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Strategic Targets in Acne: The Comedone Switch in Question

Jean-Hilaire Saurat

SCAHT – Dermatotoxicologie, Centre Médical Universitaire, Geneva, Switzerland

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Acne · Comedone switch · Comedogenesis · Pilosebaceous duct

Abstract
The sequence of events and mechanisms leading to the development of the primary acne lesion, the comedone, is revisited. Recent knowledge obtained both from lineage tracing experiments in the mouse and the pilosebaceous response to xenobiotics in humans provides robust models for further understanding key biological events at the cellular roots of comedogenesis. The focus is set on the LRIG1+ sebaceous stem cells in the isthmus of the pilosebaceous duct. The master switch that transforms a normally functioning sebaceous gland into a microcomedone and the hierarchy of factors involved in this process are reviewed. The key strategic target in acne care appears to be the naïve pilosebaceous follicle that is not involved yet in the acne cycle. The prevention of the comedone switch implies that the key switching factors are adequately controlled in the long term.

Introduction

'Although a number of different reviews have been published on acne pathogenesis, none of them gave a clearcut sequence of events and mechanisms leading to the development of a noninflamed lesion followed by its progression to an inflamed one' [1].

This is the introduction to a well-documented review in which the authors argue with the monopolistic view that a microbe, *Propionibacterium acnes,* might be the only cause of comedogenesis and retain the viewpoint that comedogenesis may occur in the absence of *P. acnes*.

In the present mini-review, I take this view forward, by setting the focus on key initial biological events at the cellular roots of comedogenesis: the LRIG1 sebaceous stem cells in the isthmus, a fact that should reconcile many opposite views [2].

Focusing on the Goals of Acne Therapy

What Are the Goals of Acne Therapy?

When asked the question 'what are the targets of acne therapy?', most dermatologists would rightly quote the 4 processes involved in the formation of acne lesions: (i) alteration of the keratinization process leading to comedones; (ii) increased and altered sebum production; (iii) inflammatory mediators released into the skin, and (iv) follicular colonization by *P. acnes* [3].

What Are You Actually Treating?

Another way to ask the question would be: 'What are you treating?' Most dermatologists would answer: inflammatory lesions (papules, pustules) and noninflam-

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Prof. Jean-Hilaire Saurat
SCAHT – Dermatotoxicologie, Centre Médical Universitaire
1, rue Michel-Servet
CH–1211 Genève 4 (Switzerland)
E-Mail Jean.Saurat@unige.ch

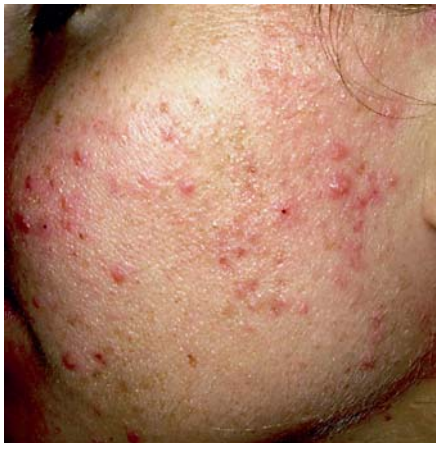

Fig. 1. Only a minimal percentage of sebaceous glands are clinically involved in any acne patient, even in severe cases (see text). SG = Sebaceous glands.

matory 'retentional' lesions (comedones and microcysts). And that answer is of course right again. Is it enough?

A further dimension may be considered: the two distinct, partially overlapping, processes occurring during the treatment of acne. One is to accelerate the healing of the few ongoing lesions. The other is to prevent the huge number of naïve sebaceous glands prone to enter the acne cycle. And this points to the often forgotten quantitative paradigm in the patient with acne: only a *minimal percentage of sebaceous glands are 'clinically lesional' in any acne patient.*

Figure 1 shows a part of the face of a moderate to severe acne case. The surface area is about 10 × 10 cm, thus 100 cm^2. According to seminal texts by Montagna [4], there are 400–900 sebaceous glands in each square centimeter of human skin on the forehead and cheeks. Therefore, in figure 1, if we take as a conservative average 500 sebaceous glands/cm^2, there should be 50,000 sebaceous glands under the surface. Let us count the acne lesions: at the most they are 131 in number. Therefore, only 0.25% of sebaceous glands are involved in visible lesions in this case, which is actually not a very mild one.

