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The emerging principles for acne biogenesis: A dermatological problem of puberty

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ABSTRACT

Acne is the most common conditional skin infection in late adolescence. It has long played the part of 'Black Spot' against Natural Beauty, characterized by non-inflammatory pilosebaceous lesions of open or closed comedons, and inflammatory lesions of papules, pustules and nodules. It is typically affected the face, neck, and upper trunk area, where sebaceous follicles is densest in population, however prevalence is about 90% in teenagers. Recent advances have been made in this area with the discovery of *Propionibacterium acnes* interaction with Toll-Like Receptors (TLRs) and free fatty acid that initiates linoleic deficiency, also the role of linoleic acid and PPARs (peroxisome proliferators-activated receptors) in inflammation. However multi-drug resistant of bacteria by biofilm formation is also a matter of concern, that render the course of treatment ineffective. With all relevant literature database search upto recent this review focuses on pathogenesis of acne and mechanisms involved in the development of inflammation.

Contents

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Introduction

The External Natural Beauty reducer and Black Spot enhancer disease is commonly known as acne vulgaris. It is one of the most common chronic diseases of pilosebaceous unit characterized by non-inflammatory lesions of open/closed comedons, and inflammatory lesions of papules, pustules and nodules of human beings [1]. It affects upto 85% of adolescents, when they undergo maximum physical, psychological and social changes [2]. There are various studies which have been reported globally for clinical relevance of its pathogenesis such as in Turkey [3], Taiwan [4], Australia [5], South India [6] Saudi Arab [7], Iran [1], Brazil [8], Mexico [9], France [10] etc. Merely 40% of acne patients had obtained general information about acne from doctors (39.5%), whereas a considerable number obtained information from the other source (35.9%). About 35% of adolescents patient use medication, without any prescriptions of a physician, remaining 40% of chronic sufferers have been seen in medical practice [11]. Due to the uncertainty of medical seeking behaviour, the exact global prevalence is unknown. But it can be conclude, in the period of life approximate everyone may suffer at least once from acne. It is typically affecting the face, neck, and upper trunk area where sebaceous follicles are densest in population, but not affect the 'General Health', while affected the 'Social Life' of human [12]; because of human face makes the first perception of social life and define the primary step of communication. Therefore the primary objective of this study was to characterize and analyse the mechanism of the actions leading the pathogen to cause acne vulgaris. In particular, the pathogenic bacterial life cycle and the allied virulence factors are discussed. In accordance to the available literature, we have tried to explore how these bacterial populations attribute themselves within the host skin and initiate virulence. However, unlike these issues, the availability of appropriate model systems to study acne pathogenesis is poorly understood. In this review, we attempted to identify the correlations between all the possible factors involve in biogenesis of acne vulgaris, so that treatment of acne vulgaris can be directed toward the known pathogenic factors.

Classification of acne

Based on the predominance lesions on epidermis, the acne is classified as: (1) comedonal, (2) papular, (3) pustular and (4) nodulocytes. Papular and pustular are inflammatory mild to moderate lesion, and comedonal is non-inflammatory mild lesion, while nodulocytes are severe [13].

What causes acne?

Hormonal changes and puberty

The sex hormone, mainly androgens are much more secreted during the puberty, causes the excess amount of sebum production by sebaceous gland leads to acne biogenesis. The male sex hormones, testosterone, dihydrotestosterone and dehydroepiendrosterone are secreted by testis, and make the puberty. It excess secretion attributes to acne genesis. Menstrual cycles and pregnancy period seem to contribute to increase the female sex hormone production, influences the acne vulgaris. Apart of these cushing syndrome and hirsutism also promoted the development of acne [14].

Western diet

The hyperglycemic food, induces the insulin like growth factor – I signalling, is the central line of endocrine pathway of sexual maturation, and play the primary role in development of acne. The western diet contains huge amount of glycaemic carbohydrate, saturated fat and milk dairy product that promoted the sebaceous lipogenesis and sebum secretion [15].

pH of skin

It is reported that the alteration of pH of skin is also consider to be one of the cause of acne. This alternation may be due to the alternation of microbial flora of skin other factors include age, skin type, gender, genetics, sweat, sebum, detergent, soap, anatomical sites, and cosmetics. The pH of skin of male should be 5.5 and 5.4–6.0 for female. Free fatty acid subsidizes acidic pH (approximately 5) on skin surface. Many common pathogens (*Staphylococcus aureus* and *Streptococcus pyogenes*) are inhibited by an acidic pH [16]. Since washing skin with soap increase the pH by 1.5–2.0, which potentiates dryness, tightness and reduces acidity that increases the risk of coetaneous acne [17].

