The Role of Inflammation in the Pathology of Acne

EMIL A. TANGHETTI, MD

Center for Dermatology and Laser Surgery, Sacramento, California

ABSTRACT

The conventional perspective of acne pathogenesis holds that *Propionibacterium acnes* colonizes the duct of the sebaceous follicle, causing an innate immune response and the progression from a so-called noninflammatory comedo to an inflammatory papule, pustule, or nodule. However, this viewpoint has come under increasing scrutiny over the last decade, as evidence has emerged supporting a role for inflammation at all stages of acne lesion development, perhaps subclinically even before comedo formation. The immunochemical pathways underlying the initiation and propagation of the inflammation in acne are complex and still being elucidated, but may involve *Propionibacterium acnes* as well as several inflammatory mediators and their target receptors, including cytokines, defensins, peptidases, sebum lipids, and neuropeptides. This review presents evidence to support the notion that acne is primarily an inflammatory disease, challenging the current nomenclature of noninflammatory versus inflammatory acne lesions and suggesting that the nomenclature is outdated and incorrect. The evidence in support of acne as an inflammatory disease also has clinical implications, in that anti-inflammatory drugs used to treat the disease can be expected to exert effects against all lesion stages, albeit via distinct mechanisms of anti-inflammation. (*J Clin Aesthet Dermatol.* 2013;6(9):27–35.)

Acne vulgaris affects almost 80 percent of adolescents and young adults, often persists well into adulthood, and can result in scarring and hyperpigmentation.[1,2] Acne lesions develop in the sebaceous follicles (the pilosebaceous unit), which are found on the cheek, forehead, chin, and back of both affected and unaffected individuals. A combination of increased sebum production and abnormal hyperproliferation of keratinocytes results in the formation of a small microscopic lesion called a microcomedo. Subsequent accumulation of sebum, enlargement of the follicle, and build-up of keratinous material within the microcomedo cause the formation of comedones.[1] The conventional perspective of acne pathogenesis holds that *Propionibacterium acnes*, which is present on normal skin, colonizes the duct of the sebaceous follicle, causing an innate immune response and the progression from a so-called noninflammatory comedo to an inflammatory papule, pustule, or nodule.[1] However, this viewpoint has come under increasing scrutiny over the last decade, as several lines of evidence have emerged suggesting that inflammation may exist throughout the lifecycle of the acne lesion, perhaps subclinically even before comedo formation. This evidence challenges the current nomenclature of noninflammatory versus inflammatory acne lesions and suggests that the nomenclature is both outdated and incorrect.

The purpose of this article is to review the current understanding of acne pathology, with a focus on the role of inflammation. Histological, immunological, and clinical evidence of the existence of subclinical inflammation during or even before comedogenesis is reviewed and applied to a reconsideration of acne lesion classification.

INFLAMMATION OCCURS IN EARLY AND LATE-STAGE ACNE LESIONS

There has been little debate about the involvement of inflammation in the later stages of acne, manifested as clinically inflamed papules and pustules. Accumulating histological and immunological evidence, but increasingly also evidence derived from a clinical platform, supports the

TABLE 1. Summary of evidence for early inflammatory events during acne lesion development

INCREASED EXPRESSION AND BIOACTIVITY OF PROINFLAMMATORY MEDIATORS

- Upregulation of inflammatory mediators in uninvolved skin and early lesions[3,4]
  - E-selectin
  - Vascular adhesion molecule-1
  - Interleukin-1
  - Integrin
- Interleukin-1α bioactivity in open comedones[5]
- Upregulation of defensin-2 immunoreactivity[6,7]
- Elevation of CD3+ and CD4+ T cells and macrophages in uninvolved skin[3]

PEPTIDASES

- Expression of proinflammatory peptidases on sebocytes and keratinocytes[8]
- Inhibition of peptidase activity leads to an anti-inflammatory profile[8,9]

NEUROPEPTIDES

- Upregulation of neuropeptides in uninvolved skin[10,11]
  - Corticotropin-releasing hormone
  - Melanocortin-1 receptor
  - Substance P

TOLL-LIKE RECEPTORS

- Activation by *Propionibacterium acnes* triggers inflammatory cytokine responses[12,13]
  - *P. acnes* is present in sebaceous follicles undergoing comedogenesis and may play a role in comedo formation[14,15]
- Activation by endogenous ligands?[16]

