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Pathophysiology of Acne Vulgaris: An Integrative Narrative Review

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Abstract:
Background: Acne vulgaris is a highly prevalent chronic inflammatory disorder of the pilosebaceous unit that affects individuals across all age groups. Its pathogenesis is complex and multifactorial, involving dysregulation of the skin microbiome, sebaceous gland hyperactivity, follicular hyperkeratinization, immune-mediated inflammation, hormonal signaling, and genetic susceptibility. Recent advances have shifted the understanding of acne

from a purely comedogenic disorder toward an immune-driven disease with early inflammatory activation.
Aim: The aim of this review is to provide an integrated overview of the current understanding of acne pathophysiology, with particular emphasis on the interplay between inflammatory mechanisms, microbial dysbiosis, sebaceous gland activity, endocrine regulation, and genetic factors.
Materials and Methods: A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar, with primary focus on peer-reviewed English-language articles published between 2000 and 2025; however, earlier seminal publications were included where relevant. Search terms included "acne vulgaris," "pathophysiology," "inflammation," "Cutibacterium acnes," "sebaceous glands," "hormones," "microbiome," and "genetics." Relevant studies were qualitatively analyzed and synthesized to summarize key molecular, cellular, and immunological mechanisms involved in acne development.
Results: Current evidence demonstrates that acne is driven by an early and persistent inflammatory response within the pilosebaceous unit, influenced by altered sebum composition, dysbiosis of the skin microbiome—particularly pathogenic *Cutibacterium acnes* phylotypes—and immune activation mediated by Th1/Th17 pathways and inflammasome signaling. Hormonal factors, especially androgens and insulin-like growth factor 1 (IGF-1), modulate sebaceous gland activity and inflammatory signaling, while genetic predisposition modulates immune responsiveness and sebaceous function. These mechanisms interact dynamically, creating a self-perpetuating inflammatory loop that underlies lesion initiation and progression.
Conclusions: Acne vulgaris should be considered a multifactorial inflammatory disease resulting from the complex interaction between microbial, sebaceous, hormonal, immune, and genetic factors. A deeper understanding of these interconnected pathways provides a foundation for the development of targeted, mechanism-based therapies aimed at modulating inflammation, restoring microbial balance, and improving clinical outcomes while minimizing adverse effects.

Keywords: acne vulgaris; pathophysiology; inflammation; Cutibacterium acnes; sebaceous gland activity; androgens; insulin-like growth factor 1 (IGF-1)

1. Introduction

Acne is a pervasive inflammatory skin disorder, clinically characterized by seborrhea, noninflammatory and inflammatory lesions, and potential scarring (1). According to the Global Burden of Disease Study 2010, acne vulgaris is among the most common skin diseases worldwide, with an estimated global prevalence of 9.38% across all age groups (2). The

pathogenesis of acne is multifactorial, involving excessive sebum production, hyperproliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), abnormal hyperkeratinization of the pilosebaceous follicles, and inflammatory processes (3).
The aim of this review is to provide an integrated overview of acne pathophysiology, highlighting the key molecular, cellular, and inflammatory mechanisms driving disease development. A thorough understanding of these mechanisms is crucial for the development of modern, targeted therapies that precisely modulate key pathogenic pathways, thereby optimizing treatment efficacy while minimizing adverse effects.

2. Determinants of Acne Vulgaris

2.1. Microbiome

Cutibacterium acnes is a gram-positive, anaerobic bacillus primarily inhabiting the follicles of human sebaceous glands and is a normal component of the skin microbiota (4). *C. acnes* is classified into six primary phylotypes: IA1, IA2, IB, IC, II, and III (5). While it colonizes both healthy and acne-prone skin, patients with acne show reduced phylotype diversity and a predominance of acne-associated variants, particularly phylotype IA1, including ribotypes RT4 and RT5, which predominate in inflammatory lesions and exhibit enhanced pathogenic potential, including biofilm formation and the production of pro-inflammatory enzymes. In contrast, ribotype RT6 functions as a commensal and lacks pathogenic properties (6). Evidence suggests that geographic factors influence regional differences in the skin microbiome, as illustrated by the higher prevalence of IA5 (a subtype of phylotype IA1) in the Japanese population. This distribution may be associated with a lower inflammatory potential of the skin microbiome and may partially explain population-specific differences in acne severity, with potential implications for acne pathogenesis across different ethnic or geographic groups (7).

