The Role of Inflammation in Acne Vulgaris

Multiple lines of evidence support a pivotal role for inflammation in the pathogenesis of acne vulgaris.

BY M. JOYCE RICO, MD

nflammation has long been recognized as important in the pathogenesis of acne; however, until recently it was considered a secondary event. Studies over the past decade have demonstrated a central role for inflammation in the development of acne lesions and have opened new opportunities for therapeutic intervention.[1,2,3] Understanding the role of inflammation in the development of acne vulgaris is important for dermatologists, as it may impact our treatment choices and identify additional targets for new treatment modalities. This review will provide a brief overview of some of the scientific literature regarding inflammation in acne. It will also review some recent auto-inflammatory acne syndromes that support the role of inflammation in acne pathogenesis, as well as discuss treatments currently available and in development with anti-inflammatory properties.

INFLAMMATORY MEDIATORS IN ACNE

Acne vulgaris is associated with excess sebum production, colonization of the follicular infundibula with *Propionibacterium acnes* (*P. acnes*), hyperkeratinization, and production of inflammatory mediators. The microcomedone, which arises secondary to ductal keratinocyte proliferation with occlusion of the infundibulum and subsequent retention of sebum, has been postulated to be the primary lesion in acne. Some studies of normal skin in acne-prone patients and early acne lesions suggest that inflammation may precede microcomedone formation and may serve as a trigger for the hyperkeratinization that leads to follicular occlusion. Figure 1 (next page) depicts some of the known major proinflammatory pathways identified in acne vulgaris.

Jeremy, et al. performed immunohistochemistry on biopsies of clinically normal follicles from uninvolved skin in patients with and without acne and demonstrated cellular, vascular, and proliferative markers of inflammation prior to microcomedone formation.[4] In these studies, skin biopsies demonstrated an increase in perifollicular and papillary dermal CD3+, CD4+ T cells, the proinflammatory cytokine IL-1, and the vascular markers VCAM and E-selectin. IL-1ß stimulates keratinocyte proliferation, which may lead to plugging of the follicular ostia and microcomedone formation. VCAM and E-selectin expression are important ligands for tethering and migration of inflammatory cells from the circulation to the dermis and are important in regulating lymphocyte trafficking in the skin.

Thiboutot and colleagues analyzed skin biopsies taken from inflammatory papules and normal skin of patients with inflammatory acne and demonstrated marked up-regulation of genes involved in inflammation and matrix repair in the inflammatory papules.[5] By gene array expression profiling, the greatest increases were in: matrix metalloproteases (MMP) 1 and 3; the cytokine IL-8; and the anti-microbial peptides (AMP) human ß-defensin 4 (hBD) and granzyme B. Quantitative PCR and immunohistochemistry confirmed increased expression of mRNA and proteins respectively for the identified genes, confirming increased protein expression. While both of the AMPs hBD 4 and granzyme B dem-
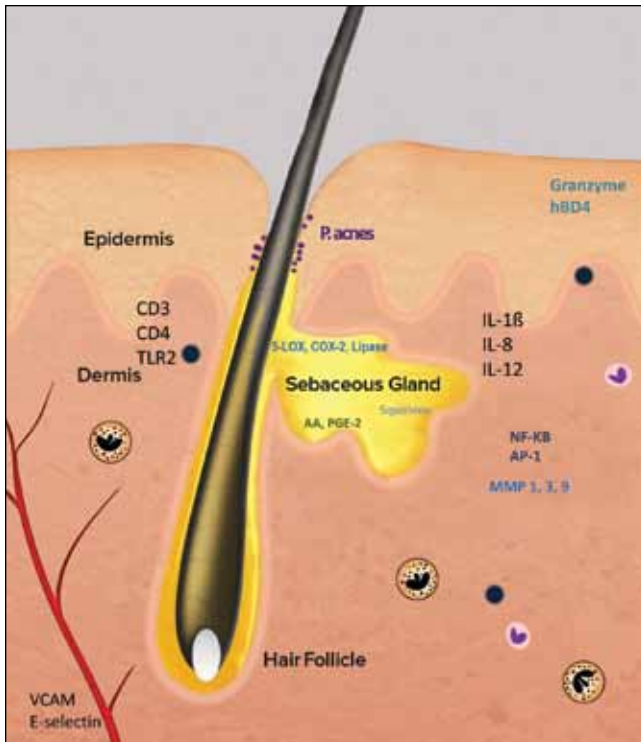
Figure 1. Inflammatory Mediators in Acne Vulgaris
In acne, pro-inflammatory transcription factors (NK-KB, AP-1), cytokines (IL-1ß, IL-8, IL-12), antimicrobial peptides (granzyme B, human beta-defensin 4), and MMPs are upregulated. Enzymes (5-LOX, COX-2, and lipase) and lipid breakdown products (squalene, arachidonic acid, prostaglandin E-2) are increased in sebum and the sebaceous gland. There is an increase in TLR-2, CD-3, CD-4 + T cells and expression of VCAM and E-selectin on endothelial cells.