CHANGES IN LIPID BIOSYNTHESIS

- Confirmed association between sebaceous lipid synthesis and inflammation[17,18]
- Peroxidated lipids trigger inflammatory responses[19]

CLINICAL TRIALS

- The anti-inflammatory dapsone is effective in treatment of "noninflammatory" lesions[20,21]
  - Dapsone has multiple anti-inflammatory properties[22–25]
- Retinoids are effective in treating "noninflammatory" lesions[26]
  - Retinoids downregulate toll-like receptor-2 and interleukin-10 expression[27,28]

notion of inflammation as a fundamental process in the early development of acne lesions (Table 1).[3–28]

Indeed, the concept that inflammation plays a role only in the late stages of acne vulgaris has been challenged repeatedly by emerging data, which are reshaping our understanding of acne pathology. Evidence for an early inflammatory response in the formation of acne lesions was provided by Norris and Cunliffe,[29] who conducted a histological examination of early acne lesions, including lesions 6 to 72 hours old. The biopsied lesions had a morphology characteristic of small papules with minimal erythematous flare, and 52 percent were classified as microcomedones. One of the earliest histological changes identified was the appearance of a lymphoid perivascular infiltrate. Accumulation of polymorphonuclear leukocytes occurred in later stages, causing distension and pustule formation. Ultimately, this distension, accompanied by

ongoing spongiosis, led to rupture of the lesion. This demonstration that inflammatory foci develop in early, apparently noninflamed, microcomedonal lesions before overt spongiosis or rupture of the pilosebaceous follicle wall, provides compelling evidence for the involvement of early inflammatory events in the development of acne lesions.[29]

Consistent with these findings, relatively recent studies have suggested that inflammatory events may also occur very early in the development of acne lesions (microcomedones), even before the initial hyperproliferative changes.[3,4] In these studies, the uninvolved skin from acne patients was found to contain elevated levels of CD3+ and CD4+ T cells in the perifollicular and papillary dermis and increased macrophage numbers similar to those seen in papules.[3,30] An example of the histological evidence for the presence of

inflammatory cells in early acne is shown in Figure 1.[31]

Clinical evidence for inflammation during early acne development is derived from an investigation by Do et al,[32] who conducted a serial photographic study of 25 acne patients. Patients were photographed every two weeks, and the digital photographs were spatially aligned and analyzed for acne lesions. A total of 3,099 lesions were counted, including closed comedones (37%), open comedones (12%), erythematous papules (26%), inflammatory papules (15%), pustules (2%), and nodules (1%). Of these 3,099 lesions, 219 (176 inflammatory papules, 35 pustules, 8 nodules) were not present at baseline and their origin was tracked. Notably, although 72 percent of these lesions were preceded by another acne lesion type or scar, 28 percent were preceded by normal-appearing skin. Thus, comedones were not detected at 28 percent of lesion sites before the appearance of the inflammatory lesions. These data support a model of acne pathogenesis in which the initiation of inflammatory events occurs early in the pathogenic process and before clinical detection of the acne lesion. However, although these studies have documented the occurrence of inflammation at the microcomedo stage and before any hyperproliferative changes, a definitive causal relationship between inflammation and the development of microcomedones from apparently normal skin still remains to be established.

Several comparative clinical trials also support the involvement of inflammation in early acne lesions. These studies investigated the effectiveness of agents with direct or indirect anti-inflammatory properties, including dapsone, retinoids, antibiotics, and benzoyl peroxide, to reduce comedonal lesions.

Dapsone is an anti-inflammatory agent with several potential mechanisms contributing to its clinical efficacy.[33] It inhibits the release of interleukin (IL)–8 from human cultured keratinocytes[25,34] and has been shown to prevent lipid peroxidation[24] and neutrophil recruitment.[22,23] In two vehicle-controlled, 12-week, double-blind, phase 3 acne clinical trials, dapsone significantly reduced both comedonal and clinically inflammatory lesions in patients with facial acne vulgaris.[20]

Topical retinoids, such as adapalene, are also known to have anti-inflammatory properties and are effective in treating patients with early-stage acne lesions.[27,28] Adapalene causes reduced expression of toll-like receptor 2 (TLR2) and IL-10 both in normal skin and in acne explants, while all-trans retinoic acid has been shown to reduce macrophage TLR2 expression.[27,28] In two large placebo-controlled, randomized, 12-week studies, significant reductions in both comedonal and clinically inflammatory lesions were experienced by acne patients treated with adapalene 0.1 percent lotion.[26]