Cutibacterium acnes contributes to pathogenesis through multiple mechanisms, including amplification of local inflammation and modulation of immune responses. It stimulates sebocytes to secrete pro-inflammatory cytokines (TNF-α, IL-6, IL-8, and IL-12) via TLR2 activation and induces IL-1β production through the NLRP3 inflammasome and caspase-1(8). Moreover, *C. acnes* promotes Th17/Th1 responses, enhancing the secretion of IL-17A and IFN-γ (9) and affects skin physiology by regulating keratinocyte differentiation, sebocyte lipid production, and reactive adipogenesis in dermal fibroblasts, thereby contributing to the inflammatory milieu characteristic of acne lesions (10).

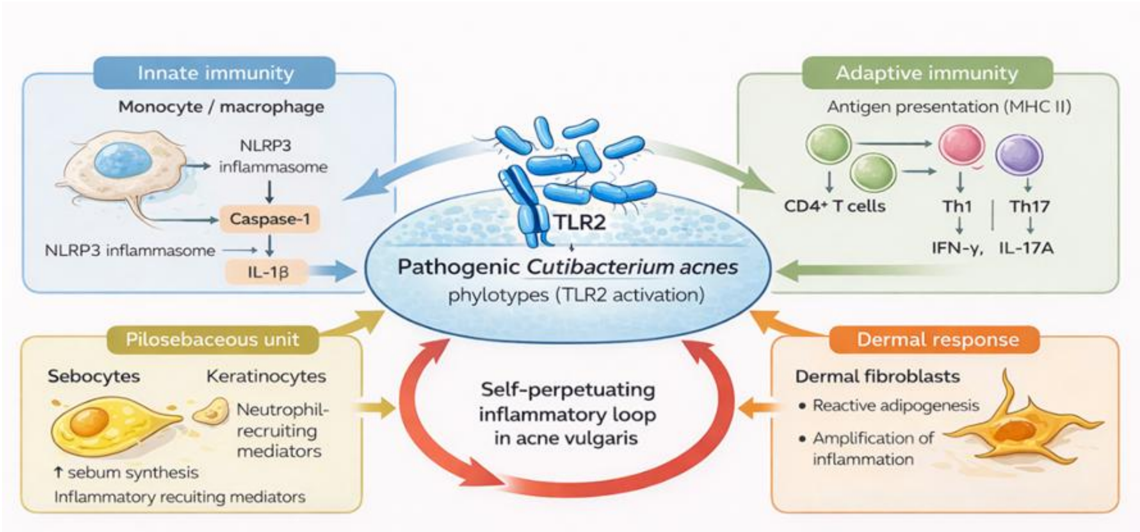

Figure 1. Schematic overview of inflammatory and immune mechanisms involved in the pathogenesis of acne vulgaris. Pathogenic *Cutibacterium acnes* phylotypes activate Toll-like receptor 2 (TLR2) signaling across multiple cell types within the pilosebaceous unit, including sebocytes, keratinocytes, immune cells, and dermal fibroblasts. This activation triggers inflammasome-dependent interleukin-1β (IL-1β) production, promotes Th1- and Th17-mediated immune responses, alters sebaceous gland activity, and induces reactive adipogenesis, collectively leading to the establishment of a self-perpetuating inflammatory microenvironment characteristic of acne lesions.

Staphylococcus species are ubiquitous residents of human skin, functioning both as potential pathogens and beneficial commensals. The skin harbors a diverse microbial community, within which *Staphylococcus*, including *S. epidermidis*, coexists with other microorganisms, contributing to skin homeostasis and disease. As members of the normal skin flora, their balance is critical; disruptions can lead to disorders such as acne. A study by Dagnelie et al. demonstrated that dysbiosis, particularly an imbalance between *C. acnes* and *S. epidermidis*, is associated with heightened inflammatory responses, underscoring the importance of maintaining a balanced skin microbiome to prevent excessive inflammation and acne progression (11).

Staphylococcus capitis (*S. capitis*) strain E12 exhibits significant antimicrobial properties, particularly against *C. acnes* (12*)*. This strain inhibits the growth of *C. acnes* more effectively than traditional antibiotics. Experimental studies involving pig skin and mice models have demonstrated the efficacy of *S. capitis* E12 in selectively targeting *C. acnes* without adversely affecting other beneficial skin bacteria (13). This selective activity highlights the potential of S. capitis E12 as a microbiome-based therapeutic candidate for acne.

