Disadvantaged, I hate adolescence, its blossoming promises and succeeded to disfigure a vast majority of teens and, better, give them a bad quality of life (2). I went even further: post adolescence, many of them still remain concerned (3).

Am I alone? No. Some of my old allies are suspected (not all yet, for comedone's sake), because these hated guys call me a multifactorial disease (4).

My good companion, the Duke of Seborrhea constantly helps me, fuelling my flame of revenge. Although now facing the 13th division of *cis*-retinoics or the anti-androgens troops, my valiant Duke never fails despite their brutal assaults. Once fortunately withdrawn, these orally borne divisions always leave my Duke ready for revival, thanks to its faithful and rapidly replenishing sebocytes (5).

I invariably succeed to build private follicular homes lodging my good fellow, Duchess Flora and her gram-positive knights (6), among which Sir Propionibacter is, without doubt, the bravest (7). They find these condominiums cosy, supplied with luxuriant

food, giving privilege to those deprived by oxygen through my squalene companion (8) or those where damn essential fatty acids cannot be found (9). Brother Sun always shines on my enterprise, helping me a lot (10).

I take pleasure in carefully selecting my victims irrespective with gender or ethnies, but rather upon their genetic profile, androgenic vigour, potent sebaceous equipment and, better, their prompt fiery reactions you call inflammation, leading to subsequent deep dermal invasions that I find so elegantly disfiguring (11,12).

From the brief achievement I have depicted, it is clear to me that my quest still prevails: Did you ever succeed in preventing my actions? Will the moment come you could mail to every Homo sapiens: acne is not any longer a human skin disorder?

You can adopt any scientific arsenal for defying me. I am confident since fewer and fewer brains pay attention to me. I am alas referring to a Kligmanian dogma where the commonest affliction is always more ignored, the only point upon which I do agree with this Philadelphian master.

Although a bewitching lady, I intend to behave as a good girl and give you a starting clue. Why does oily sebum turn to thick/solid? Look around the lipid oxidative pathways, scavenging enzymes and their dictatorial genes. Squalene and acne are specific to humans (8,13,14)... just a coincidence?

I leave you with this scientific challenge, still riding my broom
towards my 'oily' Grail...
Aetiologically yours

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Viewpoint 1

Acne: a common disease and socioeconomic problem

Acne is a most common disease affecting all ages and ethnic groups. In white Caucasian populations nearly 85% of individuals aged 12–25 present a variant clinical picture of acne. Although not life-threatening and not a major player in clinical and laboratory research, acne markedly influences quality of life and constitutes a socioeconomic problem. Not less than 15–30% of acne patients require medical treatment due to the severity of their clinical condition, 2–7% of them experience life long post-acne scars. Acne is the leading dermatologic diagnosis with 10.2 million diagnoses (25.4% of the 10 most common dermatologic diagnoses) according to a National Ambulatory Medical Care Survey conducted in 1995 in the USA. In 1996–98, 6.5 million new prescriptions at a value of over \$1 billion per year were provided to US patients for systemic antiacne medication only. The worldwide costs for systemic and topical acne treatment were calculated to represent 12.6% of the overall costs for the treatment of skin diseases.

Classical aspects of acne pathogenesis

Acne is a chronic inflammatory, exclusively human disease of the pilosebaceous unit, mostly affecting the sebaceous gland follicles – usually referred to as sebaceous follicles – located on the face, chest, shoulders, and back, where they are most common. The aetiology of acne is not yet fully clarified but it is widely accepted that its pathogenesis is multifactorial, with abnormal follicular differentiation and increased cornification, enhanced sebaceous gland activity and hyperseborrhea, bacterial hypercolonization, as well as inflammation and immunological host reaction being the major contributors.

Modern aspects of acne pathogenesis

Ongoing research is modifying the classical view of acne pathogenesis through identification of up-stream mechanisms leading to the phenotypic and laboratory findings mentioned above. Androgens, skin lipids, inflammatory signalling, and regulatory neuropeptides seem to be mainly involved in this multifactorial process. Also, there is increasing evidence that hereditary factors play an important but indirect role in acne (1).

Evidence for hereditary factors in acne point to the role of androgens and lipids

Although evidence of familial clustering exists (2) and an association of frequency and severity of acne in families with heavy course in the descendants was described (3), varying distribution and severity of acne were shown in homozygotic twins (4), and among heterozygotic twins acne was present in 54% sets only (5). Interestingly, evidence of direct genetic association of acne with androgen and lipid abnormalities has been observed: neonatal acne was found to be associated with familial hyperandrogenism (6), inadequate activity of steroid 21-hydroxylase, as well as CYP21 gene mutations have been reported to be involved in the pathogenesis of acne (7), and identical sebum excretion rates were described in homozygotic but not in heterozygotic twins (4). Moreover, the associations with biochemical markers involve lipids: lower serum levels of apolipoprotein A1 (2) and lower essential fatty acid levels in sebaceous wax esters and in epidermal acylceramides (8) were found in twins with acne rather than in non-acne twins.

