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REVIEW ARTICLE

What is new in the pathophysiology of acne, an overview

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Abstract

Acne is a chronic inflammatory disease of the pilosebaceous unit. Its pathophysiology includes hyperseborrhoea, abnormal follicular keratinization and *Propionibacterium acnes* proliferation in the pilosebaceous unit. Recent research has shed some new light on the involvement of the sebaceous gland, as well as on the pro-inflammatory activity of the cutaneous microbiome. During puberty, alteration of the sebaceous lipid profile, called dysseborrhoea, stress, irritation, cosmetics and potential dietary factors lead to inflammation and formation of different types of acne lesions. Dysbiosis, the process leading to a disturbed skin barrier and disequilibrium of the cutaneous microbiome, resulting in the proliferation of *P. acnes* strains, is another important process that triggers acne. *P. acnes* activates the innate immunity via the expression of protease activated receptors (PARs), tumour necrosis factor (TNF) α and toll-like receptors (TLRs), and the production of interferon (INF) γ, interleukins (IL-8, IL12, IL-1), TNF, and matrix metalloproteinases (MMPs) by keratinocytes, resulting in the hyperkeratinization of the pilosebaceous unit. Rebalancing the natural microbiome of the skin by restoring the natural skin barrier, limiting the proliferation of *P. acnes* on the skin by using topical antibacterials which do not cause resistance and regulating quantity and quality of sebum will be the main acne treatment challenges in the future. The aim of this article to provide an update on the involvement of the sebaceous gland, the innate immunity and the cutaneous microbiome, how all of these factors promote acne and to illustrate their links with current and future treatments.
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Conflicts of interest

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Introduction

Acne is a chronic inflammatory disease of the pilosebaceous unit.[1] It commonly occurs at puberty but is also observed in adults.[2] Its pathophysiology involves three actors, hyperseborrhoea, abnormal follicular keratinization and *Propionibacterium acnes* proliferation in the pilosebaceous unit. As a result of their interaction, the cutaneous microenvironment changes and leads to inflammatory reactions of the host that foster acne lesion progression.[2,3] Recent research has put some new light on the involvement of the sebaceous gland, as well as on the pro-inflammatory activity of the cutaneous microbiome in the pathophysiology of acne.

The objective of this article was to provide an update regarding the involvement of the sebaceous gland, the innate immunity and the cutaneous microbiome in acne. The second objective was to open a new perspective of treatment options.

Methods

The author conducted a literature review of the most recent data about the pathophysiology of acne.

The sebaceous gland

Sebum production is induced by different receptors expressed by the sebaceous gland. In addition to the well-described histamine receptor activated by histamines, the hormonal DHT receptor, activated by androgens, and the neuromodulator receptor, mainly substance P and corticotrophin-releasing hormone (CRH) receptor which are mainly activated by stress, recent molecular research has identified three other receptors that are expressed by the sebocyte and that control sebum production (Fig. 1).[4–6]

Each of these newly identified receptors is activated by a dietary substance. The peroxisome proliferator-activated receptors

(PPARα, β and γ) are stimulated by free fatty acids and cholesterol, the insulin-like growth factor (IGF)-1 receptor by sugar and leptin receptor by fat.[7–9] Leptin is a hormone secreted by adipocytes that regulates bodyweight and is also known to link lipid metabolism with inflammation in various cell types. In the sebocyte, it is responsible for creating lipid droplets within the cell and has recently been shown to induce pro-inflammatory enzyme and cytokine (interleukin (IL)-6 and IL-8) secretion as well.[9] This result suggests that leptin is a novel player in inducing inflammation and altering lipid profile in sebocytes and could be a link between diet and development of inflammatory acne.

The link between acne and diet is further supported by a recent case–control study of predictive factors for acne.[10] Apart from the well-known relationship between family history and acne, the investigators found that a high body mass index (BMI) was also a predictive factor for an increased risk of developing moderate to severe acne in adolescents and young adults. Furthermore, a population-based study of acne and BMI in adolescents reported that overweight as well as obesity may be potentially associated with acne in girls aged 18 and 19 years,[11] even though proofs are still lacking.