Several studies have evaluated the response of comedonal acne to combination treatment with topical retinoids plus other topical agents having direct or indirect anti-inflammatory properties. In these studies, combination of a retinoid with either dapsone or clindamycin/benzoyl peroxide consistently elicited significantly greater
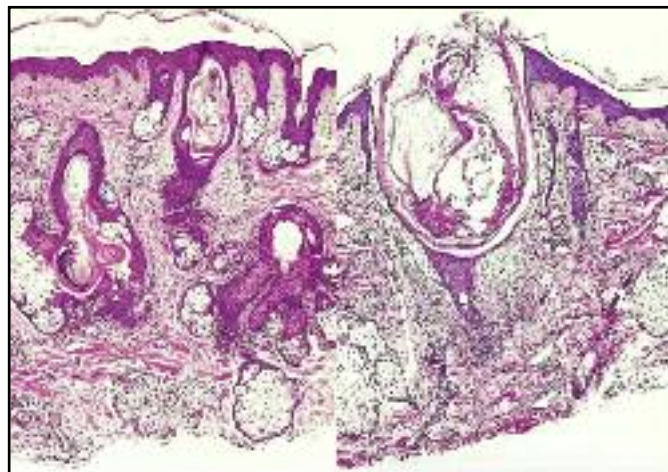

Figure 1. Inflammation in normal facial skin from a patient with acne (left); open comedo (right). Reprinted with permission from: Plewig G, Kligman AM. *Acne and Rosacea*, 3rd ed. New York: Springer-Verlag; 2000.

reductions in comedonal lesion counts than retinoid monotherapy.[21,35,36] Thus, combining a retinoid with a directly anti-inflammatory (dapsone) or indirectly anti-inflammatory (antibacterial) agent can effectively treat comedonal acne. Indeed, concurrent use of an anti-inflammatory or antibacterial agent with a retinoid appears to enhance the efficacy against comedonal acne relative to the use of the retinoid alone.

That inflammation can occur in all stages of acne is now increasingly clear. What has been unclear, however, is the mediators and events that are involved and their causal and temporal relationships. The sections that follow discuss this in more detail.

P. ACNES CAN CONTRIBUTE TO ACNE INFLAMMATION

The role of *P. acnes* in the etiology of inflammatory acne has been recognized for more than a century. Biopsy studies in patients with clinically inflamed acne vulgaris confirmed the association between *P. acnes* and clinically inflammatory acne by demonstrating that Propionibacteria are identifiable in 68 percent of one-day-old acne lesions and 79 percent of three-day-old lesions.[37] Subsequent studies demonstrated that application of *P. acnes* to unaffected areas of skin in patients with acne results in clinical inflammation and pustule development and that injection of *P. acnes* into keratinous cysts causes rupture with accompanying profound inflammation, supporting the role of *P. acnes* as a causative agent of clinically inflammatory acne lesions.[38,39]

From a clinical perspective, the *P. acnes*–inflammation relationship was further supported by studies showing that antimicrobials, such as tetracycline and minocycline, suppress *P. acnes* in patients with moderately severe acne vulgaris, with an associated substantial reduction (up to 50% in one study[40]) in the number of clinically inflammatory

lesions.[40,41] Fulton et al[42] also reported potent bacteriostatic effects of the antimicrobial agent benzoyl peroxide in patients with acne vulgaris. Thus, clinical investigations demonstrated the presence of *P. acnes* in late-stage acne lesions, the propensity for clinical inflammation and pustule development when *P. acnes* was applied to unaffected skin, and the alleviating properties of both topical and oral antimicrobials. Based on such evidence, *P. acnes* was identified as the causative agent of inflammation in acne, with inflammation accompanying *P. acnes* proliferation.

