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Research Progress on Chronic Low-Grade Inflammation and Acne

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Abstract: *This study was designed to elucidate the pivotal role and potential mechanisms of chronic low-grade inflammation in acne pathogenesis, thereby offering new perspectives for clinical management.A comprehensive review of recent literature on acne and inflammation was conducted, with emphasis on the involvement and interplay of inflammatory cytokines, immune signaling pathways, sebaceous gland function, and cutaneous microecological imbalance.Patients with acne frequently exhibit elevated circulating and local levels of key pro-inflammatory mediators, including interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP). These alterations form a pathological network in which localized skin lesions and systemic inflammatory responses mutually reinforce one another, thereby promoting disease persistence and progression. Chronic low-grade inflammation is a central driver throughout the entire course of acne, contributing to its chronicity and therapeutic resistance. Related inflammatory and metabolic biomarkers hold promise as auxiliary indicators for clinical diagnosis, disease stratification, and therapeutic efficacy evaluation.*

Keywords: *Acne; Low-Grade Inflammation; Inflammatory Cytokines; Inflammasomes; Sebaceous Glands*

1. Introduction

Acne is a chronic inflammatory disorder involving the pilosebaceous unit, affecting more than 85% of adolescents and young adults globally [1-2]. Clinically, it is characterized by comedones, papules, pustules, and nodules, and in severe cases may lead to permanent scarring, impacting both physical appearance and psychological well-being. Traditional views of acne pathogenesis have emphasized local factors such as excessive sebum production, abnormal follicular keratinization, and colonization by Cutibacterium acnes (formerly Propionibacterium acnes) [3]. However, emerging evidence suggests that the inflammatory response in acne extends beyond the local skin environment and involves a systemic component characterized by chronic low-grade inflammation [4].

CLI refers to a persistent, subclinical inflammatory state marked by mildly elevated levels of inflammatory mediators in the absence of overt infection or acute symptoms. This state is implicated in the progression of various chronic conditions, including metabolic syndrome, cardiovascular diseases, and autoimmune disorders. Clinical studies have identified elevated levels of systemic inflammatory markers in the serum and skin of acne patients, often associated with metabolic disturbances and immune dysregulation. These findings suggest that CLI may serve as a critical pathophysiological link between local acne lesions and systemic responses [5].

This review aims to systematically summarize the clinical evidence and molecular mechanisms of CLI in acne, highlighting its role as a central driver in the disease process and offering a theoretical basis for the development of precision diagnostic and therapeutic strategies.

2. Definition and Evaluation of Low-Grade Inflammation

Inflammatory cytokines play a central role in immunological processes, functioning as pivotal mediators that regulate and propagate inflammatory responses, and are primarily secreted by activated immune cells within the host. Low-grade inflammation represents a pathological state in which the

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immune system is in a persistently mild state of activation, characterized by the continuous presence of inflammatory mediators in the circulation and peripheral tissues without overt clinical manifestations of acute inflammation. This distinct inflammatory phenotype is maintained by low yet sustained levels of pro-inflammatory cytokines and acute-phase reactants, and is now recognized as both a triggering and sustaining factor in the pathogenesis and progression of a broad spectrum of chronic diseases.

In clinical practice, commonly employed biomarkers for the assessment of low-grade inflammation include interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), high-sensitivity C-reactive protein (hs-CRP), and interleukin-8 (IL-8). In addition, hematological indices such as the neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) have gained traction as indirect yet reliable parameters for estimating inflammatory activity. Collectively, these biomarkers provide a quantitative framework for evaluating subclinical immune activation and guiding individualized therapeutic strategies.

In the context of acne research, aberrant elevation of these inflammatory biomarkers reflects not only localized cutaneous inflammation but also the presence of systemic immune activation. Unlike acute inflammation, chronic low-grade inflammation occurs at a comparatively lower intensity; however, its protracted duration is sufficient to induce cellular dysfunction and pathological alterations within affected tissues. This persistent, subclinical inflammatory milieu constitutes a fundamental pathological substrate driving the chronicity and progression of acne [5].