Peripheral hyperandrogenia

Women suffering from hyperandrogenia usually present with premenstrual flare, a mild increase in serum DHEA levels and an increased antimullerian serum hormone level but with otherwise normal blood hormone levels and vellus hair on the upper lip, the peri-ocular and malar area.[12,13] Interestingly, further evidence for peripheral hyperandrogenia was recently demonstrated following the new regulations for oral contraceptive prescription put in place in France in 2013.[14] Following an increase in cerebral stroke in young women taking the third-generation pill, the French Health Agency recommended in 2012 that gynaecologists, dermatologists and general practitioners switch their patients back to second-generation contraceptives. This widespread change in contraceptive prescription from late-generation contraception to early-generation contraception turned out to be significant for dermatologists. The French survey conducted a year after the new regulations came into effect showed that the switch to a second-generation contraceptive worsened acne in 83.9% of study participants. This thus confirmed the link between peripheral hyperandrogenia and abnormal androgen receptor activation. The observations supported the investigation of the potential value of spironolactone as an alternative to isotretinoin to improve acne symptoms in this patient group.

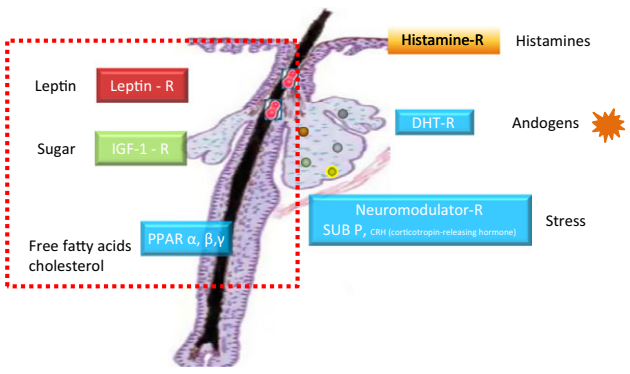

Figure 1 Receptors controlling sebum production (adapted from Zhang *et al.*[7]).

Although spironolactone is not indicated for acne by either the EMEA or FDA, there is rationale regarding its use in the condition: spironolactone interferes with the hormone-controlled sebum and sweat gland secretion, and with androgen-stimulated hair growth.[15] Based on this, a pilot study was performed in 16 patients who received 75 mg to 150 mg/day oral spironolactone and a third-generation pill and topical BPO 0.25% or a topical retinoid daily with very positive results at 6 and 12 months, confirming the clinical benefit of oral spironolactone in adult women with acne.[16] Since that time, the off-label use of spironolactone in this subgroup of patients has been tested further.[17,18] Very recently, the topical delivery of spironolactone has been shown to be superior with solid lipid nanoparticles that deliver the drug into the dermis.[19] However, further testing is required to confirm this clinically.

The endocannabinoid system

Endocannabinoids represent a class of endogenous lipid mediators that are involved in various biological processes, both centrally and peripherally.[20]

Recent studies have intriguingly suggested the existence of a functional endocannabinoid system (ECS) in the skin and implicated it in various biological processes (e.g. proliferation, growth, differentiation, apoptosis and cytokine, mediator or hormone production of various cell types of the skin and appendages, such as the hair follicle and sebaceous gland). It seems that the main physiological function of the cutaneous ECS is to constitutively control the proper and well-balanced proliferation, differentiation and survival, as well as immune competence and/or tolerance, of skin cells. The disruption of this delicate balance might facilitate the development of multiple pathological conditions and diseases of the skin.[21,22]

Recently, the ECS has attracted some interest in the treatment of acne by controlling sebum secretion.[23] An *in vitro* study performed in 2014 found that cannabidiol has lipostatic, antiproliferative and anti-inflammatory effects which could make this non-psychotrophic cannabinoid agent a promising therapy for *acne vulgaris*.[24]

