# A New Concept of Acne Pathogenesis

# 13

Christos C. Zouboulis and Clio Dessinioti

## Contents



**Core Messages**

- New insights in the pathogenesis of acne include the unraveling of the role of androgens, the identification of PPARs, the new concept of inflammation as a primary event in acne pathogenesis, the role of neuropeptides in acne, and new knowledge on the mode of action of *P. acnes*.

## 13.1 Introduction

The pathogenesis of acne, the most common disease of the pilosebaceous unit, has been traditionally attributed to increased sebum production, androgen activity, follicular hyperkeratinization, and the action of *Propionibacterium acnes* (*P. acnes*) within the sebaceous follicle [1, 2].

However, our knowledge on the pathogenesis of acne has been revolutionized in the last few years by studies on the role of sebaceous glands. The development of experimental models for the in vitro study of human sebaceous gland functions overcame the lack of an ideal animal model compatible to human sebaceous glands [3–6]. These studies have fundamentally changed the view for the human sebaceous gland from "a fossil of the skin with past but no future" [7] to the "brain of the skin" [8].

C.C. Zouboulis (✉)
Departments of Dermatology, Venereology, Allergology and Immunology,
Dessau Medical Center, Dessau, Germany
e-mail: christos.zouboulis@klinikum-dessau.de

C. Dessinioti
Department of Dermatology, Andreas Syngros Hospital, National and Capodistrian University of Athens, Athens, Greece
e-mail: cliodes@hotmail.com

C.C. Zouboulis et al. (eds.), *Pathogenesis and Treatment of Acne and Rosacea*,
DOI 10.1007/978-3-540-69375-8_13, 

New insights in the pathogenesis of acne include the unraveling of the role of androgens, the identification of PPARs, the new concept of inflammation as a primary event in acne pathogenesis, the role of neuropeptides in acne, and new knowledge on the mode of action of *P. acnes* [9].

## 13.2 New Concepts of Acne Pathogenesis

Skin (the sebaceous gland in particular) has been shown to be a steroidogenic tissue that possesses the enzymatic machinery to synthesize androgens (testosterone) de novo from cholesterol [3]. Androgens in turn play a central role in acne, not only by increasing the size of sebaceous glands and stimulating sebum production but also by stimulating keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum, thus contributing to comedone formation [2]. Increased 5α-dihydrotestosterone may act on infundibular keratinocytes leading to abnormal keratinization [10].

Peroxisome proliferation-activated receptors (PPAR) have been identified in human sebaceous glands, whereas PPAR ligands induce sebaceous lipogenesis in cultured human sebocytes [11]. Sebaceous lipids exhibit direct pro- and anti-inflammatory properties, whereas the induction of 5-lipoxygenase and cyclooxygenase-2 pathways in sebocytes leads to the production of pro-inflammatory lipids [12].

The order of events participating in acne pathogenesis has long been debated. Although traditionally inflammation was considered to succeed ductal hypercornification, new findings changed this concept. Bioactive interleukin (IL)1α-like material was found in open acne comedones from untreated patients [13], and the addition of IL1α induced hyperproliferation of follicular keratinocytes in isolated sebaceous follicle infundibula maintained ex vivo [14]. Thus, IL1α has a central role in cutaneous inflammation and keratinocyte proliferation and may influence the evolution of acne lesions [15]. Also, inflammatory events were detected in the very earliest stages of acne lesion development. Inflammatory factors (IL1α), increased CD4+ T cells, lack of neutrophils, and reduced Langerhans cells have been found in the perifollicular epidermis from uninvolved skin from acne patients prior to hyperproliferation or abnormal differentiation of the follicular epithelium [16].

New roles in the pathogenesis of acne have been attributed to *P. acnes*. A *P. acnes* biofilm, which penetrates into the sebum-like adhesive glue has been suggested to lead to the increased cohesiveness of corneocytes seen in acne. A biofilm is a complex aggregation of microorganisms that are placed within an extracellular polysaccharide lining which are secreted after adherence to a surface. So, the microcomedones may not be the central cause of acne, as traditionally thought, but rather result from the substances secreted by *P. acnes* into the sebum in its effort to attach to the follicular lining to set up a biofilm [17]. Also, Toll-like receptors (TLR), mammalian homologues of Drosophila Toll receptors, have been implicated in acne-related inflammation. *P. acnes* may activate keratinocytes and sebocytes of the pilosebaceous unit via TLR [18] and trigger inflammatory cytokine responses by activation of TLR2 [19]. *P. acnes*-conditioned medium and formalin-killed *P. acnes* were shown to augment intracellular lipid formation in hamster sebocytes by increasing de novo synthesis of triacylglycerols [20].

An exciting role has emerged for neuropeptides in acne, with the identification of the expression of melanocortin receptors 1 (MC1R) and 5 (MC5R) in human sebocytes in vitro and in situ [21–23] and increased in situ expression of MC1R in sebaceous glands of lesional skin in acne patients [24]. α-melanocyte-stimulating hormone (α-MSH) can stimulate sebocyte differentiation and lipogenesis [10]. Importantly, KDPT, a tripeptide derivative of α-MSH, has been shown to have anti-inflammatory action in SZ95 sebocytes via suppression of IL-1β-mediated cytokine expression [25]. Moreover, corticotrophin-releasing hormone (CRH) induces the synthesis of sebaceous lipids in vitro [26], and CRH expression by keratinocytes was induced by *P. acnes* [8, 27].