One may argue that many lesions might be invisible, 'the invisible comedone' according to Plewig and Kligman [5], which is correct. A significant percentage of sebaceous glands are 'clinically normal but histologically lesional' in acne-prone, normal-looking skin. Serially cut biopsy sections of normal-looking skin in an acne-prone individual will demonstrate histological features of microcomedones in up to 30% of the pilosebaceous units, which led Cunliffe et al. [6] to state: 'This finding clearly confirms the practical need to apply topical therapies to apparently noninvolved skin as well as to active acne lesions.' In clinical practice we have no tool to evaluate the number of microcomedones, except a posteriori, when a severe eruption of new lesions develops within a few days. Still we would never see more than 1,000 lesions within an area such as that shown in figure 1. This would correspond to an extraordinary situation, such as severe acute chloracne/MADISH (metabolizing acquired dioxin-induced skin hamartoma), when almost all the sebaceous glands may be involved synchronously [7].

From these observations it results that only a *minimal percentage* of sebaceous glands are 'lesional' in any acne patient, even in severe cases. The mean lifetime of each lesion is a few *days* for inflammatory and a few *weeks* for noninflammatory ones (see below). Therefore, the effects of topical acne prescription drugs are *an addition/combination* of (i) shortened time to healing of ongoing lesions *and* (ii) delayed or suppressed entry of naïve sebaceous glands into the acne cycle.

The Lifetime of Acne Lesions

The natural life cycle of acne lesions is difficult to capture, the key point being the accurate spatial tracking of lesions over time. As stated by Cunliffe et al. [6]: 'That comedones are temporary structures is self-evident to the clinician; otherwise a patient who develops acne at age 11 years and has predominantly comedonal lesions would by late adolescence have a face completely full of such lesions. Clinically this does not happen.'

Cunliffe et al. used markers of cell cycling and keratinocyte proliferation, and concluded that, like the hair follicles, normal pilosebaceous follicles and comedones undergo cyclical growth. This cycling phenomenon extended over 'a period of days or a few weeks rather than, as in the hair follicle, months'. Clinically the life cycle of whiteheads indicates that many resolved within 12 days and extracted blackheads refill over 2–6 weeks. This is consistent with posterior studies by J. Voorhees' group that the majority of visible comedones do not progress to inflammatory lesions, and they mostly resolve after 4 weeks [8]. Biopsy specimens from the normal-looking skin of acne patients that show no evidence of microcomedones or ductal hyperproliferation whatsoever have a significant inflammatory cell infiltrate around the follicle (particularly CD3+ and CD4+ cells and macrophages), which suggests that inflammatory events are involved in acne lesion initiation and may respond to anti-

