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REVIEW

From pathogenesis of acne vulgaris to anti-acne agents

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Abstract

Acne vulgaris is a cutaneous chronic inflammatory disorder with complex pathogenesis. Four factors play vital roles in acne pathophysiology: hyperseborrhea and dysseborrhea, altered keratinization of the pilosebaceous duct, *Cutibacterium acnes* (*C. acnes*) and inflammation. The main hormones responsible for the development of acne vulgaris include androgens, insulin and insulin-like growth factor-1. Other factors involved in this process are corticotropin-releasing hormone, α-melanocyte-stimulating hormone and substance P. Wnt/β-catenin signaling pathway, phosphoinositide 3-kinase (PI3K)/Akt pathway, mitogen-activated protein kinase pathway, adenosine 5′-monophosphate-activated protein kinase pathway and nuclear factor kappa B pathway participate in the modulation of sebocyte, keratinocyte and inflammatory cell (e.g. lymphocytes, monocytes, macrophages, neutrophils) activity. Among all the triggers and pathways mentioned above, IGF-1-induced PI3K/Akt/Forkhead box protein O1/mammalian target of rapamycin (mTOR) C1 pathway is the most important signaling responsible for acne pathogenesis. Commonly used anti-acne agents include retinoids, benzoyl peroxide, antibiotics and hormonal agents (e.g. spironolactone, combination oral contraceptive and flutamide). New approaches including peroxisome proliferator-activated receptor γ modifier, melanocortin receptor antagonists, epigallocatechin-3-gallate, metformin, olumacostat glasaretil, stearoyl-CoA desaturase inhibitor omiganan pentahydrochloride, K_DPT, afamelanotide, apremilast and biologics have been developed as promising treatments for acne vulgaris. Although these anti-acne agents have various pharmacological effects against the diverse pathogenesis of acne, all of them have a synergistic mode of action, the attenuation of Akt/mTORC1 signaling and enhancement of p53 signal transduction. In addition to drug therapy, diet with no hyperglycemic carbohydrates, no milk and dairy products is also beneficial for treatment of acne.

Keywords Acne · Androgen · *Cutibacterium acnes* · Insulin-like growth factor · Inflammation · Comdogenesis · Sebocyte · Keratinocyte

Introduction

Acne vulgaris is a highly prevalent cutaneous inflammatory disorder [14]. More than 85% of teenagers are affected by acne and can suffer from the disease into adulthood [120].

The high prevalence of acne vulgaris is associated with the exposome factors, such as nutrition, medication, occupational factors, pollutants, climatic factors, and psychosocial and lifestyle factors [4, 89, 110, 111]. Exposome factors have an effect on the natural skin barrier and microorganisms, causing hyperseborrhea, altered keratinization of the pilosebaceous duct, the loss of the skin microbial diversity and inflammation [102]. These factors interact and result in a chronic inflammatory response localized in the pilosebaceous units [26, 120]. Among these exposome factors, western diet characterized by hyperglycemic carbohydrates and milk consumption is an important factor which enhances the insulin-like growth factor-1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) C1 signaling [59, 84, 90, 92]. However, these external exposome factors alone are usually not capable of causing acne,since the number of sebaceous lobules per gland is reported to be higher in seborrheic acne-prone skin than in normal skin [43]. The development of acne is mainly driven by increased production of sebum, increased proliferation

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and reduced desquamation of keratinocytes in the pilosebaceous unit [24]. As sebum and keratinocytes hold together, the keratotic plug gradually forms and obstructs the pilosebaceous ducts, finally creating microcomedones. In the past, colonization with *Cutibacterium* (formerly *Propionibacterium*) *acnes* (*C. acnes*) [31] was thought to be the trigger of immune response in sebocytes, keratinocytes and monocytes. However, recent investigations suggest that the dysbiosis targeting mainly *C. acnes* together with the activation of the innate immunity might lead to the chronic inflammatory response in acne vulgaris [7, 38]. IGF-1 is also sufficient to upregulate inflammation in primary human sebocytes [55, 63]. Numerous studies have been done on the exact mechanisms involved in acne pathogenesis, which have provided substantial evidence about the specific cells, pathways, chemokines and enzymes that are part of this disease pathogenesis.

The objective of this article is to review the mechanisms mainly involved in hyperseborrhea, altered keratinization, *C. acnes* colonization and inflammatory response in pilosebaceous units. The second objective is to identify potential pharmacological approaches for treatment of acne vulgaris against the pathogenesis mentioned above.

Pathological processes in sebocytes

The main pathological processes in sebocytes include hyperseborrhea and dysseborrhea (Fig. 1). Hyperseborrhea is an aberration in sebum quantity, while dysseborrhea is the qualititative change in sebum composition. These metabolomic changes favor *C. acnes* overgrowth and biofilm formation, promote subsequent inflammation, disturb follicular barrier function and induce comedogenesis [84].