P. acnes and inflammatory mediators. *P. acnes* may trigger an innate immune reaction both in very early (microcomedogenic) and in late (inflammatory) acne lesions via the activation of TLR2. TLRs are a component of the innate immune system involved in host defense against invading micro-organisms,[12,43] and their activation ultimately triggers the expression of immune response genes, including those coding for various cytokines and chemokines that stimulate recruitment of host immune cells.[44]

P. acnes has been shown to trigger proinflammatory cytokine release and expression of antimicrobial peptides. Colonization of *P. acnes* causes activation of monocyte TLR2, resulting in the production of IL-12 and IL-8.[12] IL-12 is the major proinflammatory cytokine produced by monocytes in response to invading gram-positive organisms.[12,43] Through its activation of TLRs, *P. acnes* can also induce human β-defensin-2 (and IL-8) expression in cultured human epidermal keratinocytes.[13] The β-defensins (defensin-1, defensin-2, and defensin-3) are a family of antimicrobial peptides produced in the skin in response to microbial infection; they have been implicated in clinically inflammatory acne lesion formation. The β-defensins have a range of properties, including modification of cell migration and maturation, induction of cytokines, and chemoattraction of immunocompetent cells.[45] In a gene array analysis conducted by Trivedi et al,[46] β-defensin-2 gene expression was enhanced 33-fold in clinically inflammatory acne lesions relative to levels found in the unaffected skin of patients with acne or the skin of individuals without acne. β-defensin-2 protein levels were greater in the epidermis of inflammatory acne lesions than in the epidermis of uninvolved skin. Similarly, Philpott[47] reported relatively low β-defensin-1 protein levels and intense upregulation of β-defensin-2 protein levels in pustules of patients with acne. Interestingly, fatty acids found within sebum may act as endogenous regulators of TLR signalling,[16,45] and thus might influence the effects of *P. acnes* mediated by TLRs, but whether their effects would be proinflammatory or anti-inflammatory is not clear.

A recent study of biopsy samples from patients with acne vulgaris has suggested an alternative link between *P. acnes* and the release of inflammatory mediators.[48] *P. acnes* is known to release various exogenous proteases, which, through the activation of the protease-activated receptor-2 (PAR-2) on keratinocytes, can enhance transcription of proinflammatory cytokines, including IL-1α, IL-8, and tumor necrosis factor-α, as well as various matrix metalloproteinases and LL-37, the only known human member of the cathelicidin group of antimicrobial peptides.[48] Thus, in addition to stimulation of inflammatory processes through activation of TLRs, these data suggest another pathway, that involving PAR-2 activation, possibly linking *P. acnes* to proinflammatory events.[12,48]

Inflammation in the absence of P. acnes. Although several early reports implicated *P. acnes* as the central causative factor in the development of inflammation in acne vulgaris, numerous observations are inconsistent with this notion. Leyden et al[30] found a much higher density of Propionibacteria among patients with acne vulgaris compared with persons without acne, but failed to show an association between *P. acnes* density and severity of inflammation. Indeed, in this study, there was a lower density of *P. acnes* on the foreheads of patients with numerous large papules or pustules with or without nodulocystic lesions, than in individuals with no inflammatory lesions.[30] Similarly, Leeming et al[37] found no significant difference in the proportion of inflamed pilosebaceous units containing *P. acnes* when biopsied after 1 or 3 days of development, again failing to establish an association between *P. acnes* density and the development or progression of inflammatory lesions. Additionally, several independent studies have also shown that comedones are not universally colonized by *P. acnes*, supporting the argument that the micro-organism is not required for comedogenesis.[49–52] Lavker et al[53] studied follicular casts ("incipient or potential comedones") taken from prepuberal children and children aged 9 to 12 years with open and closed comedones. They found no evidence of *P. acnes* colonization, raising the possibility that early events in comedo formation may occur in the absence of *P. acnes*. Given that a substantial proportion of comedones have been found to be sterile,[52] it has been suggested that the micro-organisms found in inflammatory lesions are simply an extension of those already colonizing comedones and that their presence is not required for initiation of inflammation in acne.[54]

Considered collectively, these findings convincingly demonstrate that only a proportion of acne lesions, whether very early or clinically inflamed, contain micro-organisms. Thus, it appears that *P. acnes* is not required for the development of inflammation in acne lesions, regardless of the lesion type. That an inflammatory response can occur in the absence of *P. acnes* suggests that the inflammatory process is being driven via different immunochemical pathways independent of *P. acnes*. In this regard, accumulating evidence supports a significant role for the sebaceous gland in the development of inflammation in acne lesions.

