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Journal of Molecular Catalysis B: Enzymatic 22 (2003) 377–384
JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC
www.elsevier.com/locate/molcatb

Lipase inhibitors for the treatment of acne

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Accepted 2 October 2002

Abstract

Propionibacterium acnes lipase is an important factor in the pathogenesis of acne, because free fatty acids formed as a result of the effect of *P. acnes* lipase on sebaceous triglycerides induce severe inflammation. Tetracyclines have been the most common systemic therapy for acne due to their beneficial clinical effects, their inhibition of lipase activity of *P. acnes* as well as their inhibition of *P. acnes* chemotaxis. Erythromycin and *Jumi-haidoku-to* also inhibit the lipase activity of *P. acnes*. Among *P. acnes* biotypes and serotypes, stronger *P. acnes* lipase activities were seen in *P. acnes* biotype III and serotype II. Conversely, *Propionibacterium granulosum* is also isolated in acne lesions but has only a faint lipase activity, which might not be of significance. In the future, the degree of *P. acnes* lipase activity in acne, identified by genetic techniques, needs to be compared to the condition of acne rash.

Keywords: *Propionibacterium acnes* lipase; Tetracyclines; Erythromycin; *Jumi-haidoku-to*; Biotypes; Serotypes

1. Introduction

Acne is not a simple disease, which may sometimes lead to psychosomatic influence such as depression or frustration. By knowing the role of *Propionibacterium acnes* lipase that is the important pathophysiologic factor in acne, we can treat the acne patients sufficiently. Thereby, a clear comprehension of acne pathogenesis including *P. acnes* lipase is fundamental for treatment choice.

This article reviews the role of *P. acnes* lipase, agents against *P. acnes* lipase, and *P. acnes* serotypes and biotypes, and others. Among the agents, we emphasize tetracyclines and *Jumi-haidoku-to* especially.

2. Pathogenesis of acne and the role of *P. acnes* lipase

Acne, which develops chiefly in patients in age brackets of 10–30 years, is a follicular rash that starts as a comedo, then prospers inflammation which leads to the formation of red papules and pustules. Many acne patients undergo complete resolution of their lesions without any remaining symptoms, whereas other patients have continuous acne or long-term consequences, such as scarring and keloids. The initial non-inflammatory lesions were verified by light microscopy and by electron microscopy [1]. This leads to microcomedo, and it then progress to closed or open comedones. Inflammatory lesions probably begin when the proliferation of *P. acnes* attracts neutrophils to the sebaceous follicles. The contents then stream into the dermis that initiates the inflammation. In most cases, the inflammation gradually fades,

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doi:10.1016/S1381-1177(03)00053-5

remain about a few days to 2 weeks. As has been widely known, predominant organism is *P. acnes* [2]. The multiplication of *P. acnes*, the overproduction of sebum, and follicular hyperkeratinization are three consequential physiological factors in the pathogenesis of acne. It is well established that the plenty of free fatty acids detected in acne lesions forms as a result by the effect of *P. acnes* lipase on sebaceous triglycerides. Free fatty acids stimulate the follicular epithelium sufficiently to result in its breakage, which then enables those to get through the dermis and to induce inflammation. Marples et al. [3] reported that a decrease in free fatty acids precedes a decline in the numbers of *P. acnes*. Intradermal injection of free fatty acids into healthy subjects induces serious inflammation [4]. *P. acnes* lipase itself can act as a chemotactic factor [5], and it is likely that other contributing factors are involved that have been treated lightly to date [6]. Thereby, the importance of *P. acnes* lipase in acne has also been strongly confirmed [7].

P. acnes lipase has some interesting properties. It cleaves at the α and β positions of triglycerides simultaneously, producing free fatty acids and glycerol. *P. acnes* lipase is stable and is active at the pH between 5 and 8; if the pH is lower than 5, the activity of *P. acnes* lipase is feebler. *P. acnes* lipase from new *P. acnes* isolates shows greater catalytic activity than does that from the old isolates. Thereby, the degree of *P. acnes* lipase varies greatly due to its background. Although other factors have recently been discussed with respect to the pathogenesis of acne, *P. acnes* lipase has always been considered as an important component in the pathogenesis of acne.

In addition, we should not ignore the existence of acid phosphatase, hyaluronate and protease which are extracellular enzymes produced by *P. acnes* [8]. These enzymes may also be of importance in inflammatory acne.