Androgens are able to stimulate lipid synthesis and the proliferation and differentiation of sebocytes. After androgens bind to androgen receptor (AR) localized to cell nucleus, the phosphorylation of mTOR increased. It has been reported that there are a higher cytoplasmic and nuclear expression of mTOR in inflammatory sebaceous glands in acne lesion, when compared to non-lesional skin. mTOR forms the catalytic core of mTORC1, which promotes

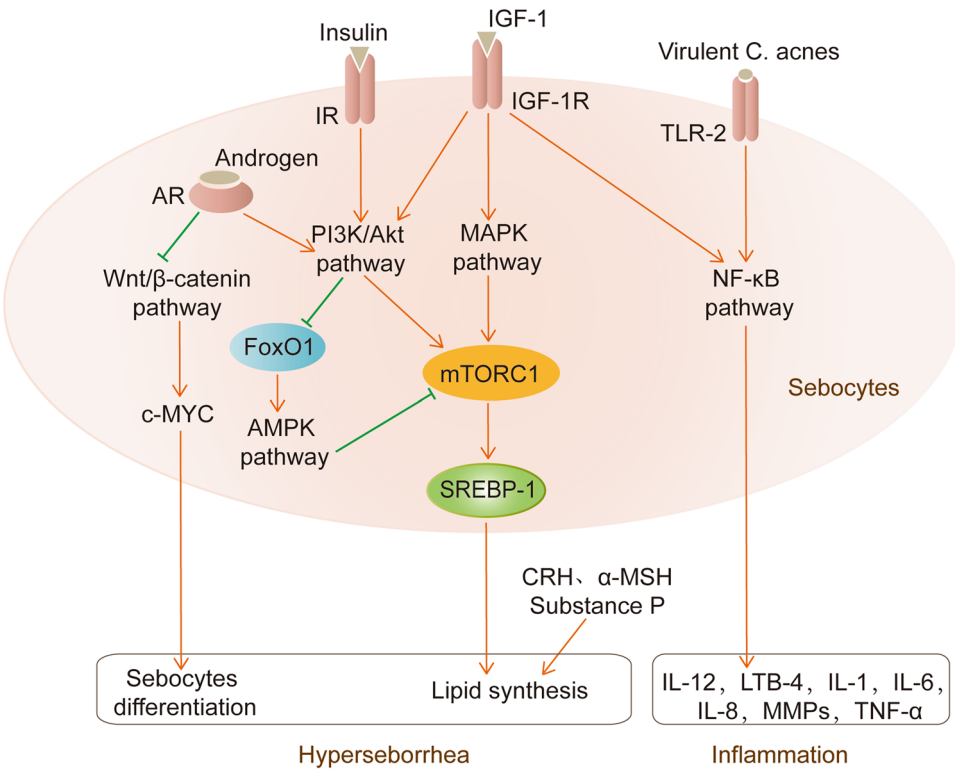

Fig. 1 The main pathological processes within sebocytes involved in acne vulgaris. Androgen stimulates altered differentiation of sebocytes by Wnt/β-catenin signaling pathway and lipid synthesis by PI3K/Akt pathway. Insulin and IGF-1 induce lipid synthesis by increasing SREBP-1 expression via PI3K/Akt/FoxO1/mTORC1 pathway and MAPK pathway. IGF-1 is also sufficient to induce proinflammatory cytokine expression in sebocytes by activating the NF-κB pathway. Other factors that affect sebum synthesis include CRH, α-MSH and substance P. *C. acnes* is recognized by TLR-2 and induces an inflammatory response in sebocytes by activating the NF-κB pathway. *AR* androgen receptor, *IR* insulin receptor, *IGF-1* insulin-like growth factor 1, *IGF-1R* insulin-like growth factor 1 receptor, *TLR* toll like receptor, *SREBP-1* sterol regulatory element-binding protein-1, *IL* interleukin, *LTB 4* leukotriene B4, *MMPs* matrix metalloproteinases, *TNF* tumor necrosis factor

lipogenesis by activating sterol regulatory element-binding protein-1 (SREBP-1) [2, 94]. Androgen also negatively regulated endogenous Wnt/β-catenin signaling pathway. As a result, the expression of Wnt/β-catenin target genes such as c-MYC is upregulated, inducing sebocyte differentiation. Differentiating sebocytes exhibit a high level of nuclear AR and peroxisome proliferator-activated receptors (PPARs) [22, 50, 69]. During this process, lipids gradually accumulate until the sebocytes are differentiated enough to release their contents into sebaceous duct in a holocrine secretion manner [105].

Although androgen signaling plays a certain role, IGF-1 signaling plays the primary role in acne pathogenesis. Laron patients, who are treated with high-dose IGF-1, develop hyperandrogenism and acne [66]. However, individuals without the overtreatment of IGF-1 never develop acne [8, 46]. These facts support that IGF-1 signaling is the central pathway in acne. Insulin and IGF-1 stimulate the PI3K/Akt cascade, which increases forkhead box protein O1 (FoxO1) nuclear export. FoxO1 is a core element in in the pathogenesis of acne. It inhibits lipogenesis not only by antagonizing the expression of SREBP-1c, but also restraining the transactivation of AR [12, 36, 60, 77]. Besides, FoxO1 also induces the activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) pathway [18], which is a key negative regulator of mTORC1 [121]. Therefore, insulin and IGF-1 increase lipid synthesis by mediating the attenuation of FoxO1 inhibition.

Other factors that are capable of controlling sebocyte activity include corticotropin-releasing hormone (CRH), α-melanocyte-stimulating hormone (α-MSH) and substance P. CRH of hypothalamic–pituitary–adrenal (HPA) axis participates in the clinical development of acne by inducing steroidogenesis and interacting with testosterone and growth hormone. In addition to HPA axis, sebaceous glands in skin with acne also express complete CRH system abundantly, and this CRH system independent of the HPA axis possibly affects immune and inflammatory processes resulting in stress-induced acne [41]. Interestingly, α-MSH has a lipogenic effect and correlates with sebocyte differentiation in primary cultures of human sebocytes derived from facial skin [40, 123] but the specific mechanism remains unclear. However, α-MSH also suppresses interleukin (IL)-8 secreted by sebocytes [11]. Therefore, whether α-MSH is a protective factor or an aggravated factor of acne pathogenesis remains to be seen. Substance P, a kind of neuropeptides associated with stress-induced acne, can induce adipogenesis by increasing PPAR-γ. It can also increase the immunoreactivities to IL-1, IL-6 and tumor necrosis factor (TNF)-α.