Certain *Staphylococcus* species, including *S. epidermidis*, naturally produce antimicrobial peptides known as bacteriocins, which selectively inhibit opportunistic pathogens (12,13). Their specificity toward harmful bacteria while sparing commensals makes them valuable for maintaining microbial homeostasis. A survey of culture-dependent human skin isolates identified 21 bacteriocins capable of inhibiting various Gram-positive bacteria, including *S. epidermidis*, methicillin-resistant *Staphylococcus aureus* (MRSA), and notably *C. acnes*, with most antimicrobial-producing isolates belonging to the *Staphylococcus* genus (14). These findings emphasize the therapeutic potential of utilizing skin-derived antimicrobials, particularly in the context of rising antibiotic resistance.

2.2. Sebum

Sebaceous glands are appendages of mammalian skin that produce a mixture of lipids known as sebum (15). Increased sebum secretion is widely recognised as an important initiating factor in the development and progression of acne (16). Sebum overproduction is often associated with the overgrowth of *C.acnes*, particularly phylotype I strains, which appear to be more closely linked to acne pathogenesis (6,17). The study by Pappas et al. demonstrated that patients with acne exhibit alterations in both the type and arrangement of fatty acids. Specifically, sebum from acne patients contains 2.2-fold more squalene, 1.84-fold more triglycerides, 1.59-fold more total sebum, 1.49-fold more sapien.

Beyond the overall quantity and composition of sebum, the anatomical distribution of sebum production also plays a significant role in acne development(19).
Facial sebum secretion has subregional variations that contribute to clinical differences in acne vulgaris (AV) lesions (20). Sebum secretion varies across facial regions, being highest on the nose, followed by the forehead, chin, and cheeks. The T-zone (forehead, nose, chin) is a high-secretion area, the O-zone (perioral) moderate-to-high, and the U-zone (cheeks) low (21,22). Importantly, sebum production in the T-zone, U-zone, and across the overall facial area is higher in patients with AV compared with those without the condition (16).

2.3. Inflammation

Inflammation is now recognized as an **early and central event** in acne pathogenesis, rather than a secondary response to follicular obstruction. Clinically uninvolved skin of acne patients exhibits increased perifollicular CD3+ and CD4+ T cells and elevated macrophage infiltration, indicating that immune activation precedes hyperkeratinization and microcomedone formation (23). Endogenous factors—including altered sebum lipids (palmitic and sapienic acid), oxidized lipids such as squalene peroxide, and oxidative stress—promote IL-1β–driven keratinocyte hyperproliferation and activate Th1 and Th17 pathways, leading to elevated IL-1β, IL-6, IL-17A, IL-23, and TNF-α. Together, these mediators establish a persistent pro-inflammatory environment within the pilosebaceous unit, driving lesion initiation, progression, and chronicity (24,25).

2.4. Hyperkeratinization

Follicular hyperkeratinization is recognized as a central driver of lesion initiation in acne vulgaris, providing the structural basis for microcomedone formation (26,27). Recent studies challenge the traditional view that increased keratinocyte proliferation within the hair follicle represents the primary abnormality in acne. Rather, these investigations highlight alterations in differentiation pathways, dysregulated expression of keratinocyte markers (such as KRT16, KRT17, and FLG), and immune-mediated signaling mechanisms (including the IL-13/IL13RA1 axis) are critical modulators of keratinocyte behavior in acne-prone follicles (28,29). Abnormalities in follicular lipid composition, together with a spectrum of local inflammatory mediators, may further facilitate keratin plug formation. Follicular hyperkeratinization therefore should be conceptualized not merely as a hyperproliferative response, but as a multifactorial disruption of terminal keratinocyte differentiation and desquamation within the follicular infundibulum (30,31). Taken together, the dynamic interplay between follicular hyperkeratinization, sebaceous activity, and immune pathways establishes a self-reinforcing pathogenic loop that drives the initiation, progression, and chronicity of acne lesions (31,32).