3. Clinical Evidence of Low-Grade Inflammation in Acne

Low-grade inflammation is typically characterized by a chronic, subclinical inflammatory response, marked by the persistent elevation of inflammatory cytokines such as IL-1β, IL-8, and TNF-α in both tissues and serum. While these responses do not give rise to obvious clinical manifestations of acute inflammation, they can substantially alter the follicular microenvironment, facilitating the occurrence of abnormal keratinization and sebaceous gland dysfunction—two key hallmarks in the initial stage of acne lesion development [6].

It has been demonstrated that Cutibacterium acnes (C. acnes) can trigger these responses by activating toll-like receptor 2 (TLR2), the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, and the nuclear factor kappa B (NF-κB) signaling pathway, thereby inducing the release of pro-inflammatory mediators. Clinically, these early inflammatory processes can be detected even during the subclinical phase—prior to the formation of visible lesions—often termed the "incipient inflammatory phase" of acne [7].

Furthermore, factors including diet, metabolic status, and skin microbiota dysbiosis contribute to the onset and recurrence of acne through systemic low-grade inflammation. For example, diets with a high glycemic index and dairy consumption are known to increase the levels of insulin-like growth factor-1 (IGF-1), which in turn upregulates sebum production and exacerbates inflammatory responses. Variations among different strains of C. acnes also lead to differences in inflammatory responses between individuals, as these strains vary significantly in their metabolic activity and immunomodulatory potential.

4. Inflammatory Mechanisms in Acne

Inflammation stands as a pivotal element in the pathogenesis of acne. Conventionally, it was regarded as a downstream event that ensues after increased sebum production, abnormal follicular keratinization, and the overgrowth of C. acnes. Nevertheless, a growing body of evidence accumulated over the past decade indicates that inflammation may precede the appearance of visible lesions, playing a role throughout the entire course of the disease. This early-stage inflammation, which often occurs at subclinical levels, has emerged as a critical focus in acne research [8-10].

4.1 Innate Immunity and Inflammasome Activation

C. acnes is recognized as a key trigger of the inflammatory response in acne. Its cell wall components, such as lipoteichoic acid and other lipoglycans, are detected by host pattern recognition receptors, particularly Toll-like receptors TLR2 and TLR4, leading to the activation of nuclear factor-kappa B (NF-κB) signaling and the transcription of inflammatory cytokines [11]. Additionally, C. acnes can penetrate keratinocytes and monocytes, where it stimulates the activation of the NLRP3 inflammasome. This

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results in the cleavage of pro-IL-1β into its active form, IL-1β, thereby initiating a robust local inflammatory cascade [12].

Studies have shown that inflammatory cytokines such as IL-1β, IL-6, and TNF-α are already upregulated in the perilesional skin of early acne, even in the absence of visible redness or papules [13]. As a key inflammatory mediator, IL - 1 β not only participates in the amplification of inflammation, but also promotes the formation of acne by regulating the differentiation and keratinization of keratinocytes.

4.2 Adaptive Immunity and the Th17/IL-17 Axis

In addition to dysregulation of the innate immune system, acne-associated inflammation is intricately linked to maladaptive responses of the adaptive immune compartment. In recent years, substantial evidence has highlighted the pivotal role of T helper 17 (Th17) lymphocytes and their signature cytokine interleukin-17 (IL-17) in acne pathophysiology [14]. IL-17 orchestrates potent pro-inflammatory effects by recruiting and activating neutrophils, thereby augmenting their capacity to generate reactive oxygen species (ROS) and release proteolytic enzymes, which collectively exacerbate local tissue damage [15].

C. acnes contributes to this process by stimulating dendritic cells to secrete interleukin-23 (IL-23), a key cytokine driving Th17 cell differentiation and expansion. Once activated, the Th17/IL-17 axis engages in synergistic crosstalk with other inflammatory mediators, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), propagating an amplified inflammatory cascade [16]. Notably, clinical and experimental observations reveal that imbalance in the Th1/Th17 immune response correlates positively with acne severity, underscoring the therapeutic potential of immunomodulatory strategies targeting the Th17/IL-17 pathway as a next-generation intervention for acne [17].