In addition to an elevated sebum production, altered sebum composition is also involved in the pathogenesis of acne. Decrease in the C16:0/C16:1 nutrition lipid ratio accompanied by increased levels of linoleic acid content is the main change [121]. The lipids including oleic acid and linoleic acid can modulate inflammatory response by regulating monocyte differentiation and secretion of cytokines [76]. It has been reported that the link between lipid metabolism and inflammation in sebocytes is leptin, which is secreted by adipocytes and can regulate weight [117].

Therapeutic implications

Some agents can inhibit androgen synthesis. For example, spironolactone can decrease production of testosterone and competitively inhibit androgens, mainly dihydrotestosterone (DHT) and testosterone, binding to androgen receptors of the skin [13, 101]. Another mechanism may be the inhibition of 5-α-reductase and the upregulation of sex hormone-binding globulin (SHBG) expression [107, 124]. The therapeutic effect of combination oral contraceptive pills (COCs) to combat acne is also based on their anti-androgenic properties. In addition to inhibiting 5-α-reductase activity, blocking androgen receptors and increasing SHBG to bind free testosterone, COCs can also decrease androgen production at the ovarian level [6, 49, 100].

Some agents are antagonists for sebocyte receptors. Recently, it was reported that flutamide, the selective blocker of androgen receptor usually used to treat prostate cancer, can be used in acne treatment. However, since this drug has not been approved by the Food and Drug Administration (FDA) as an anti-acne agent, it is not recommended and only can be used when the potential benefit warrants the risk [122]. Other agents that inhibit receptors on sebocytes include the PPARγ modifier N-Acetyl-GED-0507-34-LEVO (2016-000540-33) [126] and melanocortin receptor (MCR) antagonist (JNJ-10229570) [32]. Both of them decrease the production of sebum.

Some agents inhibit lipid synthesis via Akt/FoxO1/mTOR or AMPK signaling. For example, epigallocatechin-3-gallate (EGCG) inhibits IGF-induced lipogenesis in SZ95 sebocytes via reducing the level of mTOR and S6 ribosomal protein. Both of them are important downstream elements involved in the Akt pathway [55]. EGCG also reduces sebum production by activating the AMPK-SREBP-1 signaling pathway [121]. Oral isotretinoin is approved by the FDA as a successful treatment for most patients with severe recalcitrant acne [122]. It induces sebocyte apoptosis to decrease sebum production, since it upregulates the expression of nuclear FoxO1 and FoxO3 proteins [3]. Moderate acne with tendency to scars, significant psychosocial impairment and the high risk of recurrences is also an indication for treatment with oral isotretinoin [122]. Metformin also has favorable effects in the treatment of acne, especially proven in polycystic ovary syndrome, since it is an indirect inhibitor of

mTORC1 by activating AMPK pathway which is a negative regulator of mTORC1 [35, 71].

Other agents that exhibit such therapeutic effects inhibit enzymes involved in lipid synthesis. For example, olumacostat glasaretil, an acetyl coenzyme A carboxylase (ACC) inhibitor pro-drug, decreases triacylglycerol levels in sebocytes [9, 54]. XEN103, 6-[4-(5-fluoro-2-trifluoromethylbenzoyl)-piperazin-1-yl] pyridazine-3-carboxylic acid (2-cyclopropylethyl) amide, reduces lipid levels in sebocytes as well as the size and number of sebaceous glands by inhibition of stearoyl-CoA desaturase (SCD), an enzyme regulated by SREBP-1 [82, 96, 125]. In addition to acting as an SCD inhibitor, XEN103 also inhibits androgen-induced expression of SCD [82].

Pathological processes in keratinocytes

The main pathological processes within keratinocytes in the ductal infundibulum of skin affected by acne are hyperproliferation, aberrant desquamation and production of inflammatory mediators. Several triggers lead to follicular hyperkeratosis and inflammation (Fig. 2).

It was reported that infrainfundibular keratinocytes have an increased capacity for androgen metabolism, suggesting that androgen might be related to hyperkeratosis [115]. IL-1 is not only involved in the immune response but also hyperkeratosis of infundibular keratinocytes [47]. The possible mechanisms of action are thought to directly affect signal transduction via the IL-1 receptor or stimulate the release of other growth factors, such as vascular endothelial growth factor [33]. Alterations in composition of sebum are also associated with hyperkeratosis. Previous study reported that oleic acid, a comedogenic composition of sebum, induced ultrastructural changes on rabbit ears similar to those in human comedones [78]. Katsuta et al. found that *N*-methyl-D-aspartate (NMDA) receptors increased intracellular concentrations of calcium ions and IL-1α production, which are associated with abnormal follicular keratinization induced by oleic acid [62].

In addition to hyperkeratosis, aberrant excessive adherence is also involved in the development of acne. Overexpression and abnormal distribution of tenascin can be responsible for such a pathological process [67].

