Updates in Clinical Dermatology
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Dae Hun Suh *Editor*

Acne

Current Concepts and Management

Springer

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Preface

Acne is one of the most common skin diseases. It was in 1996 when I started researching acne and opened an acne special clinic, but until then, acne research was not actively conducted at the university level in Korea. This is probably related to the trend of taking acne lightly. People regard acne as a symbol of youth and dismiss it as a passing process. Sometimes, even doctors (excluding dermatologists) seem to have this thought. However, acne is definitely a notable chronic skin disease. It can occur not only during puberty, but also before adolescence, and often continues to last for a long time. Acne patients suffer considerably from active inflammatory/non-inflammatory lesions and scars, and there are cases of suicide attempts due to mental stress. Acne is a serious disorder and deserves meticulous attention. There tends to be a misunderstanding that acne is an "easy" disease, but there is still much to uncover about its pathophysiology, and thus research on it is increasingly active. Novel therapeutic drugs and methods are also being tried.

In 2000, I went to study in the United States with my family for a full-fledged acne research, where I could learn a lot from Prof. Thiboutot's laboratory. With the creation of the Asian Acne Board in 2005, I had the opportunity to exchange opinions with numerous acne researchers. After becoming a member of "Global Alliance to Improve Outcomes of Acne," a group of world-renowned acne researchers, I have had valuable opportunities to engage with famous scholars and hear their insights.

When Springer and Dr. Chee Leok Goh suggested I write a book about acne, I hesitated, knowing the difficulty of the task. However, the decision was made, as the collection of manuscripts written by acne researchers from around the globe should be of great help to dermatologists in the general hospital and private practice, dermatology residents, and medical students. I am grateful to the staff at Springer, including Ms. Asja Rehse and Ms. Maureen Alexander, for their efforts to complete my task. I'd also like to take this opportunity to thank my disciples and research associates for being a great help in my acne research. Last but not least, I express my gratitude to Prof. Jai Il Youn, Prof. Jouni Uitto, Prof. Joseph Gonnella, and Prof. Young Kauh for helping and encouraging me throughout my career.

The chapters' authors are all world-class acne masters, representing many regions. This combined knowledge has the advantage of being superior to the bulk of previously published books on acne. It is my great honor and glory to collaborate with these authors, and I deeply appreciate their kind and enormous work. These authors have laid out detailed and the most up-to-date

knowledge of acne pathophysiology, clinical features, differential diagnosis, treatment, and more. Pathophysiology, in particular, includes information on bacteria, immunity, endocrinologic factors, various deteriorating factors, and environmental factors. As for clinical features, adult acne, differences in clinical patterns by region and race, and acne fulminans are covered. Regarding treatment, the latest knowledge on existing treatments or treatment methods, new drugs, and core outcome measures are mentioned. The authors put forth their best efforts to bring state-of-the art knowledge to readers, sharing their expertise. I hope this book will function as an expert of acne, easily be approachable for those interested, physicians and researchers alike.

Finally, I dedicate this book to my beloved family, especially my wife and son who always remind me of the joy of life and offer me strong support. I also dedicate this book to my father and mother. My mother, who passed away in April last year due to an exacerbation of rheumatic disease, always loved her son with great pride in his communicating with world-class scholars and giving lectures around the world. Indeed, she would be most delighted with the publication of this book in heaven.

Seoul, South Korea Dae Hun Suh
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Update on *Cutibacterium acnes*

1

Marie-Ange Dagnelie, Stéphane Corvec, Amir Khammari, and Brigitte Dréno

Abbreviations

AMP	Antimicrobial peptide
CAMP	Christie-Atkins-Munch-Petersen (e.g. CAMP2, etc.)
CRISPR	Clustered regularly interspaced short palindromic repeats
D/PAMP	Damage-/pathogen-associated molecular pattern
EVs	Extracellular vesicles
hBD2	Human β-defensin 2
HYL-IA	Variant of hyaluronidase (HYL) found in phylotype IA
HYL-IB and II	Variant of hyaluronidase (HYL) found in phylotypes IB and II
IFN-γ	Interferon- γ
IL	Interleukin (e.g. IL-8, IL-6, etc.)
MMPs	Matrix metalloproteinases (e.g. MMP-9, MMP-13, etc.)
NK cells	Natural killer cells
NLRP3	NOD-like receptor family, pyrin domain containing 3
PAR-2	Protease-activated receptor-2
PCR	Polymerase chain reaction
QS	Quorum sensing
RIS-1/psoriasin	Retinoic acid-inducible skin-specific gene
RNA	Ribonucleic acid
RNases	Ribonucleases
SCORAD	Scoring atopic dermatitis
SLST	Single-locus sequence typing
TGF-β	Transforming growth factor-β
Th17/Th1	T helper 17/T helper 1 cells
TIMP-2	Tissue inhibitor of metalloproteinases (e.g. TIMP-2, TIMP-4, etc.)
TLRs	Toll-like receptors (e.g. TLR-2, TLR-4, etc.)
TNF-α	Tumour necrosis factor-α

