REVIEW ARTICLE

Recent advances in Pathogenesis of Acne

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ABSTRACT

Acne is a chronic inflammatory disease of the pilosebaceous unit. Its pathophysiology includes increased secretion of sebum, abnormal follicular keratinization, *Propionibacterium acnes* proliferation in the pilosebaceous unit and inflammation. In fact, there is much more behind the known pathogenesis that has to be highlighted for better understanding and more successful treatment. Insulin-like growth factor (IGF)-1, diet, vitamin D and stress are some of the factors affecting the sebaceous gland. Cutaneous microbiome equilibrium with 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. Inflammation and inflammatory products (TNF, IL8 and more) have a different explanations at the pathogenesis.

INTRODUCTION

Acne is an exclusively human disease and a unique condition of sebaceous follicles of the face, chest and back that begins in the prepubertal child. Spontaneous regression is common, but in about 5% of cases acne persists beyond the age of 25 and extends into the fourth and fifth decades of life.[1] Acne vulgaris is one of the most common diseases of the skin and in cases of extreme disfiguration can sometimes have severe consequences for the personality development of young people, with ensuing social and economic problems. Adolescents suffering from acne show higher levels of anxiety and greater social inhibition and aggression compared to non-affected individuals. Among skin diseases, acne vulgaris is the second highest cause of suicides.[2] Its pathophysiology involves three mechanisms: hyperseborrhoea, abnormal follicular keratinization of the sebaceous gland duct 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 (fourth element).[3] This pathogenesis which is known to all of us is like an Iceberg, and the hidden part is more than what appears on the surface. In this review we will try to unleash part of the immersed pathogenesis.

THE SEBACEOUS GLAND

Seborrhea is significantly more common in patients with acne, than in controls and contributes to lesion formation.[4] The sebaceous gland is an androgen target organ, stimulated to produce sebum at puberty and beyond by androgens. Sebaceous glands present the highest androgen receptor density in human skin.[5] The most important

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androgen is testosterone, which is converted to the more potent dihydrotestosterone (DHT) by the iso-enzyme 5a reductase (type I), the major isotype detected in skin, particularly in sebaceous gland-rich areas.[6]

More has been learned about the role of seborrhea in acne as well. Sebaceous lipids are at least partly regulated by peroxisome proliferator-activated receptors and sterol response element binding proteins. Peroxisome proliferator-activated receptor nuclear receptors act in concert with retinoid X receptors to regulate epidermal growth and differentiation and lipid metabolism.[7] Sterol response element binding proteins mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1.[8] Many factors affecting sebaceous gland other than androgen (the hidden part of the Iceberg).

1. **Insulin-like growth factor (IGF)-1:** Although serum androgens have been viewed as the major hormonal trigger in acne during puberty, recent evidence suggests a pivotal role for insulin-like growth factor (IGF)-1. Individuals congenitally deficient in IGF-1 due to Laron syndrome do not develop acne, for example. However, high-dose IGF-1 replacement therapy leads to acne and hyperandrogenism.[9] Multiple mechanisms of IGF-1 may promote the development of acne. IGF-1 has been shown to: (1) Induce androgen synthesis and increase the cutaneous availability of dihydrotestosterone; (2) Disinhibit the forkhead box O1 (FoxO1) transcription factor, which normally suppresses the androgen receptor; and (3) Activate peroxisome proliferator-activated receptor–gamma, liver X receptor–alpha, and sterol regulatory element binding protein-1c (SREBP-1c). The latter actions increase sebum triglycerides and fatty acid desaturation, leading to a proinfammatory and comedogenic monosaturated fatty acid profile. Increased sebum production also leads to increased levels of squalene. Squalene monohydroperoxide is comedogenic and results from ultraviolet A–triggered photooxidation of squalene in sebum.[10]
2. **Diet:** Compelling evidence on the roles of hyperglycemic carbohydrates (high glycemic index), dairy products, and saturated fats in promoting acne has been reported. Refined carbohydrates and dairy products lead to disinhibition of Fox O1 and activation of the mechanistic target of rapamycin complex 1 (mTORC1) through escalation of insulin and IGF-1 levels. Saturated fats directly activate mTORC1. The effect of the latter is stimulation of SREBP-1c, which is central to sebaceous lipogenesis, sebum fatty acid production, and monosaturation.[11] Diet-mediated changes in sebum quantity and composition promote *P acnes* overgrowth and biofilm formation. *P acnes* produces triglyceride lipase, which increases levels of free palmitic and oleic acids. Palmitic acid, along with *P acnes*–derived damage associated molecular patterns, stimulates toll-like receptor 2 (TLR2), thereby triggering inflammasome activation and IL-1beta signaling. Oleic acid stimulates *P acnes* adhesion, keratinocyte proliferation, and IL-1–alpha release.[12] Furthermore, oleic acid can induce formation of comedones.[11] Because high glycemic load diets (HGLDs) might increase levels of insulin-like growth factor 1 (IGF-1) activity and activation, thereby inducing proliferation of