The cutaneous microbiome

The skin microbiome is the collective genome of the resident microbial inhabitants (viruses, bacteria, fungi and parasites), also called the microbiota, present on the skin and its

appendages. It is a unique microbial fingerprint.[25,26] It controls the balance of the microbiota and of the transient microbial colonization and assists the host's innate immunity. It is constantly changing, being potentially influenced by external (mechanic factors, comedogenic cosmetics, aggressive detergents, drugs, diet) and internal factors (hormonal or genetic factors).[10,27–29]

Even though commensal, some inhabitants have been connected with inflammatory diseases of the skin, such as *P. acnes* (acne), *Malassezia furfur* (seborrhoeic dermatitis) and demodex (rosacea). Other transient microbes, such as *Staphylococcus aureus* and *Streptococcus pyogenes,* are known pathogens.[30–33]

In a balanced skin microbiome, *Staphylococcus epidermidis* limits overcolonization and the inflammatory response of the skin by the different *P. acnes* strains identified through the release of succinic acid, a fatty acid fermentation product, and suppresses *P. acnes*-induced IL-6 and TNF-α production by keratinocytes.[34–38] Conversely, *P. acnes* limits the proliferation of *S. aureus* and *S. pyogenes* in maintaining an acidic pH of the pilosebaceous follicle by hydrolysing sebum triglycerides and by secreting propionic acid.[33,39]

Therefore, any modification of the natural microbiome composition may lead to a disturbed skin barrier, an effect which is also called dysbiosis, and which triggers the activation of the innate immunity leading to inflammation.[40] In acne, dysbiosis may be paralleled by a qualitative and quantitative change of the sebum, called dysseborrhoea and in a modified profile of *P. acnes*, with all six different phylotypes differing between patients with and without acne.[41,42] As a result, inflammation worsens. As such, it has been shown that TLR-2 expression increases with the severity of the disease and that cytokines are produced as a result of the interaction between *P. acnes* and TLR-2, defensins and MMP via PAR-2R activation.[43,44] This worsening via the stimulation of TLR-2, IL-8 and MMP-9, which is diffused from the pilosebaceous gland to the dermis and epidermis, was five times more pro-inflammatory than *S. aureus* or *Streptococcus pyogenes*.[43,45–49]

Rebalancing the natural equilibrium of the microbiome, allowing the restoration of the natural skin barrier, is, therefore, one of the main aims in the treatment of acne today.

The innate immunity and *P. acnes*

Within the skin, both innate and adaptive mechanisms contribute to the host immune function.[50–52] Keratinocytes play an important role in the immune response of the skin. They express a number of pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) and protease-activated receptors (PARs) that recognize microbes through the recognition of different conserved molecular entities. While expressing a number of antimicrobial peptides (AMPs, such as dermcidin), cytokines (INF-γ, IL-8, IL-12, TNF, IL-1, MMPs) and chemokines at steady state, activation of PRRs can rapidly increase the expression of these molecules, resulting in direct antimicrobial effects as well as recruitment and education of additional immune cells.[53–55]

In the process of inflammation triggered by *P. acnes*, secretion of IL-1β by monocytes and by sebocytes through activation of the key inflammasome gene NLRP3 has been observed. This mechanism is regulated by proteases and reactive oxygen species (ROS).[56–58] Moreover, *P. acnes* promotes mixed Th17/Th1 responses by inducing the concomitant secretion of IL-17A and IFN-γ from specific CD4(+) T cells in vitro. Therefore, the presence of IL-17A-positive T cells and the activation of Th17-related cytokines in acne lesions indicate that the Th17 pathway may play a pivotal role in the disease process, possibly offering new targets of therapy.[59]

More recently, *P. acnes* was found to be highly sensitive to different concentrations of nitric oxide in nanoparticles (NO-np). NO-np significantly suppressed IL-1β, tumour necrosis factor-α (TNF-α), IL-8 and IL-6 from human monocytes, and IL-8 and IL-6 from human keratinocytes and peripheral blood mononuclear cells. These data suggest that NO-np can effectively prevent *P. acnes*-induced inflammation by both clearing the organism and inhibiting microbial stimulation of the innate immune response.[60]