Androgens, sebum and acne

Several clinical observations point to a major role of androgens in the pathogenesis of acne. Androgens play an essential role in increasing the size of sebaceous glands and stimulating sebum production (9) as well as in stimulating keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum (10,11). Acne begins to develop at the time of adrenarche when the adrenal gland starts to produce large quantities of dehydroepiandrosterone sulfate, a precursor for testosterone (12,13). Conditions of androgen excess or hyperandrogenism are associated with increased sebum production and the development of severe acne (14). Acne-prone skin exhibits a higher androgen receptor density (15) and higher 5 α -reductase activity (16) than not involved skin. Conversely, antiandrogens reduce the synthesis of sebaceous lipids and improve acne (17), whereas androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne (18).

Androgens need co-players to stimulate synthesis of sebaceous lipids

Rosenfield et al. (19) found that sebaceous lipid synthesis is stimulated by the presence of both androgens and peroxisome proliferator-activated receptor (PPAR) ligands. In addition to androgen receptors, PPAR receptors are abundantly present in human sebaceous glands (20). Among them, PPAR α has been associated with lipid synthesis. One of the strongest natural PPAR α ligands is the 5-lipoxygenation product leukotriene B₄, whose precursor, arachidonic acid, was shown to induce sebaceous lipogenesis in cultured human sebocytes (21). Not only antiandrogen treatment but also 5-lipoxygenase inhibitors were found able to significantly reduce synthesis of sebaceous lipids and acne lesions, as shown in a pilot clinical study (22).

Inflammatory signalling is involved in the initiation of acne lesions

Hyperproliferation of the follicular epithelium leads to formation of microcomedones, which are the first acne lesions and can be found in normal-looking skin (23). The sebaceous follicle undergoes a cycling process which may explain a natural resolution of microcomedones and also comedones and, on a longer term, the resolution of the disease itself (24) (Fig. 1). The very early stage of acne lesion development, namely the beginning of microcomedones, is associated with vascular endothelial-cell activation and involvement of inflammatory events (25) which corroborates the suggestion that acne may represent a genuine inflammatory disorder without involvement of bacteria in its initiation (26). Similar results have been reported by Ingham et al. (27) who found bioactive interleukin (IL)-1 α -like material in the majority of open acne comedones from untreated acne patients. There was no correlation between levels of any cytokine, in particular IL-1 α , and the numbers of follicular microorganisms. It seems that healthy sebaceous glands also express various cytokines. In our laboratories, we stressed sebocytes *in vitro* by maintaining them in serum-free medium and detected IL-1 α expression at the mRNA and protein levels (28). Antilla et al. (29) showed that IL-1 is present in normal sebaceous glands and Boehm et al. (30) detected mRNA for IL-1 α , IL-1 β , and tumor necrosis factor- α in normal sebaceous glands by *in situ* hybridization. Interestingly, IL-1 α induced hyperproliferation of follicular keratinocytes in isolated sebaceous follicle infundibula maintained *ex vivo* (31).

Which factors interrupt cycling of the sebaceous follicle?

Overstimulation of the initiation of the preclinical inflammatory process or defect negative feedback regulation may be major reasons for the interruption of the normal cycling of the sebaceous follicle and be responsible for the initiation of the clinical inflammatory process in acne (Fig. 1). As mentioned above, hereditary factors and excess androgen activity, e.g. in puberty, may cause overstimulation, thus triggering sterile inflammatory phenomena (Fig. 2). Neuroendocrinologic regulation and environmental factors, such as dietary lipids and smoking, have also been suggested to represent trigger mechanisms.

Role of neuropeptides for regulation of clinical inflammation in acne

There is current evidence that regulatory neuropeptides with hormonal and non-hormonal activity may control the development of clinical inflammation in acne. Numerous substance P immunoreactive nerve fibers were detected in close apposition to the sebaceous glands, and expression of the substance P-inactivating enzyme neutral endopeptidase was observed within sebaceous germinative cells of acne patients (32). *In vitro* experiments using an organ culture system demonstrated that substance P-induced expression of neutral endopeptidase in sebaceous glands in a dose-dependent manner. On the other hand, treatment of sebocytes with IL-1 β which resulted in marked increase of IL-8 release (33) was partially blocked by co-incubation of the cells with α -melanocyte-stimulating hormone in a dose-dependent manner (34). Corticotrophin-releasing hormone induces the synthesis of sebaceous lipids *in vitro* (33), and adrenocorticotrophic hormone evokes adrenal dehydroepiandrosterone to regulate skin inflammation (35). These current findings indicate that central (36) or topical stress (33,37) may, indeed, influence the feedback regulation, thus inducing the development of clinical inflammation in early acne lesions.

