Editorial

Inflammatory Acne: New Developments in Pathogenesis and Treatment

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Acne vulgaris is a chronic inflammatory disease that affects the majority of the population at some point in their lifetime. It is characterized by comedones, pustules, and papules. Acne pathogenesis is multifactorial with 4 primary factors that play a pivotal role in the formation of acne lesions: excess sebum production, abnormal keratinization, inflammation, and bacterial colonization of *Propionibacterium acnes* in the pilosebaceous unit.[1] Although there is a general consensus on the pathogenic factors, the sequence of events in acne development is controversial. Traditionally it was believed that abnormal keratinization resulted in the creation of the microcomedone, the earliest subclinical acne lesion.[2] Activation of sebaceous glands by androgens, excess sebum production, and keratin plug formation then were followed by *P acnes* colonization, with induction of the innate immune system culminating in inflammation.[2] Androgen-induced sebum production and follicular hyperkeratinization and plugging have been cited as initial events that alter the pilosebaceous milieu, favoring the proliferation of *P acnes*[1,3]; however, evidence suggests inflammation as the inciting factor, with proof of significant inflammatory factors surrounding the pilosebaceous unit even in clinically uninvolved skin units in acne patients.[4] Herein we will briefly review the most recent data and translational applications pertaining to the *P acnes*–triggered innate immune response via activation of toll-like receptor 2 (TLR2)[5] and importantly the inflammasome.[6,7]

A new understanding of how *P acnes* induces the inflammatory cascade may represent a paradigm shift in the management of acne. Recognition of microbes, namely *P acnes*, by the innate immune system is the body's first line of defense against pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[6] Although these pathways combat infection and prevent foreign invasion, they also result in inflammation and tissue injury. The inflammatory response to PAMPs and DAMPs is mediated by the inflammasome, a caspase 1–activating cytoplasmic complex that induces the secretion of crucial proinflammatory cytokines.[7] The exact mechanism by which *P acnes* exerts its proinflammatory activity has been somewhat unclear, though *P acnes*–induced inflammation has been shown to be mediated by proinflammatory cytokines tumor necrosis factor α, IL-1, IL-6, IL-8, and IL-12.[5,8] However, remarkable evidence recently was presented regarding triggers of inflammation and the precise mechanism involved. Qin et al[9] showed that *P acnes* is a potent trigger of IL-1β generation via activation of the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome. Specifically, the study showed that human monocytes respond to *P acnes* by upregulating caspase 1, an inflammatory caspase required for proteolytic cleavage of IL-1β. The authors correlated their in vitro findings with clinical evidence of caspase 1 and NLRP3 expression in the dermis surrounding the pilosebaceous units of biopsied lesions.[9] Kistowska et al[6] confirmed and expanded on these data by showing the inability of NLRP3-deficient myeloid cells to secrete IL-1β and induce an inflammatory response in vivo. A recent investigation demonstrated that human sebocytes can function as constituents of the innate immune response, with *P acnes* triggering sebocyte NLRP3-inflammasome activation and subsequent IL-1β secretion. These observations were further confirmed in vivo with NLRP3-deficient mice displaying an impaired inflammatory response to *P acnes*.[10]

Our understanding of TLR2 signaling in the pathogenesis of acne also has expanded. It is well established that recognition of extracellular PAMPs and DAMPs is mediated by the expression of toll-like receptors on the surface of a variety of cells within

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the skin.[11] Prior research demonstrated how *P acnes* increases TLR2 expression in keratinocytes, even in vivo.[12] Stimulation by *P acnes* was shown to induce secretion of IL-8 (promoting a T_H1 response) and IL-12 (promoting neutrophil chemotaxis) via TLR2 activation.[5] Selway et al[11] validated this finding by demonstrating that infundibular keratinocytes secrete IL-1α in response to the peptidoglycan cell wall of *P acnes*. Interestingly, Qin et al[9] determined TLR2 inhibition resulted in partial suppression of IL-1β, possibly providing new evidence of TLR2-mediated activation of the NLRP3 inflammasome. Therefore, *P acnes* activates both extracellular and intracellular triggers of the innate immune response: TLR2 activation (requiring extracellular recognition of pathogens) and inflammasome-mediated activation (requiring internalization and access of the bacterium to the interior compartments of the cells).

Overall, these findings suggest that *P acnes*–induced inflammation can be selectively targeted by agents directed at inflammasome components, IL-1β, or toll-like receptors. A phase 2 double-blind, placebo-controlled trial assessing the efficacy of the anti–IL-1β monoclonal antibody gevokizumab found that 0.6 mg/kg administered subcutaneously resulted in a significant reduction in mean inflammatory lesion count compared to placebo ($P=.077$).[13] The success of the IL-1 receptor antagonist anakinra against rare genetic autoinflammatory syndromes such as PAPA (pyogenic sterile arthritis, pyoderma gangrenosum, and acne) syndrome, an NLRP3 inflammasomopathy, sheds light onto new therapeutics that may be used to target acne vulgaris.[14] Current topical therapies such as retinoids, which have already proven efficacious in the treatment of inflammatory acne, target these pathways. In vivo data revealed that treatment with isotretinoin significantly decreased TLR2 expression in monocytes ($P<.001$) and suppressed inflammatory cytokine responses to *P acnes* ($P<.001$).[15] Adapalene, with or without benzoyl peroxide, also was shown to exert anti-inflammatory effects via TLR2 downregulation.[16]

These data and observations highlight a paradigm shift in our perception of acne. All acne is truly inflammatory, and by identifying aberrations in the immune response, we can develop targeted treatments for this chronic debilitating disease.

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