Several sebum free fatty acids (FFAs) such as linoleic and sapienic acid have antibacterial activity through stimulation of antimicrobial peptide (AMP) production against a broad range of Gram-positive bacteria such as *P. acnes*.[61] Different studies have demonstrated that AMPs are major contributors to cutaneous innate immunity.[62,63] Among those, human β-defensin (hBD)-2 is upregulated in keratinocytes during inflammation and then accumulated in the skin.[64,65] Because of their direct antimicrobial action, the secretion of these peptides provides defence against microbes such as *P. acnes*.[61] This has been confirmed by Choi *et al.*[66] through a study assessing the regional difference of inflammatory acne lesions, according to hBD-2 expression.

Based on these elements, integrating AMPs in the armamentarium of current treatments targeting inflammation, such as topical retinoids, may be considered a future for acne management.

Propionibacterium acnes and the biofilm

Propionibacterium acnes is able to create a biofilm made of extracellular polysaccharides. This biological glue increases the adherence of *P. acnes* to follicular walls, favouring the modulation of integrins. Furthermore, it regulates the bacterial growth and metabolism, induces the development of *P. acnes* colonies and confers resistance to antimicrobial agents and to host inflammatory cells, resulting in a second mechanism of bacterial resistance.[67] The *P. acnes* biofilm is observed more frequently in patients with acne.[68] In these patients, the secretion of propionic acid by *P. acnes* led to the formation of keratinocytes with irregular cellular morphologies, confirming that *P. acnes* modulates

the differentiation of keratinocytes, suggesting that it plays a role in the development of inflammatory acne lesions and in the formation of microcomedones.[69,70]

Consequently, the use of topical antibacterial compounds, such as benzoyl peroxide, or botanicals, which do not induce antibacterial resistance, may be a privileged alternative to limit the cutaneous *P. acnes* biofilm.[71]

Conclusions

In conclusion, the onset of acne involves different factors resulting in inflammation and the formation of different types of acne lesions. These factors include the quantitative and qualitative alteration of the sebum during puberty, called dysseborrhoea, triggered by internal factors such as hormonal or genetic factors, and external factors such as comedogenic cosmetics, aggressive detergents or drugs, which may stimulate mechanisms involved in the pathophysiologies of acne. The impact of stress and diet in the dysseborrhoea remains to be elucidated. Dysbiosis, the process leading to a disturbed skin barrier, and the disequilibrium of the cutaneous microbiome, resulting in the proliferation of *P. acnes* strains, are other important processes that trigger acne. *P. acnes* activates the innate immunity via the expression of PARs, TNF-α and TLRs, and the production of INF-γ, IL-8, IL-12, TNF, IL-1 and MMPs by keratinocytes, resulting in the hyperkeratinization of the pilosebaceous unit.

(i) Rebalancing the natural microbiome of the skin by restoring the natural skin barrier in targeting cytokine receptors, (ii) limiting the proliferation of *P. acnes* on the skin using topical antibacterials which do not cause resistance and (iii) regulating the sebum outflow and composition will be the main acne treatment challenges in the future.

