Acne Vulgaris: Advances in Pathogenesis and Innovations in Therapeutic Strategies

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ABSTRACT Acne vulgaris is a common dermatological condition, affecting up to 85% of adolescents and increasingly observed in adults, particularly women. Its chronic nature and visible manifestations impose significant psychological and social burdens. This review provides an updated examination of acne pathogenesis that explores emerging therapeutic approaches informed by recent molecular, genetic, and microbiome research. Findings from clinical studies, molecular biology, and immunological research published in the past decade are presented in a comprehensive overview of current advancements in acne treatment. Key databases and recent consensus guidelines have been utilized to identify novel mechanisms and therapeutic innovations. Current understanding emphasizes the role of innate immunity (e.g., toll-like receptors, inflammasomes), sebocyte biology via peroxisome proliferator-activated receptors (PPAR) signaling, and strain-specific Cutibacterium acnes dynamics. Environmental and genetic factors, including androgen receptor gene polymorphisms and lifestyle contributors, influence disease expression. Emerging treatments include selective retinoids (trifarotene), PPAR modulators, interleukin-targeting biologics, probiotics, bacteriophages, and hormonal therapies with improved safety profiles. Microbiome modulation and narrow-spectrum antibiotics are gaining attention for precision management. Integrating molecular insights with clinical practice fosters a personalized, multidisciplinary approach to acne care. Future research should prioritize microbiome restoration, novel biologics, and strategies to minimize antimicrobial resistance.

IMAJ 2025; 27: 424–428

KEY WORDS: acne pathogenesis, anti-inflammatory therapy, precision dermatology, skin microbiome, targeted therapy

Acne vulgaris is a multifactorial, chronic inflammatory disorder of the pilosebaceous unit, affecting approximately 85% of adolescents and young adults. While long considered a hallmark of puberty, recent epidemiological data highlight its increasing prevalence among adults, particularly women, due to hormonal, lifestyle, and environmental factors [1]. Clinically, acne presents with a range of lesions including comedones, papules, pustules, and nodules, which may lead to permanent scarring when inadequately treated.

Beyond its dermatological manifestations, acne carries a significant psychosocial burden. Studies consistently report associations between acne and depression, anxiety, and social withdrawal, emphasizing the condition's impact on mental health and overall quality of life [2].

The pathogenesis of acne involves a dynamic interplay between increased sebum production, follicular hyperkeratinization, microbial colonization (primarily *Cutibacterium acnes*), and inflammation. These processes are influenced by genetic predisposition, hormonal fluctuations, and environmental triggers such as diet, stress, and air pollution [3,4].

Recent advancements in molecular biology, immunology, and microbiome research have refined the understanding of these mechanisms, opening new avenues for targeted therapy. In this review I synthesized current insights into acne pathophysiology and evaluated emerging treatments that offer promise for more personalized and effective management strategies.

PATHOPHYSIOLOGICAL UPDATES

Molecular mechanisms

Recent discoveries have deepened the understanding of innate immune dysregulation in acne. Toll-like receptors (TLR-2 and TLR-4), expressed on keratinocytes and sebocytes, recognize *C. acnes* components and trigger

downstream activation of the NF-κB and MAPK pathways. This process leads to the release of key pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-8, contributing to early lesion development [5,6].

Furthermore, activation of the NLRP3 inflammasome complex by *C. acnes* enhances the maturation of IL-1β and IL-18, amplifying inflammatory responses and promoting comedogenesis [7].

SEBOCYTE REGULATION VIA PPAR-Γ PATHWAYS

Sebocyte function is increasingly understood to be regulated by peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ. Dysregulation of PPAR-γ contributes to increased sebum production and inflammatory cytokine secretion, suggesting it plays a critical role in acne pathogenesis. PPAR-γ not only regulates sebocyte differentiation and lipid synthesis but also modulates inflammatory responses, making it a potential therapeutic target for acne and other sebaceous gland disorders [8].