onstrate activity against *P. acnes* and suppress *P. acnes*-stimulated cytokine release, hBD has pro-inflammatory properties. This up-regulated AMP has chemotactic effects, induces proinflammatory chemokines and cytokines, and stimulates keratinocyte migration and proliferation.[6] Il-8 is a proinflammatory cytokine associated with polymorphonuclear leukocyte (PMN) recruitment that also stimulates keratinocyte proliferation. MMPs are involved in normal tissue repair and are highly upregulated in many inflammatory states, including acne. As MMPs selectively cleave collagen, the increase in MMPs in acne is believed to be a factor in acne scarring.

Kang, et al. identified activation of transcription factors nuclear factor -κB (NF- kB), and activator protein-1 (AP-1) and their down-stream target gene products, the proinflammatory cytokines (TNFα, IL-1ß, IL-8, and IL-10) and MMPs, in skin biopsies from patients with acne

vulgaris.[7] NF- kB is upregulated after T cell activation and translocated to the nucleus, which leads to proinflammatory cytokine transcription. The transcription factor AP1 induces transcription of mRNA for MMPs, particularly MMP1, 3, and 9 which have specificity for dermal collagens. These authors demonstrated collagen degradation in the dermis in skin biopsies from subjects with acne, consistent with the increase in MMPs.[8]

There is a complex interrelationship between *P. acnes*, sebaceous lipogenesis, and inflammation.[9] *P. acnes*, a Gram positive anaerobe that resides in the follicular infundibulum, enhances sebaceous lipogenesis, ensuring a lipid rich environment in which the bacteria can flourish. Squalene, a major component of sebum, can be oxidized in the presence of UV light or the oxidative environment associated with inflammation. Peroxidated squalene has been demonstrated to induce production of inflammatory mediators in cultured keratinocytes.[10] These inflammatory mediators induce keratinocyte proliferation, which may contribute to follicular occlusion and enhanced sebum retention. Other proinflammatory lipid by-products (ararchidonic acid [AA], prostaglandin E2 [PGE2]), and enzymes that produce inflammatory mediators (lipase, 5-lipoxygenase [5-LOX], cyclo-oxygenase-2 [COX-2]) are also increased in sebum and the sebaceous gland in patients with acne vulgaris. These lipid by-products and inflammatory mediators metabolized from AA help to perpetuate the inflammatory cascade in acne.

In addition to influencing sebum production, *P. acnes* has a direct role in inflammation, inducing production of several proinflammatory signals, via a Toll-like receptor (TLR2) regulated pathway. Toll-like receptors are a class of surface markers that selectively bind microbial pathogens and activate the transcription factor NF- kB. In acne, TLR-2 is expressed on keratinocytes and monocytes in the perifollicular macrophages of inflammatory acne.[11] *P. acnes* binding of TLR-2 leads to increased production of IL-12 and IL-8. In summary, the tightly regulated cascade of inflammation, hyperkeratinization, *P. acnes* proliferation, and sebum production appear to be closely intertwined.

CLINICAL SYNDROMES WITH ACNE
Several rare auto-inflammatory diseases include acne as a clinical manifestation and serve as a model for the role of inflammation in the pathogenesis of this disease. PAPA syndrome, a rare autosomal dominant disease, includes the triad of pyogenic sterile arthritis, pyoderma gangrenosum (PG), and acne and shares features with the aseptic abscesses syndrome. PAPA syndrome is due to a defect in PSTPIP1, which encodes proline-serine- threonine- phosphatase interactive protein 1 gene. PSTPIP1 binds to pyrin, the pro-

tein linked to familial Mediterranean fever. PSTPIP and pyrin regulate the NLRP3 inflammasome and caspase-1 mediated signaling pathway inflammation. Braun-Falco, et al. have identified a related syndrome with PG, acne, and suppurative hidradenitis (PASH) that shares some components of the follicular occlusion triad.[12] A similar aseptic abscess condition, SAPHO Syndrome, has predominately bone manifestations with Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis as key clinical features.[13] While the treatment of these aseptic abscess syndromes remains challenging, some patients with PAPA, PASH, and SAPHO have demonstrated a clinical response to anti-inflammatory agents, such as methotrexate, leflunomide, or drugs that target TNF or IL-1ß (anakinra), underscoring the critical role of inflammation in these conditions. Further characterization of the aberrant proteins, receptors, and signaling molecules involved in the pathogenesis of these inflammatory syndromes is likely to further our understanding of the role of inflammation in acne vulgaris.[14]