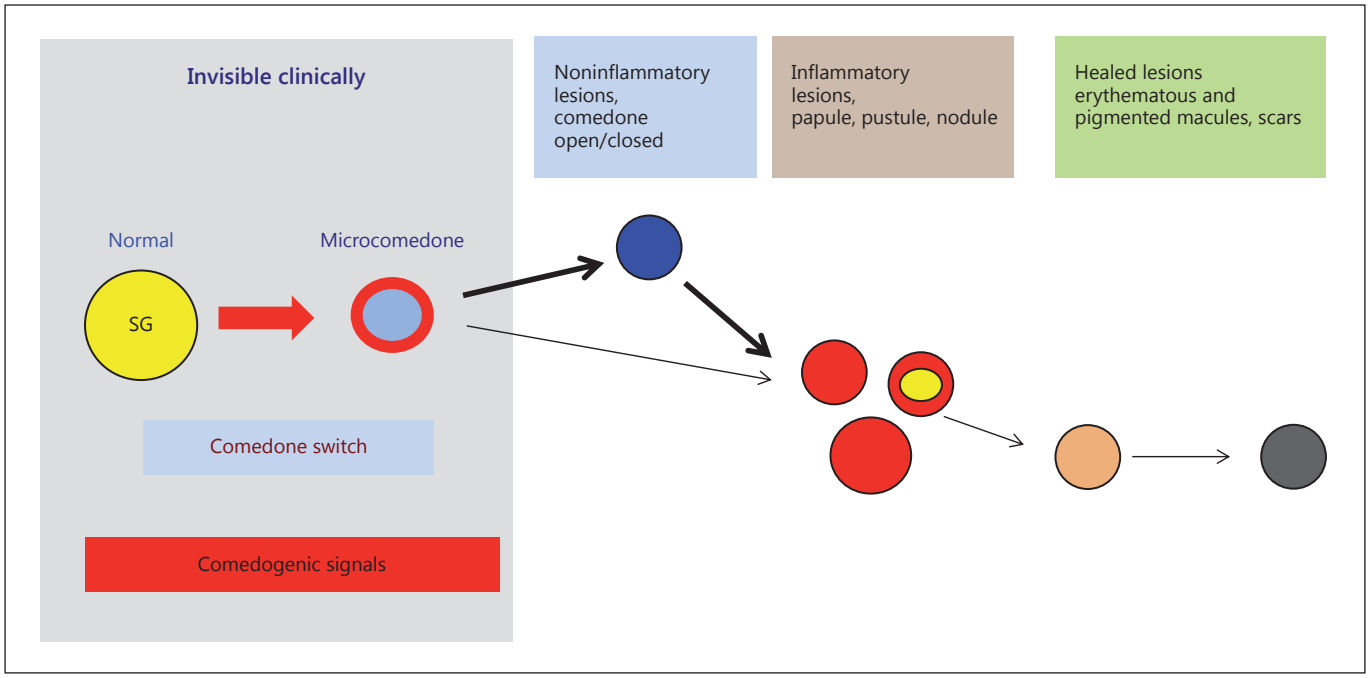

Fig. 2. The different lesions in the acne process, the acne lesional cycle [10]. SG = Sebaceous gland. Prevention of the comedone switch is the target for long-term acne therapy. This implies that normal nonlesional skin should be considered as the therapeutic target [6].

microbial agents [9]. These observations indicate that one effect of current topical prescription drugs may be the shortening of time-to-healing of ongoing lesions, a fact that has not, actually, been well demonstrated so far [10].

Delaying or suppressing the entry of naïve sebaceous glands into the acne cycle appears to be the key target, the modeling of which remains to be worked out.

The Entry of Naïve Sebaceous Glands into the Acne Cycle: The Comedone Switch

The various steps of the acne cycle have been well described (fig. 2). Factors putatively involved in each step of acne lesions have been studied by many groups worldwide in the past, but 'none of them gave a clearcut sequence of events and mechanisms leading to the development of a noninflamed lesion' [1].

It appears that the recent knowledge obtained both from lineage tracing experiments in the mouse and the pilosebaceous response to xenobiotics provides robust models for the understanding of key biological events at the cellular roots of comedogenesis [2, 7].

The Initial Steps of Comedogenesis

The initial key step for comedogenesis has been widely accepted to be an alteration of the epithelial wall of the infundibulum, particularly at the junction of the sebaceous gland duct (isthmus), with hyperproliferation of ductal keratinocytes and reduced separation of ductal corneocytes [6].

The causes of these alterations were believed to be:

- The comedogenic effects of certain sebaceous lipids
- An androgen-controlled defect (reviewed in Shaheen and Gonzalez [1])
- Local cytokine modulation (interleukin 1 augments, epidermal growth factor prevents comedogenesis)
- Retinoid control
- Ductal bacteria (review in Shaheen and Gonzalez [1])

Based on recent knowledge, this list may be summarized as follows:

- Ductal bacteria, *P. acnes,* which results from hyperseborrhea and can generate both comedogenic lipids and the innate immunity cascade [11]
- Retinoids, the metabolism of which in this specific region has now been better analyzed, and the role of vitamin deficiency in comedogenesis revisited [12, 13]