Dietary lipids and inflammatory process in acne

Topically applied linoleic acid was shown to induce an almost 25% reduction in the overall size of microcomedones over a 1-month treatment period (38). On the other hand, arachidonic acid, an essential, long-chain, pro-inflammatory ω -6 fatty acid, stimulates IL-8 and IL-6 synthesis in cultured human sebocytes (39) and enhances synthesis of sebaceous lipids (21). Leukotriene B₄ inhibition *in vivo* reduces concomitantly pro-inflammatory sebaceous fatty acids and inflammatory acne lesions (22). Inuit Eskimos, the inhabitants of the Okinawa island and Chinese have

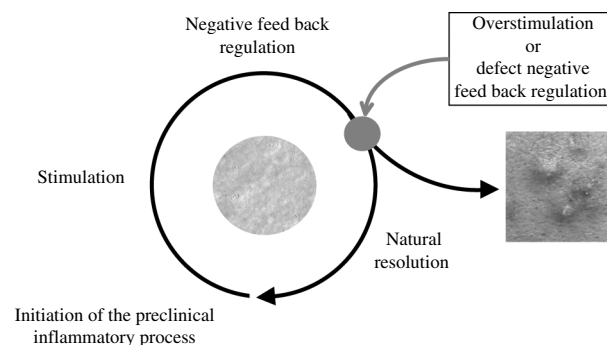


Figure 1. Natural cycling of the sebaceous follicle (microcomedone). Uncontrolled overstimulation or defect negative feedback regulation lead to the development of clinically detectable acne lesions, such as comedones and inflammatory papules.

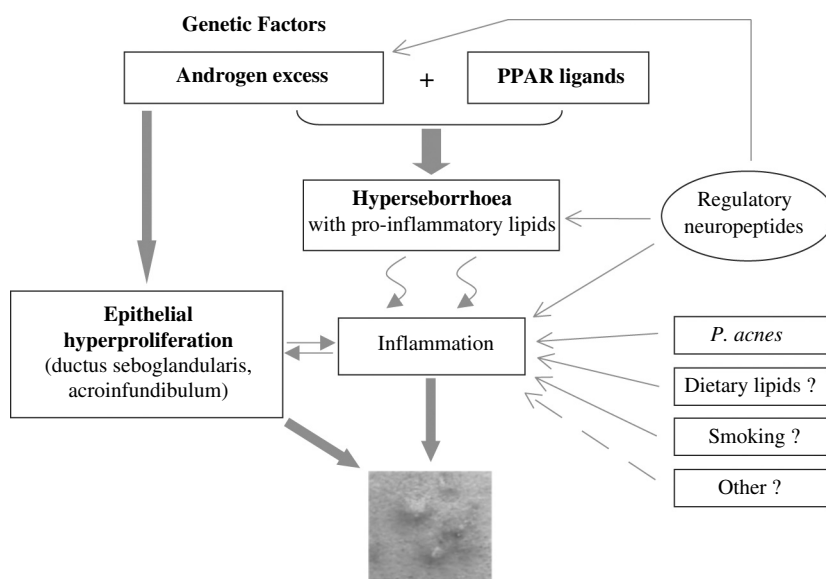


Figure 2. Modern aspects of acne pathogenesis. Androgens, peroxisome proliferator activating receptor (PPAR) ligands, regulatory neuropeptides with hormonal and non-hormonal activity and environmental factors induce hyperseborrhoea, epithelial hyperproliferation in the ductus seboglandularis and the acroinfundibulum and expression of pro-inflammatory chemokines/cytokines with comedones and inflammatory acne lesions.

been observed to develop acne with the changing of their nutrition habits (20,40,41). Westernized nutrition includes low amounts of ω -3-fatty acids and antioxidant vitamins and higher amounts of the pro-inflammatory ω -6 and *trans*-fatty acids. The ratio ω -6/ ω -3 fatty acids in westernized nutrition is 20:1, in contrast to a 1:1 ratio in traditional nutrition (42).

Overall, the role of nutrition in acne still remains controversial. A current study reported that the Kitavan islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay do not present acne (43), however, other authors suggested that these population studies may have detected a genetic background rather than a nutritional effect (44).

Smoking and acne

Smoking was currently reported to be a clinically important contributor to acne prevalence and severity (45). Recent investigations revealed that cigarette smoke contains high amounts of arachidonic acid and polycyclic aromatic hydrocarbons which induce a phospholipase A2-dependent inflammatory pathway (46); this effect may further stimulate arachidonic acid synthesis (37). On the other hand, smokers have a higher saturated fat intake with their food and much lower polyunsaturated fat intake, principally due to a lower linoleic acid intake compared with nonsmokers (47).

Are *Propionibacterium acnes* (*P. acnes*) and toll-like receptors involved in the initiation of acne lesions?