Anxiety and stress

Mental stress promoted the anxiety that can effects skin through the hypothalamic-pituitary-adrenal (HPA) axis. On sensing stress, neurons in the hypothalamus secrete corticotropin-releasing hormone (CRH) promotes lipogenesis in sebocytes through up-regulation of a key enzyme. In addition, it induces cytokines (IL-6 and IL-11) productions in keratinocytes, contributing to inflammation [18].

Makeups

Huge amount of makeups block the pore of sebaceous gland that promoted the acne [19].

Pathogenesis

Development of acne

Sebaceous glands secrete sebum, found in huge amount in entire body surface but cover larger portion in upper trunk area, chest and back side except the site where hair follicle are absent such as the palm, sole and dorsum area of feet. Sebum maintains the moisture content on skin, and protects the skin from sun light, bacterial infection and friction. It plays the active role against wound healing. The major part of sebum is lipids, excess production interfere the follicular keratinisation process leading to blockage of the pore of sebaceous gland, and the development of acne is started [20]. The events of pathogenesis is carried in following steps

Step 1. The excess production of sebum from sebaceous glands,
Step 2. Hyperkeratinisation leading to microcomedo that become enlarges into comedo,
Step 3. Growth of anaerobic bacteria leading to colonization of the follicle and
Step 4. Inflammatory responses [21].

Production of sebum and Hyperkeratinisation

Role of hormone

Hormones consider as a prime factor in initiating acne. It is reported that with the commencement of puberty the acne mostly herald, due to increased production of hormone, which tends to peak in the mid- teenage years. Hormone primarily instigates sebaceous gland. The androgenic hormones (sex hormone) like that of dihydrotestosterone stimulate and regulate the metabolic rate and size of sebaceous gland, indicating regulation of rate of hormone production. The inciting incident is believed to be stimulated by circulating androgen of pilosebaceous units. The increased