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Introduction

This book chapter focuses on *Cutibacterium acnes*, which is a commensal bacterium of the cutaneous microbiome, playing a crucial role in acne development [1–4]. This chapter will first precisely describe the identity passport of this bacterium and then focus on the interactions existing

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between *C. acnes* and the other microorganisms' resident of the human skin, mainly *Staphylococcus epidermidis*. This chapter will then describe the interactions existing between *C. acnes* and the innate immune system of the skin and finally will open on the future potential treatments that will be developed in the next years, to treat acne.

Cutibacterium acnes (Ex – *Propionibacterium acnes*) Identity Passport

The skin represents a complex ecosystem [5]. A large and diverse community of microorganisms is present on the body. Depending on the ecological niches, the bacterial distribution can vary [6]. Thus, in a lipidic area, *Actinobacteria* are more represented, and *Cutibacterium acnes* can represent until 70% [7]. This anaerobic-aerotolerant Gram-positive bacteria is a skin commensal, and its ecological niche is represented by the sebaceous follicles [8–10].

Bacteriological Description

Initially, *C. acnes* was classified as a *Corynebacterium* [11]. According to the recent literature, the microscopy morphology can be diverse leading to different subtypes [12–14]. By direct microscopy examination, the historical phylotypes I, II and III are somehow different [12, 15, 16]. New insights from integration of population community's analysis, genomic studies and biochemical and host-microorganism interactions lead to a better knowledge of this bacterium involved in inflammatory process [17, 18].

Ecological Niches

C. acnes is a major resident of the normal human skin microbiota and dominates in the pilosebaceous units which can be explained by production of different enzymes [19–21]. It can interact with other microorganisms, especially *Staphylococcus epidermidis* playing an important role in the skin health, educating the innate immune system and maintaining the skin homeostasis [22]. *S. epidermidis* could be a partner in the pathogenesis of acne, producing antimicrobial substances (bacteriocins) active against *C. acnes* leading to a disruption (dysbiosis) of the normal skin homeostasis equilibrium [23]. Its involvement in skin disorder, especially acne, has been described, but we also can recover isolates from mouth, gastrointestinal tract, prostate and device-related infections [14].

Taxonomy Modification

Following its discovery in a patient with acne, *P. acnes*, henceforth *C. acnes*, underwent a series of taxonomic changes. It was successively placed in the genus *Bacillus*, followed by *Corynebacterium* [11]. However, in 1946, Douglas and Gunter were able to demonstrate that this microorganism was more closely related to the *Propionibacterium* genus members since, like other species of this genus, it ferments lactose to propionic acid in an anaerobic atmosphere maintaining an acid pH on the skin surface and limiting pathogen development [24, 25]. Recently, a significant taxonomic revision was proposed by Scholz et al., placing all *Propionibacterium* species from the skin microbiota within this new genus *Cutibacterium* [25]. Henceforth, the main actor of the sebaceous follicles should be named *Cutibacterium acnes*. Recently, according to the three main phylotypes described at the beginning, subspecies have been proposed. Thus, phylotype I corresponds to the subspecies *C. acnes* subsp. *acnes* [26], phylotype II corresponds to the subspecies *C. acnes* subsp. *defendens* [27] (due to the presence of a CRISPR system limiting gene transfer or acquisition) [28] and phylotype III corresponds to subspecies *C. acnes* subsp. *elongatum* according to its microscopy morphology [26].

Phylogeny

Since 2005, different groups have developed molecular tools to identify if possible clusters or

lineages are more involved in different specific diseases. At the beginning, the role of specific *C. acnes* subgroups in the physiopathology of these diseases was conducted with antibodies [15]. Using different targets such as *tly* or *recA* genes, several groups developed different molecular typing methods [29]. Thereafter, phylotype multiplex PCR, different multi-locus sequence typing schemes and a useful single-locus sequence typing method which can be performed directly from samples have been proposed [30–33]. Nevertheless, to compare the phylogeny of clinical isolates recovered during different diseases, we proposed a consensus with an algorithm to identify subtypes of *C. acnes* by molecular typing methods [34]. Thus, in moderate to severe acne, different studies have proven to have highly prevalence in skin inflammatory swab specimens of phylotype IA_1 [35–41]. At the opposite, for example, another skin disease is linked to an overrepresentation of phylotype III: progressive macular hypomelanosis [42, 43].