SEBACEOUS GLAND ACTIVITY IS A DRIVER OF INFLAMMATION IN ACNE

Cytokines and inflammation in the pilosebaceous unit. IL-1 plays a central role in regulation of inflammatory and immune responses in general, and several studies have implicated a role for this cytokine in the pathogenesis of

acne vulgaris. IL-1 is produced in and secreted by noninflamed skin, has been implicated in cutaneous homeostasis, and may serve as an initial reservoir for release under conditions of environmental challenge.[55,56] There appears to be production of IL-1α and IL-1β in the sebaceous gland, reflected by the presence of both transcribed IL-1α and IL-1β mRNA and translated IL-1α and IL-1β immunoreactivity.[55,56] Furthermore, cultured normal human keratinocytes maintain a constitutive release of IL-1α, suggesting an ongoing cycle of low-level expression and secretion.[57] There is also evidence that IL-1 expression and secretion is dramatically increased during the early stages of acne lesion development. Bioactive IL-1α-like material has been detected and identified during comedogenesis in up to 76 percent of noninflamed open comedones.[5] Furthermore, in 58 percent of these comedones, the levels of IL-1α-like material exceeded 100pg/mg, a level that surpasses that known to be capable of generating a visible proinflammatory response.[5]

These expression studies of IL-1 are supported by *in vitro* studies showing that proinflammatory cytokines are capable of triggering remodelling of the pilosebaceous unit and promotion of comedogenesis.[58,59] Addition of IL-1α to pilosebaceous units maintained *in vitro* causes hypercornification similar to that seen in the development of comedones, and this effect is antagonized by IL-1 receptor blockade.[58] Notably, addition of two other cytokines—epidermal growth factor or transforming growth factor-α—to these pilosebaceous units causes disorganization of the keratinocytes in the infundibulum, resulting in rupturing similar to that seen in more severe acne. Collectively, these data strongly suggest that inflammatory mediators are both present and capable of promoting comedogenesis within the pilosebaceous unit.[58]

In an effort to understand which inflammatory and matrix remodelling proteins may be involved in inflammatory acne, Trivedi et al[46] biopsied inflammatory lesions from six acne patients and used gene array expression profiling to compare them to biopsies from uninvolved skin of the same patients, as well as with normal skin from six individuals not affected by acne. Within the inflammatory acne lesions, 211 genes were found to be upregulated relative to expression levels found in either uninvolved skin of acne patients or normal skin of individuals not affected by acne. Notably, the majority of these genes coded for proteins involved in matrix remodelling and inflammation. In regard to the latter, IL-8 expression was increased 52-fold. In an immuno-histochemical analysis of these same lesions, the investigators demonstrated the localization of IL-8 protein to the follicular and perifollicular sites of inflammation in the acne lesions, while IL-8 protein expression was "relatively absent" in normal skin. IL-8 is crucial in attracting neutrophils to the site of inflammation in acne vulgaris, the pilosebaceous unit.[12,43] Release of lysosomal enzymes by these neutrophils leads to rupture of the follicular epithelium and further inflammation.[60]

Consistent with these findings, a separate cytokine mRNA analysis of biopsied inflammatory acne lesions revealed that facial acne lesions expressed significantly greater mRNA levels of tumor necrosis factor-α and the interleukins.[61] In particular, levels of IL-8 were 3,000-fold higher in the acne lesions than in adjacent uninvolved skin from acne patients.[59] Levels of IL-10 had a less dramatic 46-fold increase.[61]

Defensins and the sebaceous gland. The defensins have been implicated in early acne lesion formation. There is constitutive β-defensin mRNA and protein expression in the sebaceous glands of healthy skin, where the defensins may play a role in protecting the pilosebaceous unit from microbial invasion.[6] Notably, there is a marked upregulation of β-defensin-1 and β-defensin-2 in most acne vulgaris lesions.[6] β-defensin-1 protein expression, in particular, is markedly elevated in comedones, even more so than in pustules.[6,47] In comedones, β-defensin-1 immunoreactivity was found in the suprabasal layers of lesional and perilesional epithelium, the pilosebaceous duct, sebaceous gland, and hair follicle inner root sheath.[6,47] Given that proinflammatory cytokines can upregulate β-defensins, the observed upregulation of β-defensin-1 in comedones may be a secondary response to perilesional infiltrates.[6,47]