3. Effects of systemic antibiotics against *P. acnes* lipase

Systemic antibiotic therapy has been a mainstay of acne treatment for more than 30 years. The clinical effects as well as the psychological factors involved in treating acne have been chiefly achieved by antibiotics that are thought to decrease the number of propionibacteria [9] and hence to reduce free fatty acids in the sebum. Results by antibiotics are very often excellent. Antibiotic therapy must be sometimes continued for a long time and they are effective in inhibiting *P. acnes* lipase production by virtue of their bactericidal or growth inhibitory activities, thus preventing worsening of the inflammatory lesions. Much interesting insight into *P. acnes* lipase began in the 1950s when Strauss and Mescon [10] demonstrated lipolytic activity in comedones. In Japan, the uses of other agents, such as benzoyl peroxide, azelaic acid (a naturally occurring dicarboxylic acid analogue) and isotretinoin (an anti-androgen drug), to treat acne is not officially permitted, even if those agents are effective in treating inflammatory and non-inflammatory lesions or can suppress the emergence of resistant strains. Taking into account these therapeutic methods, systemic antibiotics have been widely prescribed to treat acne lesions [11].

Tetracyclines in particular have been the most common and effective antibiotics available for the treatment of acne [12], probably due to their beneficial clinical effects and their anti-lipase effects on *P. acnes*. Fortunately, side effects from tetracyclines are quite rare. Cunliffe et al. [13] obtained adequate results in acne patients treated with tetracycline hydrochloride for 3 months. Many studies have revealed that tetracyclines decrease the production of free fatty acids in acne patients [14]. Investigations about the role of *P. acnes* lipase and the effects of various agents, including antibiotics, were mainly conducted in the 1970s and 1980s, but have continued until now. Oral tetracyclines, such as minocycline, have been widely used in Japan for the past 20 years and it is a risk that *P. acnes* might secure specific resistance. Indeed, minocycline resistant *P. acnes* strains have been reported [15], and reports of tetracyclines resistant *P. acnes* have gradually increased in the late 1990s around the world.

P. acnes lipase activity can be inhibited by tetracycline at serum concentrations of less than 2 μg/ml [16]. However, such an effect might not be seen at tetracycline concentrations found in the pilosebaceous follicles. It seems more likely that tetracyclines reduce the amount of free fatty acids by inhibiting lipase production by *P. acnes*. In the initial stage, the lipolytic activity of hog pancreatic lipase was shown to be inhibited by antibiotics [17,18]. Shalita and Wheatley [18] reported that tetracyclines were able to inhibit *P.*

acnes lipase completely, while penicillins are not able to inhibit *P. acnes* lipase activity. Gordon [19] reported that, using hydrolysis of tributyrin emulsion, tetracycline is a potent inhibitor of *P. acnes* lipase, producing 89% inhibition at 8.0×10^{-4} M. This effect is influenced greatly by pH, and at pH 6.0 there is no inhibition. This pH dependence should be emphasized when considering lipase inhibition by tetracycline in sebaceous follicles where the pH may be below pH 7. Webster et al. [20] evaluated the inhibition of *P. acnes* lipase production in *P. acnes* by low doses of tetracycline. Production of lipase activity at detectable levels was never reached in *P. acnes* supernatants, which supports the conclusion that even low concentrations of tetracycline inhibit lipase, as reported by Puhvel and Reisner [21]. They reported that tetracyclines inhibited *P. acnes* lipase activity by 70–80% at a concentration of 500 μg/ml and that neomycin or penicillins had no inhibitory effect on *P. acnes* lipase activity. Other researchers also reported that tetracyclines inhibited *P. acnes* lipase activity at sub-minimal inhibitory concentration (sub-MIC) [22,23].

The inhibition of *P. acnes* lipase activity could be reinforced by adding calcium chloride and could be completely inhibited by tetracycline at 10^{-4} M, and partially inhibited at 10^{-6} M [24]. Weaber et al. [24] hypothesized that (i) tetracycline has an affinity for calcium-activated lipase, and (ii) the tetracycline–calcium complex is a specific inhibitor of lipase. Otherholm et al. [25] also recognized the inhibitory effect of calcium chloride to *P. acnes* lipase using a colorimetric method.