Toll-like receptors 2 and 4 as well as CD14 are expressed in human monocytes. Chemokine/cytokine synthesis in these cells is induced through activation of Toll-like receptor 2 by *P. acnes* (48). These findings in combination with the expression of active Toll-like receptors 2 and 4 and of CD14 in human keratinocytes (49) have implicated *P. acnes* and Toll-like receptors in acne inflammation. However, *P. acnes* was unable to induce IL-1 α expression in human keratinocytes *in vitro* (50), therefore, *P. acnes* seems to induce later events not being involved in the initiation of acne lesions. The successful therapeutic action of antibiotics in acne has been attributed to an antibacterial activity but it may also be seen as a para-antibiotic, anti-inflammatory effect.

Conclusion

Acne vulgaris is likely to be a genuine inflammatory disease with androgens, PPAR ligands, regulatory neuropeptides, and environmental factors being agents able to interrupt the natural cycling of the sebaceous follicles and lead microcomedones to form comedones and inflammatory lesions (Figs. 1 and 2). Pro-inflammatory lipids and chemokines/cytokines seem to act as mediators for the initiation of acne lesions. *P. acnes* is not initially involved but may mediate later inflammatory events leading to worsening of the lesions.

This concept of acne pathogenesis may be controversially discussed, however, it initiates a fruitful discussion for better understanding this most common disease.

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Viewpoint 2

Dermatologists primarily attack acne from the outside in. Of the three factors long incriminated in the pathogenesis of acne, sebaceous duct obstruction, infection, and excessive production of sebum (1), first-line therapy focuses on the first two: drying or exfoliating agents are used to keep the duct open, and hygiene, antiseptics, and antibiotics are used to control the infectious element. When all of this fails, a toxic systemic retinoid is used to trigger sebocyte atrophy.

Our perspective is that an improved inside-out approach should be developed. The fundamental problem is the sebocyte differentiation that underlies sebum production. Acne will not develop without sebum, and sebum will not be produced without androgenic stimulation of sebocytes. Male-hormone stimulation is a prerequisite and an incitant for acne vulgaris, to paraphrase Hamilton's classic observation on common baldness (2). Androgen is necessary for the growth and development of the sebaceous gland (3–5). Common inflammatory acne only occurs when androgens rise at puberty (6). Furthermore, acne is one of the manifestations of hyperandrogenism (7). This underlies about half of the cases of even mild acne in women when it persists into adulthood (8). The vast majority of androgen excess is due to polycystic ovary syndrome (PCOS). PCOS is extraordinarily pleomorphic, lacking the classic anovulatory symptoms and obesity 20–50% of the time (9). The possibility of PCOS is

often ignored by dermatologists, although, it not only causes infertility but is associated with the metabolic (insulin resistance) syndrome, which carries cardiovascular risk. Basic research suggests that the compensatory insulin excess independently aggravates the acne. Estrogen-progestin combination pills or antiandrogens are effective treatments because they, respectively, suppress gonadal androgen production or androgen action. However, the side effects make them unacceptable for the most severely affected teenage boys.

Targeting the branch point in androgen action that is specific to the sebaceous gland would seem likely to revolutionize the treatment of acne. Unfortunately, nature has not readily revealed much about the postreceptor aspects of androgen action in any of its target glands, the sebaceous gland included. While androgens have a proliferative effect on cultured human sebocytes (10,11), they have only a minimal effect on differentiation of sebocytes in culture, and this effect pales beside that of peroxisome proliferator-activated receptor (PPAR) agonists (12).

PPAR agonists are master regulators of lipid metabolism that, in the presence of insulin, glucocorticoid, and a cyclic AMP generator, initiate differentiation of rat prepubertal sebocytes (Fig. 1). Intriguingly, the PPAR agonist that increases sebocyte

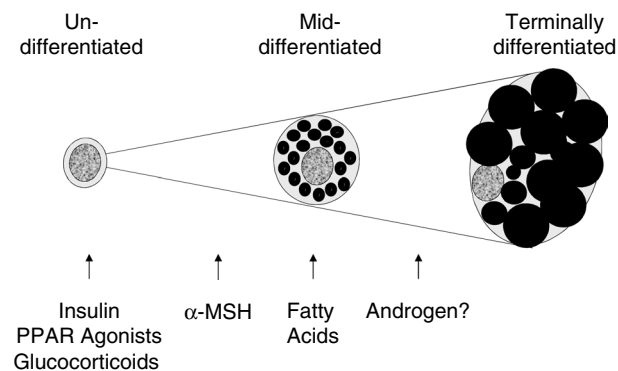


Figure 1. Diagram of working hypothesis about the site of hormonal and metabolic signaling in the induction of sebocyte differentiation. Insulin-like growth factor-I partially substitutes for insulin, and growth hormone is synergistic with insulin in inducing sebocyte differentiation. The major site of androgen action is postulated to be late in sebocyte differentiation.

differentiation the most in both cultured rat prepubertal sebocytes, which are immature, and cultured human SZ95 sebocytes, which are partially mature, is the essential long-chain fatty acid, linoleic acid (11,13). We suspect that this is because the PPAR agonist aspect of its action is to induce an early aspect of sebocyte differentiation, which brings the sebocyte to the mid-differentiated state at which fatty acids reach the critical level required for them to become signaling molecules for the next step in sebocyte differentiation.