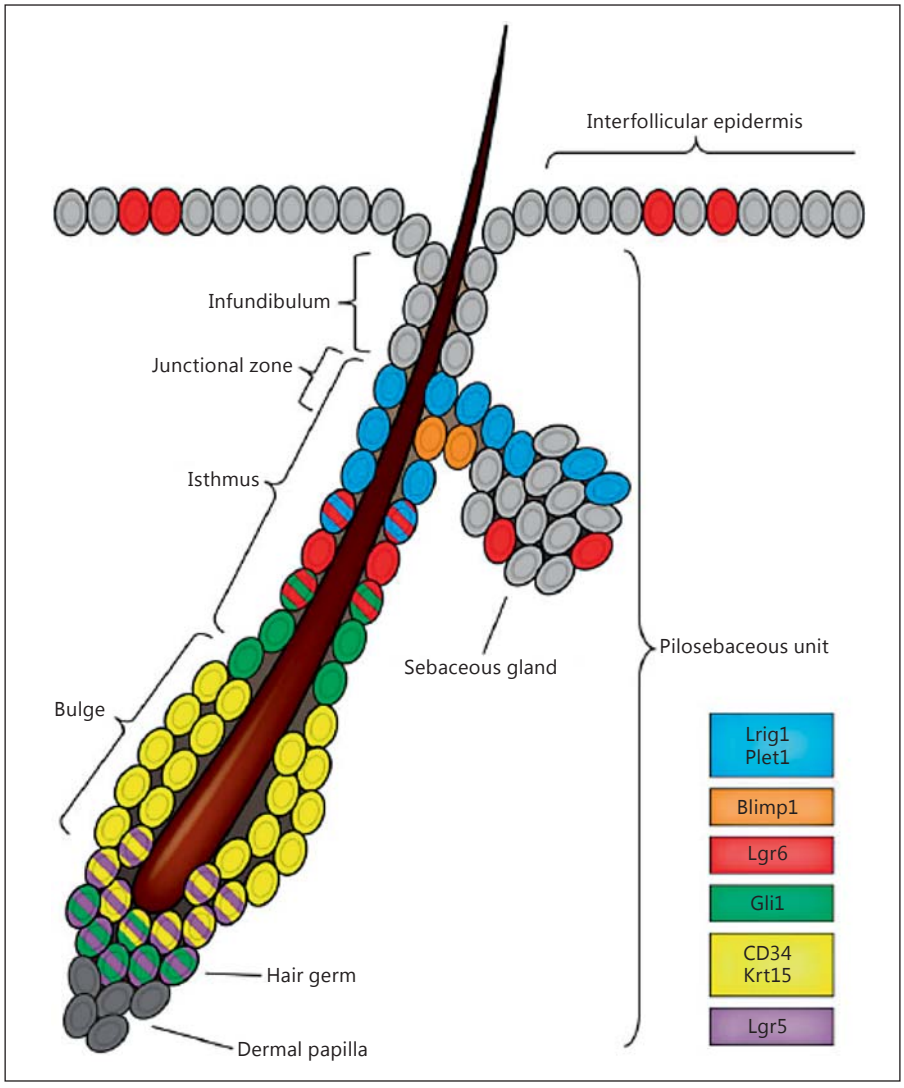

Fig. 3. LRIG1+ sebaceous gland stem cells are localized in the isthmus' epithelium. Cells are the sebaceous stem cells. Different stem cell populations are shown in the mouse resting (telogen) adult hair follicle. Each stem cell compartment is defined by distinct protein expression and gene promoter activity (see key); cells with multiple colors express multiple markers. Reprinted from Schepeler et al. [27].

- Xenobiotic comedogens whose historically suspected role is currently amenable to better analysis [7, 14–16]

The Master Switch for Microcomedone Formation

The master switch that transforms a normally functioning sebaceous gland into a microcomedone (fig. 2) and the hierarchy of factors involved in it remain to be fully understood. The prevalent 'switching agent' may appear to be *P. acnes*, at least in adolescent acne. *P. acnes* has mainly been considered as a proinflammatory factor. However, the role of *P. acnes*-derived products in initiating comedogenesis in the absence of clinical inflammation appears now as a most plausible option. This does not exclude many other switching agents that may be operative in the absence of *P. acnes,* as stressed by Shaheen and Gonzalez [1], and to which many xenobiotics should be added (see further).

Topology of the Master Switch for Microcomedone Formation

Where are these switching agents supposed to act at the tissue/cellular level?

Recent data from lineage tracing of sebaceous stem cells [2], as well as on the localization of the cellular targets of comedogenic xenobiotics [7, 16], allow to focus on the topology of the comedogenic switch at the tissular level. It is accepted that the isthmus (the zone where the sebaceous gland duct joins the hair duct) is the zone where the microcomedone develops (fig. 3), which suggests the following scenario.