both keratinocytes and sebocytes as well as simulating androgen production, some have proposed that HGLDs might be pathogenic in acne.[13] Milk consumption, like HGLDs, has been suggested to play a potential role in the pathogenesis of acne by increasing insulin and IGF-1 levels. In addition, it has been noted that milk contains bovine IGF-1, which is able to bind to the human IGF-1 receptor and contains dihydrotestosterone precursors including placenta-derived progesterone, 5a pregnanedione, and 5a-androstanedione that might promote acne. Last, given that whey protein constitutes 20% of protein in cow's milk, its insulin-promoting component could help to explain the possible link between milk and acne.[14] Although, there are many positive researches about relation of diet and milk association with acne, there are also other articles that deny the relation. This needs to be sustantiated with further researches.

3. **Vitamin D:** An additional area of interest that has recently emerged is the action of vitamin D in the skin. Sebocytes are capable of metabolizing and synthesizing the primary vitamin D metabolite 1,25-dihydroxy vitamin D3. Several lines of evidence suggest that the vitamin D endocrine system is involved in regulating sebocyte function and physiology, including production of sebum. Further, vitamin D analogues may potentially be useful in normalizing sebaceous gland physiology in patients with acne.[15]
4. **Stress:** The sebaceous gland acts as an independent endocrine organ in response to changes in androgens and hormones, and is the control center for a complex regulatory neuropeptide program that acts like the hypothalamus-pituitary-adrenal axis. From cell-culture experiments there is evidence that human sebocytes possess a complete corticotropin-releasing hormone (CRH)-receptor system. CRH is a coordinator for neuroendocrine and behavioral responses to stress. It has been concluded that CRH may function as an important autocrine hormone with a homeostatic pro-differentiation activity. Clinical observations suggest an influence of stress on the course of acne, which may be explained via this hormonal pathway.[16]

FOLLICULAR KERATINIZATION

Recent studies support the latter hypothesis by demonstrating that an increase in IL-1 activity occurs before the hyper proliferation around uninvolved follicles and this triggers the activation of the keratinocytes. Jeremy et al, investigated the initiating events for acne lesions, and found that immune changes and inflammatory responses occur before hyper proliferation of keratinocytes, with a pattern similar to a type IV delayed hypersensitivity response. The immune response is led by CD 41 lymphocytes and macrophages. These researchers hypothesize that the subsequent production of cytokines activates local endothelial cells, up-regulating inflammatory vascular markers (E-selectin, vascular cell adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1], and human leukocyte antigen-DR [HLA-DR]) in the vasculature around the pilosebaceous follicle. They further have postulated that the entire process is initiated by interleukin (IL)-1a up-regulation in response to a relative linoleic acid deficiency caused by excess sebum and perturbation of barrier function within the follicle.[17]