Similar to sebocytes, keratinocytes are also involved in the inflammatory response. *C. acnes* activates Toll-like receptor (TLR) -2 and TLR-4 on keratinocytes leading to activation of signaling cascades including NF-κB pathway and MAPK pathway. Subsequently, keratinocytes produce IL-1, IL-8, IL-6, granulocyte–macrophage colony stimulating factor (GM-CSF), TNF-α, matrix metalloproteinases (MMPs) and human β-defensin-2 (hBD-2) [44, 58, 95]. In addition to TLR-2 and TLR-4, scavenger receptor CD36 expressed on keratinocytes is also involved in the recognition of *C. acnes* [104]. After *C. acnes* is recognized by CD36, reactive oxygen species (ROS), especially superoxide anions originating from cytosolic enzymes NAD(P)H oxidase, are rapidly produced by keratinocytes. These ROS are then used to eliminate bacteria and generate inflammation [45].

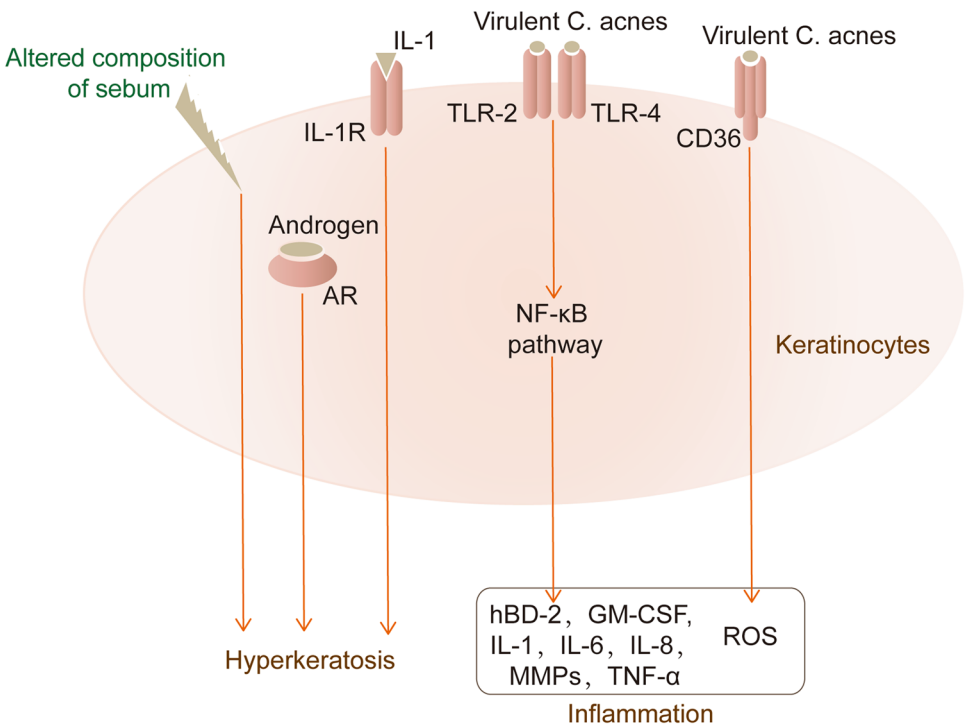

Fig. 2 The main pathological processes within keratinocytes involved in acne vulgaris. Androgen, IL-1 and altered composition of sebum can induce hyperkeratosis; however, the specific mechanisms are unclear. *C. acnes* is recognized by TLR-2 and TLR-4 and induces an inflammatory response in keratinocytes by activating the NF-κB pathway. *C. acnes* is recognized by CD-36 and increases ROS rapidly produced by keratinocytes. *AR* androgen receptor, *IL* interleukin, *IL-1R* interleukin 1 receptor, *TLR* toll like receptor, *CD36* cluster of differentiation 36, *hBD-2* human β-defensin-2, *GM-CSF* granulocyte–macrophage colony stimulating factor, *MMPs* matrix metalloproteinases, *TNF* tumor necrosis factor, *ROS* reactive oxygen species

Therapeutic implications

The anti-acne agents acting against the pathological processes associated with keratinocytes include retinoids, minocycline, azelaic acid and EGCG. Topical retinoids have comedolytic and anti-comedogenic efficacy [114, 122]. Retinoids prevent the formation of microcomedones by inhibiting disturbed differentiation and hyperproliferation of keratinocytes in the follicular [73, 116]. It has been reported that oral isotretinoin, the major and most effective anti-acne treatment, inhibits hyperkeratosis by increasing the expression of the key transcription factor FoxO1 and p53 in primary human keratinocytes. FoxO1 and p53 enhance differentiation and apoptosis of keratinocytes [98, 108]. In fact, it has been recently proposed that increasing the expression of p53 can correct all the acne-related abnormality of molecular pathways. And all common anti-acne drugs operate by increasing the expression of p53 [87, 91].

Upregulation of p53 mediated by isotretinoin also explains isotretinoin's teratogenicity [88]. Retinoids can also suppress the production of cytokines from keratinocytes (e.g. IL-6, IL-8, TNF-α and superoxide anions) [45, 103]. Topical use of 20% azelaic acid is recommended to be mildly effective as an agent with comedolytic effects [122]. EGCG can inhibit hyperkeratosis by decreasing the level of IL-1 in keratinocytes [121].

