ABSTRACT

Acne vulgaris is the most common disorder seen in ambulatory dermatology practice. Acne causes significant morbidity and the direct costs associated with it exceed $2.2 billion per year in the United States (U.S.). The pathogenesis is multifactorial, and our understanding of the mechanisms involved in the development of acne lesions has improved with time. Follicular hyperkeratinization, sebum production, presence of Propionibacterium acnes (P. acnes), inflammatory mediators, and androgens have been identified as key components of acne pathophysiology. Recent advances have been made in this area with the discovery of P. acnes interaction with Toll-like receptors (TLRs), vaccines targeting P. acnes or its components, antimicrobial peptides and the role of hormones.

INTRODUCTION

Acne vulgaris is a common disorder of the pilosebaceous unit. It affects approximately 40-50 million Americans, and it is estimated that nearly 85% of people have acne at some point in the course of their lifetime. The disease causes significant morbidity and affects patients both physically and psychologically in terms of scarring, depression, anxiety and low self esteem. (1) The direct costs related to acne exceed $2.2 billion annually in the U.S., when factors such as loss of productivity and depression are taken into account. The pathogenesis of acne vulgaris is multifactorial and is thought to involve the following factors: follicular hyperkeratinization, sebum production, presence of Propionibacterium acnes (P. acnes), inflammatory mediators and androgens.

Evolution of Lesions

Lesions of acne vulgaris can be divided into non-inflammatory (open and closed comedones) and inflammatory (papules, pustules and nodules). Microcomedones are the precursor lesions that can then develop into non-inflammatory and/or inflammatory lesions. The formation of a microcomedo is presently thought to result from both follicular keratinization and reduced desquamation of keratinocytes in the infundibulum, or upper portion of the pilosebaceous unit. (2) Recent reports have hypothesized a possible role of biofilm in the formation of a microcomedo by acting as biological glue. (3) A biofilm is a complex aggregation of microorganisms encased within an extracellular polysaccharide lining secreted by bacteria, including P. acnes.

A recent study by Do et al. illustrated formation of inflammatory lesions not only in areas of pre-existing comedones but also in areas of normal-appearing skin. (4) Serial digital photography in 25 patients was taken at baseline and every two weeks over a period of 12 weeks and evolution of untreated inflammatory lesions was assessed using serial digital photography. It was observed that 28% of lesions were preceded by normal-appearing skin without the presence of comedones forming initially. The authors postulated that de novo formation of inflammatory lesions could have arisen from microcomedones that were not clinically visible. De novo formation of inflammatory lesions has also been proven utilizing biopsy specimens of normal-appearing pilosebaceous units which showed inflammatory features, such as upregulation of the proinflammatory cytokine interleukin-1 (IL-1), and increased numbers of macrophages, without any features of microcomedone formation. (5)

Role of Propionibacterium acnes

P. acnes is a gram-positive anaerobic bacteria that is normally found in the sebaceous follicle. Increased numbers of P. acnes have been commonly found in the follicles of acne patients and reduction in these counts correlates with clinical improvement in acne patients. (6) Accordingly, antimicrobial agents and antibiotics have been a mainstay of acne therapy targeting P.acnes colonies. Antibiotic resistance to P. acnes is increasing and various factors, such as biofilm production by P. acnes and the inability of P. acnes to be killed or ingested by neutrophils and macrophages. (7-9) The biofilm excreted by P. acnes is a glycocalyx polymer and may contribute to its persistence and immunogenicity. (3), (10)

P. acnes plays an important role, both directly and indirectly, in the development of inflammatory acne. Overgrowth of the bacteria can lead to precipitation of an innate immune response and, in some cases, follicular wall rupture may occur.
initiating a host inflammatory reaction leading to inflammatory acne. P. acnes releases many enzymes, such as proteinases, lipases, hyaluronidases and chemotactic factors that are integral in the inflammatory cascade. (11) P. acnes directs immune reactions by modulation of the TH1/TH2 response and induction of monocyte-derived dendritic cell maturation. (12)

**Propionibacterium acnes and Toll-Like Receptors**

P. acnes stimulates the host innate immune response by activating Toll-like receptors (TLRs). TLRs are a group of pattern recognition receptors that are involved in the response of the host against microorganisms including bacteria, fungi and parasites. (13) Pattern recognition receptors recognize pathogen-associated molecular patterns (PAMPs). TLRs are present on keratinocytes, monocytes/macrophages, Langerhans cells, T and B lymphocytes, mast cells and endothelial cells. (13-15) The structure of a TLR is a transmembrane protein with a leucine-rich extracellular domain and an intracellular domain which is homologous to the cytoplasmic domain of the interleukin-1 (IL-1) receptor. (13)