4.3 Sebaceous Gland Inflammatory Response

Beyond functioning as the principal site for lipid biosynthesis and holocrine secretion, the sebaceous gland is increasingly recognized as a dynamic immunoendocrine organ that actively shapes cutaneous immune responses. Sebocytes possess innate immune sensing machinery, notably Toll-like receptor 2 (TLR2), enabling the detection of *C. acnes* and the rapid induction of a pro-inflammatory cascade marked by the secretion of cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) [18]. Perturbations in the qualitative profile of sebum—exemplified by a decline in linoleic acid and a relative enrichment of saturated fatty acids—undermine epidermal barrier integrity, thereby amplifying the activation of keratinocytes and resident as well as infiltrating immune cell populations [19].

In particular, free fatty acids, including oleic acid and stearic acid, exert direct pro-inflammatory effects on keratinocytes, driving the production of inflammatory mediators and potentiating aberrant keratinization within the follicular infundibulum [20]. These biochemical and immunological perturbations form a critical nexus linking sebaceous gland activity to the initiation and propagation of acne-associated inflammation.

4.4 Interaction between Oxidative Stress and Inflammation

Elevated oxidative stress is a well-recognized biochemical signature in the lesional and perilesional skin of patients with acne. Excessive accumulation of reactive oxygen species (ROS) compromises keratinocyte plasma membrane integrity, facilitates lipid peroxidation processes—most notably the generation of malondialdehyde (MDA)—and triggers the activation of redox-sensitive signaling cascades, including the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, thereby intensifying local and systemic inflammatory responses [21].

Beyond direct cytotoxicity, ROS exert pathogen-modulatory effects by altering the metabolic state and biofilm dynamics of *C. acnes*, leading to enhanced secretion of pro-inflammatory mediators [22]. This dual mechanism not only sustains a chronic low-grade inflammatory milieu but also exacerbates follicular keratinization abnormalities through oxidative modification of epidermal and sebaceous components. Clinical evidence demonstrating that antioxidants—such as vitamin C, vitamin E, and N-acetylcysteine—attenuate inflammatory severity when used as adjunctive interventions further substantiates the concept of a reciprocal, self-reinforcing axis between oxidative stress and inflammation in acne pathophysiology.

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4.5 Dysbiosis of Skin Microbiota and Inflammation

The composition of the healthy skin microbiome is predominantly characterized by Cutibacterium acnes, Staphylococcus epidermidis, and Malassezia species. Within this microbial consortium, certain non-pathogenic strains—particularly specific subtypes of C. acnes—play a pivotal role in preserving cutaneous immune homeostasis. They achieve this by exerting competitive inhibition against the proliferation of pathogenic microorganisms and by secreting bioactive metabolites, such as short-chain fatty acids, which possess antimicrobial and immunomodulatory properties [23].

Conversely, disruption of the microbial equilibrium can facilitate the overgrowth of distinct "pro-inflammatory" C. acnes lineages, such as the IA1 phylotype, which intensify inflammatory processes through the release of virulence factors, including peptide-based toxins and lipolytic enzymes [24]. Empirical evidence indicates that individuals with acne vulgaris exhibit a markedly reduced microbial diversity on the skin surface, accompanied by a disproportionate enrichment of these inflammatory C. acnes strains. This microbial dysbiosis is increasingly recognized as a potential key contributor to the initiation and perpetuation of chronic low-grade inflammation [25].

4.6 Hyperkeratosis and Inflammation Mutually Promote Each Other

Aberrant follicular keratinization and inflammation are intricately interconnected, engaging in a bidirectional pathogenic crosstalk that fuels a self-sustaining vicious cycle in acne development. Under the influence of inflammatory mediators, keratinocytes undergo phenotypic alterations characterized by the upregulated expression of hyperproliferation-associated keratins, notably keratin 6 (K6) and keratin 16 (K16), which culminates in the formation of keratinous plugs that obstruct the follicular infundibulum [26]. Such physical blockage establishes a hypoxic, lipid-rich microenvironment within the follicular unit, which is highly conducive to the overgrowth of *C. acnes*. The ensuing bacterial proliferation triggers Toll-like receptor (TLR)-mediated immune activation, further intensifying local inflammatory cascades and amplifying keratinization abnormalities, thus perpetuating the cycle.

