Current Concepts in Acne Pathogenesis: Pathways to Inflammation

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Abstract

Acne is a disease of pilosebaceous inflammation. Pivotal in pathogenesis are the roles of hormones (insulin, insulin-like growth factor-1, androgens), *Propionibacterium acnes*, lipogenesis, and a proinflammatory lipid profile. Innate immune responses are induced through interaction with toll-like receptors and inflammasome activation initially and subsequently through adaptive immune activation. These insights into pathogenic inflammatory pathways can translate into novel therapeutic approaches for acne.
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Keywords

Acne; caspase-1; inflammasome; nitric oxide; *P acnes* phylotypes; pathophysiology; toll-like receptor

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Acne pathogenesis is characterized by hyperproliferation and abnormal differentiation of the follicular epithelium; excess sebum production; inflammation; and proliferation and biofilm formation of *Propionibacterium acnes*.[1,2] Inflammation is present in all acne lesions, including preclinical microcomedones.[3,4] Immunohistochemical studies show higher levels of CD4 cells, macrophages, and interleukin (IL)-1–alpha in uninvolved skin of patients with acne compared with skin of those without acne. These findings suggest that inflammation precedes hyperproliferation in the development of acne.[4] "Noninflammatory acne" is thus a misnomer; it appears that all primary acne lesions are inflammatory.

Although serum androgens have been viewed as the major hormonal trigger in acne during puberty, recent evidence suggests a pivotal role for insulin-like growth factor (IGF)-1. Individuals congenitally deficient in IGF-1 due to Laron syndrome do not develop acne, for example. However, high-dose IGF-1 replacement therapy leads to acne and hyperandrogenism.[5]

Multiple mechanisms of IGF-1 may promote the development of acne. IGF-1 has been shown to: (1) induce androgen synthesis and increase the cutaneous availability of dihydrotestosterone; (2) disinhibit the forkhead box O1 (FoxO1) transcription factor, which normally suppresses the androgen receptor; and (3) activate peroxisome proliferator-activated receptor–gamma, liver X receptor–alpha, and sterol regulatory element binding protein-1c (SREBP-1c). The latter actions increase sebum triglycerides and fatty acid desaturation, leading to a proinflammatory and comedogenic monosaturated fatty acid profile.[6] Increased sebum production also leads to increased levels of squalene. Squalene monohydroperoxide is comedogenic and results from ultraviolet A–triggered photooxidation of squalene in sebum.[7]

Compelling evidence on the roles of hyperglycemic carbohydrates (high glycemic index), dairy products, and saturated fats in promoting acne has been reported.[6] Refined carbohydrates and dairy products lead to disinhibition of FoxO1 and activation of the mechanistic target of rapamycin complex 1 (mTORC1) through escalation of insulin and IGF-1 levels. Saturated fats directly activate mTORC1. The effect of the latter is stimulation of SREBP-1c, which is central to sebaceous lipogenesis, sebum fatty acid production, and monosaturation.[2,6]

Diet-mediated changes in sebum quantity and composition promote *P acnes* overgrowth and biofilm formation. *P acnes* produces triglyceride lipase, which increases levels of free palmitic and oleic acids. Palmitic acid, along with *P acnes*–derived damage-associated molecular patterns, stimulates toll-like receptor 2 (TLR2), thereby triggering inflammasome activation and IL-1–beta signaling. Oleic acid stimulates *P acnes* adhesion, keratinocyte proliferation, and IL-1–alpha release.[8-10] Furthermore, oleic acid can induce formation of comedones (**Figure**).[6,11,12]

P acnes acts on the innate immune system through multiple proinflammatory pathways.[3,13] It activates TLR2 on monocytes, leading to the release of proinflammatory cytokines IL-12 and