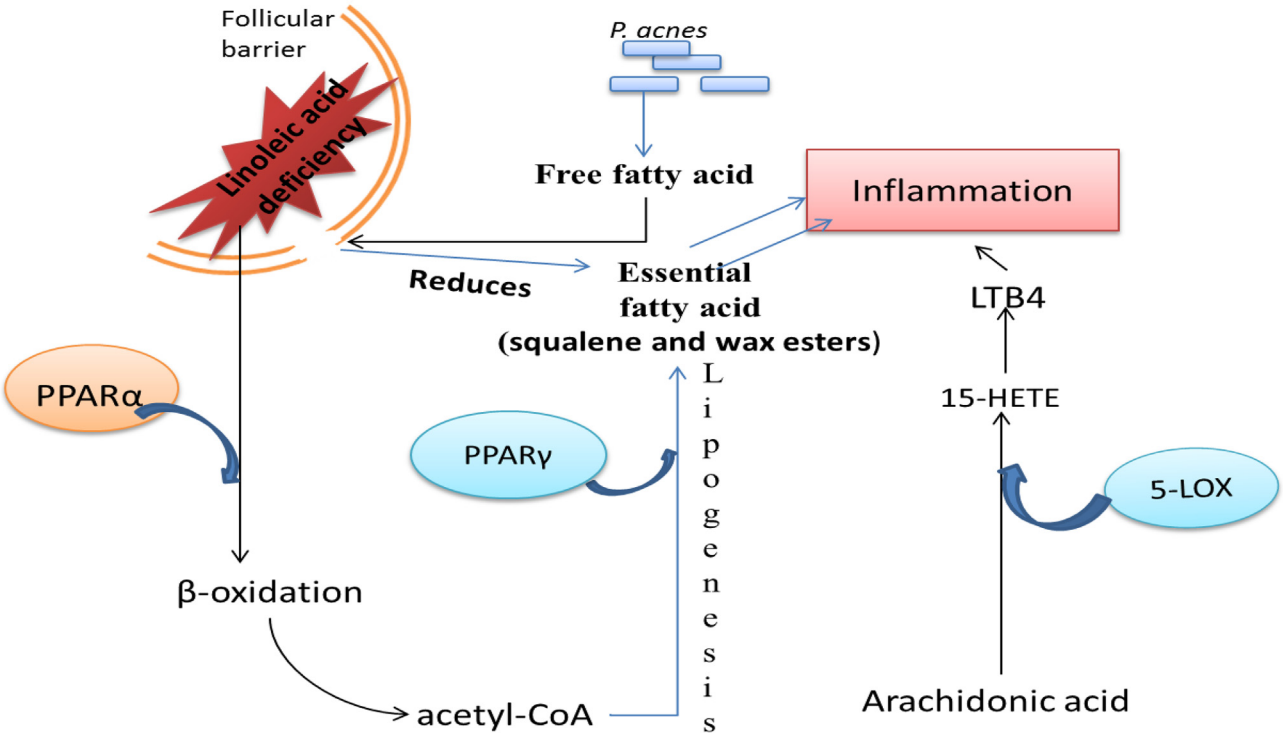

Fig. 1. Schematic representation of role of fatty acid: deficiency of linoleic acid impairs the follicular barrier that creates a way for other free fatty and bacteria. Reduced essential fatty acid initiate inflammation, fatty acid distribution and lipid peroxidation activate PPARs. Its isoform PPARα and PPARγ induce β-oxidation of fatty acids and lipid synthesis respectively. 15-HETE with arachidonic acid (ligand of PPARα and PPARγ respectively) produces LT-B4, catalyse by 5-LOX. Ultimately sustenance inflammation.

sebum production initiates retention of hyperkeratosis and abnormal desquamation of follicular epithelium. The combination of cells and sebum creates an environment for the proliferation of anaerobic bacteria. The shed keratinocytes form a plug at follicular infundibulum level, hence the blocked infundibulum dilates and form comedone and prevents sebum from being extruded to the skin surface. The follicular plugging and colonization of bacteria (*P. acnes*), causes inflammatory mediators to release in the skin. Further the affected and plugged pilosebaceous unit expands until the comedo ruptures; creating inflammation [22]. It reported that acne-prone skin exhibits a higher androgen receptor density and higher 5a-reductase activity than healthy skin. On the other hand, anti-androgen reduces synthesis of sebaceous lipids and provide improve acne [23].

Role of linoleic acid

Linoleic acid is an essential fatty acid that the sebaceous glands use as a normal component of sebum. Initially it was suggested that linoleic deficiency on the skin surface is significantly observed in pathogenesis of acne. The deficiency of linoleic acid impairs the follicular barrier that creates a pathway for other free fatty (which may produce from bacterial lipases activity or by sebocytes metabolism) [24] (Fig. 1). As these free fatty acid move in epithelium, induces localized deficiency of essential fatty acid. Further, lower level of the essential fatty acid in wax esters (sebum-specific lipids) suggest that linoleic acid is directly involved in the incorrect regulation of lipid metabolism however uptake of circulating lipid and β-oxidation are essential steps involved in it [25]. Apparently, sebaceous gland selectively utilizes fatty acids, whereas linoleic acid only appears to subject to β-oxidation. It transformed into precursors (two carbon units) for the generation of acetyl-CoA that are incorporated into different metabolic route such as the biosynthetic pathway leading to squalene and wax esters synthesis [26]. The reduced linoleic acid content in the sebum suggest to effect sphingolipids (sphingolipids in human epidermis maintain a barrier between the environment and the human body) composition in the follicle. The sphingolipids with reduced linoleic acid has been postulated to involve in the follicular hyperkeratosis, which is an essential incident in the comedones formation [27] (Fig. 1).

