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The Pathogenesis of Acne

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SUMMARY Acne vulgaris is a multifactorial disease of as yet incompletely elucidated etiology and pathogenesis. The following have been identified as the most significant factors: follicular hyperkeratosis, increased sebum secretion, *Propionibacterium (P.) acnes*, and inflammation. Increased sebum production and follicular hyperkeratosis result in the development of microcomedones, and changes in follicular milieu in intensive growth of *P. acnes. P. acnes* secretes several proinflammatory products, which play an important role in the development of inflammation. These include lipases, proteases, hyaluronidases, and chemotactic factors. Immune response to *P. acnes* includes humoral and cell-mediated immunity as well as complement activation. Recent results indicate that keratinocytes and sebocytes, as major components of pilosebaceous unit, may act as immune cells and may be activated by *P. acnes via* toll-like receptors (TLRs) and CD14, and through CD1 molecules may recognize altered lipid content in sebum, followed by the production of inflammatory cytokines.

KEY WORDS: acne vulgaris; pathogenesis

INTRODUCTION

Acne vulgaris is a multifactorial disease, which includes hormonal, microbial and immune mechanisms. The process occurs in pilosebaceous unit, resulting in microcomedo due to hyperkeratinization and increased sebum production, and afterwards open and closed comedo. These are non-inflammatory acne lesions. Further process may result in inflammatory acne lesions, i.e. papules, pustules and nodules. Most patients have a mixture of lesions. The lesions are localized in the so-called acne-prone areas (cheeks, nose, forehead, midline chest and back). The changes occur primarily in adolescents with the secretion of androgen hormones, which regulate the activity of sebaceous glands. It is characterized by spontaneous resolution at approximately age 25, although the hormone level remains the same. However, the background of this process remains unclear. A possible explanation for the resolution of lesions may lie in the follicular cycling process, similar to the terminal hair follicles (1,2).

INCREASED SEBUM PRODUCTION

All acne patients have increased sebum production. Sebum production is greater in patients with more severe acne. Sebum secretion is different in follicles, depending on the follicle type and localization. It is most pronounced in so-called acne-prone follicles distributed in acne-prone areas. Sebaceous glands are characterized by their hyperresponse to androgens, which is genetically determined. Investigations in monozygotic twins

showed a significant influence of the genetic factor (3). Most patients have normal blood androgen levels. Skin has a cellular mechanism to convert testosterone into more potent dihydrotestosterone (DHT) in the presence of the 5α-reductase (type 1) enzyme. An increased activity of this enzyme was detected in acne-prone areas such as the face, correlating with other areas on the legs or hands (4). Antiandrogens, estrogens and retinoid, which decrease sebaceous gland activity, control acne (5). Besides increased sebum secretion, there are changes in the composition of lipids. The levels of free fatty acids, squalene and squaling oxide are increased, while the concentration of linoleic acid is lower.

Sebum secretion is also affected by stress. Sebaceous glands may be stimulated in a way similar to the hypothalamic-pituitary-adrenal (HPA) axis. Corticotrophin-releasing hormone (CRH) is the most proximal element of HPA axis and it acts on neuropeptide receptors stimulating lipid synthesis as a response to stress (6). CRH and CRH receptors were detected in human sebaceous glands. CRH induced a biphasic increase in the synthesis of sebaceous lipids and up-regulated in mRNA levels of 3β-hydroxysteroid dehydrogenase/δ (5-4) isomerase, important for testosterone synthesis in human sebocytes (7). The role of stress in acne could be related to the release of neuromediators such as substance P (SP), which stimulates sebum production. Data from immunologic, physiologic and chemical studies have also shown that this substance is close to sebaceous gland. *In vitro* exposure of normal skin to the activity of this substance resulted in a significant increase in the size of sebaceous gland and number of sebum vacuoles in sebaceous cells. Recent data have also shown that receptors to neuromediators are present in sebaceous glands, e.g., SP and α-melanocyte stimulating hormone (8,9).