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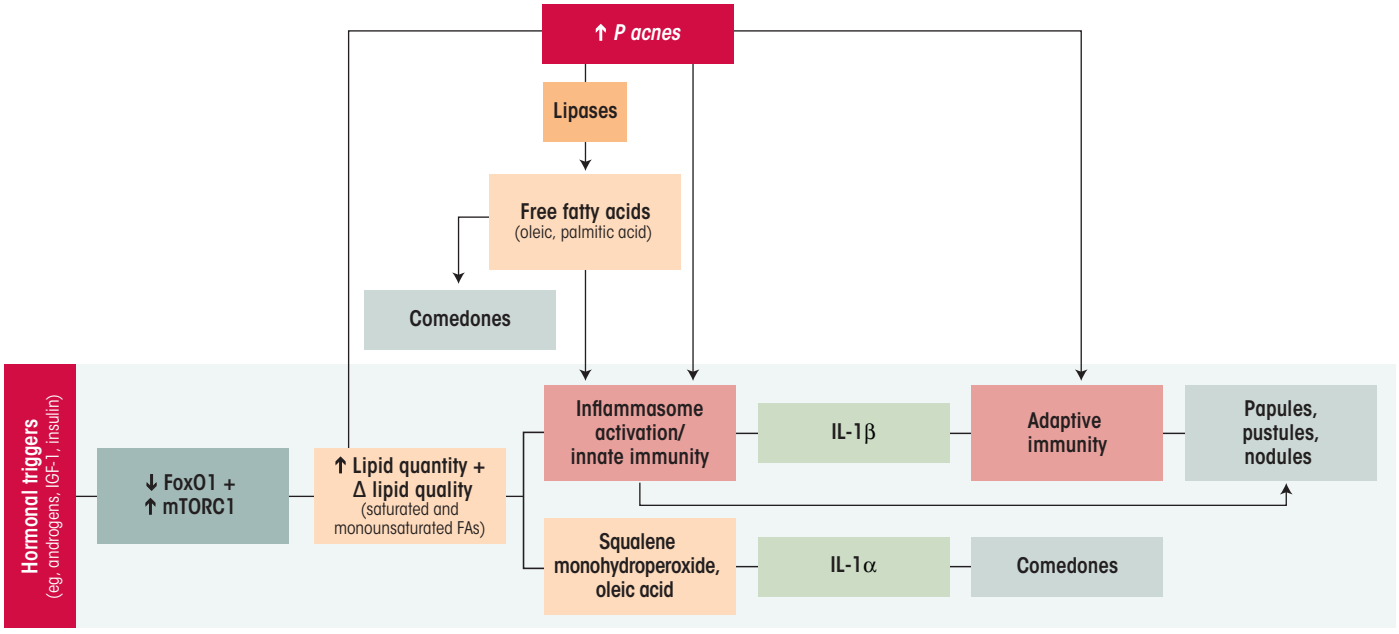

FIGURE Pathways to Inflammation in Acne Pathogenesis

Hormonal initiators in acne include elevated insulin, IGF-1, and androgen levels. These lead to disinhibition of FoxO1 and activation of mTORC1, resulting in increased local pilosebaceous androgenesis, lipogenesis, and increased squalene, fatty acid production, and desaturation. Increased sebum production results in proliferation of *Propionibacterium acnes*, and the attendant lipase catalysis of triglycerides to the free fatty acids palmitic and oleic acid, leading to inflammasome activation. The latter, plus IL-1–beta upregulation and subsequent adaptive immune response activation, leads to development of inflammatory papules, pustules, and nodules. Comedo formation results from the direct effect of squalene monohydroperoxide and oleic acid from lipogenesis (oleic acid) and UVA photooxidation of squalene (monohydroperoxide) or from the degradative effect of *P acnes* lipases on triglycerides (oleic acid).

FAs=fatty acids; FoxO1=forkhead box O1; IGF-1=insulin-like growth factor-1; IL=interleukin; mTORC1=mechanistic target of rapamycin complex 1; UVA=ultraviolet A.

Sources: Melnik BC[6]; Lovászi M, et al.[12]

IL-8.[14] It promotes secretion of the proinflammatory cytokines IL-1–beta and IL-18 through an inflammasome pathway involving caspase-1 and the nucleotide oligomerization domain-like receptor protein (NLRP) 3.[15,16] The inflammasome is a group of intracellular proteins that convert procaspase-1 to caspase-1. Caspase-1 converts the inactive precursor of IL-1–beta to its active form.[17] Additionally, *P acnes* induces monocyte production of matrix metalloproteinases. These enzymes are associated with numerous inflammatory conditions and may play a role in matrix degradation and formation of acne scars.[18,19]

P acnes also stimulates an adaptive immune response, inducing IL-17A and interferon (IFN)-gamma secretion from $CD4^+$ T cells in vitro. Type 17 helper T cells (T_H17) and type 1/type 17 helper T cells (T_H1/T_H17) that react to *P acnes* stimulation are found in the peripheral blood of patients with and without acne, but cells from patients with acne displayed stronger responses to *P acnes*.[20]

