Comments

Dermatology

Dermatology 2003;206:96–105
DOI: 10.1159/000068476

The Role of Innate Immunity in the Pathogenesis of Acne

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Key Words
Acne · Toll-like receptors · CD1d molecule

Abstract
Acne is a multifactorial disease of the pilosebaceous follicle. The most significant pathogenetic factors of acne are: abnormal ductal keratinization, increased sebum secretion, abnormalities of the microbial flora and inflammation. The pilosebaceous unit is an immunocompetent organ. Keratinocytes and sebocytes may act as immune cells capable of pathogen recognition and abnormal lipid presentation, and they might have an important role in initiating and perpetuating the activation of both innate and adaptive immune responses. The elements of the skin immune system are involved in the development of both noninflammatory and inflammatory acne lesions.

Acne is a chronic inflammatory disease of the pilosebaceous unit. The lesions are localized in the so-called acne-prone areas (the cheeks, the nose, the forehead, the midline chest and the back), where sebaceous follicles are most common.

Acne lesions can be divided into noninflammatory and inflammatory lesions. The noninflammatory lesions are represented by microcomedones and comedones. The microcomedo is the first pathogenic feature of acne that can be found in normal-looking skin and can only be identified microscopically [1].

Inflammatory acne lesions consist of papules, pustules and nodules. In these lesions the follicular epithelium is damaged, and a dermal inflammation occurs. Duct rupture can occur but is certainly not an early phenomenon [1, 2]. If rupture occurs the comedo content elicits an intense inflammatory response in the dermis. Long-lasting dermal inflammation may give rise to indurated nodules. Most patients have a mixture of noninflammatory and inflammatory lesions. An interesting feature of acne is the spontaneous resolution of the disease in the majority of young adults and of particular lesions during the disease. The background of this process is still unknown. A possible explanation for the resolution of lesions, especially of microcomedones and comedones, may be represented by the follicular cycling process [3].

There is a general agreement that acne is a multifactorial disease. The most significant pathogenetic factors of acne have been identified as: abnormal ductal keratinization resulting in comedogenesis, increased sebum production resulting in seborrhea, abnormalities of the microbial flora and inflammation [2, 4].

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Abnormal Ductal Keratinization

Microcomedones and comedones show ductal hyperkeratinization and subsequent obstruction of sebaceous follicles. The hyperproliferation of ductal keratinocytes has been confirmed by immunohistochemical staining with monoclonal antibody Ki-67, by an increase in ^{3}H-thymidine labeling of comedones and the presence of keratins 6 and 16 [5–7]. The mechanism by which this process occurs is not elucidated. One important factor that induces this hyperproliferative state of ductal keratinocytes may be the modified lipid composition of the sebum [2, 8]. Lipids, which have been incriminated in comedogenesis are linoleic acid, free fatty acids and squalene [9]. Several studies have shown that keratinocyte proliferation and differentiation could be influenced by lipids. N-acylated forms of sphingolipids, such as ceramides, have been shown to promote keratinocyte differentiation, and sphingosine and sphingosylphosphorylcholine have been demonstrated to promote keratinocyte proliferation [10].

Beside hyperproliferation of ductal keratinocytes comedogenesis may be related to the failure of ductal keratinocytes to separate: however, conflicting results are available from studies concerning terminal differentiation of keratinocytes and desmosome expression [11, 12]. In comedogenesis hormones could also have a role [2].

Cytokines are another important factor that may induce proliferation of keratinocytes. In experiments performed by Guy and Kealey [13], comedogenesis was induced experimentally by interleukin (IL) 1α and was blocked by IL-1 receptor antagonist. IL-1α has been found to be present in high amounts in noninflammatory acne lesions. In contrast, epidermal growth factor markedly reduced comedo formation in vitro [13].

Increased Sebum Production

Almost all acne patients have increased sebum production, but excessive sebum production is not sufficient for the development of acne. It has been demonstrated that in acne patients a considerable heterogeneity in individual follicular sebum secretion exists, which suggests the existence of 'acne-prone' follicles [14]. The induction of sebum hypersecretion in acne is not fully elucidated. Acne generally begins at puberty, when androgen levels increase significantly and stimulate sebum secretion. In young adults acne usually wanes, whereas androgen levels remain high. Several studies have found increased 5α-reductase levels and increased expression of androgen receptors in sebaceous glands of acne patients [15, 16]. These findings suggest that an end-organ hyperresponse of the sebaceous glands to androgens is probably the most likely explanation for the seborrhea.