Activation of the TLR leads to activation of nuclear factor (NF)-κB which, in turn, promotes expression of genes responsible for production of chemokines, cytokines and adhesion molecules. Currently, 10 TLRs have been identified in humans and each TLR recognizes a distinct PAMP. P. acnes activates TLR-2, resulting in increased levels of IL-8, IL-12, tumor necrosis factor-α, and IL-1β. (13-15) The presence of TLR-2 on macrophages surrounding pilosebaceous follicles in histological specimens of acne lesions has been demonstrated. (15) Furthermore, the number of TLR-2 positive cells was found to increase with increasing age of acne lesions, thereby strengthening the integral role played by TLRs in acne pathogenesis.

Since TLR-2 activation leads to inflammation in acne patients which, in turn, translates into visible inflammatory lesions, therapies that down-regulate TLRs may be of benefit. All-trans retinoic acid (ATRA) has shown to specifically down-regulate the cell surface expression of TLR-2 and CD14 resulting in the inhibition of various cytokines (IL-12p40, TNF-α and IL-6) released by monocytes. (19) ATRA has also been shown to reduce P. acnes-induced cytokine release. Jalian et al. showed that treatment of monocytes with ATRA resulted in decreased metallopeptidase 9 (MMP-9) expression. Both MMP-9 and MMP-1 induction was inhibited when monocytes were treated with ATRA and P. acnes. (20) Zinc salts have shown to inhibit in vitro TLR-2 surface expression by keratinocytes. (21)

Adapalene, a synthetic retinoid, has been shown to decrease expression of TLR-2 and IL-10 in explants of normal skin and explants of skin from acne patients. (22) Tenaud et al. incubated explants of normal human skin and explants of skin from acne patients with adapalene for 24 hours. (22) Epidermal expression was then evaluated using immunohistochemistry, which revealed increased expression of CD1d and decreased expression of TLR-2 and IL-10 in acne explants. The decreased expression of TLR-2 and IL-10 may be responsible for the anti-inflammatory effects seen with adapalene.

Corticosteroids have known to cause acneform eruptions or exacerbate acne vulgaris despite their anti-inflammatory and immunosuppressive effects. Shibata et al. demonstrated that glucocorticoids, such as Cortisol and dexamethasone, enhance TLR-2 gene expression in human keratinocytes, which when further stimulated by P. acnes may be responsible for the exacerbation of acne vulgaris. (23)

**Propionibacterium acnes and Vaccines**

Antibodies against P. acnes have been found in patients but have not been known to confer protective immunity against developing future acne lesions. Vaccines against P. acnes or its components have been described. (24) Killed P. acnes-based vaccines exert their effects by modulating non-specific immune response. Nakatsuji et al. recently reported vaccines consisting of killed-whole organism P. acnes and a cell wall-anchored sialadase. (11) Nakatsuji et al. illustrated that mice immunized with heat or ultraviolet-killed P. acnes produced antibodies against P. acnes specific proteins. Furthermore, P. acnes-induced ear swelling was effectively suppressed by the vaccination. Antibodies elicited by P. acnes vaccine provided protective immunity and lowered P. acnes-induced production of IL-8, a proinflammatory cytokine. (25) Cell wall-anchored sialadase, one of at least five siala-dases in the P. acnes genome, is important for P. acnes adhesion and infection. In the past, sialadase has been used as a vaccine target for influenza and bacterial pneumonia. (24) Sialadase antibodies were not produced when mice were immunized with heat-killed P. acnes but were produced when immunized with recombinant sialadase. A sialadase-based acne vaccine was shown to confer protective immunity. Sialadase-immunized mice were shown to have decreased P. acnes ear swelling and decreased
production of cytokine MIP-2 without affecting body microflora. (24), (25) Antibodies against sialadase were also shown to decrease P. acnes induced cell death and reduced levels of IL-8 in human sebocytes. (25)

Vaccines targeting specific components of P. acnes, which are involved in producing a specific inflammatory response, may be of benefit in the future. (26)