Lipid metabolism is the key to sebocyte differentiation, which occurs by the accumulation of lipid droplets. Every model of sebaceous gland hypoplasia, other than that brought about by androgen deprivation, involves defects in lipid metabolism (14–17). Of these, the knockout of the melanocortin 5 receptor is particularly interesting because this receptor has been identified in sebocytes (18,19), where it would seem to mediate the augmentation of androgen-induced sebogenesis by α -melanocyte-stimulating hormone (20).

In summary, the root of acne seems to lie at the juncture of hormone action and lipid metabolism in sebocyte differentiation. Optimal acne therapy can only be expected to evolve from research in this area.

Viewpoint 3

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

Sir William Bragg

As a microbiologist, I should try and convince everyone that acne without propionibacteria would be like tuberculosis without mycobacteria – but I cannot. I do not believe that bacteria play a part in the onset of acne or that they contribute to the fundamental abnormality that differentiates acne-prone from non-acne-prone follicles. I have argued before that inflamed lesions resemble chronic infections of functionally blocked follicles (1),

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and I still believe that this is true. Within such follicles, propionibacterial multiplication leads to tissue damage whereas in normal follicles it does not, despite the similar numbers of organisms present. In terms of inflammatory potential, where and how propionibacteria die may be just as significant as where and how they live.

The fate of an individual follicle may be sealed when a number of independent events occur, by chance, in a precise order. The challenge is to identify what the precipitating or first event might be. Accumulating evidence suggests that an early event (but not the earliest event) is the release of interleukin-1 α (IL-1 α) from

ductal keratinocytes. Non-lesional follicles in acne-prone skin are subclinically inflamed, and the pattern of expression of various markers is indicative of an innate response triggered by IL-1 α (2). These follicles show no evidence of microcomedone formation or loss of basement-membrane integrity. Given that less than 20% of healthy-looking follicles in acne-prone skin contain viable propionibacteria (3) [compared with 91% of normal follicles in healthy skin (4)], then it follows either that propionibacteria were never present and thus did not trigger the innate response or that proliferation of *P. acnes* induces an innate response so potent that the organisms are rapidly eliminated. Comedones from prepubertal children do not contain propionibacteria suggesting that involvement of the organisms in lesion formation is a relatively late event (5). In organ culture, IL-1 α alone can promote comedogenesis (6).

If propionibacteria do not induce IL-1 α secretion, then what does? Release of IL-1 α can be facilitated by biological (e.g. substance P, bacterial heat shock proteins, and ligation of CD59) and physical factors. Mechanical trauma is an important exogenous stimulus for release of IL-1 α (7,8), of recognized importance in psoriasis. Thus, local injury is the most probable inducer of IL-1 α secretion. During the adrenarche, the first flow of sebum through the previously empty duct might create shear forces of sufficient magnitude to release IL-1 α from keratinocytes in the infrainfundibular region where fewer cell layers are present. Might adrenal androgens also drive the accumulation of IL-1 α ? Fluctuations in the sebum excretion rate or turbulence in sebum flow may predispose to subsequent waves of IL-1 α release.

What makes follicles in acne-prone skin so susceptible to IL-1 α -driven inflammation? Do they contain an inducer of its synthesis/release? Are factors (such as IL-1Ra or IL-1RII) that neutralize its biological activities less abundant? Often overlooked is the fact that IL-1 α can diffuse across an intact basement membrane (9) into the dermis where it could induce the expression of endothelial adhesion molecules and drive the accumulation of CD4⁺ Th-1 cells. If any of these T cells encounter their antigen (the predominantly Th-1 response is consistent with an intracellular microbial pathogen or an auto-antigen) in a perifollicular location, they will become activated and thereby engage the adaptive immune response leading to visible inflammation.