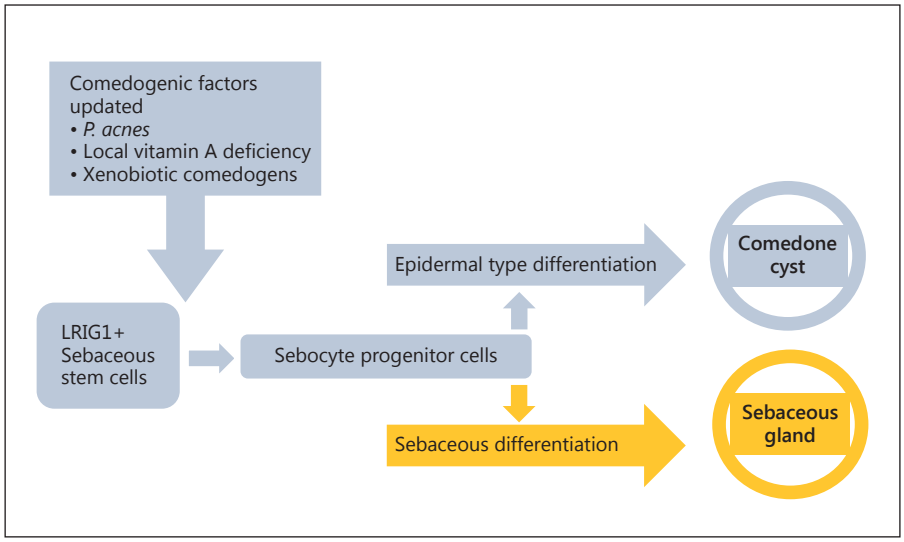

Fig. 4. The comedone switch in the differentiation of sebaceous gland stem cells.

Scenario for the Master Switch for Microcomedone Formation

Where Are Sebaceous Gland Progenitor Cells (LRIG1 Cells) Located?

The epithelium of the isthmus is the residence for sebaceous gland progenitor cells (LRIG1 cells), the so-called sebaceous gland stem cells. Lineage tracing experiments in the mouse have shown that the progeny of LRIG1 cells contributes to the epithelium of the isthmus and populates sebaceous glands [2, 26].

LRIG cells may therefore differentiate toward either an *epithelial type* or a *sebaceous type* and should therefore be primary targets for comedogenic factors.

This population may therefore be the root of the comedone switch. This may also explain the well-accepted observation that 'the more comedones, the less mature sebocytes' in the histology of acne [5, 6].

What Is the Fate and Subsequent Differentiation of the Sebaceous Gland Progenitor Cells (LRIG1 Cells)?

The regulation of the LRIG1 cells' fate and subsequent differentiation is not fully established yet. The following observations are relevant to the comedone switch:

(i) The location of LRIG1 cells in the epithelium of the isthmus where many potential modifying factors do occur, the main one, at least quantitatively, being *P. acnes* when seborrhea allows its proliferation, opens further questions (see below) [17].

(ii) Topical retinoic acid induces a selective expansion of LRIG1 cell clones into the sebaceous glands in the mouse [2].

(iii) Retinoic acid synthesis, from retinol and retinaldehyde, is present in the cells of the isthmus, at the site of stem cells. Therefore comedogenic factors may alter the process on vitamin A metabolism, thereby inducing vitamin A deficiency [12].

(iv) Strong and durable activation of the aryl hydrocarbon receptor (AhR) pathway by tetrachlorodibenzodioxin alters sebogenic differentiation towards epithelial type differentiation with infundibular acanthosis, hyperkeratosis and macrocomedones/MADISH formation [7, 15].

(v) An important observation was that of the high susceptibility of LRIG1 cells to the major comedogenic factor tetrachlorodibenzodioxin/dioxin, through the AhR pathway activation. This indicates that xenobiotics do specifically activate the AhR pathway in sebaceous gland stem cells both in animals and humans [7, 14, 16]. That AhR activation directs progenitor cell differentiation is a currently well accepted concept [18].

(vi) Besides the tetrachlorodibenzodioxin paradigm, an endless list of AhR pathway modulators is present in the human environment, mainly in foods, tobacco smoke, etc. [19–23]. These modulators of the AhR pathway might have both negative and positive effects on acne, depending on their distribution and metabolism [14, 20].

(vii) Even microbes can produce activators for the AhR pathway [24], and the future will tell whether *P. acnes* might generate such AhR activators.

In summary, this scenario (fig. 4) offers a simple master switch model for comedone formation that articulates the different etiological agents as well as the potential mode of action of therapeutic and preventive interventions.

Indeed, if the key target in acne care is understood to be the naïve follicle that is not involved yet, then prevention of the comedone switch implies that the switching factors are adequately targeted.

Preventing the Comedone Switch?