Role of peroxisome proliferators-activated receptors

Peroxisome proliferators-activated receptors (PPARs) are nuclear transcription factors involved in the control of lipid metabolism and inflammation. Alteration in sebum composition, fatty acid distribution and lipid peroxidation are capable of stimulating synthesis of pro-inflammatory cytokines and activation of PPARs. The PPARα and PPARγ are main isoform where, PPARα appears to associate with β-oxidation of fatty acids and lipid catabolism and PPARγ activation seems to associate with synthesis of lipid [28]. The most effective and natural PPRA ligands is 5-lipooxygenase produces leukotriene B4 (LTB4) *via* 15-HETE (hydroperoxy-ecosatetraenoic acid) with arachidonic acid as a precursor, both consider as ligands of PPARα and PPARγ, respectively (Fig. 1). Remarkably, the enzymes involved in their metabolic pathway, including 5-lipoxygenase (5-LOX), have reported in higher extent in acne-path skin comparison to the skin of healthy subjects. LOX products have been involved in inflammation by keratinocytes hyper-proliferation and induced IL-6 and IL-8 expression in human sebocytes. Therefore along with the anti-androgen, 5-lipoxgenase inhibitor treatment significantly reduce synthesis of sebaceous lipid hence acne lesions (Fig. 1) [29].

Bacterial infection

Propionibacterium acnes are gram-positive, facultative, anaerobic rod shaped bacteria that is a main inhabitant of the human skin accounting for 87% of the clones [30] with other *Staphylococcus,*

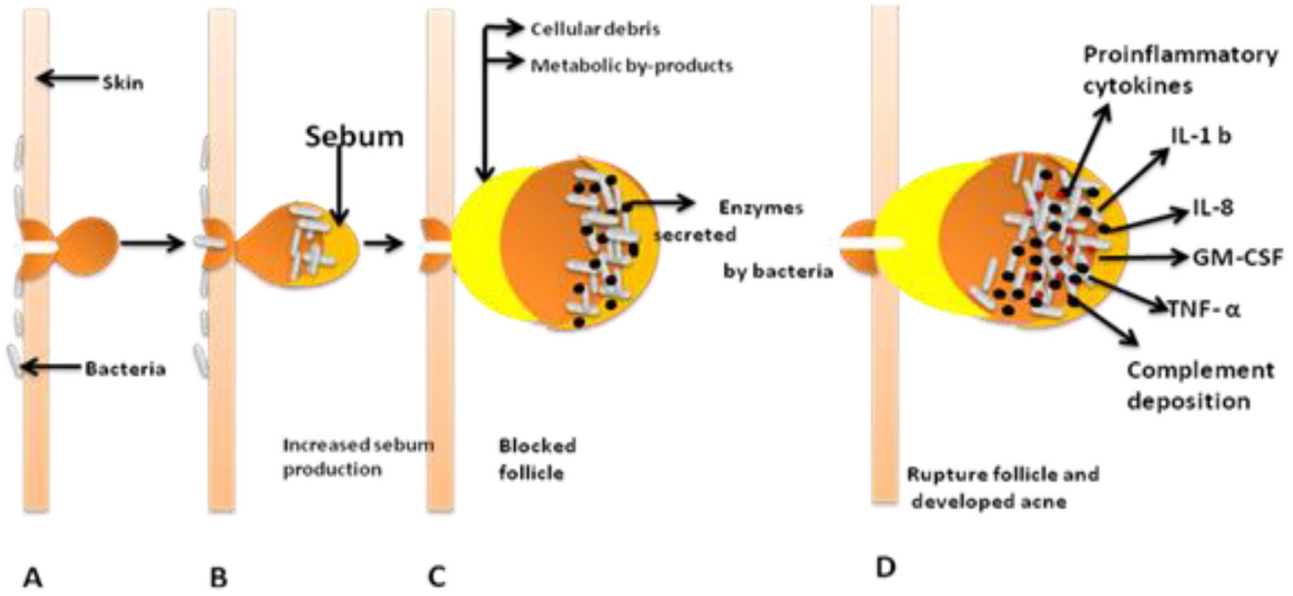

Fig. 2. Diagrammatic representation of bacterial pathogenesis: A. infestation of bacteria on the skin; B. stimulation of excessive sebum production; C. the cellular debris and metabolic by-product clog the follicular pore and create environment suitable for anaerobic bacterial (*P. acnes*) growth; D. that initiate the proinflammatory cytokines and other inflammatory responses.