Cutibacterium acnes colonization

Cutibacterium acnes is a dominant cutaneous commensal bacterium both in acne patients and normal individuals. However, it is noteworthy that hypercolonization of *C. acnes* is not the key factor in acne pathogenesis since acne patients do not harbor more *C. acnes* in follicles compared with healthy individuals. Instead, the loss of the skin microbial diversity together with the activation of the innate immunity might lead to the chronic inflammatory condition, which is mentioned in "Inflammation" part below [7, 38, 75]. *C. acnes* with virulence properties and antibiotic resistance, CC18 strains and ST3 clone, are dominant types on acne patient skin [75]. The virulence factors secreted by *C. acnes*, which induce host-tissue degradation and inflammation, include lipases, several proteases, hyaluronate lyase, endoglycoceramidases, neuraminidases, Christie–Atkins–Munch–Petersen (CAMP) factors and low-molecular chemotactic factors (peptides) (Fig. 3). Lipase has chemoattraction for neutrophils and can also hydrolyze triglycerides in the sebum to free fatty acids with a pro-inflammatory and keratosis effect [51, 62, 72]. Proteases and hyaluronate lyase potentially aid *C. acnes* invasion by degrading an important constituent of the extracellular matrix. Endoglycoceramidases and neuraminidases also possess degradation activities [53, 79, 112]. When the extracellular matrix breaks down, inflammatory cells such as dendritic cells, leukomonocytes, neutrophils and monocytes infiltrate the follicular wall and inflammation gradually spreads even to the dermis. It has been reported that CAMP factors produced by *Streptococcus*

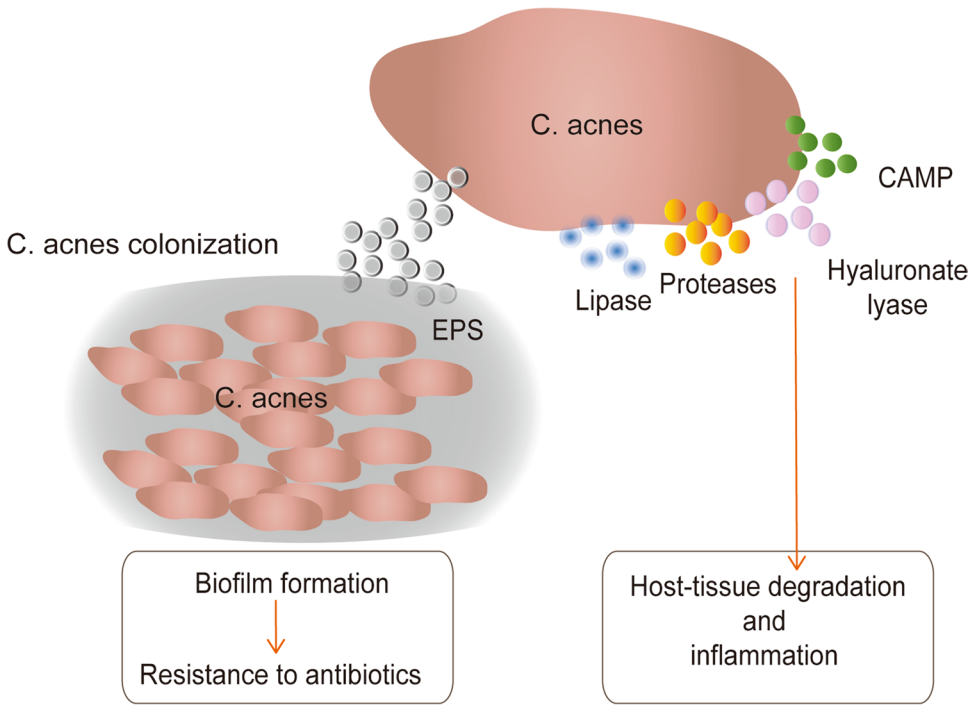

Fig. 3 The main pathological processes induced by *C. acnes* in acne vulgaris. *C. acnes* can secrete metabolites causing host-tissue degradation and inflammation, including lipases, proteases, hyaluronate lyase and CAMP factors. *C. acnes* can also secrete EPS and form biofilms leading to antibiotic resistance. *EPS* extracellular polymeric substances, *CAMP* cyclic adenosine monophosphate

possess pore-forming toxicity [70]. Denda et al. found that increased CAMP levels in keratinocyte induced calcium influx [29], which delayed the recovery of epidermal barrier function after skin barrier disruption [28].

Another pathological process of *C. acnes* is the formation of biofilms (Fig. 3). A biofilm is a complex aggregation of sessile microbes encased in an extracellular polymeric substance (EPS) secreted by organisms in order to adhere to the skin surface. The EPS is a system that regulates growth and metabolism of microorganisms and confers resistance to host inflammatory cells and antibacterial agents [15, 118]. The complete *C. acnes* genome sequence provides evidence for the formation of biofilms. Genes associated with the biosynthesis of glycocalyx polymers are present in the genome of *C. acnes* which are secreted by organisms account for surface adhesion [16]. Skin biopsies have provided further evidence. Jahns et al. directly observed *C. acnes* in skin samples using immunofluorescence microscopy. They found a higher prevalence of follicular *C. acnes* colonization and biofilm formation in acne samples than in control samples [56].

Biofilm also cause resistance to antimicrobial agents. Coenye et al. found that *C. acnes* strains that can form biofilms in vitro show more obvious resistance towards antibiotics commonly used in treatment of acne than in planktonic cells. This finding partly explains the reason why antimicrobial therapy of acne failed. They also found that production of extracellular lipase and quorum-sensing molecule autoinducer-2 (AI-2), putative virulence factors, in the supernatant of sessile cells drastically increasing compared to planktonic cells [20]. Donlan has summarized the reasons for antimicrobial resistance of biofilms. In terms of the intrinsic antimicrobial resistance, EPS blocks contact between antimicrobial and organisms by retarding antimicrobial diffusion, and the mechanisms include chemically reacting with the antimicrobial molecules or limiting antimicrobial transport rate. Reduced growth rates of organisms in the biofilm minimize the rate of antimicrobial agent ingestion and, therefore, impair their inactivation effect. Furthermore, the environment that immediately surrounds the cells in a biofilm may further protect microorganisms. With respect to acquired resistance, it has been reported that plasmids may encode resistance to some antibiotics, under a number of conditions, which can transfer between different organisms growing in biofilms through conjugation [30].