In the development of acne, an important feature may be represented beside the increased quantity of sebum by its abnormal composition in certain lipid components.

Abnormalities of the Microbial Flora

A pathogenic factor of acne is the proliferation of normal flora and especially of *Propionibacterium acnes.* Acne is not an infectious disease, but the role of *P. acnes* is outlined by several data [17]. Sebum production shows a high correlation with *P. acnes* levels, so the increased sebum secretion of affected follicles provides a very good environment for the growth of *P. acnes* [18]. In some studies the number of *P. acnes* was found increased in acne lesions, but there was no correlation between the number of *P.* acnes and the severity and outcome of the disease [17]. Other studies found no difference between the numbers of *P. acnes* in affected follicles and control ones [19]. However, the importance of *P. acnes* is further suggested by the successful antibiotic therapy of acne and by the observation that the presence of resistant strains of *P. acnes* may be associated with therapeutic failure.

Several studies have demonstrated that in acne patients and especially in subgroups with severe forms, the immune response against *P. acnes* is abnormal [20]. Ashbee et al. [21] reported that patients with severe acne have significantly higher levels of complement fixing antibodies to *P. acnes.* Puhvel et al. [22] showed that lymphocyte stimulation by *P. acnes* is significantly increased in patients with nodulocystic acne. Kersey et al. [23] demonstrated that delayed skin test reactivity to *P. acnes* correlates with the severity of the disease. Recent studies performed by Jappe et al. [24] revealed that *P. acnes* could activate both peripheral blood mononuclear cells of adults and cord blood mononuclear cells and that the reactions produced are both antigenic and T cell mitogenic. These results are in concordance with other immunological studies, which revealed that the initial cells that infiltrate acne lesions are T helper lymphocytes [1]. *P.* acnes secretes various biologically active molecules like enzymes and chemotactic factors, which may have a role in the initiation and perpetuation of the local inflammatory response and even in the induction of keratinocyte hyperproliferation [25].

Inflammation

The fourth main factor in the pathogenesis of acne is inflammation. It is widely accepted that inflammation in acne vulgaris may be mainly induced by an immunological reaction to *P. acnes*. Chemotactive substances released by bacteria attract cells of the immune system such as neutrophils, monocytes and lymphocytes [20, 25]. *P. acnes* may also activate the complement system with the formation of the potent chemoattractant C5a, which further amplifies the recruitment of immune cells [26]. *P. acnes* produces soluble factors that are able to activate immune cells with the consecutive secretion of various proinflammatory cytokines (IL-8, tumor necrosis factor α, IL-1α) [25, 27].

Recent results indicate a key role for leukotriene B_4 in the development of tissue inflammation in acne. Leukotriene B_4 is a proinflammatory mediator synthesized from arachidonic acid. Synthesis of leukotriene B_4 is catalyzed by 5-lipoxygenase and leukotriene A_4 hydrolase and is increased by inflammatory mediators including endotoxin, complement fragments tumor necrosis factor α and interleukins [28, 29]. Zouboulis [30] showed that administration of a specific lipoxygenase inhibitor significantly decreased the inflammatory lesions in a small cohort of patients with inflammatory acne. In these patients, a significant reduction in total lipids and especially in free fatty acids in sebum as well as a substantial decrease in lipoperoxides was found. Bivariate analysis indicated that the decrease in total serum lipids, and especially in proinflammatory lipids, was directly correlated with the improvement in inflammatory lesions [30]. In cultured human sebocytes, 5-lipoxygenase was induced at the mRNA and protein levels under arachidonic acid and calcium ionophore treatment. Furthermore, leukotriene A_4 hydrolase and peroxisome proliferator-activated receptor α were expressed in sebocytes at the mRNA and protein levels. The presence of the enzymes 5-lipoxygenase, and leukotriene A_4 hydrolase and the detection of peroxisome proliferator-activated receptor α in human sebocytes provide strong evidence that eicosanoids may play an important role in inflammatory sebaceous gland disorders, including acne [31].

These results also support the view that sebum lipids induce inflammation in acne, independent of the presence of bacteria or increased systemic levels of proinflammatory molecules [32]. Ceramides could induce degranulation of neutrophils and increased integrin expression on leukocytes [33]. Ceramides and sphingosylphosphorylcholine have been shown to modulate T lymphocyte proliferation [34]. Modification in the lipid composition also leads to a diminished epidermal barrier function and favors the diffusion of proinflammatory mediators through the follicular epithelium into the dermis [35].