Recent molecular discoveries in acne pathogenesis, including toll-like receptors signaling, inflammasome activation, sebocyte biology, and microbiome shifts, are reshaping therapeutic approaches toward precision dermatology.

SEBOCYTE MODULATION VIA CANNABIDIOL

Cannabidiol, a non-psychoactive cannabinoid, has demonstrated promising anti-acne effects by modulating sebocyte activity. Studies have shown that cannabidiol can normalize excessive lipid synthesis induced by pro-acne agents and significantly reduce sebocyte proliferation. In addition, cannabidiol exhibits potent anti-inflammatory properties, suppressing the expression of key cytokines such as TNF-α, IL-1β, and IL-6 in sebocytes. These effects suggest that cannabidiol offers a multifaceted approach to acne management by targeting both sebum production and inflammation [9,10].

Other molecular players include antimicrobial peptides such as LL-37 and β-defensins, which modulate local immune responses and microbial balance. Aberrant expression of these peptides has been implicated in acne lesion persistence [11].

MICROBIOME CONSIDERATIONS

Advances in metagenomic sequencing reveal that acne is not simply associated with bacterial overgrowth but rather with a shift in *C. acnes* strain composition. Pathogenic IA1 phylotypes are enriched in severe acne, whereas non-pathogenic II and III phylotypes are dominant in healthy skin [12].

Skin dysbiosis, characterized by reduced microbial diversity, disrupts homeostasis and enhances inflammation. Beneficial species such as *Staphylococcus epidermidis* produce antimicrobial substances (e.g., succinic acid) that inhibit pathogenic *C. acnes* strains [13]. Strategies aimed at restoring microbial balance rather than eradicating bacteria entirely represent a promising therapeutic frontier.

GENETIC AND ENVIRONMENTAL FACTORS

Genetic susceptibility to acne involves polymorphisms in key genes regulating androgen signaling (e.g., androgen receptor [AR] gene), innate immunity (e.g., TLR2, NLRP3), and inflammatory mediators (e.g., TNF, IL1A) [14]. Genome-wide association studies have identified several loci associated with acne risk, supporting the concept of an inherited predisposition.

Environmental factors such as high-glycemic diets, dairy consumption, psychosocial stress, and urban air pol-

Table 1. Summary of emerging acne therapies

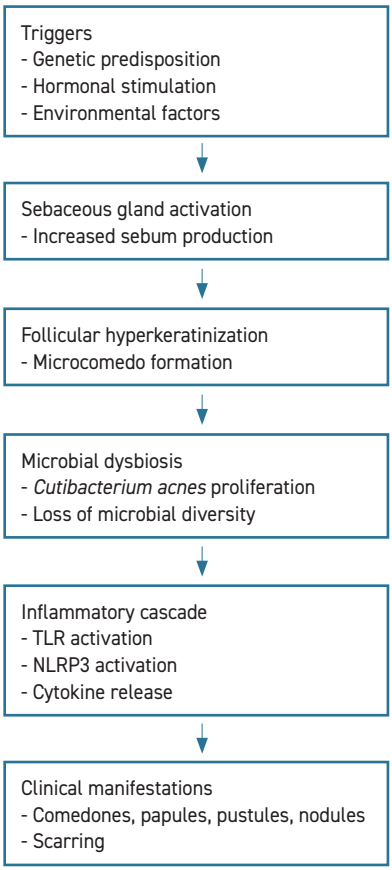
Treatment	Mechanism of action	Development stage
Trifarotene	Selective RAR-γ agonist; enhances keratinocyte differentiation	Approved (topical)
PPAR Modulators	Regulates sebocyte activity; reduces sebum and inflammation	Phase II trials
Biologics (IL-17/IL-23 inhibitors)	Targets specific pro-inflammatory cytokines	Investigational
JAK inhibitors	Inhibits cytokine signaling pathways (JAK-STAT)	Early trials
Topical probiotics	Restores skin microbiome balance; reduces inflammation	Pilot studies
Bacteriophage therapy	Targets and lyses pathogenic *Cutibacterium acnes* strains	Preclinical development
Clascoterone	Blocks androgen receptors in sebocytes; reduces sebum production	Approved (topical)
Sarecycline	Narrow-spectrum antibiotic with anti-inflammatory properties	Approved (oral)