Ductal *P. acnes* control may be obtained primarily by reducing sebum production, which feeds the bacterial growth. This may account for the effect of oral isotretinoin, even at low (off-label) dose use. Obviously, a topical agent with a significant sebum suppressive effect, and clean safety profile for long-term use, would appear as a 'disease-modifying' breakthrough compound. The threshold of sebum suppression necessary to maintain *P. acnes* 'commensality' is still to be determined. Indeed, this approach would necessitate complex, long and costly 'disease-modifying' studies, provided, that a candidate topical drug with a significant sebum suppressive effect emerges.

Ductal *P. acnes* control may be obtained also by antiseptics and antibiotics. It is sad that no major progress has been made for decades, this field being currently crowded with 'me-too' products both in the prescription and over-the-counter market. The hope is that with the progress in understanding the biology of *P. acnes,* new and simple methods for targeted ductal bacterial control will emerge, which may be used in the long term.

Retinoids may participate in comedone switch prevention. The effects of topical retinoic acid which, according to Plewig and Kligman [5], would 'explain the efficacy of this drug in acne' were said to be 'proliferation and comedolytic effect'. Retrospectively, these 'proliferative and comedolytic effects' can all be assigned to the effect of retinoic acid on any epidermal type epithelium, and by extension to the epithelium of the infundibulum/isthmus. Thus, topical retinoic acid induces a hypervitaminosis A state in the epithelium of the infundibulum/isthmus. In mice, topical retinoic acid induces a selective expansion of LRIG1 cell clones into the sebaceous glands [2].

Therefore, the state of local vitamin A deficiency that contributes to the abnormal differentiation observed in the infundibulum/isthmus epithelium and leads to microcomedones [13, 25] might well be corrected by topical retinoids.

Topical retinoid therapy appears to act towards restoring adequate retinoid signaling in the infundibulum/isthmus epithelium, and this should prevent the abnormal differentiation resulting in the comedone switch and stem cell commitment. Topical retinoid use should therefore be revisited as targeting acne-prone normal-looking skin in a preventive dimension, rather than just only as comedolytic.

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Disclosure Statement

The author declares no conflict of interest.

References

1 Shaheen B, Gonzalez M: Acne sans *P. acnes*. J Eur Acad Dermatol Venereol 2013;27:1–10.
2 Jensen KB, Collins CA, Nascimento E, Tan DW, Frye M, Itami S, Watt FM: Lrig1 expression defines a distinct multipotent stem cell population in mammalian epidermis. Cell Stem Cell 2009;4:427–439.
3 Williams HC, Dellavalle RP, Garner S: Acne vulgaris. Lancet 2012;379:361–372.
4 Montagna W: The sebaceous glands; in Montagna W, Ellis RA, Silver AF (eds): Advances in Biology of the Skin. Oxford, Pergamon Press, 1963, pp 167–187.
5 Plewig G, Kligman AM: Acne and Rosacea. Berlin, Springer, 1993.
6 Cunliffe WJ, Holland DB, Jeremy A: Comedone formation: etiology, clinical presentation, and treatment. Clin Dermatol 2004;22:367–374.
7 Saurat JH, Kaya G, Saxer-Sekulic N, Pardo B, Becker M, Fontao L, Mottu F, Carraux P, Pham X, Barde C, Fontao F, Zennegg M, Schmid P, Schaad O, Descombes P, Sorg O: The cutaneous lesions of dioxin exposure: lessons from the poisoning of V. Yushchenko. Toxicol Sci 2012;125:310–317.
8 Egbers R, Do T, Voorhees JJ, Sachs D, Kang S: Computer-assisted alignment and tracking of comedones in patients with predominantly comedonal acne indicate that most resolve within 4 weeks and do not become inflammatory lesions. J Invest Dermatol 2010;130:S58.
9 Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ: Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121:20–27.
10 Do TT, Zarkhin S, Orringer JS, Nemeth S, Hamilton T, Sachs D, Voorhees JJ, Kang S: Computer-assisted alignment and tracking of acne lesions indicate that most inflammatory lesions arise from comedones and de novo. J Am Acad Dermatol 2008;58:603–608.
11 Contassot E, French LE: New insights into acne pathogenesis: *Propionibacterium acnes* activates the inflammasome. J Invest Dermatol 2014;134:310–313.
12 Everts HB: Endogenous retinoids in the hair follicle and sebaceous gland. Biochim Biophys Acta 2012;1821:222–229.