Neuropeptides may also have an important role in the development of inflammatory acne lesions. Seiffert et al. [36] have demonstrated that human sebocytes express neuropeptide receptors and that their agonists possess stimulatory effects on cytokine production. Böhm et al. [37] have shown that the paracrine and/or endocrine actions of β-endorphin are mediated by the μ-opioid receptors expressed by human sebocytes. The presence of melanocortin 1 receptor in human sebocytes has also been demonstrated [38]. Recently, the role of corticotropin-releasing hormone as an autocrine hormone that stimulates lipogenesis in human sebocytes has also been established [39].

Beside the professional cells of the immune system, ductal keratinocytes and sebocytes are also able to secrete amounts of cytokines following various stimuli [40]. Released cytokines stimulate the expression of adhesion molecules on endothelial cells, have chemotactic properties, activate antigen-presenting cells and leukocytes and stimulate the formation of new inflammatory mediators such as leukotrienes and prostaglandins. Even before the rupture of the duct all the immunologically active substances diffuse through the follicular epithelium, which is already thinned. After the disruption of the duct, keratin, hair and lipids from the extruded sebum directly initiate inflammation and the formation of a macrophage giant-cell foreign-body reaction.

Both in follicular hyperproliferation of keratinocytes, which is the primary cause of comedo formation, and in the development of inflammatory lesions, growth factors, cytokines and hormones produced locally in the pilosebaceous unit have been supposed to play an important role. The immune system has a high capacity of producing these growth-promoting factors and inflammatory cytokines. In acne lesions, these mediators were found to be upregulated, and activated immune cells could be detected in inflammatory acne lesions. These data suggest that elements of the skin immune system (SIS) might be responsible for producing these mediators and be involved in the development of both noninflammatory (hyperproliferative) and inflammatory acne lesions (table 1).

Table 1. Characteristic features of noninflammatory and inflammatory lesions in acne

	Noninflammatory acne lesions	Inflammatory acne lesions
Type of lesions	Microcomedo Comedo (open and closed)	Papules Pustules Nodules
Responsible cells	Keratinocytes Sebocytes?	Keratinocytes Sebocytes Monocytes, neutrophils T lymphocytes, NKT cells?
Responsible mediators	Abnormal lipids? Growth factors Cytokines (IL-1α) Hormones	Proinflammatory cytokines (IL-1α, IL-8, TNF-α) Metabolites of arachidonic acid (leukotrienes, prostaglandins) Enzymes Complement Growth factors Hormones Neuropeptides
Pathogens	*P. acnes?*	*P. acnes*

Skin Immune System

The immune system of vertebrates has two components: innate immunity and adaptive immunity. These two systems utilize two very different mechanisms for host defense. The innate immune system relies on a set of germline-encoded receptors that are expressed on a wide variety of cells, like macrophages and neutrophils as well as on epithelial cells situated at host-environment boundaries. The skin represents the largest organ of the human body. In addition to its structural functions, a specific immunological environment has developed in the skin. The theory of the SIS was introduced in 1987, by Bos et al. [41]. The SIS consists of professional immune cells, such as macrophages, neutrophils, dendritic cells and lymphocytes, and nonprofessional immune cells, such as keratinocytes and sebocytes.

The most important function of the innate immune system is to recognize foreign invaders and self-molecules with modified structures. This is a crucial event necessary for the activation of both innate and adaptive defense mechanisms. Abnormal reactions to such stimuli could lead to the development of pathological features. Considering the peculiar aspects of the pilosebaceous unit, which is constantly hosting *P. acnes* and is especially rich in lipids, two mechanisms could have an outstanding role in the development of acne lesions: recognition of pathogens by Toll-like receptors (TLRs) and presentation of abnormal lipids by CD1d molecules, which results in the activation of natural killer T (NKT) cells. NKT cells could further activate both the cells of the innate immune system and the cells of the adaptive immune system; they represent a link between innate and adaptive immunity.

TLRs in the Skin: Recognition of Pathogens

Effective host defense against invading microorganisms requires the detection of foreign pathogens. The recognition of invading pathogens is mediated by germline-encoded receptors that are specific for common constituents of pathogenic microorganisms that are called pattern recognition receptors (PRRs). PRRs recognize invariant molecular structures called pathogen-associated molecular patterns (PAMPs) that are relatively invariant within a given class of microorganisms (table 2). Such a PAMP is the lipopolysaccharide (LPS) of gram-negative bacteria, mannan in the yeast cell wall, the mycobacterial cell wall component lipoarabinomannan and the peptidoglycan of gram-positive bacteria. In the past 10 years, a number of PRRs have been described that mediate complement activation, opsonization and phagocytosis. However, until recently only little has been known about the receptors responsible for the induction of immune and inflammatory genes. Recent studies on the recognition of PAMPs have highlighted the critical role of one group of PRRs, the TLRs in innate host defense. TLRs play crucial roles in the induction of antimicrobial responses in different