Corynebacterium, Streptococcus, and *Pseudomonas* spp.[31]. In a strain level and genome level study of *P. acnes*, the sub-total of 11,009 ribotypes (each unique 16S rDNA sequence as a 16S rDNA allele type, called a ribotype) was assigned to the *P. acnes* 16S rDNA sequences. Analysis of the top ten ribotypes showed three most abundant ribotypes (RT1, RT2 and RT3) were found in both, acne affected and normal pilosebaceous follicle. Ribotypes 4, 5, 7, 8, 9 and 10 were found predominantly in acne patients. Further study demonstrates a strong association between strains of RT4 and RT5 with acne and strains of RT6 and healthy skin, each with unique genetic elements [30]. However, presence of these strains in healthy and diseased follicles suggest, it may be a matter of the threshold number of bacterial cells that may decide the prerequisite root of infection [32]. This organism remains dormant prior to puberty, but on the onset of puberty, hormone increase the levels of sebum by which bacteria get activated and react by proliferating. It lives primarily on fatty acids in sebum, secreted by sebaceous glands. In the follicles, bacteria use sebum, cellular debris and metabolic by-products from the surrounding skin tissue as their primary sources of energy and nutrients. Hence blockage of the follicle can create appropriate environment for bacteria to flourish. It is reported that follicular shed extracted from acne lesions consist of protein. The most distinctive proteins reported are myeloperoxidase, neutrophil elastase, lactotransferrin, inhibitor, and unpredictably, vimentin. And interestingly, these proteins were identified as bacterial protein exclusively from P. acnes. Among the P. acnes associated protein surface exposed dermatan sulphate adhesins, unrecognized lipase and CAMP factors are most abundant in follicular casts of acne affected as well as normal human skin [33]. The chemotactic factors released by bacteria attract lymphocytes and neutrophils, as well as producing other proinflammatory molecules within and around the affected pilosebaceous unit [34,35] (Fig. 2). Further the Toll-like receptors have shown their role in pathogenesis, activated by bacterial (*P. acnes*) cell wall peptidoglycan that testify a molecular demonstrate for inflammation in acne [36]. *P acnes* also reported to stimulate follicular keratinocytes to release proinflammatory cytokines, interleukin-1b (IL-1 b), IL-8, granulocyte–macrophage colony-stimulating factor (GM-CSF), tumors necrosis factor α (TNF-α) and complement deposition, which causes keratinocytes to proliferate and subsidize to form preclinical microcomedo (Fig. 2) [37].

Bacterial biofilm

After all the discussion of considering sole role of *P. acnes* in dermal infection, there are some studies that allegate this perception. The antimicrobial therapy must provide complete treatment if *P. acnes* had had sole role, but it is a matter of concern that topical or systemic antibacterial treatments often show incomplete responses. By the course of treatments, there reported the reoccurrence of inflammation indicates failure of treatment. Since the specific antibiotic may not be effective against other bacterial strain, signifying *P. acnes* is not the only player in the pathogenesis of acne vulgaris [38]. The conclusions regarding reoccurrence may be the emerging antibiotic resistance in bacterial strain or due to formation of biofilm that confer antibiotic tolerance. This become a matter of great concern, and attracted scientific researches therefore many studies have put forward, with pertinence toward biofilm formation in *P. acnes* might have role in persisting chronic infection [39,40]. Bacterial biofilms are formed when unicellular organisms associate to form a community that is attached to a substratum and encased in an exopolysaccharide (endo or exogenously produced polysaccharides, protein and extracellular DNA) matrix. Biofilms can be made up of single or multiple bacterial species. These cells in biofilms exhibit varied phenotype, gene expression and protein production other planktonic microbial cell [41]. The pathogens in biofilms have enhanced pathogenicity and increased resistance to antimicrobial agents. One potential reason for this increased resistance may be the penetration barrier that biofilm may confer to antimicrobials; the possible causes may be the exopolysaccharide matrix prevents the access of antibiotics diffusion through the biofilm. Either the reaction or adsorption of compound to the component of biofilm can hinder the transportation of antibiotics to the cell within biofilms (Fig. 2) [31]. Therefore biofilm microorganisms have much enhanced resistance to antimicrobial agents than do planktonic bacteria [42] (Fig. 3).