FOLLICULAR HYPERKERATOSIS

Why follicular hyperkeratosis occurs remains largely unknown. There are several theories. One of them is that there is a reduction in the amount of lamellar granules in stratum spinosum, secreting enzymes that dissolute cement substance in stratum corneum, enabling their separation (10,11). Increased expression of tenascin, an extracellular matrix glycoprotein that can interact with cells and alter them to adhere, migrate and proliferate, has been associated with the development of acne lesion (12). Androgens regulate sebaceous gland function and play an important role in the development of hyperkeratosis in infundibulum, because keratinocytes in infundibulum have a greater capacity to metabolize androgens (13). Other investigators have reported that a disorder in the normal process of keratinization in follicular channel could be caused by a modified lipid composition, leading to increased cohesion of cells in the follicle (14-16). Cytokines, such as interleukin-1α (IL-1α), are an important factor that may induce proliferation of keratinocytes, while epidermal growth factor (EGF) reduces comedo formation. Comedogenesis was induced experimentally by IL-1α, and was blocked by IL-1 receptor antagonist. Cytokine IL-1α has been found to be present in high amounts in noninflammatory acne lesions (17).

PROPIONIBACTERIUM ACNES

Propionibacterium (P.) acnes is an anaerobic pleomorphic diphtheroid, which normally resides in the follicle. Increased sebum secretion of the affected follicles provides a very good environment for the development of this bacterium. It ingests sebum and dilutes triglycerides into glycerol and free fatty acids, which have proinflammatory and comedogenic features. The usual treatment of inflamed acne by antibiotics decreases inflammation, however, the presence of *P. acnes* resistance to antibiotics may be associated with therapeutic failure. According to normal standards, *P. acnes* is not pathogenic, because it is localized in the follicles free from acnes, so there is minimal correlation between the number of *P. acnes* and the severity of clinical signs and type of acne. *P. acnes* has been shown serologically and biochemically to be identical to *Corynebacterium parvum,* a potent stimulator of the reticuloendothelial system (18,19).

INFLAMMATION

Inflammation in acne is the result of the body response to *P. acnes*. This bacterium produces different enzymes and chemotactic factors, attracting polynuclears. Upon phagocytosis, attracted polynuclears release proinflammatory mediators such as reactive oxygen species (ROS) and cytokines. ROS produced by activated neutrophils cause damage to the follicular wall epithelium, expelling the follicle content into the dermis and resulting in inflammation. Tetracyclines, especially minocycline hydrochloride, that are the first choice in inflamed acne treatment, inhibit the formation of ROS by neutrophils, thus reducing inflammation (20,21).

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Stimulation of cytokine production by *P. acnes* could be important in the pathogenesis of inflammatory acne vulgaris and may have wider implications for immunomodulation of the human system by commensal skin microorganisms. The mechanism of cytokine production remains unclear, however, it has been assumed to occur in several ways. Besides keratinocytes, which are the main source of cytokines in epidermis, they are also produced by polymorphonuclears, attracted by chemotactic factors of *P. acnes* in the follicle.

P. acnes hydrolyzes triglycerides to free fatty acids, which are toxic for the follicle wall cells. Various proinflammatory cytokines are involved, e.g., interleukin 1α (IL-1α), transforming growth factor α (TGF-α), tumor necrosis factor α (TNF-α), interferon γ (INF-γ), epidermal growth factor (EGF), IL-8 and IL-12. EGF and TGF-α cause disorganization of keratinocytes in the hair follicle, leading to infundibular rupture and resulting in sebum entry into the dermis and development of inflammation. IL-1α influences inflammatory response, stimulating the production of vascular endothelial growth factor in dermal papillae and follicular keratinocytes of pilosebaceous unit (11). IL-1 is multifunctional and mediates a wide spectrum of inflammatory, metabolic, physiologic and immune reactions (22,23). IL-1 plays a central role in inflammation induction of inflammatory response, specific for various dermatoses. In acne, IL-1α causes hyperkeratosis in hair infundibulum resulting in microcomedones and can be found at increased concentrations in the as yet noninflamed acne lesions. In vitro experiments showed it to be possible to induce hyperkeratosis in infundibulum similar to that found in comedone (5,17,24). The stimulus that triggers IL-1α production by ductal keratinocytes is unknown (25). There is a hypothesis that the induction of IL-1α production could be caused by a deficit of the essential fatty acid, linoleic acid, in the follicular wall keratinocytes, found in acne (26). It is considered that the altered sebum content and increased rate of its secretion may precipitate IL-1α from keratinocytes in infundibulum, stimulating comedogenesis (12). Besides IL-1, other cytokines such as TNF-α, IFN-γ, EGF and TGF-α, may also be involved (7).