Therapeutic implications

The anti-acne agents for *C. acnes* colonization include tetracycline antibiotics (e.g. doxycycline, minocycline), clindamycin, benzoyl peroxide (BP), omiganan pentahydrochloride, azelaic acid and EGCG.

Tetracyclines bind to the 30S subunit of the bacterial ribosome to inhibit protein biosynthesis, consequently killing the microorganism [27]. However, since acne is not an infectious disease, tetracyclines are utilized primarily for their anti-inflammatory properties via inhibiting neutrophilic chemotaxis, production of proinflammatory cytokines and MMP activity [34, 109]. Although there is inadequate evidence to support the use of doxycycline over minocycline in terms of efficacy, a recent cochrane review of clinical trials highlighted the uncertain safety profile of minocycline. Antibiotic resistance is an unavoidable problem in the use of tetracyclines. Subantimicrobial dosing of doxycycline is effective in patients with moderate inflammatory acne since it provides anti-inflammatory effects without exerting selection pressure causing antibiotic resistance [37, 122].

The efficacy of clindamycin is based on its antimicrobial property [68]. The therapeutic effect of BP is due to the killing of *C. acnes* via release of free oxygen radicals as well as mild comedolytic action [23, 39]. Omiganan pentahydrochloride is a cationic antimicrobial peptide (AMP) having antibacterial (both gram positive and gram negative) and antifungal activity in experimental pig skin colonization models. It is capable of reducing the number of comedo inflammatory lesions [119]. Its primary mechanism coincides with the non-receptor-mediated mechanism of antibacterial action for other cationic peptides [48]. To be more precise, the action of omiganan is related to its membrane depolarization effect on the cytoplasmic membranes of bacteria and fungi, inhibition of macromolecular (e.g. nucleic acid and protein) synthesis and cell death [93]. In addition to comedolytic effects, topical use of azelaic acid also has antibacterial and anti-inflammatory properties [122]. EGCG suppresses the growth of *C. acnes* in vitro models; however, the mechanism remains unclear [121].

Inflammation

More and more research has found that inflammation plays an important role in the onset, development and resolution of acne vulgaris. IGF-1 and virulent *C. acnes* are the most important factors to induce inflammatory response in acne.

Previous studies have demonstrated that IGF-1 is sufficient to induce pro-inflammatory cytokine expression in primary human sebocytes [55, 63]. Increased expression of NF-κB, IL-1β, IL-6, IL-8, and TNF-α in cultured sebocytes was observed after stimulation with IGF-1. However, the level of these inflammatory biomarkers was decreased in NF-κB inhibitor-pretreated sebocytes after IGF-1 treatment [63]. In addition to IGF-1, androgen might have similar effects, since androgen can increase IGF-1 level in serum in normal men [52]. After the stimulation of IGF-1, sebocytes release cytokines and MMPs and recruit inflammatory cells into the pilosebaceous unit [81]. MMPs are capable of breaking the follicular membrane, causing fatty acid spillage

to the dermis and dissolution of the extracellular matrix [97] (Fig. 1).

Cutibacterium acnes is identified by TLR-2 expressed on monocyte/macrophage lineage cells, which induce IL-20 p40 promoter activity and production of IL-12 and IL-8 [64]. *C. acnes* also upregulates caspase-1 and NLPR3 gene expression while inducing the activation of monocyte–macrophage NLRP3-inflammasome depending on phagocytotic activity, lysosomal breaks with release, and activation of cathepsin B, generation of ROS and efflux of potassium, resulting in the abundant production of IL-1β [99] (Fig. 4). *C. acnes* also have a mitogenic effect on T lymphocytes [57]. The lymphocytes involved in the *C. acnes*-induced adaptive immune response are CD4 + T cells, specifically T helper (Th) 1 and Th17 cells. *C. acnes* triggers the secretion of IL-1β, IL-6 and transforming growth factor-β (TGF-β) in peripheral blood mononuclear cell (PBMCs) inducing naive CD4 + CD45RA T cells differentiation into Th17 cells [1]. This process is potentially done in a major histocompatibility complex II (MHC II)-dependent manner. As a result, the secretion of IL-17 and interferon (IFN)-γ, the Th effector cytokines, in the same areas in acne biopsies, are upregulated [65]. In addition to inflammatory mediators, neutrophils also mediate inflammation by increasing hydrogen peroxide generation [5] (Fig. 4).

Therapeutic implications

Most anti-acne agents have anti-inflammatory action. Retinoids exhibit an anti-inflammatory effect by suppressing the expression of TLR-2 on monocytes [74], enhancing phagocytic function, inhibiting the release of pro-inflammatory cytokines including IL-6, IL-12, TNF-α and IFN-γ [61], decreasing the production of transcription factor activator protein (AP-1) [25] and inhibiting vascular cell adhesion molecule-1 gene expression [42]. The anti-inflammatory effects of antibiotics include inhibition of *C. acnes* colonization, neutrophilic chemotaxis, production of proinflammatory cytokines and MMP activity.