Growth Culture Conditions

Conventional microbial culture of *C. acnes* from skin samples requires some attention, but in a well-trained microbiology laboratory, it remains easy. Different media can be used, sometimes with supplementation with tween, for example [14]. Schaedler agar, Brucella agar, or chocolate agar plates can be seeded and incubated anaerobically for at least 7–10 days at 37 °C [13]. In acne lesions, different colony aspects can be observed regarding colour and haemolysis [44].

Virulence Factors

C. acnes is able to produce numerous virulence factors [45]. Thus, it produces short-chain fatty acids (leading to a local inflammation); thiopeptides; bacteriocins [46]; degradative enzyme such as lipases [20], endoglyceramidases, sialidase and hyaluronidase [21]; and other molecules with inhibitory properties against pathogens such as *Staphylococcus aureus* or *Streptococcus pyogenes*. *C. acnes* is able to trigger innate immune system via Toll-like receptor 2 (TLR-2) activation. Different TLR-2 ligands can be involved in this immune stimulation: lipoteichoic acids and peptidoglycan fragments [45] but also cell surface proteins like Christie-Atkins-Munch-Petersen (CAMP) factors which have co-haemolytic activity and cytotoxin properties [47, 48]. *C. acnes* lipase has a crucial role in hydrolysing triglycerides of sebum leading to the release of irritating fatty acids within pilosebaceous follicles which partly explain acne pathogenesis [13]. Interestingly, phylotype IA_1 recovered in 80% of acne lesion produces more lipase than other phylotypes [49].

Hyaluronidase is another extracellular enzyme implicated in the bacterial pathogenesis (involvement in penetrating the extracellular matrix) leading to total hyaluronic acid degradation for HYL-IB/II variant versus a partial degradation for the HLY-IA variant [13, 21, 50]. Certain *C. acnes* strains, especially those involved in acne, belonging to phylotype I can produce haemolysins with cytotoxin properties. Valanne et al. demonstrated the presence of the five CAMP factors in the different *C. acnes* subgroups. However, the *camp2* gene seems to be the most relevant and active co-haemolytic factor but in the IA phylotype *C. acnes* genetic background [13, 44, 47]. At last, the ability of *C. acnes* clinical strains to produce biofilm has been largely investigated, especially in device-related infections [51, 52]. In acne field, in 2008, Coenye et al. suggested the impact in acne of sessile *C. acnes* cells either highly resistant to antimicrobial agents or tolerant to with potential increased production of virulence factors and quorum sensing molecule regulation [53]. In biofilm condition, lipase has a greater extracellular activity [8]. In 2012, the presence of *C. acnes* macrocolonies within the pilosebaceous follicles has been described. Interestingly, different phylotypes were contained and coexisted [54]. Recently, Kuehnast et al. suggested that biofilm formation correlates with the phylotype, rather than the anatomical isolation site. In their model, phylotype IA_1 (SLST types A1 and A2) demonstrated higher biofilm production [55].

Resistance in Acne Context

C. acnes is susceptible to a large range of antibiotics [14]. Nevertheless, in acne context, antibiotics should be used for a short treatment period. Indeed, from 1979, the first resistant strains have been reported [56]. Henceforth, erythromycin resistance is largely higher than tetracycline one [57, 58]. According to antibiotic treatment habits, the epidemiological resistance of *C. acnes* is different: topical or systemic treatment, doses, combination, duration, etc. Thus, macrolide resistance rate can vary from less than 25% in Columbia to almost 90% in Spain [57]. The tetracycline situation is better with less than 10% in France to almost 50% in India [57]. The mechanism involved in these resistances is systematically point mutation in the chromosomal gene targets: 23S encoding gene and to a lesser extent L4 or L22 proteins for macrolides and 16S encoding genes for tetracycline [14]. Recently, in Japan, the impact of fluoroquinolone topical use has been reported with the emergence of resistant *C. acnes* strains [59] but also a worrying problem linked to the collateral damages with the impact on resistance in the microbiota and therefore *Staphylococcus epidermidis* fluoroquinolone selection [60].