It was suggested that on acquiring optimal environment *P. acnes* biofilm binds with extracellular matrix and plasma proteins

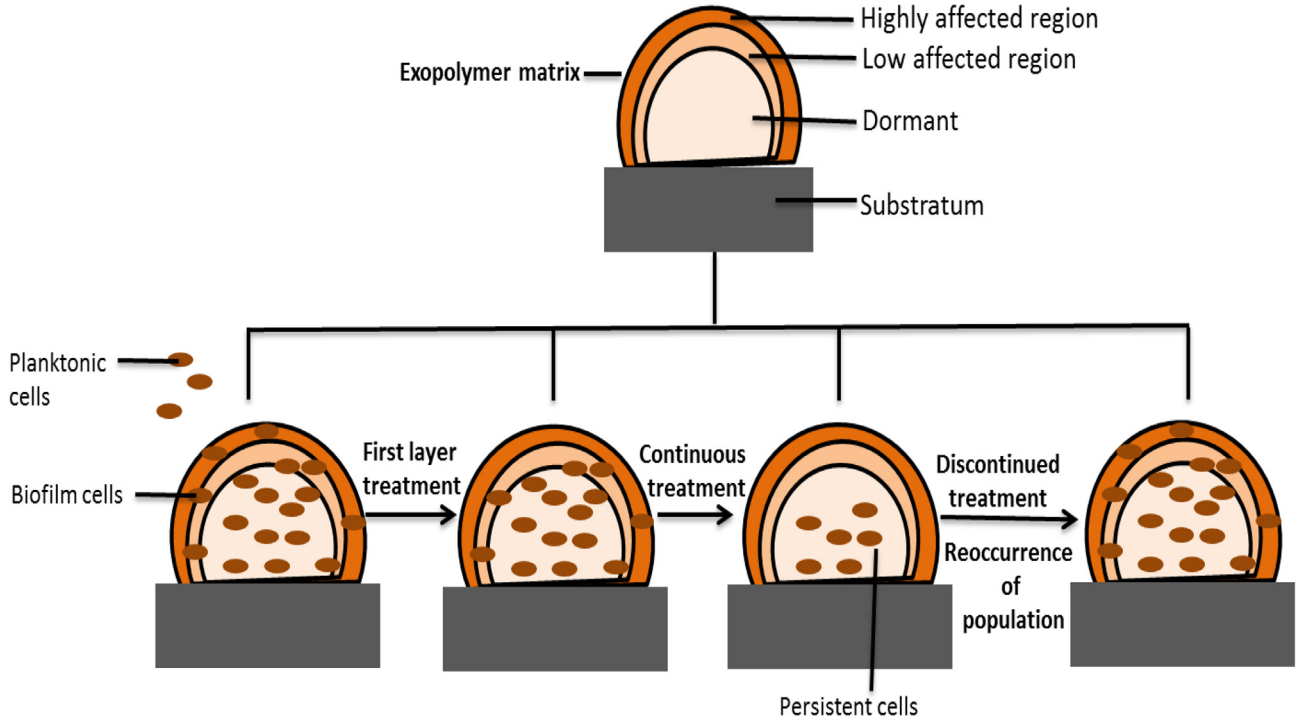

Fig. 3. The diagrammatic approaches of biofilm strata resistance: A. different strata according to antibacterial resistance these strata confer. B. Planktonic cells accumulate and secrete Exopolymer matrix to form biofilm in which cell distributed evenly. C. First layer treatment exterminates cells from the upper strata. D. Continuous treatment can eradicate mass of bacterial cell. E. By discontinuous treatment bacterial cell get opportunity to reoccur.

(fibronectin Fn, laminin, and fibrinogen) this might be consider as initial step of infection in affiliation with foreign materials [43]. *P. acnes* produce a lipoglycan established cell envelope that may be a significant adherence to skin tissue and for biofilm formation [44]. Moreover, *P. acnes* mediate the increased lipase activity that attracts neutrophils. And these host immune cell often have to experience phagocytosis thereby lysing cells, add to the exopolymeric component of the biofilm. The biofilm contours in several layers, upper few layers may get affected by the antibiotics but the inner core region remains dormant and unpretentious. The aggregation of neutrophils and frustrated phagocytosis might have inflammatory role. It is reported that the clusters of gene of the *P. acnes* have role in biofilm matrix formation, clusters encode UDP-N-acetyl-D-mannose aminuronate dehydrogenase, UDP-N-acetyl glucosamine-2-epimerase, mannose-1-phosphate guanyl transferase, Exo A (succinoglycan biosynthesis protein), and various glycosyl transferases [45]. Hence, it can be concluded that sessile biofilm of *P. acnes* cells are less vulnerable to antimicrobial agents than their planktonic equivalents [46]. The sustained application of antibiotics might affect biofilm upto upper exposed layer to some extent, but to the core dormant region. The bacterial cell in the core region persists; on attaining favourable opportunity (that may be discontinued antibiotics treatments) the persisting cell reproduce and increases their population again. That might be a major cause to render topical or systemic therapy inefficient.