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References

1 Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. *Nat Rev Dis Primers* 2015; **1**: 15029.
2 Taylor M, Gonzalez M, Porter R. Pathways to inflammation: acne pathophysiology. *Eur J Dermatol* 2011; **21**: 323–333.
3 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.
4 Pelle E, McCarthy J, Seltmann H *et al.* Identification of histamine receptors and reduction of squalene levels by an antihistamine in sebocytes. *J Invest Dermatol* 2008; **128**: 1280–1285.
5 Zouboulis CC. Sebaceous gland receptors. *Dermatoendocrinology* 2009; **1**: 77–80.
6 Krause K, Schnitger A, Fimmel S, Glass E, Zouboulis CC. Corticotropin-releasing hormone skin signaling is receptor-mediated and is predominant in the sebaceous glands. *Horm Metab Res* 2007; **39**: 166–170.
7 Zhang L, Li WH, Anthonavage M, Eisinger M. Melanocortin-5 receptor: a marker of human sebocyte differentiation. *Peptides* 2006; **27**: 413–420.
8 Trivedi NR, Cong Z, Nelson AM *et al.* Peroxisome proliferator-activated receptors increase human sebum production. *J Invest Dermatol* 2006; **126**: 2002–2009.
9 Torocsik D, Kovacs D, Camera E *et al.* Leptin promotes a proinflammatory lipid profile and induces inflammatory pathways in human SZ95 sebocytes. *Br J Dermatol* 2014; **171**: 1326–1335.
10 Di Landro A, Cazzaniga S, Parazzini F *et al.* Family history, body mass index, selected dietary factors, menstrual history, and risk of moderate to severe acne in adolescents and young adults. *J Am Acad Dermatol* 2012; **67**: 1129–1135.
11 Halvorsen JA, Vleugels RA, Bjertness E, Lien L. A population-based study of acne and body mass index in adolescents. *Arch Dermatol* 2012; **148**: 131–132.
12 Peigne M, Villers-Capelle A, Robin G, Dewailly D. Hyperandrogenism in women. *Presse Med* 2013; **42**: 1487–1499.
13 Tuten A, Sahmay S, Oncul M *et al.* Serum AMH levels in the differential diagnosis of hyperandrogenemic conditions. *Eur J Obstet Gynecol Reprod Biol* 2014; **177**: 121–125.
14 Leclerc-Mercier S, Buisson V, Dreno B. New regulations for oral contraceptive prescription in France in 2013: what is the impact on adult female acne? *Eur J Dermatol* 2016; **26**: 345–349.
15 Salavastru CM, Fritz K, Tiplica GS. Spironolactone in dermatological treatment. On and off label indications. *Hautarzt* 2013; **64**: 762–767.
16 Saint-Jean M, Ballanger F, Nguyen JM, Khammari A, Dreno B. Importance of spironolactone in the treatment of acne in adult women. *J Eur Acad Dermatol Venereol* 2011; **25**: 1480–1481.
17 Kim GK, Del Rosso JQ. Oral spironolactone in post-teenage female patients with acne vulgaris: practical considerations for the clinician based on current data and clinical experience. *J Clin Aesthet Dermatol* 2012; **5**: 37–50.
18 Lessner E, Fisher S, Kobraei K *et al.* Spironolactone and topical retinoids in adult female cyclical acne. *J Drugs Dermatol* 2014; **13**: 126–129.
19 Kelidari HR, Saeedi M, Akbari J *et al.* Formulation optimization and in vitro skin penetration of spironolactone loaded solid lipid nanoparticles. *Colloids Surf B Biointerfaces* 2015; **128**: 473–479.
20 Pucci M, Pirazzi V, Pasquariello N, Maccarrone M. Endocannabinoid signaling and epidermal differentiation. *Eur J Dermatol* 2011; **21**(Suppl 2): 29–34.
21 Biro T, Toth BI, Hasko G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci* 2009; **30**: 411–420.
22 Kendall AC, Nicolaou A. Bioactive lipid mediators in skin inflammation and immunity. *Prog Lipid Res* 2013; **52**: 141–164.
23 Dobrosi N, Toth BI, Nagy G *et al.* Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. *Faseb J* 2008; **22**: 3685–3695.
24 Olah A, Toth BI, Borbiro I *et al.* Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. *J Clin Invest* 2014; **124**: 3713–3724.
25 Kong HH, Oh J, Deming C *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; **22**: 850–859.
26 Cundell AM. Microbial ecology of the human skin. *Microb Ecol* 2016; DOI: https://doi.org/10.1007/s00248-016-0789-6 [Epub ahead of print]
27 Oh J, Byrd AL, Park M, Kong HH, Segre JA. Temporal stability of the human skin microbiome. *Cell* 2016; **165**: 854–866.
28 Kazandjieva J, Tsankov N. Drug-induced acne. *Clin Dermatol* 2017; **35**: 156–162.
29 Dreno B, Bettoli V, Perez M, Bouloc A, Ochsendorf F. Cutaneous lesions caused by mechanical injury. *Eur J Dermatol* 2015; **25**: 114–121.
30 Findley K, Grice EA. The skin microbiome: a focus on pathogens and their association with skin disease. *PLoS Pathog* 2014; **10**: e1004436.
31 Grice EA, Kong HH, Renaud G *et al.* A diversity profile of the human skin microbiota. *Genome Res* 2008; **18**: 1043–1050.