In addition to tetracyclines, erythromycin has also been well studied as to its effects on *P. acnes* lipase, since erythromycin is also clinically effective for treating acne patients [26]. Erythromycin is usually given as a secondary treatment in Japan and some other countries. The inhibition of *P. acnes* lipase is observed at a low dose of erythromycin [19,27]. It is likely that erythromycin acts solely via its bacteriostatic action, or alternatively, it might damage *P. acnes* lipase. It might be clever to use erythromycin in order to avoid *P. acnes* growth that is resistant to other antibiotics (including tetracyclines), and at that juncture, one should be careful to avoid the occurrence of erythromycin resistant *P. acnes*, which have been reported since the late 1980s [28]. According another view, protein synthesis-inhibiting antibiotics, such tetracyclines and erythromycin, might decrease the production of inflammatory factors and thus might reduce the inflammatory ability of *P. acnes* before decreasing the bacterial counts, and calcium chloride might elongate the action of some antibiotics somewhere in that process. Other agents, such as propylene phenoxetol, have also been reported to decrease the growth and lipase activity of *P. acnes* [29].

P. acnes is well known to produce many factors which stimulate chemotaxis and complement activation, and tetracycline or erythromycin resistant *P. acnes* fail to show a distinct suppression of chemotactic factor production. Many evidence revealed that tetracyclines and erythromycin suppressed chemotaxis of polymorphonuclear leukocytes in vitro [30–34]. Whereas, treatment with a sub-MIC of ampicillin failed to have any effect [33].

A new technique to measure *P. acnes* lipase activity using gas chromatography has been reported. Isolates were examined for production of propionic acid as an indicator of *P. acnes* growth and for butyric acid as a measure of *P. acnes* lipase activity [35]. The effect of minocycline to inhibit *P. acnes* lipase and to decrease *P. acnes* growth was seen. In contrast, a few opposite findings have been seen. For example, Unkles and Gemmell [27] reported that while tetracyclines inhibited *P. granulosum* lipase, they found that it did not inhibit *P. acnes* lipase.

Studies correlating antibiotics other than tetracyclines and erythromycin with effects on lipase activity of *P. acnes* have been reported, but many dermatologists are unconcerned with these antibiotics. Lincomycin and clindamycin could inhibit *P. acnes* lipase with little effect on their growth [27], while streptomycin sulfate, neomycin sulfate and penicillin G potassium did not inhibit *P. acnes* lipase [18]. Penicillin, which does not suppress *P. acnes*, generates a poor clinical reaction in the treatment of acne [36]. Correlations between changes in *P. acnes* lipase and the degree of acne rash following antibiotic therapy are still required.

4. Effects of agents other than antibiotics on *P. acnes* lipase

The effects of agents other than antibiotics on *P. acnes* lipase have been often examined. Halopyridyl

phosphorus compounds, such as *O*,*O*-dimethyl-*O*-phosphate and fospirate, proved to be potent inhibitors of *P. acnes* lipase at 10^{-8} M, as assessed by potentiometric titration [37]. Suppression of free fatty acids by topical fospirate therapy is clinically as effective as that obtained by systemic tetracycline. Whereas, the degree of acne skin rash did not reform. Diisopropyl phosphofluoridate at 10^{-7} M completely inhibited *P. acnes* lipase as well as polymorphonuclear leukocyte chemotaxis elicited by *P. acnes* lipase [5]. A similarity to fully inhibition of *P. acnes* lipase activity was seen by diisopropylfluorophosphate, but benzoyl peroxide at a low concentration was unable to suppress *P. acnes* lipase activity [38]. In contrast, *p*-chloromercuricbenzoate and phenylmethanesulfonyl fluoride had no ability to inhibit *P. acnes* lipase [39].

Free fatty acids, which occupy 16% of the sebum and mainly consist of palmitic acid, stearic acid and oleic acid. Free fatty acids are able to accelerate or suppress *P. acnes* growth. A minor free fatty acid, lauric acid, was able to suppress *P. acnes* lipase as well as *Staphylococcus epidermidis* lipase activities, through inhibition of their growth, and oleic acid has the same effect against *S. epidermidis*, not but against *P. acnes* [40]. *P. acnes* has a tendency to proliferate during the accumulation of oleic acid at a follicular depth. *P. acnes* growth was inhibited in medium containing 200 μg/ml lauric acid but was not inhibited in medium containing oleic acid, palmitic acid or stearic acid at more than 200 μg/ml concentration [41]. She further indicated a decrease in *P. acnes* colonies and a shortening of their rod structures, which leads to the suppression of *P. acnes* lipase, was distinctly observed in medium containing 200 μg/ml lauric acid using electron microscopy. However, free fatty acids other than lauric acid did not influence the morphology of *P. acnes* and *P. acnes* lipase. On the contrary, *S. epidermidis* growth was inhibited in medium containing 200 μg/ml lauric acid and even further by 100 μg/ml oleic acid. By oleic acid, *S. epidermidis* lipase might be more influenced than is *P. acnes* due to its morphology as a coccus, not as a rod.