Inflammation

The studies have shown that active IL-1b, mRNA and IL-1b form are abundant in acne lesion with inflammation [47]. Further biopsies collected from acne lesions confirm the elevation of cytokines of the Th17 lineage. However cytokines involved in Th17 lineage differentiation (IL-1β, IL-6, TGF-β, and IL23p19) were induced at the RNA level. Most remarkably studies have revealed the significantly elevated number of IL-17A positive T cells and CD83 dendritic cells in the acne lesions. Further they demonstrate the presence of IL-17A positive T cells and the activation of Th17-related cytokines in acne lesions, indicating that the Th17 pathway is activated [48]. Therefore, the elevated incidence of interleukins and cytokines in the inflammatory acne lesions might be the reason to incite inflammation.

Furthermore, *P. acnes* colony in pilosebaceous unit disrupt the epithelium of follicle, from where the bacterial cell leaks out and get into contact with myeloid cells (like macrophage). It acts on TLR-2 that induce release of interleukins (IL-6 and IL-8) from follicular keratinocyte and IL-8 and IL-12 from macrophages [49]. Bacterial supernatants PBMCs (human peripheral blood mononuclear cells) stimulation is sufficient to inspire the CD4 and CD45RA T cells differentiation into Th17 cells [47]. Besides, it triggers activation of monocyte–macrophage NLRP3-inflammasome [50], deterioration of lysosome, cellular Kþ efflux, reactive oxygen species which is phagocytosis dependent. Subsequently bioactive IL-1b, and neutrophil-rich local inflammation Cat. B, cathepsin B, DNA, mitochondrial DNA, ROS, TLR, Toll-like receptor releases. Therefore, *P. acne* proves to induce IL-1b and the NLRP3 inflammasome dependent inflammatory responses and triggering an innate immune response [51].

The multiple activator of NLRP3-inflammasome stimulates Ca^{2+} signaling, which in turn damage mitochondria and release cellular stress [52,54] referred to as signal 2, equivalent to signal 1, which is provided by TLRs [53] (Fig. 4). After the activation of NLRP3-inflammasome, caspase-1 activates, and secrets mature IL-1b in human monocytes, this pathway involves K^+ efflux. The instigation of inflammation depends on entrance of bacteria to myeloid cells as well as their capability to phagocytose the bacteria. Such findings suggest that molecules targeting IL-1b and/or the NLRP3 inflammasome may constitute new treatment possibilities for acne vulgaris [55]. The damage caused by *P. acnes* and the associated