Acne in the Genomic Era

As the skin ecosystem is a dynamic and evolving environment with numerous bacterial interactions, genomic, transcriptomic and metabolomic approaches will help us better understand the role of these specific bacterial communities in acne pathogenesis and inflammation (Table 1.1).

Table 1.1 Summary of nomenclatures of *Cutibacterium acnes* phylotypes and clonal complexes based on the two main MLST schemes and the SLST typing methods

Typing based on multiplex PCR	MLST9Aarhus scheme156 ST	MLST8Belfast scheme152 ST	SLST142 types
IA_1	CC18	CC1	A1-45
	CC3	CC3	C1-6
	CC28		D1-5
	CC31	CC4	E1-11
IA_2	CC28	CC2	F1-18
IB	CC36	CC5	H1-10
IC	Singletons	CC107	G1
II	CC53	CC6	K1-27
	CC60	CC72	
III	CC43	CC77	L1-10

Note that Aarhus MLST scheme can detect CC28 in IA_1 and IA_2 clades
CC clonal complex, *MLST* multi-locus sequence typing, *SLST* single-locus sequence typing, *ST* sequence type
Last update MLST9: September 22, 2019
Last update MLST8: September 22, 2019
Last update SLST: September 22, 2019

Cutibacterium acnes and Cutaneous Microbiome Interactions

The human skin microbiome is a unique and complex mixture of different groups of microorganisms. Human skin harbours bacteria (anaerobic, aerotolerant, or facultative anaerobic), virus, fungi and bacteriophages. Interspecies cross talks exist between these cutaneous microbial communities. These interactions take place through different ways, notably growth regulation, quorum sensing, biofilm synthesis regulation and extracellular vesicles exchanges. This fragile balance between growth and inhibition of each cutaneous species is the guarantor of skin homeostasis and functional skin barrier.

First of all, growth regulation is possible through the production of certain type of bioactive molecules able to kill and/or inhibit the growth of certain bacteria. To illustrate this phenomenon, Christensen et al. showed that *Staphylococcus epidermidis* strains possess an arsenal of mechanisms to inhibit *C. acnes* growth. These growth regulations result from the production of bioactive molecules called bacteriocins, such as the epidermin produced by *S. epidermidis* in that case [22]. These molecules act on the cytoplasmic membrane of Gram-positive bacteria. Another example of bioactive molecule is gallidermin. This molecule was successfully tested in a topical formulation on rat skin showing antibacterial potential against *C. acnes* and *S. aureus* [61]. Another example was reported by Wang et al. concerning

the inhibitory potential of *C. acnes* on the growth of methicillin-resistant *Staphylococcus aureus*, using an in vitro model [62].

Secondly, quorum sensing (QS) is a way to communicate between bacteria enabling the regulation of bacterial gene expression in response to changes in cell density. It permits them to sense bacterial numbers among their population (cell density), integrate and process the environmental parameters and synchronously alter their behaviour by expressing specific target genes [63, 64]. Nowadays, more and more evidences relate interspecies, inter-genera and inter-kingdom communications using largely diffusible small molecules named "quoromones" or "autoinducers" [65]. In Gram-positive bacteria such as *Cutibacterium acnes*, these molecules are often oligopeptides [65]. On the clinical point of view, it was recently suggested that QS mutants of human pathogens were attenuated for virulence [66, 67] quickly leading to the concept of using QS inhibitors to control some diseases [63]. Then, QS appears as a way to regulate microbial populations among skin microbiome, as previously suggested [68], and even more could be involved in the physiopathology of dermatoses such as acne [69].

Then, interspecies interactions are also described through biofilm synthesis regulation. This kind of mechanism was previously reported between *Staphylococcus aureus* and *C. acnes* [70]. In this study, authors demonstrated that *C. acnes* may have an effect on the behaviour of *S. aureus*. This study suggests that *C. acnes* may produce a factor or provide a promoting environment for staphylococcal biofilm formation. Since coproporphyrin III is known to induce *S. aureus* aggregation in cutaneous isolates, it is possible that this molecule could also induce biofilm formation or there may be a different mechanism currently not described [71].