PROPIONIBACTERIUM ACNES

Acne is not an infectious disease and, therefore, not contagious. Among the bacteria species that colonize normal skin as resident flora, only those able to colonize the follicular duct and multiply there can be pathogenic for acne. Only three species of microorganisms could therefore be associated with the development of acne lesions: propionibacteria, coagulase-negative staphylococci, and yeasts of the species Malassezia. However, acne did not improve after antifungal treatment, so yeasts could not be associated with the pathogenesis of acne. Staphylococci could also be excluded, because these develop antibiotic resistance during the first weeks of treatment in most patients, and the numbers quickly rise. Scientific interest has therefore been focused on propionibacteria.[18] Propionibacteria are gram-positive, non-motile, pleomorphic rod-shaped cells that ferment sugars to yield propionic acid as one of the end products in this metabolic process. *P acnes* is the predominant resident microorganism on sebaceous gland-rich areas of skin in adults. On human skin, propionibacteria can be found from birth until death.[19] Bacteriological analysis and sebum production investigated in multiple body areas demonstrated a high association between *P acnes* levels and sebum production.[20] The pathogenicity of propionibacteria is thought to be due to, first, the production of exocellular enzymes and other bioactive exocellular products, which could act as virulence determinants, and, second, on the microorganism` 's interaction with the immune system. Propionibacteria resist phagocytosis and can persist intracellularly within macrophages for prolonged periods.[21] First significant hints of an influence of *P acnes* on acne were obtained from *in vivo* studies on the injection of highly concentrated viable propionibacteria into sterile cysts of Steatocystoma multiplex patients; this induced prominent inflammation. Intradermal application of dead *P acnes* cells as well as the injection of viable *Staphylococcus epidermidis* cells were unable to reproduce this effect.[22] *P acnes* is not always pathogenic, however. The organism is present in both healthy and acne-affected skin, and all *P acnes* strains do not exert the same effects. Immune system responses to *P acnes,* rather than microbial density may influence progression to disease. Some *P acnes* phylotypes are associated with healthy skin rather than with skin affected by acne; others are more likely found in skin affected by acne than in healthy skin.[23] Acne associated *P acnes* phylotypes have been shown to induce higher levels of IFN-gamma and IL-17 in peripheral blood mononuclear cells than those associated with healthy skin. While, phylotypes associated with healthy skin induced higher levels of IL-10, an anti-inflammatory cytokine.[24] Whereas staphylococci acquire antibiotic resistance very rapidly via plasmids, *P acnes* develops resistance to tetracyclines, erythromycin and clindamycin over a long period of time via mutational change which is transferred vertically. According to recent results, *P acnes* antibiotic resistance is commonly associated with mutations in 16S and 23S mRNA, which are present in bacterial isolates from Japan, Australia, U.S.A., and Europe.[25]

THE CUTANEOUS MICROBIOME

The skin microbiome is the collective genome of the resident microbial inhabitants (viruses, bacteria, fungi and parasites), also called the mi-

crobiota, present on the skin and its appendages. It is a unique microbial fingerprint.[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).[27] Even though commensal, some inhabitants have been connected with inflammatory diseases of the skin, such as *P acnes* (acne), Malassezia furfur (seborrheic dermatitis) and demodex (rosacea). Other transient microbes, such as *Staphylococcus aureus* and *Streptococcus pyogenes*, are known pathogens.[28] In a balanced skin microbiome, *Staphylococcus epidermidis* limits over colonization 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-a production by keratinocytes.[29] 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.[30] 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.[31] 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.[32] 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. 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*.[33]

INFLAMMATION

P acnes acts on the innate immune system through multiple proinfammatory pathways. It activates TLR2 on monocytes, leading to the release of proinfammatory cytokines IL-12 and IL-8.[34] It promotes secretion of the proinflammatory cytokines IL-1–beta and IL-18 through an inflammasome pathway involving caspase-1 and the nucleotide oligomerization domain like receptor protein (NLRP).[35] The inflammasome is a group of intracellular proteins that convert procaspase-1 to caspase-1. Caspase-1 converts the inactive precursor of IL-1–beta to its active form.[36] Additionally, *P acnes* induces monocyte production of matrix metalloproteinases. These enzymes are associated with numerous inflammatory conditions and may play a role in matrix degradation and formation of acne scars.[37] *P acnes* also stimulates an adaptive immune response, inducing IL-17A and interferon (IFN)-gamma secretion from CD4+ T cells *in vitro*. Type 17 helper T cells (TH17) and type 1/type 17 helper T cells (TH1/TH17) that react to *P acnes*-stimulation are found in the peripheral blood of patients with and without acne, but cells from patients with acne displayed stronger responses to *P acnes*.[38] *P acnes* influences the development of acne in ways beyond promoting inflammation. *P acnes* biofilm formation has been detected in the

sebaceous follicles of patients with acne. Biofilm formation leads to increased *P acnes* virulence, manifested in part by the increased expression of *P acnes* triglyceride lipase, which increases the sebum concentration of palmitic and oleic acids. These changes in sebum lipid composition contribute to inducing inflammatory acne. As noted, oleic acid increases *P acnes* adherence and growth. Therefore, *P acnes* triglyceride lipase may indirectly contribute to biofilm formation by promoting increased concentration of oleic acid.[12] *P acnes* was found to be highly sensitive to different concentrations of nitric oxide in nanoparticles (NOnp). NO-np significantly suppressed IL-1b, tumor necrosis factor-a (TNF-a), 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.[39] Oxidized squalene can stimulate hyper proliferative behavior of keratinocytes, suggesting that this lipid may be partly responsible for comedo formation.[40] Zouboulis et al, have hypothesized that lipoperoxides exert a proinflammatory effect on the pilosebaceous duct. Lipoperoxides produce leukotriene B4, which is a powerful chemoattractant that can recruit both neutrophils and macrophages, and stimulate production of proinflammatory cytokine.[41]