Kampo formulations, officially authorized in 1976 in Japan, are traditional medicinal prescriptions that have seen increased use in treating acne, either alone or in conjunction with Western therapy. Excellent clinical effectiveness of acne patients treated with 12 weeks oral administration of Kampo formulations in fine granules form was reported [42], and the effective rates of red papules (78%) and pustules (68%) (inflammatory lesions) were higher than those of comedo (33%) (non-inflammatory lesion). Target group of *Jumi-haidoku-to* (one representative Kampo formulation) was acne as well as mild exudation transition to purulent dermatitis [43]. Many of the 10 Kampo crude drugs composing *Jumi-haidoku-to* have antibacterial and anti-inflammatory activities. *Jumi-haidoku-to* significantly inhibited *P. acnes* growth and secondary decreased the *P. acnes* lipase activity. Detachment of the cell wall, and the cytoplasmic degeneration of *P. acnes* grown in medium containing sub-MIC of *Jumi-haidoku-to* was observed using electron microscopy [35]. The inhibition of *P. acnes* lipase activity by *Jumi-haidoku-to* was considered to be due chiefly to its ingredients, *Glycyrrhizae radix* and *Platycodi radix*. Flavonoids are important ingredients of *G. radix*, which have a strong anti-organismic activity, particularly against Gram-positive bacteria, and thus lead to the suppression of *P. acnes* lipase [44]. It is well known that saponin, which is an ingredient of *P. radix*, has an antibacterial activity as well as an anti-inflammatory activity. *Shiunko*, a Kampo ointment, has many activities including an antimicrobial activity [45], and has been used more recently, acne [46]. A similar tendency to inhibit *P. acnes* lipase to levels elicited by *Jumi-haidoku-to* was also seen in *Shiunko*. *Shiunko* (0.01 and 0.1%) suppressed *P. acnes* lipase activity about 8 and 14%, respectively [47]. If the clinical effects of *Jumi-haidoku-to* or *Shiunko* differ at various acne sites, the inhibition of *P. acnes* lipase activity might also differ at those sites. Among the Kampo crude drugs, distinct differences in *P. acnes* lipase inhibition were observed [48]. Kampo formulations and antibiotics that inhibit *P. acnes* lipase activity should be synergistic when they are combined. Indeed, synergistic actions have already been observed between *Seijyo-bofu-to* and *Keigai-rengyo-to*, and or between *Jumi-haidoku-to* and minocycline [35,49]. Akamatsu et al. [50] emphasized that the clinical effects of Kampo formulations in treating acne might be due to their antioxidant actions on infiltrating neutrophils as well as on their inhibition of *P. acnes* lipase activity.

As one particular method, oral zinc had been evaluated for treating acne, especially in the 1970s and

1980s [51], and some patients showed low serum zinc values. Zinc was proved to inhibit pancreatic lipase [52]. *P. acnes* lipase activity was inhibited about 86% at a zinc concentration of 2.0 mM/l (measured as ^{3}H-labeled oleic acid), and the body zinc influenced *P. acnes* lipase activity in vitro [53].

In addition, isotretinoin has been used to acne therapy since 1982 and provided advantage to the patients. Isotretinoin, that is an anti-androgen with the effect of atrophy of the sebaceous gland, is usually indicated for nodulocystic acne or for severe acne lesions that show poor response to ordinary acne therapy. Significant decrement of resistant *P. acnes* to some antibiotics by isotretinoin and efficacy of isotretinoin were addressed [54,55]. These might accelerate anti-*P. acnes* lipase activity followed by decrement of numbers of *P. acnes*.