Could there be a parallel pathway towards inflammation that is initially antigen and IL-1 α independent but which sets a similar series of events in motion? Might sebum alone induce an innate response and, if so, how does it do it? The IL-1 receptor belongs to the same superfamily as Toll-like receptors (TLRs). Binding of their respective agonists triggers a cascade of intracellular events leading to the activation of NF- κ B and the induction of early response genes including those encoding pro-inflammatory cytokines, chemokines, and adhesion molecules. Thus activation of TLRs will, to a significant extent, mimic the action of IL-1 α and also promote its synthesis. Researchers interested in the possible role of TLRs in acne pathogenesis immediately targeted *P. acnes* as the most obvious source of the pathogen-associated molecular pattern recognized by TLR-2. Subsequent experiments confirmed that TLR-2 was up-regulated on perilesional macrophages and that *P. acnes* could indeed activate TLR-2 and trigger release of IL-8 and IL-12 from peripheral blood mononuclear cells (10). IL-12 promotes Th-1-cell differentiation whereas IL-8 is chemotactic for neutrophils. Early acne lesions are characterized by a paucity of neutrophils. They are more likely to be involved later in the generation of pustules.

Human β -defensin 2 (HBD-2) is an antimicrobial peptide and endogenous agonist of TLR-4 that is induced via TLR activation. HBD-2 is up-regulated within comedones and inflamed acne lesions (11). Theoretically, HBD-2 could be produced in response to activation of TLR-2 by *P. acnes*, but in our search for the earliest effector of pathological change, neither *P. acnes* nor HBD-2 are contenders. There is accumulating evidence for a variety of other endogenous mechanisms of TLR activation (12) that fits with the danger model of the innate response proposed

by Matzinger (13). Several putative physiological ligands of TLRs including human heat shock proteins, oligosaccharides of hyaluronan [comedones contain hyaluronidase activity (14)], and most intriguingly, fatty acids may be involved in acne pathogenesis. Polyunsaturated dietary fatty acids (n-3) inhibit whereas the saturated fatty acid, lauric acid, potentiate the ligand-specific activation of NF- κ B via TLR-2 or TLR-4 (15). This raises the obvious question of whether fatty acids in sebum might also modulate TLR-mediated activation of NF- κ B and induction of early response genes. Human sebum contains two unique fatty acids, sapienate (C16:1 Δ 6) and its two carbon extension products, sebaleate (C18:2 Δ 5,8) together with variable amounts of the essential fatty acid, linoleate (C18:2 Δ 9,12). Sebum from prepubertal children contains higher amounts of Δ 9 fatty acids and Δ 6 fatty acids are less abundant. As sebum excretion rises in response to increasing amounts of adrenal androgens (especially DHEAS), the concentration of Δ 9 fatty acids falls and the concentration of Δ 6 fatty acids increases. Moreover, sebum from acne patients contains more sapienate and sebaleate than sebum from non-acne subjects (16). Sebocytes derive sapienate from palmitate via the action of a Δ 6 desaturase that preferentially converts linoleate into γ -linolenate (17). Sebocytes also produce 15-lipoxygenase-2 that competes with the desaturase for linoleate (arachidonate is a preferred substrate) (18). Additionally, sebum linoleate is susceptible to degradation via beta oxidation (19). Thus, multiple mechanisms deplete linoleate and thereby alter the content of both pro- and anti-inflammatory metabolites in native sebum (including activators of PPAR α and γ). Modification of sebum composition during the late adrenarche/early gonadarche may exert a critical influence on pro-inflammatory events, comedogenesis, and the expansion of the propionibacterial flora. Components of sebum that may act as endogenous modulators of TLR signaling could turn acne on or off.

Where does this leave propionibacteria? Amongst the CD4⁺ T-cell infiltrate around early inflamed acne lesions are a sub-population that recognize antigens from *P. acnes* (20). Multiplication, death analysis of the organisms within subclinically inflamed and functionally blocked follicles might represent the next stage of lesion development, but that is another story.

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Commentary 1

Does variation in the innate immunity of the skin predispose some individuals to acne?

Most people get acne to some degree, and some are born with a predisposition to certain types of acne. Similarities in the patterns of acne lesion, duration, and severity are reported to run in families. Although hypercornification of the distal Outer Root Sheath (ORS) of the hair follicle and the pilosebaceous duct in concert with increased sebum production and abnormalities of the microbial flora are considered to be major factors in the pathogenesis of acne vulgaris (1–3). The role of microbial agents in acne is still not clear. Why do some colonized ducts become inflamed and others not? Why do some acne vulgaris patients respond well to antibiotic drugs and others not? If microbial agents are so important, why is there little relationship between the numbers of bacteria on the skin surface and the severity of acne (4,5)?

It has been suggested that variation in the microenvironment of the duct may be important. Such microenvironmental variations are likely to influence the production and activity of inflammatory mediators such as lipases, neuramidases, phosphatases, and proteases (6–8). However, an alternate hypothesis might be that acne vulgaris patients suffer from a dysregulation of the production of innate and specific antimicrobial peptides.