13 Rollman O, Vahlquist A: Vitamin A in skin and serum – studies of acne vulgaris, atopic dermatitis, ichthyosis vulgaris and lichen planus. Br J Dermatol 1985;113:405–413.
14 Saurat JH, Sorg O: Chloracne, a misnomer and its implications. Dermatology 2010;221: 23–26.
15 Schäfer M, Willrodt AH, Kurinna S, Link AS, Farwanah H, Geusau A, Gruber F, Sorg O, Huebner AJ, Roop DR, Sandhoff K, Saurat JH, Tschachler E, Schneider MR, Langbein L, Bloch W, Beer HD, Werner S: Activation of Nrf2 in keratinocytes causes chloracne (MADISH)-like skin disease in mice. EMBO Mol Med 2014;6:442–457.
16 Fontao F, Fontao L, Barnes L, Kaya G, Sorg O, Saurat JH: High susceptibility of LRIG1 sebaceous stem cells to TCDD in mice. Submitted.
17 Lwin SM, Kimber I, McFadden JP: Acne, quorum sensing and danger. Clin Exp Dermatol 2014;39:162–167.
18 Smith BW, Rozelle SS, Leung A, Ubellacker J, Parks A, Nah SK, French D, Gadue P, Monti S, Chui DH, Steinberg MH, Frelinger AL, Michelson AD, Theberge R, McComb ME, Costello CE, Kotton DN, Mostoslavsky G, Sherr DH, Murphy GJ: The aryl hydrocarbon receptor directs hematopoietic progenitor cell expansion and differentiation. Blood 2013;122:376–385.
19 De Waard WJ, Aarts JM, Peijnenburg AC, De Kok TM, Van Schooten FJ, Hoogenboom LA: Ah receptor agonist activity in frequently consumed food items. Food Addit Contam Part A Chemistry Anal Control Expo Risk Assess 2008;25:779–787.
20 Connor KT, Harris MA, Edwards MR, Budinsky RA, Clark GC, Chu AC, Finley BL, Rowlands JC: AH receptor agonist activity in human blood measured with a cell-based bioassay: evidence for naturally occurring AH receptor ligands in vivo. J Expo Sci Environ Epidemiol 2008;18:369–380.
21 Heath-Pagliuso S, Rogers WJ, Tullis K, Seidel SD, Cenijn PH, Brouwer A, Denison MS: Activation of the Ah receptor by tryptophan and tryptophan metabolites. Biochemistry 1998; 37:11508–11515.
22 Lowe MM, Mold JE, Kanwar B, Huang Y, Louie A, Pollastri MP, Wang C, Patel G, Franks DG, Schlezinger J, Sherr DH, Silverstone AE, Hahn ME, McCune JM: Identification of cinnabarinic acid as a novel endogenous aryl hydrocarbon receptor ligand that drives IL-22 production. PLoS One 2014; 9:e87877.
23 Stejskalova L, Dvorak Z, Pavek P: Endogenous and exogenous ligands of aryl hydrocarbon receptor: current state of art. Curr Drug Metab 2011;12:198–212.
24 Moura-Alves P, Fae K, Houthuys E, Dorhoi A, Kreuchwig A, Furkert J, Barison N, Diehl A, Munder A, Constant P, Skrahina T, Guhlich-Bornhof U, Klemm M, Koehler AB, Bandermann S, Goosmann C, Mollenkopf HJ, Hurwitz R, Brinkmann V, Fillatreau S, Daffe M, Tummler B, Kolbe M, Oschkinat H, Krause G, Kaufmann SH: AhR sensing of bacterial pigments regulates antibacterial defence. Nature 2014;512:387–392.
25 Skazik C, Amann PM, Heise R, Marquardt Y, Czaja K, Kim A, Ruhl R, Kurschat P, Merk HF, Bickers DR, Baron JM: Downregulation of STRA6 expression in epidermal keratinocytes leads to hyperproliferation-associated differentiation in both in vitro and in vivo skin models. J Invest Dermatol 2014;134: 1579–1588.
26 Barnes L, Puenchera J, Saurat JH, Kaya G: Lrig1 and CD44v3 expression in human folliculosebaceous unit. Dermatology 2015; 231:116–118.
27 Schepeler T, Page ME, Jensen KB: Heterogeneity and plasticity of epidermal stem cells. Development 2014;141:2559–2567.