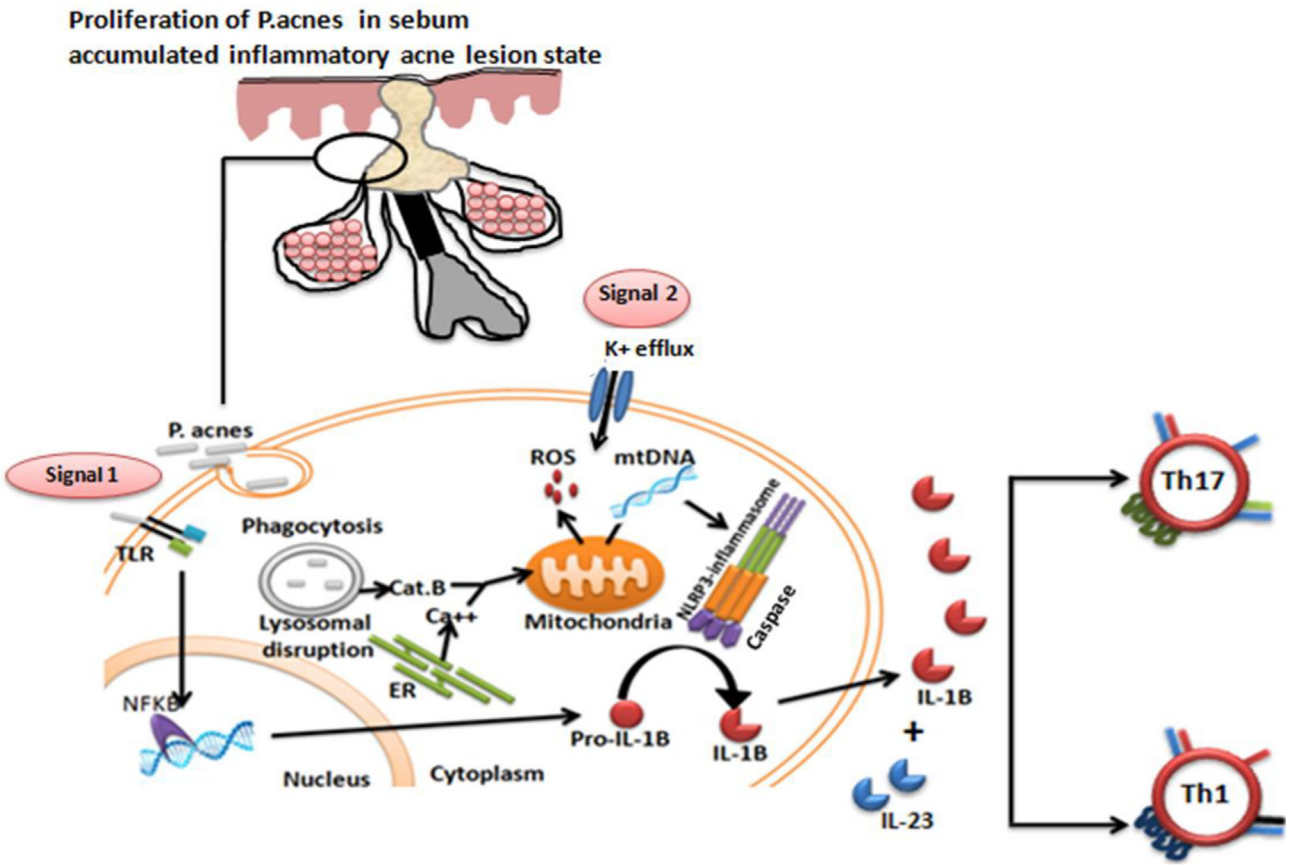

Fig. 4. Proliferation of *P. acnes* in sebum accumulated inflammatory acne lesion state at molecular level.

inflammation make the affected tissue more susceptible to colonization by opportunistic bacteria, such as *Staphylococcus aureus* [56].

The present review has discussed all possible pathogenic factors so that management of acne vulgaris can be focused on the known pathogenic factors, including follicular hyper proliferation, excess sebum production, microbial, biofilm formation and inflammation. The most appropriate treatment is based on the grade and severity of the acne. Some of the basic treatment types and discussed in brief as follows

Pharmacotherapy

The following medications are used in the treatment of acne vulgaris:

- Retinoid-like agents (eg, topical tretinoin, adapalene, tazarotene, isotretinoin).
- Antibiotics (eg, tetracycline, minocycline, doxycycline, trimetho prim/sulfamethoxazole, clindamycin, topical clindamycin, topical erythromycin, daptomycin).
- Selective aldosterone antagonists (eg, spironolactone, cyproterone acetate).
- Estrogen/progestin combination oral contraceptive pills (eg, ethinyl estradiol, drospirenone, and levomefolate; ethinyl estradiol and norethindrone; ethinyl estradiol and norgestimate; ethinyl estradiol and drospirenone).
- Adjunct with antibiotic (eg, erythromycin and benzoyl peroxide, clindamycin and tretinoin, clindamycin and benzoyl peroxide, azelaic acid, benzoyl peroxide).

Physical treatment

- Lesion removal (eg. Comedones extractor, aspiration of active deep inflammatory lesions).
- Phototherapy (e.g., use of limited spectrum wavelength, such as blue light (peak at 415 nm), and mixed blue and red light (peak at 415 and 660 nm, photodynamic therapy).

Diet therapy, such as a low-glycaemic diet to manage acne vulgaris [57].

Conflict of interest

None.

Funding resource

None.

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