32 Grice EA, Kong HH, Conlan S *et al.* Topographical and temporal diversity of the human skin microbiome. *Science* 2009; **324**: 1190–1192.
33 Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011; **9**: 244–253.
34 Wang Y, Kuo S, Shu M *et al.* Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of *Propionibacterium acnes*: implications of probiotics in acne vulgaris. *Appl Microbiol Biotechnol* 2014; **98**: 411–424.
35 Wang Y, Kao MS, Yu J *et al.* A precision microbiome approach using sucrose for selective augmentation of Staphylococcus epidermidis Fermentation against *Propionibacterium acnes*. *Int J Mol Sci* 2016; **17**: E1870.
36 Skabytska Y, Biedermann T. Staphylococcus epidermidis sets things right again. *J Invest Dermatol* 2016; **136**: 559–560.
37 McDowell A, Valanne S, Ramage G *et al. Propionibacterium acnes* types I and II represent phylogenetically distinct groups. *J Clin Microbiol* 2005; **43**: 326–334.
38 Xia X, Li Z, Liu K, Wu Y, Jiang D, Lai Y. Staphylococcal LTA-induced miR-143 inhibits *Propionibacterium acnes*-mediated inflammatory response in skin. *J Invest Dermatol* 2016; **136**: 621–630.
39 Shu M, Wang Y, Yu J *et al.* Fermentation of *Propionibacterium acnes*, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant Staphylococcus aureus. *PLoS ONE* 2013; **8**: e55380.
40 Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. *Clin Cosmet Investig Dermatol* 2015; **8**: 479–483.
41 McDowell A, Nagy I, Magyari M, Barnard E, Patrick S. The opportunistic pathogen *Propionibacterium acnes*: insights into typing, human disease, clonal diversification and CAMP factor evolution. *PLoS ONE* 2013; **8**: e70897.
42 Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol* 2015; **8**: 371–388.
43 Jugeau S, Tenaud I, Knol AC *et al.* Induction of toll-like receptors by *Propionibacterium acnes*. *Br J Dermatol* 2005; **153**: 1105–1113.
44 Dreno B, Gollnick HP, Kang S *et al.* Understanding innate immunity and inflammation in acne: implications for management. *J Eur Acad Dermatol Venereol* 2015; **29**(Suppl 4): 3–11.
45 Bruggemann H, Henne A, Hoster F *et al.* The complete genome sequence of *Propionibacterium acnes*, a commensal of human skin. *Science* 2004; **305**: 671–673.
46 Nagy I, Pivarcsi A, Koreck A, Szell M, Urban E, Kemeny L. Distinct strains of *Propionibacterium acnes* induce selective human beta-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. *J Invest Dermatol* 2005; **124**: 931–938.
47 Nakatsuji T, Liu YT, Huang CP, Zoubouis CC, Gallo RL, Huang CM. Antibodies elicited by inactivated propionibacterium acnes-based vaccines exert protective immunity and attenuate the IL-8 production in human sebocytes: relevance to therapy for acne vulgaris. *J Invest Dermatol* 2008; **128**: 2451–2457.
48 Trompezinski S, Weber S, Cadars B *et al.* Assessment of a new biological complex efficacy on dysseborrhea, inflammation, and *Propionibacterium acnes* proliferation. *Clin Cosmet Investig Dermatol* 2016; **9**: 233–239.
49 Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *J Eur Acad Dermatol Venereol* 2014; **28**: 527–532.
50 Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. *Nat Rev Immunol* 2004; **4**: 211–222.