JAK = Janus kinase, PPAR = peroxisome proliferator-activated receptors, RAR-γ = retinoic acid receptor gamma

lution exacerbate acne through mechanisms that include insulin-like growth factor-1 (IGF-1) stimulation, sebocyte activation, and inflammatory cytokine induction [15,16] [Figure 1].

Figure 1. Schematic representation of the main pathogenic factors involved in acne vulgaris: sebaceous gland hyperactivity, follicular hyperkeratinization, microbial dysbiosis, and inflammation

NLRP3 = NOD-like receptor family pyrin domain containing 3, TLR = toll-like receptors



EMERGING THERAPEUTICS

TARGETED MOLECULAR THERAPIES

The development of more selective and tolerable molecular agents marks a major advance in acne management. Trifarotene, a novel fourth-generation retinoid, demonstrates high specificity for retinoic acid receptor gamma (RAR-γ), predominantly expressed in the skin. Clinical trials showed trifarotene's efficacy in both facial and truncal acne with an improved tolerability profile compared to earlier retinoids [17].

PPAR modulators are investigated for their ability to regulate sebocyte differentiation and sebum production. Early-phase studies indicate that selective PPAR-γ agonists may reduce seborrhea and inflammation without the side effects associated with systemic retinoids [18].

Biologics targeting key inflammatory cytokines (IL-17, IL-23, IL-1β) represent a theoretical therapeutic approach for severe acne based on shared inflammatory pathways with other skin diseases. Preliminary evidence suggests IL-17 pathway activation in acne lesions, although large-scale clinical trials specifically for acne are still needed [19].

To the best of my knowledge, there is no published research suggesting that Janus kinase (JAK) inhibitors have a therapeutic role in treating acne. However, multiple studies have identified acne as a common adverse effect associated with JAK inhibitor therapy, particularly in dermatologic conditions such as atopic dermatitis. A systematic review and meta-analysis published in *JAMA Dermatology* found that patients treated with JAK inhibitors had a 3.83-fold higher risk of developing acne compared to those receiving placebo, with a notably higher risk associated with abrocitinib and upadacitinib [20].

Recent evidence has indicated that JAK inhibitors are associated with acne development as an adverse effect rather than offering therapeutic benefit. The JAK-STAT pathway may contribute to inflammatory responses in acne, but this finding has not translated into therapeutic applications.

Further research is necessary to explore any potential therapeutic roles of JAK inhibitors in acne management [21].

MICROBIOME-BASED INTERVENTIONS

Recognition of the skin microbiome's complexity has spurred interest in probiotic and bacteriophage therapies. Topical probiotics, such as *Lactobacillus plantarum* and *Bifidobacterium breve*, may enhance barrier function, competitively inhibit pathogenic *C. acnes*, and modulate local inflammation [22].

Bacteriophage therapy that selectively lyses pathogenic *C. acnes* strains is in preclinical development as a targeted alternative to traditional antibiotics with the potential to reduce the development of resistant bacterial strains [23].

Microbiome transplantation, although still experimental, aims to restore skin microbial balance by applying healthy skin-derived microbiota to lesional sites, similar to approaches used in gut microbiome therapy.

HORMONAL AND SYSTEMIC APPROACHES

Hormonal therapies remain a cornerstone for patients with hormonally driven acne, particularly women. Combined oral contraceptives and selective androgen receptor inhibitors such as clascoterone cream have demonstrated efficacy by reducing sebaceous gland activity [24].

Isotretinoin, the gold standard for severe acne, continues to evolve with modified low-dose regimens designed to maintain efficacy while minimizing adverse effects [25].