Finally, extracellular vesicle (EV) exchanges are nowadays considered as a crucial player in bacteria communications [72]. All bacteria are capable of producing this type of natural messenger, including Gram-positive ones [73]. Recently, *C. acnes* was described as able to produce EVs [74]. These bacterial EVs enable the communication between bacteria themselves but also between them and host cells such as keratinocytes in cutaneous context, notably via TLR2-mediated signalling pathways [75]. Indeed, Choi et al. described that the entry of *C. acnes*-derived EVs into keratinocytes is mediated by clathrin-dependent endocytosis, and this way, the internal cargo of these EVs can be delivered into keratinocytes. In this example, Choi et al. demonstrated that *C. acnes*-derived EVs were able to induce an acne-like phenotype in keratinocytes and confirmed their results in a reconstituted human epidermis model. In addition, one specific study reports the possible regulation between bacterial populations from different microbiotas using EV pathway, to protect the skin from inflammation induced by a pathogen. Indeed, it was previously reported that EVs from *Lactobacillus plantarum*, which is a commensal found in digestive tract, were able to protect from atopic dermatitis induced by *S. aureus*-derived EVs. Clinical applications are then suggested using *L. plantarum*-derived EVs, based on their modulation potential towards cutaneous pathogens like *S. aureus*. Another clinical outlook was suggested in the literature, based on the inhibition of the release of EVs from *C. acnes* to avoid inflammatory cytokine releases from keratinocytes and acne phenotype occurrence [75].

Taken together, these elements of the literature underline the importance of appropriate interspecies cross talks. Indeed, an imbalance in these microbial interactions could potentially jeopardize the relationships between skin microbiota and host cells and may result in skin inflammatory diseases where dysbiosis is often cited as a potent actor.

Skin microbiota appears as a complex and multifactorial organ part of the skin, for which modulation is nowadays thought to be able to treat inflammatory dermatoses, as recently suggested in acne context [76]. Indeed, as antibiotic resistance is an increasing phenomenon especially in acne disease [77, 78], probiotic solutions are nowadays considered as an interesting alternative to antibiotic treatments and also a new option added to the current therapeutic arsenal of clinicians (Fig. 1.1).

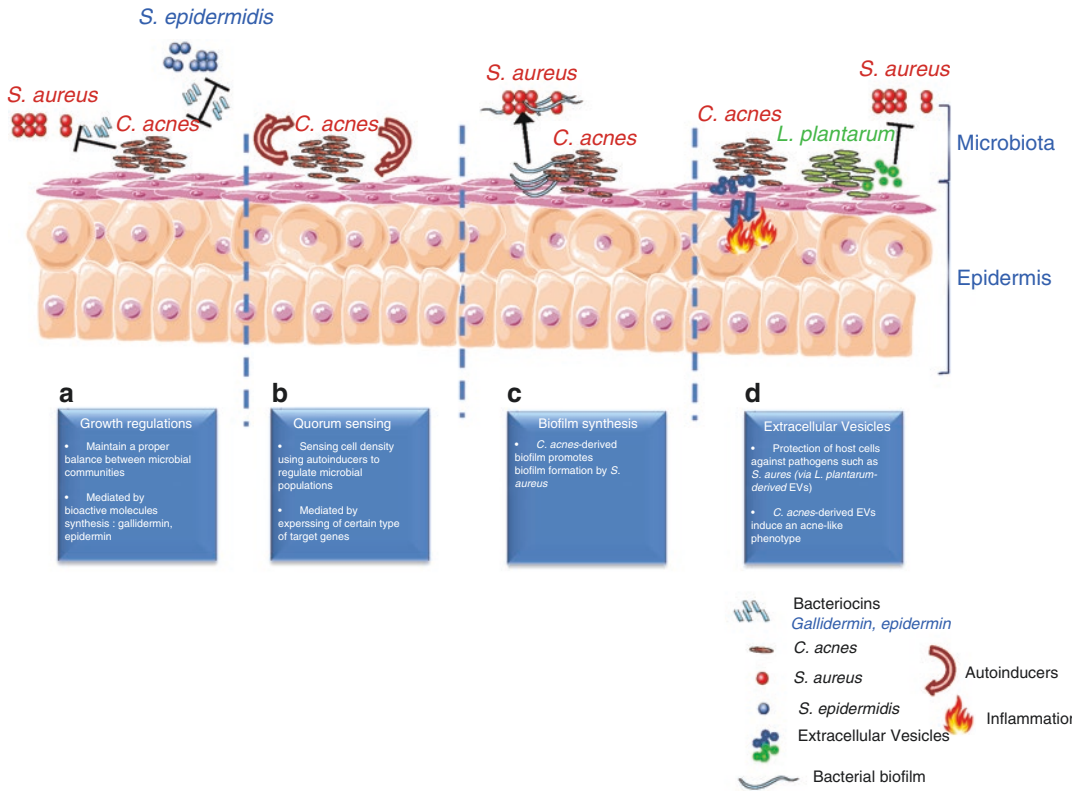

Fig. 1.1 *Cutibacterium acnes* and cutaneous microbiome interactions. Summary of the different interactions existing between *C. acnes* and the different skin microbial communities. (**a**) Growth regulations are mediated through different bioactive molecules (epidermin, gallidermin). (**b**) Quorum sensing is one of the pathways possible for interaction between bacteria. (**c**) Interactions between *C. acnes* and skin microbiota also take place through biofilm synthesis. Indeed, recent studies reported that *C. acnes*-derived biofilm was able to promote biofilm synthesis by *S. aureus*. (**d**) Extracellular vesicles are able to carry signals promoting interspecies communications and also host/microbiota communications