Table 2. Common PAMPs and their PRRs [97, 98]

PAMPs	PRRs
LPS	LBP, CD14, TLR_4, TLR_2
Lipoproteins	TLR_2
Peptidoglycan	CD14, TLR_2
CpG	TLR_9
Lipoarabidomannan	TLR_2, CD1
N-formyl-Met	f-Met receptors 1 and 2
Mannans, mannoproteins, zymosan	mannose-R, MBP, mannose-, glucan-R, TLR_2
Heat shock proteins	undefined (TLR_4?)
Flagellin	TLR_5

CpG = Deoxycytidylate-phosphate-deoxyguanylate; LBP = lipopolysaccharide-binding protein; R = receptor; MBP = mannose-binding protein.

cells [42]. In the past few years, at least 9 different human TLRs have been identified. Biochemical studies on an in vitro model and investigations on mice deficient in TLR_4 indicated that TLR_4 primarily mediates cellular signaling induced by gram-negative bacteria [43]. Targeted disruption of the TLR_4 gene resulted in abrogation of the response to LPS [44]. In humans, common mutations in the TLR_4 gene are associated with differences in LPS responsiveness [45]. While TLR_4 is highly specific for LPS and is associated with CD14, a coreceptor for LPS, TLR_2, is implicated in the recognition of multiple products of gram-positive bacteria, mycobacteria and yeast. TLR_2 is required for proinflammatory signaling to lipoteichoic acid, peptidoglycan, lipoproteins, lipoarabinomannan and zymosan [42, 46–48]. The common downstream signaling pathway of TLR_2 and TLR_4 leads to the activation of NF-κB through the myeloid differentiation protein (MyD88) and IL-1-receptor-associated kinase in various cell types [49, 50].

Keratinocytes have been demonstrated to play important regulatory roles in cutaneous inflammatory and immune responses by producing various kinds of cytokines. Keratinocyte-derived cytokines are pivotal in mobilizing leukocytes from the blood and in signaling other cutaneous cells. Keratinocytes are able to produce proinflammatory cytokines such as IL-8 in response to microbial compounds providing initial chemotactic stimuli for neutrophils.

In addition to regulating immunological and inflammatory responses, the epidermal keratinocytes contribute to the protective barrier of the epithelia and participate in the host defense by killing invading microorganisms. It was earlier demonstrated that epidermal keratinocytes have direct candidacidal activity, which can be further increased by UV light [51, 52], IL-1 [53], IL-8 and α-melanocyte-stimulating hormone [54]. IL-1, prostaglandin E_2 and platelet-activating factor have also been demonstrated to be involved in *Candida* killing by human epidermal cells [55], but the mechanism of killing remained unknown. Recently it has been shown that keratinocytes express a new type of mannose binding receptor on their surface, which has a role in the binding and subsequent killing of *Candida albicans* [56]. Keratinocytes have been shown to produce inducible antimicrobial products such as nitric oxide [57], LL-37 [58], antileukoprotease [59] and β-defensins [60]. Keratinocyte-derived nitric oxide and antimicrobial peptides in the epidermis might be responsible for the killing of invading pathogens in the epidermis and for the prevention of systemic invasion by microbes [61, 62].

It was demonstrated that keratinocytes express TLR_2 and TLR_4 and that TLRs are involved in the microbial compound-mediated induction of proinflammatory cytokines in keratinocytes [63, 64]. Microbial compounds induce the nuclear translocation of NF-κB transcription factor, and the activation of NF-κB is required for the killing of *Candida* [63].

Recent studies have revealed that the pilosebaceous duct is also characterized by many features of immunological activity such as classical and nonclassical MHC class I expression, presence of intraepithelial Langerhans cells and expression of CD14, TLR_2 and TLR_4 [65, 66]. TLR_2 expressed by sebocytes might have a role in *P. acnes*-triggered induction of inflammatory response [67]. Antimicrobial peptides such as human β-defensins are also expressed in pilosebaceous follicles [68]. Investigation of the recently described immortalized sebaceous cell line might give better insight into the role of sebocytes in the innate immunity [69, 70].