ANTI-INFLAMMATORY APPROACHES TO ACNE

Several agents commonly prescribed to treat acne vulgaris have known effects on one or more components of the inflammatory pathways reviewed above. While the exact mechanism of action for some of our therapeutic armamentaria remains unknown, studies *in vitro* and *in vivo* have identified anti-inflammatory activity of retinoids, dapsone, antibiotics and other treatments prescribed by dermatologists to control the signs and symptoms of acne vulgaris. Several drugs in development have demonstrated anti-inflammatory activity *in vitro*, and novel anti-inflammatory mechanisms are being explored for additional development opportunities.

Retinoids are traditionally viewed as keratolytics, promoting keratinocyte differentiation and turn-over to prevent follicular occlusion. Modlin and co-workers demonstrated that all-trans retinoic acid down-regulates TLR2 expression and function as well as the TLR2 co-receptor CD14.[15] *In vitro* studies have also demonstrated retinoid inhibition of arachidonic acid induced ear swelling in mice and inhibition of peritoneal macrophage lipoxygenase activity.[2]

Antibiotics, used both topically and systemically in the treatment of acne, have both anti-microbial and anti-inflammatory properties. In addition to direct anti-microbial activity targeting *P. acnes*, clindamycin has multiple activities on macrophages and leukocytes including: inhibiting cytokine release from bacterially stimulated macrophages, modulating the stimulated production of reactive oxygen species by macrophages, and potentiating the activity of phagocytic leukocytes.[16,17] Clindamycin has also been shown to decrease lipase production, thereby decreasing proinflammatory free fatty acids in the sebum. Clindamycin and tetracy-

clines inhibit the release of neutrophil chemotactic factor from neutrophils exposed to *P. acnes* and production of IL-1ß. Inhibition of neutrophil chemotactic factor decreases inflammatory cell migration into early acne lesions, while a decrease in IL-1 ß would decrease keratinocyte proliferation and hyperkeratinization.

Dapsone is administered systemically to treat a wide range of inflammatory dermatologic diseases and is particularly prescribed in conditions characterized by a PMN predominant infiltrate such dermatitis herpetiformis, bullous systemic lupus erythematosus, and Sweet's syndrome. Sweet's syndrome, which is also known as acute febrile neutrophilic dermatosis, shares some features with the auto-inflammatory family of disorders described above. Topical dapsone gel has been approved for the treatment of acne vulgaris. *In vitro*, a wide range of anti-inflammatory affects have been associated with dapsone including inhibition of: IL-8 release from cultured keratinocytes; leukocyte migration via inhibition of integrins; signal transduction after G-protein activation; calcium-dependent neutrophil function; release of prostaglandins, leukotrienes, and lysosomal acid hyrolases; and formation of 5 lipoxygenase metabolites.[18] In a randomized study of tazarotene cream alone or in combination with dapsone gel, the addition of topical dapsone resulted in greater efficacy than monotherapy, suggesting that the addition of an anti-inflammatory agent to a retinoid-based regimen provided clinical benefit to patients with acne.[19]

Dermatologists have also used anti-inflammatory agents not approved for the treatment of acne vulgaris in select circumstances to help control acne when our usual treatment options have been unsuccessful. Examples of such treatments include the addition of dapsone, methylprednisolone, and non-steroidal anti-inflammatory agents (NSAIDs) to treatment regimens.[20] In a four-arm, randomized study in 60 subjects with acne vulgaris, concomitant administration of oral ibuprofen and tetracycline was more effective than either agent alone.[21]

Another agent with reported anti-inflammatory activity is zinc, which has been used both topically and orally to treat acne vulgaris.[22] A combination erythromycin-zinc topical solution is approved for treatment of acne vulgaris in Europe and other ex-US countries.

DRUGS IN DEVELOPMENT

There are several novel agents in development for acne vulgaris that target inflammation as a major component of their mechanism of action. Agents in early development with a mechanism of action that targets the inflammatory pathway include: Topical epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea; NVN1000, a nitric oxide-

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releasing compound; and gevokizumab, a systemically administered monoclonal antibody that targets IL-1ß.