51 Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol* 2009; **9**: 679–691.
52 Afshar M, Gallo RL. Innate immune defense system of the skin. *Vet Dermatol* 2013; **24**: 32–38. e8-9.
53 Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. *Semin Immunol* 2013; **25**: 370–377.
54 Gallo RL, Nizet V. Innate barriers against infection and associated disorders. *Drug Discov Today Dis Mech* 2008; **5**: 145–152.
55 Schittek B, Paulmann M, Senyurek I, Steffen H. The role of antimicrobial peptides in human skin and in skin infectious diseases. *Infect Disord Drug Targets* 2008; **8**: 135–143.
56 Eady EA, Goodwin CE, Cove JH, Ingham E, Cunliffe WJ. Inflammatory levels of interleukin 1 alpha are present in the majority of open comedones in acne vulgaris. *Arch Dermatol* 1991; **127**: 1238–1239.
57 Ingham E, Eady EA, Goodwin CE, Cove JH, Cunliffe WJ. 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.
58 Guy R, Green MR, Kealey T. Modeling acne in vitro. *J Invest Dermatol* 1996; **106**: 176–182.
59 Kistowska M, Meier B, Proust T *et al. Propionibacterium acnes* promotes Th17 and Th17/Th1 responses in acne patients. *J Invest Dermatol* 2015; **135**: 110–118.
60 Qin M, Landriscina A, Rosen JM *et al.* Nitric oxide-releasing nanoparticles prevent *Propionibacterium acnes*-induced inflammation by both clearing the organism and inhibiting microbial stimulation of the innate immune response. *J Invest Dermatol* 2015; **135**: 2723–2731.
61 Nakatsuji T, Kao MC, Zhang L, Zouboulis CC, Gallo RL, Huang C-M. Sebum free fatty acids enhance the innate immune defense of human sebocytes by upregulating [beta]-defensin-2 expression. *J Invest Dermatol* 2010; **130**: 985–994.
62 Nizet V, Ohtake T, Lauth X *et al.* Innate antimicrobial peptide protects the skin from invasive bacterial infection. *Nature* 2001; **414**: 454–457.
63 Zasloff M. Antimicrobial peptides of multicellular organisms. *Nature* 2002; **415**: 389–395.
64 Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. *J Allergy Clin Immunol* 2002; **110**: 823–831.
65 Froy O. Regulation of mammalian defensin expression by Toll-like receptor-dependent and independent signalling pathways. *Cell Microbiol* 2005; **7**: 1387–1397.
66 Choi DK, Li ZJ, Chang IK *et al.* Regional difference of inflammatory acne lesions according to beta-defensin-2 expression. *J Invest Dermatol* 2014; **134**: 2044–2046.
67 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**: 722–724.
68 Jahns AC, Lundskog B, Ganceviciene R *et al.* An increased incidence of *Propionibacterium acnes* biofilms in acne vulgaris: a case-control study. *Br J Dermatol* 2012; **167**: 50–58.
69 Tax G, Urban E, Palotas Z *et al.* Propionic acid produced by *Propionibacterium acnes* strains contributes to their pathogenicity. *Acta Derm Venereol* 2016; **96**: 43–49.
70 Jarrousse V, Castex-Rizzi N, Khammari A, Charveron M, Dreno B. Modulation of integrins and filaggrin expression by *Propionibacterium acnes* extracts on keratinocytes. *Arch Dermatol Res* 2007; **299**: 441–447.
71 Fisk WA, Lev-Tov HA, Sivamani RK. Botanical and phytochemical therapy of acne: a systematic review. *Phytother Res* 2014; **28**: 1137–1152.