Cutibacterium acnes and Innate Immunity

The skin with its microbiome develops a wide range of innate immune responses to protect the body against infection. In contrast to the gut microbiome that is physically separated from the epithelium by a dense mucus layer in the colon, the skin microbiome is in close contact with the epidermis. It is important that the immune response is primed to recognize and tailored to respond to an appropriate threat, as any immune reaction towards commensal agents could lead to chronic disease. Keratinocytes and sebocytes are the main cell types of the epidermis and actively participate in innate immunity, as a source of antimicrobial peptides and cytokines that trigger inflammation when the epithelium is exposed to damage-/pathogen-associated molecular patterns (D/PAMP), mainly represented by Toll-like receptor 2, 4 and 6 (TLR) ligands and protease-activated receptor (PAR)-2 ligands that link with the corresponding receptors expressed on/in the keratinocytes and sebocytes [79]. The activation of innate immunity seems different according to the type of the skin and phylotype of *C. acnes*. In one study, type IC isolated in the normal skin would induce higher secretion of IL-8 in keratinocytes than type IA [80]. In contrast, types IA and IB of *C. acnes* were found to induce greater levels of the human β-defensin 2 (hBD2) from cultured sebocytes than a type II isolate [81, 82]

which demonstrated that *C. acnes* type III had the highest pro-inflammatory potential by upregulating the expression of PAR-2, TNF-alpha, MMP-13 and TIMP-2, whereas *Cutibacterium avidum* had the weakest by upregulating only MMP-13 and TIMP-2 [82].

C. acnes can induce IFN-γ from NK cells by mechanism involving the release of RNA and an innate pathway dependent on activation of TLR8 and the secretion of IL-12p40 and IL18 [83]. In addition of IL-8, in the process of inflammation triggered by *C. acnes*, secretion of IL-1β by monocytes and sebocytes throughout the activation of the key inflammasome gene NLRP3 has been observed [84]. This mechanism is regulated by proteases and reactive oxygen species. Moreover, *C. 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 [85]. Recently it has been shown that IL-17 was increased in the serum of acne patients [86]. In addition of cytokines, antimicrobial peptides (AMPs) are important modulator of cutaneous inflammation and belong to the innate immunity. There is strong evidence that AMP plays a role in the pathogenesis of inflammatory acne lesions. Skin-derived AMPs comprise the family of β-defensins, S100 proteins, RNases and the cathelicidin LL-37. While some AMPs are constitutively secreted, hBD-2 and hBD-3 and LL-37 are upregulated in acne lesions and induced by culture supernatants of *C. acnes* in vitro both in keratinocytes [48] and in sebocytes [87]. RIS-1/psoriasin is an epithelial antimicrobial peptide, whose expression is upregulated in inflammatory skin diseases including acne and is induced by retinoids. Inflammation modifies the compartmentation of RIS-1/psoriasin in sebaceous glands and the follicular root sheaths with an increase of its expression, thus making this AMP a new target of acne treatments [88].

Acne is associated with scar development in many patients. Recently, we showed that in the skin of acne patients prone to scars versus not prone to scars, TLR-4, IL-2, IL-10, TIMP-2 and JUN were significantly overexpressed and the MMP-9 protein level was decreased. Similar results were obtained in inflammatory papules, except for TLR-4. Thus, these results suggest a link between the early events of inflammation with levels of activation of innate immunity in the normal epidermis of acne patients and the development of scars showing how crucial it is to treat inflammation in acne to prevent the development of scars [89]. TGF-β1 could also play a role in the development of scars as it is strongly elevated in lesions of acne patients who were prone to scars [90].