Changes in sebogenesis as a precursor to inflammation. Although seborrhea does not correlate directly with acne lesion development, it does affect lesion inflammatory changes. Synthesis of free fatty acids without bacterial involvement but accompanied by marked IL-1 expression has been observed in cultured sebocytes, leading investigators to suggest that sebocytes might initiate acne lesions by an intrinsic mechanism.[62] Indeed, sebaceous gland lipids can have proinflammatory effects,[63] and some lipids, such as oleic acid or palmitoleate, also have been shown to have antibacterial activity *in vitro* and *in vivo*.[64] The mechanism by which lipids kill bacteria is not known, but as noted previously, may involve lipid-activated TLR-2. These data support the existence of an inducible lipid-based microbicidal effector pathway in the skin.[64] Given the expression of TLRs in the sebaceous glands, and the antimicrobial activity of lipids, it has been postulated that the sebaceous gland plays a prominent role in the innate immune defense of the skin.[64]

Postsynthetic modifications in lipid composition also occur during acne lesion formation, and accumulation of lipid peroxides may be responsible for inflammatory changes in comedones.[63] Lipid peroxides exist at significantly higher concentrations in comedones in patients with acne vulgaris than in healthy skin.[18] Lipid peroxides stimulate the production of proinflammatory cytokines, and activate peroxisome proliferator activated receptors (PPARs).[63] PPARs are nuclear transcription factors that regulate lipid metabolism and inflammation. Specifically, the peroxidation products of squalene, a characteristic human sebaceous lipid, are comedogenic and also possess proinflammatory activity: They can stimulate keratinocyte proliferation and lipo-oxygenase activity, induce PPAR expression, and increase expression and secretion of proinflammatory cytokines.[19] This suggests the direct involvement of squalene
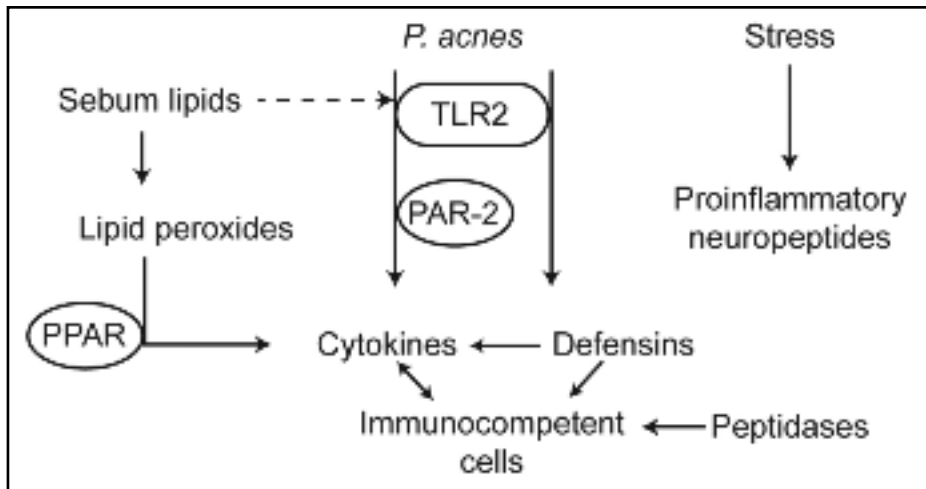
Figure 2. Elucidating the biochemistry of inflammation in early- and late-stage acne lesions.

	FOUND IN ACNE LESIONS	
INFLAMMATORY MEDIATOR	**EARLY-STAGE ACNE LESIONS**	**LATE-STAGE ACNE LESIONS**
Propionibacterium acnes	✓	✓
Cytokines	✓	✓
Defensins	✓	✓
Peptidases	✓	
Neuropeptides	✓	
Immunocompetent cells	✓	✓

TABLE 2. Inflammatory mediators that have been associated with early- and late-stage acne lesions

peroxidation products in the onset of an inflammatory state in early acne lesions.[19] Thus, although increased sebum *per se* has not been found to cause acne,[65] it appears that changes in sebum lipid composition may initiate a previously unsuspected inflammatory cascade early in the development of acne lesions.