There are some other novel potent agents for the treatment of acne vulgaris, for example, K_DPT, afamelanotide, apremilast, various biological agents and EGCG. K_DPT is a tripeptide derivative of the C-terminal end of α-MSH with no melanotropic activity. It has potential anti-inflammatory properties. K_DPT inhibits inflammation through a variety of mechanisms: (1) suppressing IL-1β-induced expression of IL-6 and IL-8 by binding to IL-1RI and decreasing IL-1β-mediated NF-κB signaling in sebocytes; (2) reducing IL-1β-mediated generation of intracellular ROS [80]. Afamelanotide is an α-MSH analog with anti-acne properties [10] and possibly blocks IL-8 release induced by IL-1β

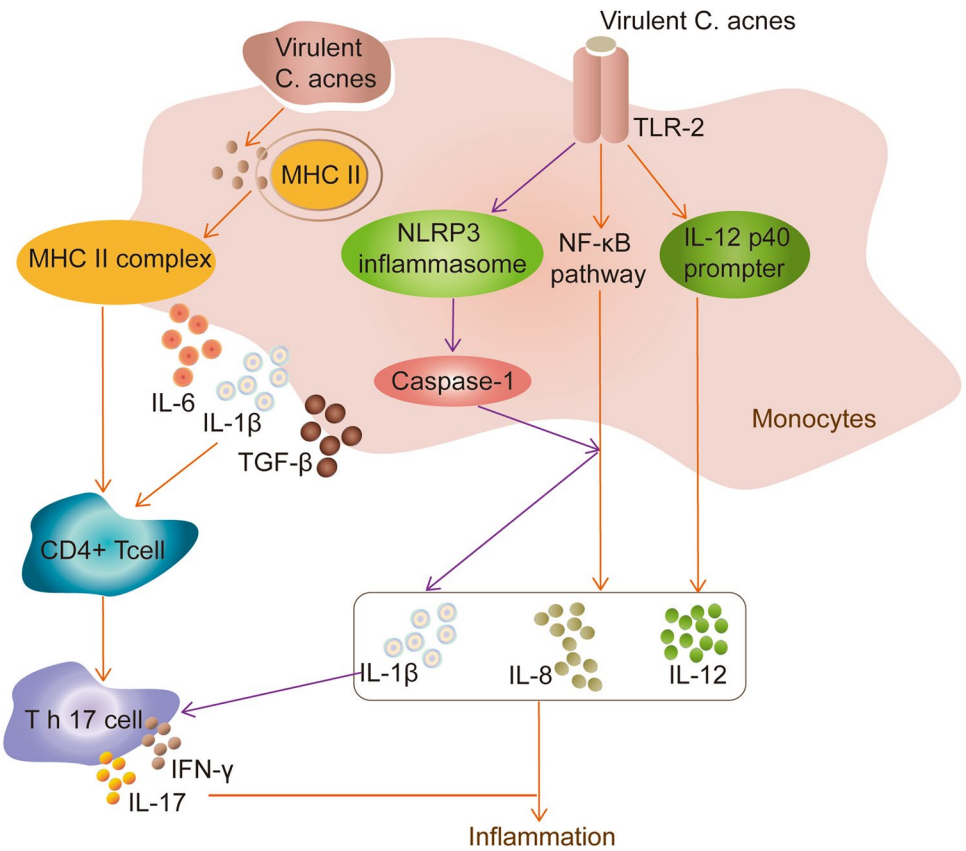

Fig. 4 Inflammatory events in acne vulgaris. *C. acnes* triggers the secretion of IL-1β, IL-6 and TGF-β in mononuclear cell inducing naive CD4 + T cells differentiating into PPAR in an MHC II-dependent manner. IL-1beta is a key signal for Th17 cell differentiation. *C. acnes* increases the production of inflammatory mediators by activation of NF-κB pathway, enhancing IL-12 p40 prompter activity and activation of NLRP3-inflammasome. *MHC II* major histocompatibility complex II, *Th 17 cell* T helper 17 cell, *IL* interleukin, *TGF* transforming growth factor, *TLR* toll-like receptor, *IFN* interferon