A crucial question in the microbiome field is why do cells switch from a state of immunological tolerance to a chronic inflammatory state in the absence of an infection. In the case of acne development, a dynamic shift in the microenvironment of the follicle induced by hyperseborrhea can trigger a different transcriptional response of the microbiome. Thus, culturing *C. acnes* in a lipid-rich, hypoxic environment similar to that of an occluded hair follicle promotes anaerobic fermentation and production of short-chain fatty acids that activate an epigenetic mechanism to enhance the TLR2-mediated production of IL-6, IL-8 and TNFα in human keratinocytes [91] (Fig. 1.2).

What Alternatives in the Future?

The development of new treatments against pathology requires a good and strong knowledge of the physiopathology and the pathways involved in order to better target the factors involved in the pathology and by inducing few side effects. Currently, the exact pathophysiological mechanisms of acne are only partially known. The predominant involvement of *C. acnes* is questionable since the latest knowledge shows that acne state and induced inflammation are governed by complex association of multiple factors. These factors mainly depend on the microbiological microenvironment, gender, age and individual intrinsic factors.

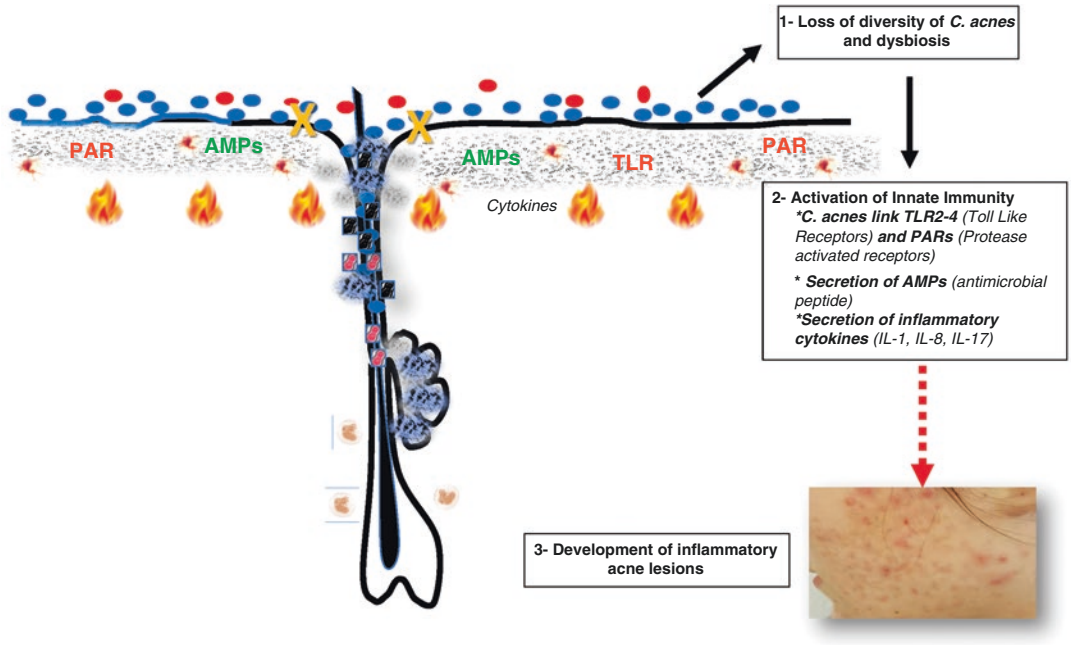

Fig. 1.2 *C. acnes* cross talks with the cutaneous innate immunity

In the current therapeutic arsenal, the management of acne varies mainly according to acne severity. Management algorithms are published [92] including topical treatments (antibiotics, retinoids, benzoyl peroxide and salicylic/azelaic acids) and systemic treatments (antibiotics, retinoids, zinc) [93]. Some studies pointed that the main research goal of acne treatment is to target *C. acnes* and the induced inflammatory status, the sebum hypersecretion and hyperkeratinization [94]. In parallel, antibiotics modulate *C. acnes* and have an anti-inflammatory effect [95]. Benzoyl peroxide and azelaic acid inhibit *C. acnes* colonization and have comedolytic and anti-inflammatory/antibacterial effects [96–98]. Oral retinoids or isotretinoin are more likely used to treat severe acne. These molecules impact on sebum production and regulate *C. acnes*/TLR-2-mediated innate immune response [99]. Systemic retinoids might indirectly regulate skin microbes and reduce the number of *C. acnes*, inducing changes in microbial diversity [93, 100].

Despite some proven efficacy of current treatments, cutaneous side effects of topical products, systemic effects as for isotretinoin, antibiotic-induced bacterial resistance and acne chronicity encourage the research to explore targeted therapies, respecting the microbiome diversity and inducing fewer side effects. Currently, there are four main axes in development: probiotics, vaccines, phages and antimicrobial peptide therapies.