More than 500 antimicrobial peptides have been described in plants, insects, amphibians, and mammals, with broad-spectrum activity against bacteria, fungi, and viruses and as such represent an integral part of innate immunity (9,10). Of particular interest are the mammalian defensins, a family of cationic antimicrobial peptides, 28–42 amino acids long, containing three disulphide bonds. They have been divided into two subtypes, the α -defensins and the β -defensins (11). The α -defensins are found in neutrophil granules or in the paneth cells of the small intestine (12). The three β -defensins so far identified, human β -defensin 1 (hBD1), human β -defensin 2 (hBD2), and human β -defensin 3 (hBD3) are produced in various epithelia (13–16). hBD1 and hBD2 are expressed in human terminal hair follicles in the distal ORS, surrounding the hair canal and in the pilosebaceous duct of the hair follicle (16). This finding is consistent with the concept that these regions are highly exposed to microbial invasion as well as to the physiological skin microflora. In contrast, hair follicle compartments that are rarely exposed to microbial invasion such as the proximal ORS and Inner Root Sheath (IRS) as well as the hair follicle bulb, including the dermal papilla, showed only very weak hBD1 and hBD2 expression.

Both hBD1 and hBD2 show differential up-regulation in lesional and perilesional acne skin when compared to normal back skin from healthy controls and interlesional epithelium of the same patient. However, marked variations in hBD1 and hBD2 Immuno-reactivity (IR) intensity have been reported between sex- and age-matched patients, between face and back skin as well as between different hair follicle types (16,17). This suggests that some individuals have higher levels of constitutive, innate, immunity in the skin and that some may also have a much stronger response to external stimuli. We suggest that the observed differences in expression of defensins in normal human skin may

explain why some people are prone to acne and others not, why some colonized ducts become inflamed and others do not. Why some people have a predisposition to certain types of acne and why the patterns of acne lesion, duration, and severity run in families. Finally, we also suggest that good responders to antibiotic antiacne treatment may differ in their β -defensin levels and/or activity from bad responders (18–20).

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Commentary 2

Les jeux sont fait: put your bets on FGFR2

Now is the time to place your bets in the acne casino. Studies in molecular genetics determined the pathogenesis of many disorders, but even in Cockayne's (1) classic on genodermatology acne was not discussed. Present in many complex genetic syndromes, the keys to acne's pathogenesis may be discovered through genetic studies. Recent findings related to two genetic syndromes and a large twin study exemplify the potential of genetic studies in understanding acne.

Apert syndrome (OMIM 101200) is a sporadic form of craniosynostosis, with premature sutural closure and cranial and facial malformations and limb changes, including mitten-type symmetrical syndactyly. Apert Syndrome is caused by a dominant mutation of paternal origin in fibroblast growth factor receptor 2 (FGFR2) (OMIM 176943). Over 30 years ago, nine Apert Syndrome patients were carefully studied and found to have extensive comedonal and cystic acne on their forearms, face, back, and chest (2). Extension of acne beyond its usual body sites is characteristic of this syndrome, confirmed by subsequent studies, as have frequent hyperhidrosis of the scalp and palms, wrinkling of the forehead, and interrupted eyebrows (related to bony defects) (3).

The mutations of Apert Syndrome are frequently activating (gain of function) mutations which increase FGFR2 interactions and the receptor's affinity for fibroblast growth factors, including keratinocyte growth factor. Epidermal mosaicism for a comedonal nevus with a Blaschko line distribution in a patient without Apert syndrome was associated with a typical Apert ser252trp mutation in affected skin but not in normal skin (4,5). There were 508 potential SNPs (Single Nucleotide Polymorphisms) for *FGFR2* in the NCBI database on December 28, 2004, that could be used for acne genotyping. The gain-of-function Apert mutation leads to FGF down-regulation of noggin with resulting interference with cranial suture formation (6). Noggin has a role in hair follicle formation as well (7,8). In a knockout model for one of the alternatively spliced forms of FGFR2 there was marked impairment of hair follicle development (9). The acne in Apert syndrome responds to isotretinoin, and the effect of retinoids on FGFR2 will be of interest as well (10). Thus FGFR2 is a candidate for extensive study in acne; focusing such studies on the follicle and sebaceous gland has a high probability of success.

PAPA syndrome (OMIM 604416)

Pyogenic sterile arthritis, pyoderma gangrenosum, and severe cystic acne (beginning in infancy in some patients) are associated in a syndrome with mutations in a CD2-binding protein (CD2BP1). The syndrome is dominantly inherited and is associated with reduced binding between CD2BP1 and its effector proteins (11). Pysin, the protein in Familial Mediterranean Fever, binds to this molecule as well (12). This inflammatory system and

its control deserve more study in patients with acne and without the syndrome.

XYY Phenotype

The most complete article on nodulocystic acne as a feature of the XYY genotype is over 30 years old and even then ascertainment bias was recognized (13). Save your chips.

Twin Studies and Population Studies

A recent study of over 1500 pairs of monozygotic and dizygotic twins showed that 81% of the variance in acne was attributable to additive genetic factors (14). It will take a large grub stake – adding molecular genetic studies to well characterized family studies – but those studies may have a real long-term payoff.