Table 1 Anti-acne agents

Agents	Effects and mechanisms
Agents controlling sebum production	
Spironolactone	(1) Decreasing testosterone production (2) Competitively inhibiting androgens (mainly testosterone and DHT) binding to androgen receptors of the skin (3) Inhibiting 5-α-reductase activity (4) Increasing sex hormone-binding globulin
COCs	(1) Reducing 5-α-reductase activity (2) Blocking androgen receptors (3) Increasing sex hormone-binding globulin to bind free circulating testosterone (4) Decreasing androgen production at the ovary level
Flutamide	Nonsteroidal selective androgen receptor blocker
N-Acetyl-GED-0507-34-LEVO (2016-000540-33)	PPARγ modifier
JNJ-10229570	MCR antagonist
EGCG	(1) Reducing critical downstream elements (mTOR and S6 ribosomal protein) in the Akt pathway (2) Activating the AMPK–SREBP-1 signaling pathway
Olumacostat glasaretil	Inhibiting the acetyl coenzyme A carboxylases
XEN103	(1) Inhibiting SCD activity (2) Inhibiting SCD expression in human sebocytes
Retinoids (topical and systematic use)	Upregulating the expression of nuclear FoxO1 and FoxO3 proteins
Metformin	Indirect inhibitor of mTORC1 by activating AMPK pathway
Agents normalizing altered keratinization within the pilosebaceous duct	
Retinoids	(1) Inhibiting disturbed differentiation and hyperproliferation of keratinocytes (2) Suppressing cytokines (e.g. IL-6, IL-8 and TNF-α) production in keratinocytes and superoxide anions
Azelaic acid	Comedolytic effect
EGCG	Inhibiting hyperkeratosis by decreasing the level of IL-1 in keratinocytes
Agents acting against C. acnes colonization	
Tetracycline antibiotics	Killing *C. acnes* by releasing free oxygen radicals as well as the mild comedolytic action
BP	(1) *C. acnes* death by release of free oxygen radicals (2) Mild comedolytic action
Omiganan pentahydrochloride	(1) A cationic antimicrobial peptide having membrane depolarization effect on the cytoplasmic membranes of bacterium and fungal (2) Bactericidal effect by inhibiting macromolecular (e.g. nucleic acid and protein) synthesis (3) Reducing comedo inflammatory lesions
Azelaic acid	Antibacterial property
EGCG	Inhibiting the growth of *C. acnes*
Clindamycin	Antimicrobial property
Agents with anti-inflammatory action	
Retinoids	(1) Suppressing TLR-2 expression on monocytes (2) Enhancing phagocytic function (3) Inhibiting the release of pro-inflammatory cytokines including IL-6, IL-12, TNF-α and IFN-γ (4) Decreasing AP-1 production (5) Inhibiting vascular cell adhesion molecule-1 gene expression
Tetracycline antibiotics	(1) Inhibiting *C. acnes* colonization (2) Inhibiting neutrophilic chemotaxis (3) Suppressing proinflammatory cytokines production and MMP activity
K_DPT	A tripeptide derivative of the C-terminal end of α-MSH (1) Suppression of IL-1β-induced IL-6 and IL-8 expression by binding to IL-1RI and decreasing IL-1β-mediated NF-κB signaling in sebocytes (2) Reducing IL-1β-mediated intracellular ROS generation
Afamelanotide	An α-MSH analog possibly capable of blocking IL-8 release induced by IL-1β
Apremilast	Phosphodiesterase 4-inhibitor capable of inhibiting the neutrophil infiltration and TNF-α, IL-8 production
Biologics	IL-1 monoclonal antibodies and IL-17 monoclonal antibodies
Azelaic acid	Anti-inflammatory property
EGCG	(1) Suppressing NF-κB and AP-1 signaling pathways (2) Reducing IL-1α and IL-6 in sebocytes stimulated by IGF-1

COCs combination oral contraceptive pills, *MCR* melanocortin receptor, *EGCG* epigallocatechin-3-gallate, *SCD* stearoyl-CoA desaturase, *BP* benzoyl peroxide, *IL* interleukin, *TNF* tumor necrosis factor, *RA* retinoic acid, *TLR* toll-like receptor, *IFN* interferon, *AP* transcription factor activator protein, *MMP* matrix metalloproteinase, *MSH* melanocyte-stimulating hormone, *ROS* reactive oxygen species

[11]. Apremilast is a phosphodiesterase 4-inhibitor capable of inhibiting neutrophil infiltration and TNF-α, IL-8 production [126]. Biologics for acne mainly include IL-1 monoclonal antibodies and IL-17 monoclonal antibodies [126]. However, there is still no convincing evidence to confirm the efficacy of these antibodies in acne treatment, and both of them are expensive and thus may be reserved for rare acne variants such as acne fulminans or severe cases of acne conglobate instead of routine clinical treatment. EGCG is an mTORC1 inhibitor with the property of inhibiting lipid synthesis in sebocytes and might have some effect when applied topically. In fact, the agent also has anti-inflammatory effect by suppressing IL-1α and IL-6 in sebocytes stimulated by IGF-1 [55, 121].

In addition to drug therapy, the dietary treatment of acne should not be neglected. Compelling evidence indicates that western diet is a major cause of epidemic mTORC1-driven acne vulgaris [17, 83, 106] and the incidence of acne in people living in nonwesternized societies is lower [21]. Therefore, diet with no hyperglycemic carbohydrates, no milk and dairy products is beneficial for therapy of acne [19, 85, 86, 113].

Conclusion

In conclusion, acne vulgaris is a highly prevalent cutaneous inflammatory disorder with a high psychosocial impact. The pathology of this disease is multifactorial including hyperseborrhea, altered keratinization of the pilosebaceous duct, colonization with *C. acnes* and inflammation.

Androgen, insulin and IGF-1 are the main factors responsible for the development of acne vulgaris. Moreover, CRH, α-MSH and substance P are also involved in the pathogenesis. *C. acnes* is a microorganism well suited to almost every pathogenesis pathway of acne. Wnt/β-catenin signaling pathway, PI3K/Akt pathway, MAPK pathway, AMPK pathway and NF-κB pathway participate in signal transmission modulating the activity of sebocytes, keratinocytes and inflammatory cells.

Commonly used topical anti-acne agents include retinoids, BP and antibiotics. Systemic therapies commonly include antibiotics and hormonal agents (e.g. COCs, spironolactone and flutamide). Numerous new approaches in the treatment of acne have been developed such as EGCG, omiganan pentahydrochloride, K_DPT, afamelanotide, apremilast, and various biological agents. However, these agents are experimental or ideas for efficaciousness only instead of the established drugs according to evidence.

We summarized all the anti-acne agents mentioned in this review and found that one agent may have diverse pharmacological action against multifactorial causative factors of acne vulgaris (Table 1). Besides drug therapy mentioned above, avoiding western diet also plays an important role in the treatment of acne.

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Compliance with ethical standards

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