Proinflammatory peptidases in the sebaceous gland. Peptidases, such as dipeptidyl peptidase IV (DP-IV) and amino-peptidase N (APN), are ubiquitously expressed enzymes that affect many biological processes, including growth, differentiation, cell-cell interactions, and transformation.[8] The pharmacological inhibition of these enzymes affects growth, cytokine activity, and T-cell function. Both DP-IV and APN are expressed on normal human keratinocytes and are upregulated in hyperproliferative skin disorders.[8] Thielitz et al studied the expression and functional relevance of these enzymes in three cell types that exhibit an altered phenotype in early acne lesions. They found that these peptidases were expressed on human sebocytes and that their pharmacological inhibition suppressed proliferation, differentiation, and cytokine production in sebocytes and keratinocytes, which are involved in the initiation of acne.[8,9] Furthermore, their inhibition also suppressed IL-3 production by *P. acnes*-stimulated T cells *ex vivo* and enhanced the expression of the immunosuppressive cytokine transforming growth factor-β1.[8] These data suggest a functional role for DP-IV and APN in the sebaceous gland apparatus and a proinflammatory role in early acne pathogenesis.[8,9]

Proinflammatory neuropeptides in the sebaceous gland. Changes in the expression of neuropeptides have been identified during the early stages of acne, suggesting a potential neurogenic element to the early stages of lesion development. The expression of corticotropin-releasing hormone (CRH), a hormone involved in the stress response, is higher in the sebocytes of acne-involved skin (regardless of the stage of acne differentiation) than in those of uninvolved skin.[10,11] Melanocortin-1 receptor (MC-1R) expression is also increased in the sebocytes and cells of the ductus seboglandularis, with MC-1R immunoreactivity being higher in skin with acne than in the skin of unaffected individuals.[10,11] Both CRH and MC-1R possess proinflammatory properties.[66,67] Substance P (SP) is also upregulated in the vicinity of sebaceous glands in patients with acne, but is rarely seen in skin samples from those without acne.[68] SP is a potent initiator of neurogenic inflammation and it has been proposed that SP-induced neurogenic inflammation may represent a central process in stress-induced acne.[11]

CHRONIC INFLAMMATION IN ACNE: CLINICAL CONSEQUENCES

Several converging lines of evidence indicate that inflammation may be present throughout the development of acne lesions, both during the latter stages where

inflammatory papules, pustules, and nodules are present, and also during the early stages of lesion development, in microcomedones and comedones. Indeed, many of the same classes of proinflammatory mediators have been implicated in the development of inflammation in both (Table 2, Figure 2). The evidence for inflammation during microcomedogenesis—a proinflammatory role for sebaceous lipids, the upregulation of proinflammatory mediators, early involvement of TLRs and PPARs, and a potential neurogenic component driven by neuropeptide upregulation in what have historically been regarded as noninflammatory lesions—is gaining credibility. Sufficient evidence for inflammation in early lesions now exists to reconsider acne lesion nomenclature. Based on the data presented within this review, it may be argued that classification of early stage lesions as noninflammatory is misleading and incorrect. Early stage lesions have inflammatory properties and are effectively treated with anti-inflammatory drugs. Thus, current lesion classification convention should be reconsidered in light of our expanding understanding of acne pathology.

Consideration of acne as a chronic inflammatory disease also raises important questions regarding acne treatment. Treatment guidelines have traditionally advocated the use of a topical retinoid for the treatment of comedonal acne.[69] Given the findings regarding chronic inflammation in acne, combining a retinoid with an anti-inflammatory that has a nonoverlapping mechanism of action may provide an incremental gain in efficacy.[21]

DISCUSSION AND CONCLUSION

Emerging data indicate that acne vulgaris is a primary inflammatory disease, with histological, immunological, and clinical evidence suggesting that inflammation occurs at all stages of acne lesion development. The immunochemical pathways underlying the initiation and propagation of the inflammation in acne are complex and still being elucidated, but may involve *P. acnes*.[19] However, given that an inflammatory response can also occur in the absence of *P. acnes*, in both early and clinically inflammatory lesions, other pathways of inflammation, in addition to those requiring *P. acnes* for activation or propagation, must exist. These include various inflammatory pathways activated within and around the sebaceous gland, and perhaps other as yet unidentified pathways. Thus, because inflammation is critical to all types of acne lesions and is multifactorial, anti-inflammatory drugs can be expected to exert effects against all lesion stages, albeit via distinct mechanisms of anti-inflammation.

ACKNOWLEDGMENT

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