**Antimicrobial Peptides**

Antimicrobial peptides (AMPs) play an integral role in the skin's immune defense system by direct microbial toxicity and also by modulating components of innate and adaptive immune systems. AMPs are produced by keratinocytes, monocytes, mast cells, sebocytes, neutrophils and natural killer cells. (27), (28) Although there are many AMPs produced, cathelicidins, [beta]-defensins and granulysin are among the most frequently described. Human cathelicidin (LL-37) has been shown to influence the function of TLRs. Nagy et al. demonstrated the upregulation of human [beta]-defensin 2 (hBD2) and IL-8 by genotypically P. acnes via TLR-2 and TLR-4. (29) Granulysin is found in the cytotoxic granules of T and natural killer cells and is known to have activity against pathogenic bacteria. (30) Granulysin-derived peptides have been reported to possess both antimicrobial (bactericidal) and antiinflammatory activity against P. acnes. (28) P. acnes induces expression of cathelicidin and hBD2 in human SZ95 sebocytes. (31-33)

Nelson et al. demonstrated that 13-cisretinoic acid (isotretinoin) upregulates lipocalin 2, which encodes the neutrophil gelatinase-associated lipocalin (NGAL), a protein involved in innate immunity and apoptosis. (34) Biopsies were done one week prior and at one week during treatment with 13-cis retinoic acid with demonstration of apoptosis of sebocytes mediated by NGAL. It is unknown whether NGAL has any effect on P. acnes or whether P. acnes can stimulate NGAL.

**Acne and Hormones**

Androgens have long been implicated in acne pathogenesis. (35-37) Hormones not only exert their effects on sebaceous glands but they also may play a role in follicular hyperkeratinization. (38) Increased sebum is seen in acne patients and functional androgen receptors must be present for the production of sebum. (35) Androgens, such as testosterone, dehydroepiandrosterone sulfate (DHEAS) and dihydrotestosterone (DHT), are known to regulate genes responsible for sebaceous gland growth and sebum production. (39-41) DHT is converted from testosterone by the action of 5-a reductase. Higher activity of type 1 5-[alpha] reductase is seen in acne patients whereas higher levels of DHEAS is usually seen in prepubertal acne patients.

The exact mechanism of estrogen in acne pathogenesis is unclear but is known to suppress sebum production in sufficient amounts. (42), (43) Estrogen may exert its effects through several mechanisms: direct opposition effect on androgens, inhibition of androgen secretion or modulating genes involved in sebaceous gland growth and function. (35)

Growth hormone is secreted by the pituitary and it stimulates the production of insulin-like growth factors (IGF). (43) Sebocytes express receptors for IGF-1 which may interact to cause growth of the sebaceous gland. (44) Propiomelanocortin, corticotropin-releasing hormone (CRH), and corticotropin-releasing hormone receptor (CRHR) genes are present in the skin. (45) CRH has been reported to promote lipogenesis and to enhance mRNA expression of [DELTA]5-3-[beta]-hydroxysteroid dehydrogenase, the enzyme that converts dehydroepiandrosterone to testosterone, in human sebocytes. (46) Ganceviciene et al. studied the involvement of CRH system in acne pathogenesis. (47) Facial biopsies were obtained from 33 acne patients and were compared to noninvolved thigh skin of the same patients and normal skin of eightagematched healthy volunteers. Strong CRH expression was seen in sebocytes, of all differentiation stages, of acne-involved skin whereas the CRH expression in uninvolved and normal skin was dependent on the differentiation stage of the sebocyte. (47) The authors hypothesized that CRH may interact with immune factors causing a release of inflammatory mediators in acne. CRHRBP expression was intense in differentiating sebocytes of acne-involved skin, which may be as a result of local stress reaction in acne. The authors concluded that CRH acts as a central director, via the CRHR-1, for behavioral and neuroendocrine response to stress and is involved in stress-induced exacerbation of acne. (47)

**CONCLUSION**

Acne is a common disorder with significant physical and psychological impact. Vaccines targeting specific components of P. acnes may be effective as more antigens and their specific effects are discovered. In addition, the role of TLRs in acne pathophysiology is key and therapies targeting them or reducing their expression may be effective in treating acne vulgaris.
DISCLOSURES

Dr. Del Rosso has served as a consultant, speaker, and researcher for Allergan, Amgen, Arcutis, Coria, Galderma, Graceway, Intendis, Medicis, Obagi Medical Products, Ortho Dermatology, Onset Therapeutics, QLT, Quinnova, Ranbaxy, SkinMedica, Stiefel, Triax, Warner-Chilcott and Unilever.

Drs. Bhambri S and Bhambri A have no relevant conflicts of interest to disclose.

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