We have come a long way since 1975, when Dr. Albert M. Kligman described acne as "a bewitching lady, pursued with more passion than intelligence" [28]. The multifaceted acne has been pursued with dedication and many new signaling pathways have been unraveled through robust experimental data. Nevertheless, acne never ceases to bewitch us and the search for new discoveries is yet to be over.

## References


1. Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol. 2005;22:360–6.
2. Zouboulis CC, Eady A, Philpott M, et al. What is the pathogenesis of acne? Exp Dermatol. 2005;14: 143–52.
3. Thiboutot D, Jabara S, McAlister J, et al. Human skin is a steroidogenic tissue: Steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). J Invest Dermatol. 2003;120:905–14.
4. Xia L, Zouboulis C, Detmar M, et al. Isolation of human sebaceous glands and cultivation of sebaceous gland-derived cells as an in-vitro model. J Invest Dermatol. 1989;93:315–21.
5. Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterization of an immortalized human sebaceous gland cell line (SZ95). J Invest Dermatol. 1999;113:1011–20.
6. Zouboulis CC, Xia L, Akamatsu H, et al. The human sebocyte culture model provides new insights into development and management of seborrhea and acne. Dermatology. 1998;196:21–31.
7. Kligman AM, Wheatley VR, Mills OH. Comedogenicity of human sebum. Arch Dermatol. 1970;102: 267–75.
8. Ganceviciene R, Graziene V, Fimmel S, et al. Involvement of the corticotropin-releasing hormone system in the pathogenesis of acne vulgaris. Br J Dermatol. 2008;160:345–52.
9. Kurokawa I, Danby FW, Ju Q, et al. New development in our understanding of acne pathogenesis and treatment. Exp Dermatol. 2009;18:821–32.
10. Thiboutot DM, Knaggs H, Gilliland K, et al. Activity of type 1 5 alpha-reductase is greater in the follicular infrainfundibulum compared with the epidermis. Br J Dermatol. 1997;136:166–71.
11. Wrobel A, Seltmann H, Fimmel S, et al. Differentiation and apoptosis in human immortalized sebocytes. J Invest Dermatol. 2003;120:175–81.
12. Alestas T, Ganceviciene R, Fimmel S, et al. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. J Mol Med. 2006;84:75–87.
13. Ingham E, Eady EA, Goodwin CE, et al. Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. J Invest Dermatol. 1992;98: 895–901.
14. Guy R, Green MR, Kealey T. Modeling acne in vitro. J Invest Dermatol. 1996;106:176–82.
15. Dessinioti C, Katsambas AD. The role of *Propionibacterium acnes* in acne pathogenesis: facts and controversies. Clin Dermatol. 2010;28:2–7.
16. Jeremy AH, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003;121:20–7.
17. Burkhart CG, Burkhart CN. Expanding the microcomedone theory and acne therapeutics: *Propionibacterium acnes* biofilm produces biological glue that holds corneocytes together to form plug. J Am Acad Dermatol. 2007;57:722–4.
18. Jugeau S, Tenaud I, Knol AC, et al. Induction of toll-like receptors by *Propionibacterium acnes*. Br J Dermatol. 2005;153:1105–13.
19. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine response. J Immunol. 2002;169:1535–41.
20. Iinuma K, Sato T, Akimoto N, et al. Involvement of *Propionibacterium acnes* in the augmentation of lipogenesis in hamster sebaceous glands in vivo and in vitro. J Invest Dermatol. 2009;129:2113–9.
21. Bohm M, Schiller M, Stander S, et al. Evidence of melanocortin-1 receptor in human sebocytes in vitro and in situ. J Invest Dermatol. 2002;118:533–9.
22. Zhang L, Li WH, Anthonavage M, et al. Melanocortin-5 receptor: a marker of human sebocyte differentiation. Peptides. 2006;27:413–20.
23. Zouboulis CC. Sebaceous gland receptors. Dermatoendocrinol. 2009;1:77–80.
24. Ganceviciene R, Graziene V, Bohm M, et al. Increased in situ expression of melanocortin-1 receptor in sebaceous glands of lesional skin of patients with acne vulgaris. Exp Dermatol. 2007;16:547–52.
25. Mastrofrancesco A, Kokot A, Eberle A, et al. KDPT, a tripeptide derivative of α-Melanocyte-stimulating hormone, suppresses IL-1β-mediated cytokine expression and signaling in human sebocytes. J Immunol. 2010; 185:1903–11.
26. Zouboulis CC, Seltmann H, Hiroi N, et al. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. Proc Natl Acad Sci USA. 2002;99:7148–53.
27. Isard O, Knol AC, Castex-Rizzi N, et al. Cutaneous induction of corticotrophin releasing hormone by *Propionibacterium acnes* extracts. Dermatoendocrinol. 2009;1:96–9.
28. Plewig G, Kligman AM. Acne. 1st ed. Berlin: Springer; 1975.