Among the inflammatory mediators implicated, interleukin-1 alpha (IL-1α) has emerged as a pivotal regulator of keratinocyte behavior in acne lesions. In vitro evidence indicates that IL-1α directly stimulates abnormal keratinocyte hyperproliferation and accelerates keratin plug formation, representing a critical molecular driver in the early morphogenesis of microcomedones [27]. This IL-1α–keratinization axis not only bridges innate immune activation with structural follicular alterations but also provides a plausible mechanistic link between chronic low-grade inflammation and comedogenesis.

5. Chronic low-grade Inflammation and Acne Related Serum Markers

Low-grade inflammation plays a central and indispensable role in the onset, progression, and persistence of acne vulgaris. This inflammatory state arises from multifaceted and bidirectional interactions between the immune system and metabolic pathways, giving rise to a complex inflammatory network that extends from localized cutaneous lesions to systemic physiological responses. Mounting evidence has redefined acne from being merely a sebaceous gland dysfunction to a complex immunopathological disorder characterized by the intricate cross-regulation of innate immunity, adaptive immune responses, and metabolic signaling cascades.

In recent years, a growing body of clinical evidence has demonstrated that multiple inflammatory mediators are consistently elevated in both the serum and cutaneous tissues of acne patients, underscoring the widespread presence of systemic low-grade inflammation. For instance, Li Shanshan *et al.* reported that circulating levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were significantly elevated in the peripheral blood of acne patients and showed a positive correlation with the severity of skin lesions[28]. Particularly noteworthy is interleukin-8 (IL-8), which is markedly upregulated in pustular acne, where it acts as a potent chemotactic factor, promoting the recruitment and aggregation of neutrophils to inflammatory sites, thereby amplifying local tissue damage and inflammatory burden.

From a mechanistic perspective, TNF-α, a prototypical pro-inflammatory cytokine, serves as a critical driver of persistent acne inflammation by activating the nuclear factor κB (NF-κB) signaling pathway, thereby inducing downstream inflammatory mediator release. Moreover, TNF-α acts synergistically with interleukin-1β (IL-1β) to contribute to aberrant follicular keratinization and sebaceous gland dysregulation. High-sensitivity C-reactive protein (hs-CRP), an established biomarker of systemic low-grade inflammation, has been found to be significantly elevated in patients with moderate-to-severe acne,

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making it a valuable serum indicator for assessing inflammatory activity.

In addition to these inflammatory mediators, metabolic factors—particularly insulin-like growth factor-1 (IGF-1)—are frequently elevated in acne patients. IGF-1 exacerbates acne pathology by potentiating androgen receptor signaling, stimulating lipid biosynthesis, and activating key intracellular pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK). These effects collectively promote sebaceous gland hyperplasia and excessive lipid accumulation, while also establishing a close association with insulin resistance and hyperinsulinemia [29].

Taken together, these inflammatory and metabolic serum biomarkers not only illuminate the underlying mechanisms of low-grade inflammation in acne but also provide potential molecular targets and objective parameters for clinical phenotyping, prognostic assessment, and personalized therapeutic strategies.

6. Conclusion

The pathogenesis of acne is no longer viewed solely as a localized disorder of sebaceous gland hyperactivity or aberrant follicular keratinization; rather, it is increasingly recognized as being tightly interwoven with a persistent state of chronic low-grade inflammation. This inflammatory milieu is sustained through the activation of multiple, intersecting signaling pathways, including innate immune responses, adaptive immune modulation, sebaceous gland reactivity, and oxidative stress, thereby establishing a self-perpetuating inflammatory network. Such a network not only exacerbates cutaneous lesions but may also predispose to systemic immune dysregulation and metabolic disturbances.

Clinically, elevated levels of inflammatory and metabolic biomarkers—such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), high-sensitivity C-reactive protein (hs-CRP), and insulin-like growth factor-1 (IGF-1)—provide objective evidence of inflammatory activity in acne, underscoring their potential utility in disease stratification and personalized therapeutic decision-making. Future treatment paradigms for acne should thus extend beyond localized antimicrobial and sebum-suppressive strategies, with greater emphasis on identifying and modulating the underlying low-grade inflammatory state. Such an approach could facilitate the transition from symptom-focused control toward mechanism-targeted intervention, thereby advancing the quality and durability of clinical remission.

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