5. *P. acnes* biotypes and serotypes

P. acnes can be subdivided into five biotypes and two serotypes. Kishishita et al. [56] advocated the division of *P. acnes* into biotype I, II, III, IV or V based on the results of fermentation test for ribose, erythritol and sorbitol. Sugar-specific pH for each carbonate (ribose, erythritol and sorbitol) was calculated by the equation: SpH = (pH of carbohydrate medium − pH of culture of carbohydrate medium) − (pH of basal medium − pH of culture of basal medium). SpH > 0.35 is shown as (+), and SpH < 0.35 as (−) (Table 1). Some studies referring to biotypes have been reported. Akamatsu et al. [57] mentioned that medium containing a sub-MIC of minocycline strongly suppressed the neutrophil chemotaxis of all biotypes, but that other antibiotics only suppressed some biotypes. He further indicated that a sub-MIC of minocycline was able to suppress all biotypes lipase activity. Among biotypes, biotype III occupies the major part and might more severely aggravate the acne rash [58]. Biotype III is isolated from more severe skin rashes than are other biotypes, and might multiply more quickly in acne lesions than do the other biotypes. A proportional change in *P. acnes* lipase activity, rash degree of acne patients and *P. acnes* growth has also been recognized. Therefore, stronger *P. acnes* lipase activities was seen in biotype III [59] (Table 2). The tendency towards increased *P. acnes* lipase activity at each of those sites might be influenced by the distribution of biotype III, but, among biotypes, no significant differences in the degree of inhibition of *P. acnes* lipase by *Jumi-haidoku-to* were seen [60]. The growth of biotype III was inhibited by

Table 1
Biotypes of *P. acnes*

	Ribose	Erythritol	Sorbitol
Biotype I	+	+	+
Biotype II	+	+	−
Biotype III	+	−	+
Biotype IV	+	−	−
Biotype V	−	−	−

(+) SpH > −0.35, acid production from fermentation reaction; (−) SpH < 0.35, no acid production, i.e. no fermentation reaction.

Table 2
Rash degree, *P. acnes* biotype and production of free fatty acids (meq./ml) in acne patients

Strain number	Rash degree in acne patients	*P. acnes* biotype	24 h after inoculation production of		48 h after inoculation production of	
			Propionic acid	Butyric acid	Propionic acid	Butyric acid
P. acnes TM 1	Mild	III	1.82	2.68	2.56	3.05
P. acnes TM 2	Moderate	III	1.96	2.50	2.85	4.02
P. acnes TM 3	Mild	II	0.80	1.20	1.91	3.55
P. acnes TM 4	Mild	IV	1.60	1.96	1.83	2.43
P. acnes TM 5	Mild	I	0.86	1.91	2.09	3.28
P. acnes TM 6	Severe	III	2.98	4.10	3.92	5.60
P. acnes TM 7	Mild	I	1.51	2.02	1.79	3.06
P. acnes TM 8	Mild	III	2.05	3.16	2.63	4.50
P. acnes TM 9	Moderate	III	2.50	3.33	2.90	4.88
P. acnes TM 10	Mild	II	1.80	2.43	2.31	2.85

Propionic acid production indicates degree of *P. acnes* growth. Butyric acid production indicates degree of *P. acnes* lipase activity.

Table 3
Relationship between biotype and serotype of *P. acnes*

Serotype I–galactose (−)	Biotype I
	Biotype II
	Biotype III
	Biotype IV
	Biotype V
Serotype II–galactose (+)	Biotype I
	Biotype II

tetracycline, and the average peak serum concentration after oral tetracycline (250 mg) was 2.02 μg/ml; while the intradermal concentration was 3 μg/ml [14]. Taking that into consideration, it is conceivable that oral tetracycline might fully inhibit the growth of all biotypes in follicles, and could also inhibit lipase production by all biotypes. Lipases produced by biotypes I, II, III and IV are stimulated by oleic acid [61], a finding identical to the report of Nakagawa et al. [41]. Whereas, differences in the inhibition of lipases produced by different biotypes by oleic acid remain unknown.

Serotypes can be identified by the technique described by Johnson and Cummins [62]. Serotype I has galactose as a cell wall sugar, but serotype II lacks galactose. Biotypes I and II belongs to *P. acnes* serotype I or II, while biotypes III, IV and V belong to *P. acnes* serotype I (Table 3) [14]. Serotype I is predominantly distributed on the cheek and the nose, while serotype II is predominantly distributed on the forehead [63]. Although the difference in the distribution of each serotype might be due to the existence of oleic acid [62], *P. acnes* lipase activity might be higher on the cheek and the nose since serotype I contains biotype III.