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Commentary 3

Blinded by the obvious

I cannot remember whether it was Albert (as in Kligman) or Sam (as in Shuster) who commented that we would only make significant advances in dermatology when there is the first blind dermatologist. We can all be blinded by science – and I am no

exception much to the delight of our adversary – the beguiling acne witch.

She is laughing at us for missing some of the obvious experiments which have been staring us in the face for the last many years. Patients are aware that acne resolves, but many investigational dermatologists have not recognized this naturally

occurring event which could provide us with some very useful information. The number of publications on resolution of acne can be counted on one hand.

There are two aspects of the resolution. There is resolution of individual lesions and of the disease as a whole.

We have been obsessed with looking at initiating factors, and yet, some wonderful pharmacological agent may be found by investigating this natural event of resolution.

We also, for too long, have been obsessed with measuring total skin-surface phenomenon, such as total skin-surface lipids, total surface-lipid composition and surface bacteria. At times, the limitations of technology have not been sophisticated enough to allow measurement from individual follicles. Pleasingly, some recent studies have focussed on individual follicles. There is no doubt that acne is likely to be disease of genetically acne-prone follicles. We need, when possible, to compare acne-prone follicles with non-acne-prone follicles.

Furthermore, many investigators including myself have also collected samples from patients with different types of acne and pooled the samples.

Acne patients do differ. There are many phenotypes in which different genetic and some environmental factors might be playing the role. In the future, studies on acne must precisely define the acne phenotype from which the sample is collected.

The following factors may be relevant: the age of onset and its relationship to puberty, the age of resolution, site of disease; not all patients with the same level of seborrhoea have the same degree of acne, thus seborrhoea is likely to be a distinct phenotype. Some patients have predominantly inflammatory acne, others predominantly come-donal acne. Even within those patients with many comedones there are variations. Some patients are characterised by having many blackheads others many whiteheads. Up to 8% of individuals have sandpaper acne and more infrequently macrocomedones or submarine comedones.

We also need to record the specific type of inflammation; the inflammation may be superficial or deep. Very infrequently the patients may have sinus tracts or acne conglobata.

We also should note the presence and type of scars. It is likely that the inflammation which leads to scarring is different than that seen in non-scarrers. This difference may be genetically determined.

Many patients have mixed types of such lesions; sometimes, even in the same patient certain lesions are seen more characteristically at one specific site. Thus, whenever a sample is taken from the acne patient these phenotypic facts should be recorded.

Response to treatment may be determined genetically. Some patients seem to respond more quickly than others; some patients relapse more quickly than others, and this appears to be true especially following oral isotretinoin.

There is a wide expression in the severity of acne. Most university dermatology departments see the tough end of the disease.

Therefore they tend to carry out research on this type of acne patient, which may not always represent the disease as a whole. Acne patients who are not treated by academia probably have a shorter duration of acne, and comparative investigations on this group of acne patients and those with more severe and longer lasting disease could throw useful light on the issue of resolution.

We have also been blinded by the witchcraft of clinical trials, upon which much of our clinical database depends. Clinical trials, however, do not often reflect our patients in the clinic. With the exception of drugs such as oral isotretinoin, clinical trials usually incorporate patients with less severe disease. Clinical trial subjects are almost a different race compared to the patients we see in the clinic. Many clinical trial patients usually have had shorter disease, fewer treatments and therefore less likely to be resistant to the effect of antibiotics.

We frequently fail to ignore just what the patient believes about treatments. Can a patient distinguish a (significant) 10% difference between two treatments? Some recent studies have appropriately included, as an important endpoint, the patient's thoughts about the treatment. We have over 30 years or more conducted clinical trials in a rather standardized way without too much thought as to how the outcomes relate to management of the patient in the clinic. Patient's perceptions, albeit difficult to quantify, should be included in clinical trials.

The acne witch is persistent; she produces much suffering over many years, but the clinical trials provide information only over a 3-4-month period; rarely are clinical trials performed for longer than 4 months. We desperately need data from the clinic as how to optimally manage acne patients in the clinic. Most dermatologists prescribe combined therapies and have done so for many years. Despite this habit there are very few clinical trials on combination therapy, although some recent studies support that what we do in the clinic is possibly correct. We need to address not only the long-term benefit of therapy but also the safety and the cost of the multiple treatments which we can prescribe. These are in excess, a 1000 treatment combinations in most countries!

I hope that some of the suggestions, which I should have acted upon many years ago, will be taken forward.

We desperately need more investigators; the acne wizards of the world [AI (two of them), John, Jim, Sam Bill, and others] are all now well past the age of 60-70 years of age. There are relatively few doctors and scientists tackling the formidable problem of acne.

Acne may not be attractive to the sufferer, but it is an extremely attractive and challenging condition to investigate. Best of luck!

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