P acnes influences the development of acne in ways beyond promoting inflammation. *P acnes* biofilm formation has been detected in the sebaceous follicles of patients with acne. Biofilm formation leads to increased *P acnes* virulence, manifested in part by the increased expression of *P acnes* triglyceride lipase, which increases the sebum concentration of palmitic and oleic acids. These changes in sebum lipid composition contribute to inducing inflammatory acne. As noted, oleic acid increases *P acnes* adherence and growth. Therefore, *P acnes* triglyceride lipase may indirectly contribute to biofilm formation by promoting increased concentration of oleic acid.[8]

P acnes is not always pathogenic, however. The organism is present in both healthy and acne-affected skin, and all *P acnes* strains do not exert the same effects. Immune system responses to *P acnes* rather than microbial density may influence progression to disease. Some *P acnes* phylotypes are associated with healthy skin rather than with skin affected by acne; others are more likely found in skin affected by acne than in healthy skin.[21] Acne-associated *P acnes* phylotypes have been shown to induce higher levels of IFN-gamma and IL-17 in peripheral blood mononuclear cells than those associated with healthy skin. In recent studies, phylotypes associated with healthy skin induced higher levels of IL-10, an anti-inflammatory cytokine.[22,23] Future studies might determine whether *P acnes* strains associated with healthy skin can reduce T_H1 or T_H17 inflammation.[23]

These current pathogenic concepts suggest new targets for therapy, including FoxO1, mTORC1, TLR2, the NLRP3 inflammasome, caspase-1, and IL-1–beta.[14,15] Consumption of foods that increase FoxO1 or inhibit mTORC1 and inflammasome activation should alleviate acne. A paleolithic diet—ie, eliminating hyperglycemic carbohydrates and dairy products—and consumption of vegetables, berries, sea fish, and green tea may be a nutritional therapy for acne.[6]

Treatments eradicating *P acnes* may leave a microbiome vacuum that could be repopulated by *P acnes* strains promoting anti-inflammatory profiles. Sebum production and altered proinflammatory lipid content represent additional targets for acne therapies. An analysis of clinical trials found that sebum reduction

is associated with acne improvement.[24] Acetyl coenzyme A carboxylase (ACC) catalyzes the rate-limiting step in synthesis of fatty acids that become components of sebaceous lipids.[25] IGF-1 and androgens upregulate expression of a transcription factor that promotes ACC expression.[26] Investigational acne therapies include a topical antiandrogen medication and a topical inhibitor of ACC (see **Advances in Acne and Rosacea Therapy**, page S63).

Another potential intervention involves nitric oxide. Nitric-oxide–releasing nanoparticles (NO-np) have been shown to suppress IL-1–beta, tumor necrosis factor–alpha, and IL-8 release from human monocytes, and IL-8 and IL-6 release from human keratinocytes. NO-np reduce IL-1–beta secretion in part by inhibition of caspase-1. NO-np also kill *P acnes* in vitro.[27] A nitric-oxide–releasing macromolecule formulated in an alcoholic gel is under study for the treatment of acne.[28] (For more information, see **Advances in Acne and Rosacea Therapy**, page S63.) Current therapies address some elements of pathogenic pathways. Azelaic acid 15% gel; an oral contraceptive (drospirenone 3 mg/ethinyl estradiol 20 µg); the topical retinoids adapalene, tazarotene, and tretinoin; and oral isotretinoin have each been associated with reduced expression of TLR2.[29-34] Azelaic acid has demonstrated anti-inflammatory action in vitro by inhibiting the generation of reactive oxygen species.[35]

Summary

Inflammation plays a central role in acne pathogenesis and insulin. IGF-1 and androgens are prime orchestrators, with initiation likely due to consumption of dairy foods and a high glycemic index diet. The hormones lead to increased sebum production and a more inflammatory composition of sebaceous lipids. These changes promote *P acnes* overgrowth and inflammation through multiple pathways, triggering both innate and adaptive immune activation (**Figure**). TLR2, caspase-1, the inflammasome, IL-1–beta, and mediators of sebum production offer possible therapeutic targets in acne. All *P acnes* phylotypes do not act in the same way; some have been associated with healthy skin, rather than acne, and have anti-inflammatory effects. Beneficial *P acnes* phylotypes may lend themselves to future therapies.

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