6. Organisms other than *P. acnes* isolated from acne lesions

Among organisms other than *P. acnes* isolated from acne lesions, *S. epidermidis* is the most common. More than 30% of *S. epidermidis* are resistant to macrolides, such as erythromycin and roxithromycin, and the resistant *S. epidermidis* to those agents increased after the long-term therapy [64]. Nevertheless, the role of *S. epidermidis* lipase and the significance of *S. epidermidis* in acne have seldom been assessed due to its non-pathogenicity. Even though *P. acnes* and *S. epidermidis* are simultaneously isolated from acne lesions, *S. epidermidis* seems to have no effect on *P. acnes* lipase activity. There is additionally no evidence relating *S. epidermidis* at the follicular depth to the pathogenesis of acne. *S. epidermidis* lipase acts similarly to pancreatic lipase and cleaves the α position of triglycerides more rapidly than the β position, producing monoglyceride intermediates. Triglycerides are thus dehydrated as free fatty acids and glycerol. Thereby, the properties of *S. epidermidis* lipases are not identical with lipase in comedones, and *S. epidermidis* lipase may be closely related to *S. aureus* lipase according to their phylogeny and calculations of their amino acid sequence homologies [65].

P. granulosum has been isolated in acne lesions, but its existence has generally been ignored by many dermatologists. One reason is that *P. acnes* occurs at much greater frequency than *P. granulosum* in acne

Table 4
Inhibitory effects of minocycline against *P. granulosum*

Strain number	Control		Decrease of acids production (meq./ml)			
	Propionic acid	Butyric acid	Minocycline (0.1 μg/ml)		Minocycline (0.5 μg/ml)	
			Propionic acid	Butyric acid	Propionic acid	Butyric acid
P. granulosum TM 22	0.12	0.21	0.10 (83)	0.16 (76)	0.05 (42)	0.07 (33)
P. granulosum TM 23	0.18	0.34	0.16 (89)	0.26 (76)	0.08 (44)	0.13 (38)
P. granulosum TM 24	0.23	0.33	0.18 (78)	0.24 (73)	0.07 (30)	0.07 (21)
P. granulosum TM 25	0.36	0.50	0.25 (70)	0.30 (60)	0.09 (25)	0.08 (16)
Average ± standard error (%)	100	100	80.0 ± 4.7	71.3 ± 4.4	35.3 ± 5.3	27.0 ± 5.9

Propionic acid production indicates degree of *P. granulosum* growth, Butyric acid production indicates degree of *P. granulosum* lipase activity. Figures in parenthesis indicate percentage of acids produced in the medium added with minocycline to those in the control medium.

lesions [66,67]. *P. granulosum* lipase activity is feebler than *P acnes* lipase activity, and it is more influenced by each agent than is *P. acnes* lipase activity (Table 4) [59,68]. Conversely, a minor opinion exists that *P. granulosum* lipase activity is stronger in acne patients with or without tetracyclines [67], and that *P. granulosum* might thus play a more consequential role in acne [69,70]. However, *P. granulosum* lipase might not be of significance in the etiology of acne [71]. In fact, the significance of *P. granulosum* in acne has gained more notice because of its immunologic considerations, but not for its enzymatic activity.

7. Chemotactic factor in acne

Lee et al. [5] found that *P. acnes* produced higher-molecular-weight chemotactic factors, one of which was the lipase molecule itself. 5α-Reductase and cytokines referred to acne have been studied. Cilotti et al. [72] reported that 5α-reductase inhibitors seemed the ideal agent for baldness, benign prostative hyperplasia and acne. Shaw [73] also emphasized the clinical efficacy of 5α-reductase inhibitors for acne. Suh et al. [74] mentioned that IL-10 and IL-1 receptor antagonist might play importance in the immunoregulation in acne. Though it is unclear what kinds of cytokines are more important for acne and *P. acnes* lipase in detail, the development of clinical application of cytokines and 5α-reductase inhibitors has been expected.

8. Conclusion

We now have a greater understanding of *P. acnes* lipase and its inhibitors. Although the phases of inflammation that occurs in acne and the catalytic activity of *P. acnes* lipase have been well studied, it is not yet known why acne, in most cases, will spontaneously ameliorate and even disappear. It has been unclear whether inhibitors of *P. acnes* lipase might influence that phenomenon.

Recently, genetic research in bacteriology has become widespread, and *P. acnes* lipase has been confirmed to be related to the production of a 33 kDa lipase [75]. Comparison between the degree of *P. acnes* lipase identified by genetics and the skin grade of acne needs to be assessed in greater detail.

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