2.5. Hormones

The activation of inflammatory pathways within the pilosebaceous unit represents a critical step in the pathogenesis of AV lesions, involving both innate and adaptive immune mechanisms (33). Androgens are thought to modulate this process by influencing the expression of proinflammatory cytokines in sebaceous glands. The addition of dihydrotestosterone (DHT) to cultured sebocytes significantly elevates levels of IL-6 and tumor necrosis factor α (TNF-α) (34).
The critical role of androgens in regulating sebaceous gland activity and sebum production is underscored by the marked absence of sebum observed in individuals with androgen insensitivity or mutations in the androgen receptor (AR) gene (35,36).
In addition to being a target of circulating androgens, cells within the pilosebaceous unit are capable of both *de novo* androgen synthesis from cholesterol and biosynthesis of testosterone and DHT from androgenic precursors *via* local enzymatic activity (37,38). Interestingly, skin biopsy sections from individuals with AV demonstrate localization of the type 2 isoform of 5α-reductase within comedonal walls and endothelial cells from sections of inflammatory lesions (37), suggesting a possible role of 5α-reductase type 2 in the development of AV lesions.
While the importance of androgens in the pathophysiology of AV is well established, it is important to acknowledge that most AV patients do not demonstrate laboratory evidence of abnormal hormone levels (33). This suggests that the relationship between androgen concentration and acne severity is not linear, and/or that circulating levels of androgens are not necessarily reflective of their biological activity at ARs or of sebaceous gland activity. Serum levels of testosterone and DHT are commonly higher in female patients with AV compared with those without AV (39–45) but are still mostly within the normal range (46). The marked increase in the prevalence of acne during adolescence compared to adulthood, even though circulating concentrations of androgen remain relatively stable until middle-to-late adulthood (47), also suggests that a key driver of hormone-induced AV is fluctuations in androgen production and not solely androgen excess. The influence of hormonal fluctuation on AV severity is further supported by the reported prevalence of premenstrual exacerbation of adult female AV (48–51).

In addition to ARs, sebocytes express several other hormone receptors that act to modulate inflammatory pathways and sebum production, including insulin and insulin-like growth factor 1 (IGF-1). Dietary factors, particularly a high dietary glycemic load

or glycemic index, have long been implicated in the pathophysiology and clinical severity of acne vulgaris (AV) (33,52–56). Accumulating evidence further suggests that insulin resistance may increase susceptibility to AV (56–60).
These associations may be attributable to increases in the concentration of IGF-1, which promotes sebum production and increases the expression of proinflammatory cytokines in cultured sebocytes (61). Moreover, elevated serum IGF-1 concentrations have been consistently reported in patients with AV compared with acne-free controls (53,62–64). However, the causal relationship between dietary factors, IGF-1 signaling, and acne severity remains complex and likely influenced by multiple metabolic and genetic variables.

2.6. Genetics

Acne vulgaris is a multifactorial disease influenced by both genetic and environmental factors. Specific genes have been linked to the occurrence and severity of acne, particularly those involved in immune and inflammatory responses. Interleukins (IL) provide a clear example, with recent studies focusing on IL-1α, IL-1β, IL-4, IL-6, IL-8, IL-10, and others (65). Genes regulating inflammatory pathways, such as TNF, as well as sebaceous gland function, including CYP17A1 and FST, have also been associated with acne susceptibility and severity across populations (66).

The study by Bataille et al. (2002) supports a strong genetic basis for acne, reporting that 81% of the variation in acne scores among adult twins in the U.K. could be attributed to genetic factors. Furthermore, family history confirmed significant familial clustering of the disease. These findings are consistent with two earlier twin studies, which estimated acne heritability between 50% and 90% (Friedman, 1984; Kirk et al., 2001) (67). Further investigation into genetic susceptibility will improve our understanding of acne pathogenesis, allowing better risk assessment, prognostic evaluation, and identification of potential targets for gene-based therapies (66).

3. Conclusions

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, driven by the interplay of microbial, sebaceous, immune, endocrine, and genetic factors. Early inflammation, often triggered by pathogenic *Cutibacterium acnes* strains, precedes visible lesions and sustains disease progression. Sebaceous glands contribute through altered sebum production and lipid composition, while sebocytes actively participate in local immune signaling. Subclinical immune activation, including Th1/Th17 responses and pro-inflammatory cytokine production, establishes a self-perpetuating inflammatory loop. Androgens and IGF-1 further modulate sebaceous activity and inflammation, with local hormone metabolism and receptor sensitivity playing a critical role. Genetic predisposition shapes individual susceptibility and disease severity. Recognizing acne as an integrated inflammatory disorder supports targeted, mechanism-based therapies aimed at restoring microbial balance, modulating immune pathways, and addressing hormonal and metabolic contributors, enabling more effective and personalized management.

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Resources: [AK], [JD]
Data curation: [NM], [KT], [MK]
Writing -orginal draft: [NM]
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