Sarecycline, a narrow-spectrum tetracycline derivative, offers antibacterial and anti-inflammatory effects with a reduced risk of antimicrobial resistance and fewer gastrointestinal side effects compared to traditional tetracyclines [26].

Emerging targeted therapies such as selective retinoids (trifarotene), peroxisome proliferator-activated receptors modulators, IL-targeted biologics, and microbiome interventions offer promising alternatives to traditional acne treatments, emphasizing efficacy with improved safety profiles.

CONCLUSION AND FUTURE DIRECTIONS

Acne vulgaris remains one of the most common dermatological disorders, exerting a significant burden not only on skin health but also on psychological and social well-being. Although substantial advances have been made in understanding its complex pathogenesis, many therapeutic challenges persist. Current treatments often fail to achieve complete disease control, especially in cases of severe, nodulocystic, or recalcitrant acne. Relapses after treatment discontinuation remain a frequent issue, underscoring the need for more durable and preventive strategies.

The recent elucidation of molecular mechanisms, including the role of TLR signaling, inflammasome activation, sebocyte biology, and the microbiome, has opened promising new avenues for targeted interventions. Emerging therapies such as selective retinoids, PPAR modulators, IL-targeted biologics, and microbiome-based interventions represent a shift toward precision dermatology. Nevertheless, these innovations are still in various stages of development, and long-term safety, cost-effectiveness, and accessibility require further validation, particularly for adolescent and young adult populations who are most affected by acne.

Future research directions should prioritize several key areas. These areas include the refinement of microbiome modulation strategies, such as the use of engineered probiotics and bacteriophage therapy, the development of biologics that selectively target pathogenic inflammatory pathways while preserving host immunity, and exploration of gene-environment interactions that predispose individuals to severe or persistent disease. Advances in pharmacogenomics and skin microbiome profiling may soon enable truly personalized acne therapies tailored to individual biological signatures.

Ultimately, integrating molecular insights with holistic, patient-centered care holds the potential to transform acne management. Future therapies should aim to clear visible lesions and to also modify the underlying disease course, reduce the risk of scarring, improve quality of life, and prevent recurrence. Achieving these goals will require multidisciplinary collaboration across dermatology, immunology, microbiology, and precision medicine fields.

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Capsule

Feedback from higher-level visual processing centers in the brain influences the early stages of object recognition.

Visual recognition is thought to start with basic object features in the primary visual cortex, reaching the level of object representation at higher cortical areas after processing. However, there is increasing evidence for top-down influences in these pathways. **Altavin**i and colleagues took recordings from electrode arrays in several rhesus monkey cortical areas during a delayed match-to-sample task that measured the effect of cued objects on neuronal responses to a range of objects. Top-down influences were involved in object recognition at several visual pathway stages. Many neurons changed their selectivity with different cues even at the earliest processing stages. This indicates that internal representations of object identity are continually being fed back to all cortical areas in the ventral visual stream.

Proc Natl Acad Sci U S A 2025; 122 (13): e2406684122.
Eitan Israeli

Capsule

Systemic inflammation impairs myelopoiesis and interferon type I responses in humans

Keramati and co-authors leveraged a controlled, human in vivo model of lipopolysaccharide (LPS)-induced systemic inflammation encompassing both phases. Single-cell RNA sequencing during the acute hyperinflammatory phase identified an inflammatory *CD163+SLC39A8+CALR+* monocyte-like subset (infMono) at 4 hours post-LPS administration. The late immunosuppressive phase was characterized by diminished expression of type I interferon (IFN)-responsive genes in monocytes and impaired myelopoiesis. It also included a pronounced attenuation of the immune response on a secondary LPS challenge 1 week after the first. The infMono gene program and impaired myelopoiesis were also detected in patient cohorts with bacterial sepsis and coronavirus disease. IFNβ treatment restored type-I IFN responses and proinflammatory cytokine production and induced monocyte maturation, suggesting a potential treatment option for immunosuppression.

Nature Immunol 2025; 26: 737
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