THE ENDOCANNABINOID SYSTEM

Endocannabinoids represent a class of endogenous lipid mediators that are involved in various biological processes, both centrally and peripherally.[42] 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.[43,44] An in vitro study performed in 2014 found that cannabidiol has lipostatic, ant proliferative and anti-inflammatory effects which could make this non-psychotrophic cannabinoid agent a promising therapy for acne vulgaris.[45]

LINOLEIC ACID DEFICIENCY

Linoleic acid is incorporated into sphingolipids in the follicular epithelium, which participates in the formation of the intracellular lipid lamellae. Zouboulis showed that linoleic acid is able to regulate interleukin (IL-)8 secretion and, as a consequence, the inflammatory reaction.[46]

IN SUMMARY;

Inflammation plays a central role in acne pathogenesis. And insulin, IGF-1 and androgens are prime orchestrators, with initiation likely due to consumption of dairy foods and a high glycemic index diet. The hormones lead to increased sebum production and a more inflammatory composition of sebaceous lipids. Other receptors on sebaceous glands, such as corticotropin-releasing hormone (CRH)- receptor and The endocan-

nabinoid have to be kept in mind while managing Acne. The pathogenesis of Acne is not that four known elements. There is more affecting those factors, that's the hidden part of the Iceberg.

REFERENCES

1. Cunliffe WJ. Natural history of acne. In: Cunliffe WJ, ed. Acne. London: Martin Dunitz, 1989: 2-10.
2. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol 1998; 139: 846-50.
3. Taylor M, Gonzalez M, Porter R. Pathways to inflammation: acne pathophysiology. Eur J Dermatol 2011; 21: 323-33.
4. Harris HH, Downing DT, Stewart ME, Strauss JS. Sustainable rates of sebum secretion in acne patients and matched normal control subjects. J Am Acad Dermatol 1983; 8: 200-203.
5. Bla¨uer M, Vaalasti A, Pauli SL, Ylikomi T, et al. Location of androgen receptor in human skin. J Invest Dermatol 1991; 97: 264-68.
6. Thigpen AE, Silver RI, Guileyardo JM, Casey ML, et al. Tissue distribution and ontogeny of steroid 5a-reductase iso-enzyme expression. J Clin Invest 1993; 92: 903-10.
7. Trivedi NR, Cong Z, Nelson AM, Albert AJ, et al. Peroxisome proliferator-activated receptors increase human sebum production. J Invest Dermatol 2006; 126: 2002-09.
8. Smith TM, Cong Z, Gilliland KL, Clawson GA, Thiboutot DM. Insulin-like growth factor-1 induces lipid production in human SEB-1 sebocytes via sterol response element-binding protein-1. J Invest Dermatol 2006;126:1226-32.
9. Ben-Amitai D, Laron Z. Effect of insulin-like growth factor-1 defciency or administration on the occurrence of acne. J Eur Acad Dermatol Venereol. 2011; 25: 950-54.
10. Chiba K, Yoshizawa K, Makino I, Kawakami K, Onoue M. Comedogenicity of squalene monohydroperoxide in the skin after topical application. J Toxicol Sci. 2000; 25: 77-83.
11. Melnik BC. Linking diet to acne metabolomics, infammation, and comedogenesis: An update. Clin Cosmet Investig Dermatol. 2015; 8: 371-88.
12. Gribbon EM, Cunliffe WJ, Holland KT. Interaction of Propionibacterium acnes with skin lipids in vitro. J Gen Microbiol. 1993; 139: 1745-51.
13. Cordain L, Lindeberg S, Hurtado M, Hill K, et al. Acne vulgaris: a disease of Western civilization. Arch Dermatol. 2002; 138 (12): 1584-90.
14. Bronsnick T, Murzaku EC, Rao BK. Diet in dermatology: Part I. Atopic dermatitis, acne, and nonmelanoma skin cancer. J Am Acad Dermatol. 2014; 71(6): 1039.e1-1039.e12.
15. Zouboulis CC, Baron JM, Bohm M, Kippenberger S, et al. Frontiers in sebaceous gland biology and pathology. Exp Dermatol 2008; 17: 542-51.
16. Zouboulis CC, Seltmann H, Hiroi N, Chen WC, et al. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. www.pnas.org/cgi/doi/10.1073.
17. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003; 121: 20-7.
18. Marples RR, McGinley KJ. Corynebacterium acnes and other anaerobic diphtheroids from human skin. J Med Microbiol 1974; 7: 349-57.
19. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Age related changes in the resident bacterial flora of the human face. J Invest Dermatol 1975; 65: 379-81.
20. McGinley KJ. Regional variations in the density of cutaneous propionibacteria: correlation of Propionibacterium acnes populations with sebaceous secretions. J Clin Microbiol 1980; 12: 672-75.
21. Webster GF, Leyden JJ, Musson RA, Douglas SD. Susceptibility of Propionibacterium acnes to killing and degradation by human neutrophils and monocytes in vitro. Infect Immun 1985; 49: 116-21.
22. Kirschbaum JD, Kligman AM. The pathogenic role of Corynebacterium acnes in acne vulgaris. Arch Dermatol 1963; 88: 832-33.
23. Fitz-Gibbon S, Tomida S, Chiu BH, et al. Propionibacterium acnes strain populations in the human skin microbiome associated with acne. J Invest Dermatol. 2013; 133: 2152-60.
24. Yu Y, Champer J, Agak GW, Kao S, Modlin RL, Kim J. Different Propionibacterium acnes phylotypes induce distinct immune responses and express unique surface and secreted proteomes. J Invest Dermatol. 2016; 136: 2221-28.
25. Ross JI, Snelling AM, Eady EA, Cove JH, et al. Phenotypic and genotypic characterisation of antibiotic-resistant Propionibacterium acnes isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. Br J Dermatol 2001; 144:

339-46.
26. Cundell AM. Microbial ecology of the human skin. Microb Ecol 2016; DOI: https://doi.org/10.1007/s00248-016-0789-6.
27. Oh J, Byrd AL, Park M, Kong HH, Segre JA. Temporal stability of the human skin microbiome. Cell 2016; 165: 854-66.
28. Findley K, Grice EA. The skin microbiome: a focus on pathogens and their association with skin disease. PLoS Pathog 2014; 10: e1004436.
29. 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: 411-24.
30. 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.
31. Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. Clin Cosmet Investig Dermatol 2015; 8: 479-83.
32. 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.
33. Jugeau S, Tenaud I, Knol AC, et al. Induction of toll-like receptors by Propionibacterium acnes. Br J Dermatol 2005; 153: 1105-13.
34. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers infammatory cytokine responses. J Immunol. 2002; 169: 1535-41.
35. Qin M, Pirouz A, Kim MH, Krutzik SR, et al. Propionibacterium acnes induces IL-1ß secretion via the NLRP3 infammasome in human monocytes. J Invest Dermatol. 2014; 134: 381-88.
36. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of infammatory diseases. Blood. 2011; 117: 3720-32.
37. Jalian HR, Liu PT, Kanchanapoomi M, Phan JN, et al. All-trans retinoic acid shifts Propionibacterium acnes-induced matrix degradation expression profle toward matrix preservation in human monocytes. J Invest Dermatol. 2008; 128: 2777-82.
38. Kistowska M, Meier B, Proust T, et al. Propionibacterium acnes promotes TH17 and TH17/ TH1 responses in acne patients. J Invest Dermatol. 2015; 135: 110-18.
39. 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: 2723-31.
40. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, et al. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. J Invest Dermatol 2006; 126: 2430-37.
41. Zouboulis CC. Leukotrien-antagonisten bie atopischen Erkrankungen und Akne. Akt Dermatol 2003; 29: 419-25.
42. Pucci M, Pirazzi V, Pasquariello N, Maccarrone M. Endocannabinoid signaling and epidermal differentiation. Eur J Dermatol 2011; 21 (Suppl 2): 29-34.
43. 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: 411-20.
44. Kendall AC, Nicolaou A. Bioactive lipid mediators in skin inflammation and immunity. Prog Lipid Res 2013; 52: 141-64.
45. Olah A, Toth BI, Borbiro I, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J Clin Invest 2014; 124: 3713-24.
46. Zouboulis C. Update on sebaceous gland physiology: induction of inflammation and its clinical implications. J Eur Acad Derm Venereol 2001; 15 Suppl. 2: 102.