SUMMARY

Multiple lines of evidence support a pivotal role for inflammation in the pathogenesis of acne vulgaris. Many currently available acne treatments have demonstrated anti-inflammatory activity, although it is difficult to separate the anti-inflammatory effects from other actions of these agents. A greater understanding of the inflammatory pathways relevant in acne may identify targets for additional treatment options. ■

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1. Stein Gold LF, What's new in acne and inflammation, J Drugs Dermatol. 2013; 12(6):s67-s69.

2. Weiss JS, Messages from molecules: deciphering the code, J Drugs Dermatol. 2013; 12(6):s70-s72.

3. Bellew S, Thiboutot D, Del Rosso JQ, Pathogenesis of acne vulgaris: what's new, what's interesting and what may be clinically relevant, J Drugs Dermatol. 2011;10 (6):582-585.

4. Jeremy AHT, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion Initiation, J Invest Dermatol. 2003;121:20-27.

5. Trivedi NR, Gilliland KL, Zhao W, Liu W, Thiboutot D. Gene Array Expression Profiling in Acne Lesions Reveals Marked Upregulation of Genes Involved in Inflammation and Matrix Remodeling, J Invest Dermatol. 2006; 126:1071-1079.

6. Harder J, Tsuruta D, Murakami M, Kurokawa I. What is the role of antimicrobial peptides (AMP) in acne vulgaris? Experimental Dermatology 2013; 22:386-391.

7. Kang S, Cho S, Ho J, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and Extracellular Matrix Degradation Mediated by Activated Transcription Factors Nuclear Factor-κB and Activator Protein-1 in Inflammatory Acne Lesions in Vivo. Am J Pathol. 2005;166:1691-1699.

8. Kang S, Cho S, Ho J, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and Extracellular Matrix Degradation Mediated by Activated Transcription Factors Nuclear Factor-κB and Activator Protein-1 in Inflammatory Acne Lesions in Vivo. Am J Pathol. 2005;166:1691-1699.

9. Zouboulis C. Propionibacterium acnes and Sebaceous Lipogenesis: A Love-Hate Relationship? J Invest Dermatol. 2009; 129:2093-2096.

10. Ottaviani M, Alestas T, Flori E, Mastorfrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris? J Invest Dermatol. 2006; 126: 2430-2437.

11. Kim J, Ochoa MT, Krutzik SR, Takeuchi O, Uematsu S, Legaspi AJ, Brighbill HD, Holand D, Cunliffe WJ, Akira S, Sieling PA, Godowski PJ, Modin RL. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol. 2002; 169 (3): 1535-41.

12. Braun-Falco M, Kovnerystyy O., Lohse P, Ruzicka T, Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)—a new auto inflammatory syndrome distinct from PAPA syndrome, J Am Acad Dermatol. 2012; 66: 409-15.

13. Nguyen MT, Borchers A, Selmi C, Naguwa SM, Cheema G, Gershwin ME. The SAPHO syndrome. Semin Arthis Rheum 2012; 42 (3): 254-65.

14. Chen W, Obermayer-Pietsch B, Hong JB, Melnik BC, Yamasaki O, Dessinioti C, Ju Q, Liakou AI, Al-Khuzaei S, Katsambas A, Ring J, Xouboulis CC, Acne-associated syndromes: models for better understanding of acne pathogenesis, J Eur Acad Dermatol Venereol. 2011; 25: 637-646.

15. Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: all-trans retinoic acid down-regulates TLR2 expression and function. J Immunol 2005; 174 (5): 2467-70.

16. Lyte P, Sur R, Nigam A, Southall MD. Heat killed Propionibacterium acnes is capable of inducing inflammatory responses in skin. Exp Derm 2009; 18: 1070-1072.

17. Del Ross JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. Cutis. 2010; 85: 15-24.

18. Kircik L. Harnessing the anti-inflammatory effects of topical dapsone for management of acne. J Drugs Dermatol. 2010; 9(6): 667-671.

19. Tanghetti E, Dhawan S, Green L, Ling M, Downie J, Germain MA, Kasteler JS, Kireik L, Oefelein MG, Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. J Drugs Dermatol. 2011; 10 (7): 783-792.

20. Kaminsky A. Less common methods to treat acne. Dermatology. 2003; 206(1): 68-73.

21. Wong RC, Kang S, Heezen JL, Voorhees JJ, Ellis CN. Oral ibuprofen and tetracycline for the treatment of acne vulgaris. J Am Acad Dermatol. 1984; 11 (6); 1076-81.

22. Brandt S. J Drugs Dermatol. 2013; 12(5): 542-545.