The *P. acnes* immune response is another way of inflammation initiation in acne. Circulating immune complexes have been reported to be elevated in some acne patients. The degree of elevation correlated with the severity of acne inflammation (18). Complement-fixing antibody titers are elevated and in correlation with the severity of inflammation. They are reported to be largely of the IgG class (16,18). Antibodies against *P. acnes* may increase inflammation activating complements *via* classic or alternate pathways, causing the release of comedogenic (IL-1α), inflammatory (TNF-α and IFN-γ) and disruptive (TGF-α) cytokines from the cells of inflammatory and immune system (26). Activated complement may form the potent chemoattractant C5a, which further amplifies the recruitment of immune cells (27).

The role of cell-mediated immunity is far from having been proven. However, skin tests done with common recall antigens such as trichophytin, mumps, or purified protein derivative have demonstrated that patients with severe acne may have a depressed or absent reactivity. In addition, sensitization to dinitrochlorobenzene may not occur (18). Heat-killed *P. acnes* skin test has strongest response in the most severe acne cases (28).

Recent investigations have shown that microbial antigens can directly influence the release of proinflammatory cytokines (IL-1α, TNF-α, IFN-γ, TGF-α), activating toll-like receptors (TLRs). Two mechanisms could play an important role in the development of inflammation in acne (16,24): recognition of pathogens by TLRs and CD14 receptors, and abnormal lipid presentation by CD1d molecule.

Keratinocytes and sebocytes have been demonstrated to play important roles in acne pathogenesis; these are major components of pilosebaceous unit, which is constantly hosting *P. acnes* and is especially rich in lipids. Keratinocytes and sebocytes have TLRs, CD14 and CD1d receptors, although they do not belong to immune system cells like macrophages, neutrophils, dendritic cells and lymphocytes. These receptors belong to the innate immunity and first line defense against pathogens. In contrast to adaptive, innate immunity represents an older system of defense against pathogens and is activated through a limited number of antigens specific for conserved microbial structures. Recognition of these structures by the innate immune system induces costimulators, cytokines, and chemokines, which recruit and activate antigen-specific lymphocytes and initiate adaptive immune response (29,30).

TLRs belong to a wide group of related receptors called pattern recognition receptors (PRRs) that are specific for common constituents of pathogenic microorganisms. By means of TLRs, keratinocytes and sebocytes receive signals from microorganisms (bacteria, viruses and fungi), enabling response to infection. Toll receptors were

first identified in Drosophila and recent studies suggest that mammalian toll homologs, TLRs, mediate immune response to microbial ligands (31). Recent studies of TLRs have suggested that these receptors are necessary elements for the host defense against pathogens, activating innate immunity as a prerequisite for induction of adaptive immunity (29,32).

PRRs recognize relatively invariant structures within a given class of microorganisms. These include various components in the bacterial cell wall such as lipopolysaccharides (LPS), peptidoglycans, lipopeptides, flagellin, and bacterial DNA. These components are called pathogen-associated molecular patterns (PAMPs). In PRRs, TLRs have the crucial role in the recognition of PAMPs, and they induce antimicrobial response in different cells. TLRs require the presence of coreceptors to initiate the signaling cascade (16,29,31).

On keratinocytes and sebocytes from the group of TLR receptors, TLR2 and TLR4 receptors are present and can be activated directly by *P. acnes* antigens. Further, the recognition of *P. acnes* by TLR is strongly induced by CD14. CD14 is also a coreceptor necessary to initiate the signaling cascade. Keratinocytes, activated in this way, directly produce proinflammatory cytokines, i.e. TNF-α, IL-1β, IL-8 and IL-12, stimulating macrophages for the production of these cytokines (9,24). Macrophages around the pilosebaceous follicle in acne disease also have TLR2 receptors and present evidence for a mechanism mediated by TLR to occur at the site of disease (24).