Microbiome and Probiotics Approach

The use of antibiotic therapy to eliminate, as a priority, *C. acnes* considered for a long time as major acne agent is less and less recommended especially in oral monotherapy [92] for at least two major reasons: development of resistance to antibiotics and disruption of the skin and gut microbiome (bacterial diversity loss) which is a crucial condition in normal healthy status. Furthermore, it is known that phylotype IA1 is overrepresented and involved in moderate to severe acne [37–39]. In parallel, dysbiosis in acne patient is associated with a decreased number of *S. epidermidis* which is able to control *C. acnes* proliferation via releasing of succinic acid and fatty acid fermentation product [23]; this way, the systematic eradication of *C. acnes* no

longer seems a relevant strategy. In consequence, it will now be necessary to take into account the other types of bacteria that constitute the skin microbiome. The steady state of the microbiome and its preservation is complex and little known. Recently, data from a clinical study showed that *Propionibacteriaceae* and *Staphylococcaceae* family were significantly overrepresented respectively in healthy controls and acne patient [101].

Without targeting only *C. acnes*, the new research orientations aim at the development new per os treatments or topical formulations based on probiotics. These innovative approaches aim to restore skin microbiome diversity and eliminate pathogenic species and induced inflammation in acne and other inflammatory diseases [79, 93, 102].

Recent knowledge demonstrated that microbial dysbiosis in the skin and the gut was implicated in many chronic inflammatory diseases. The improvement of dysbiosis and restoration of a normal skin microbiome are promising therapeutic strategies that have been tested in intestinal dysbiosis by oral administration of probiotics, living microorganisms that are beneficial to the host's health or by faecal transplantation with a pill which encapsulates stool of a healthy donor containing its intestinal microbiota. Faecal transplantation has been used in *Clostridium difficile* infections, in the irritable bowel syndrome or in inflammatory colitis. The faecal microbiome transplants have been demonstrated to be safe and effective for patients with *Clostridium difficile* infections [103].

The therapeutic approach for cutaneous dysbiosis is currently poorly developed, and some trials have been conducted in inflammatory conditions such as atopic dermatitis, psoriasis and acne [76, 104]. Topical treatment consisting of the commensal bacterium *Vitreoscilla filiformis* used in patients with atopic dermatitis showed significant clinical improvement with decreasing SCORAD (scoring atopic dermatitis) score and pruritus [104]. Moreover, the approach based on specific bacterial strains selected from the skin microbiome to treat atopic dermatitis patients has been shown to eliminate *S. aureus* and restore a balanced microbiome [105].

Some data have shown that probiotics could induce *C. acnes* inhibition with antimicrobial proteins such as *Streptococcus salivarius* which suppresses the growth of *C. acnes* by secreting a bacteriocin-like inhibitory substance [106]. Topical treatment with cream containing *Streptococcus thermophiles* was shown to display antimicrobial activity against *C. acnes* by ceramide production [107]. Probiotics could also act on immune response by inhibiting pro-inflammatory cytokine IL-8 from keratinocytes [108], by suppression of substance P-induced skin inflammation [109].

Some clinical trials have been conducted in acne patients to investigate the clinical benefit of probiotics [93]. Topical *Enterococcus faecalis* treatment has shown significant reduction of inflammatory acne lesions versus placebo [110]. *Lactobacillus plantarum* treatment also induces a decrease of acne severity and associated erythema [111]. Interestingly, association of freeze-dried *Bifidobacterium bifidum* and *L. acidophilus* used as a supplement to acne treatment showed greater resolution of acne compared with the non-supplemented group [112].

The new concept in acne drug development, despite *C. acnes* implication in acne, takes into account that *C. acnes* might also play a protective role in the skin by preserving a permanent low level of innate immunity activation, and thus therapeutic options that respect *C. acnes* equilibrium are an adequate alternative to treat acne [94]. An ongoing clinical study investigates the role of the skin microbiome and the potential use of a topical probiotic cream (YUN ACN cream) for acne treatment [113].

Recently some data postulated the beneficial effect of *S. epidermidis* in the physiopathology of acne by limiting *C. acnes*-induced colonization of the skin and inflammation [23]. However, overexpression of *S. epidermidis* could induce nosocomial infections. Therefore, to respect the balanced skin homeostasis, future treatments may be based on probiotics derived from *S. epidermidis* to allow a restoration of the normal skin microbiota and to target the regulation of the host's AMP mediators, without increasing *S. epidermidis* population [23].