Two major components of the gram-positive cell wall, reported to induce immune response of keratinocytes and sebocytes by TLRs, are peptidoglycan-polysaccharide (PG-PS) complexes and lipoteichoic acid. It is suggested that *P. acnes* acts in a similar way (16,21,27). Stimulation of TLRs by PAMPs initiates a signaling cascade leading to the activation of the transcription factor NF-κB, which induces the secretion of proinflammatory cytokines that direct the adaptive immune response (23,33,34).

CD14 is a glycosylphosphatidylinositol (GPI)-anchored membranous protein that acts as a bacterial pattern recognition receptor. CD14 is found in macrophages, neutrophils, B lymphocytes, keratinocytes and sebocytes. CD14 is member of the heteromeric lipopolysaccharide (LPS) receptor complex, which also contains TLR4. This receptor is associated with TLR4, initiating signaling. It also interacts with TLRs as a response to different microbial infections (23).

CD1 molecules represent a family of nonpolymorphic glycoproteins, and they could function as "sensory" molecules, sensing alterations in cellular lipid content. CD1 molecule is expressed by a variety of cells: thymocytes, activated T cells, B lymphocytes, professional antigen-presenting cells, and intestinal epithelial cells. CD1d molecule is considered to present abnormal lipids in sebocytes and keratinocytes from pilosebaceous unit, and to activate NKT cells to secrete different cytokines, thus developing inflammation (16).

It is considered that leukotrienes have an important role in the development of tissue inflammation. Leukotrienes belong to a family of highly potent biologic substances, eicosanoids, derivatives of arachidonic acid (24,35). Leukotriene B4 is a proinflammatory mediator with a key role in the development of tissue inflammation in acne as well as in other skin diseases with inflammation and hyperkeratosis, especially psoriasis. It is synthesized from arachidonic acid. The synthesis of leukotriene B4 is catalyzed by 5-lipooxygenase. Leukotriene B4 is a natural ligand for peroxisome proliferator-activated receptor α (PPARs), enabling the synthesis of free fatty acids (24). Zouboulis *et al.* showed the inflammation in acne to decrease by inhibiting the synthesis of leukotriene B4. This is a strong evidence that eicosanoids may play an important role in the development of inflammation in acne. These results also support the view that lipids induce inflammation in acne, independently of the presence of bacteria or increased systemic levels of proinflammatory molecules (35). The administration of a specific inhibitor, 5-lypooxygenase, resulted in reduced inflammation, significant reduction in total lipids and especially in free fatty acids in sebum. Among several diseases, hyperkeratotic inflammatory skin diseases and especially psoriasis seem to respond to this therapy. Using this therapy, reduction of inflammation is greater than with local or oral antibiotics (clindamycin, erythromycin) (24,35).

It is known that biologic activity of retinoids on the skin occurs *via* specific nuclear receptors, retinoic acid receptors (RARs) (36-38). The favorable activity of locally applied retinoids in acne occurs through down-regulation of the expression of TLRs, receptors involved in *P. acnes* recognition (16,35,39). Retinoids reduce the activation of AP-1 by reducing the increase of collagenase in the dermis, and prevent decomposition of collagens, thus diminishing the possibility of scar formation in acne (38,40,41).

CONCLUSION

Several factors are involved in the pathogenesis of acne: seborrhea, follicular hyperkeratosis, *P. acnes* proliferation, and inflammation. An immune response, including humoral and cellular immunity, and activation of complements develop to *P. acnes.* Recent studies have shown that *P. acnes* acts through TLRs, CD14 and CD1 receptors on keratinocytes, sebocytes and macrophages, resulting in the production of multiple proinflammatory cytokines. All these factors cause development of comedones and progression into inflammed acne forms. Better understanding of these processes and trigger factors that induce their initiation is important for the improvement of this disease treatment.

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