CD1d Molecule in the Skin: Link between Innate and Adaptive Immunity

The CD1 molecules represent a family of conserved nonpolymorphic cell surface glycoproteins with a role in the presentation of nonpeptide antigens to T cells. The human CD1 gene family is composed of 5 members (CD1a, b, c, d and e); 4 of these genes are expressed in vivo (CD1a–d). The overall structure of the CD1 molecules resembles that of classical MHC class I molecules; however, the amino acid sequence homology to MHC class I is low which suggests a marked difference in function. On the basis of nucleotide and amino acid sequence homology, CD1 molecules are divided into two groups: group I, consisting of CD1a, b and c, and group II, comprising CD1d [71].

CD1d molecules are capable of presenting lipid and glycolipid antigens to a special type of T cells, the NKT cells [71]. The natural ligands of CD1d molecules are still unknown. In vitro and in vivo experiments have demonstrated that CD1d molecules are capable of binding synthetic glycolipids with a α-anomeric structure, α-galactosylceramide and α-glucosylceramide, and of presenting and stimulating NKT cells with these antigens. Interestingly α-mannosylceramide has been shown to be incapable of stimulating NKT cells, and the same proved to be true for all these ceramides with β-anomeric structure [72]. Additionally, the search for the natural antigen presented by CD1d to NKT cells identified that CD1d is capable of binding cellular phospholipids as phosphatidylinositol and glycosylphosphatidylinositol, and that this association is accomplished in the endoplasmic reticulum, but this complex is inert to the immune system [73].

Joyce [73] has suggested that CD1d molecules could function as 'sensor' molecules, sensing alterations in cellular lipid content. The presentation of a neo-self glycolipid, presumably induced by infectious assaults, such as viral and bacterial infections, activates NKT cells [73].

The CD1d molecule is expressed by a variety of cells: the thymocytes, activated T cells, B lymphocytes, professional antigen-presenting cells and also by intestinal epithelial cells [74–76]. Recently, the expression of CD1d in the skin was also elucidated. Keratinocytes, the major cell type of the epidermis have been shown to express CD1d, as well as sebocytes, dermal dendritic cells and endothelial cells [77]. Moreover, at least two forms of CD1d, one of 30 kD and the other of 47 kD, were found in keratinocytes by Western blot analysis [78].

The role of the CD1d molecule is to present glycolipid antigens to NKT cells [79]. These cells have the ability to rapidly secrete large amounts of cytokines following activation and without prior sensitization. NKT cell clones secrete type 1, type 2 or both types of cytokines, which could influence the differentiation of Th0 cells towards Th1 or Th2 cells, depending on the stimulus [80]. Recent studies have suggested that NKT cells also play an important role in cross-talk between components of the innate immune system as well as the adaptive immune system [81]. The rapid activation of these cells is characteristic of innate immunity and probably serves two purposes: to provide a first line of defense against pathogens and to orient the adaptive immune response in an adequate fashion with the nature of the pathogen. The role of CD1d in host defense has been suggested by studies performed in CD1d-deficient mice. *Borrelia burgdorferi* infection of CD1d-deficient mouse strains normally resistant to this pathogen resulted in arthritis, suggesting that CD1d is important in host defense against spirochetes [82]. CD1d-deficient mice also showed a significantly reduced clearance of *Pseudomonas aeruginosa* from the lung compared to wild-type mice [83]. CD1d has also been suggested to play a role in the host defense against *Mycobacterium tuberculosis, Toxoplasma gondii, Listeria monocytogenes, Plasmodium falciparum* and respiratory syncytial virus [84, 85].

CD1d expression is rapidly induced on keratinocytes in normal skin by physical trauma that disrupts barrier function [86]. This could represent an additional protective mechanism of the skin immune system.

CD1d-activated NKT cells have been suggested to play a role in the pathogenesis of several autoimmune diseases such as diabetes mellitus, rheumatoid arthritis, systemic sclerosis and psoriasis [87, 88].

Lipid antigen presentation in the skin by CD1d-expressing cells could be of major importance both in host defense against pathogens and in the pathogenesis of autoimmune disorders. The skin and especially the epidermis and the pilosebaceous unit are structures rich in lipids. The presence of glycolipids with modified structures could represent an important factor in the initiation and maintenance of immune responses. Bonish et al. [86] have recently shown that coculture of CD1d-positive keratinocytes with an NKT cell clone isolated from patients with psoriasis leads to activation and cytokine release, especially γ-interferon. This reveals that keratinocytes are able to function as nonconventional antigen-presenting cells and activate NKT cells by presenting lipid antigens with the help of CD1d molecules. Many pathogens also possess lipid antigens, which may represent potential antigens for presentation by CD1d-expressing cells to NKT cells.

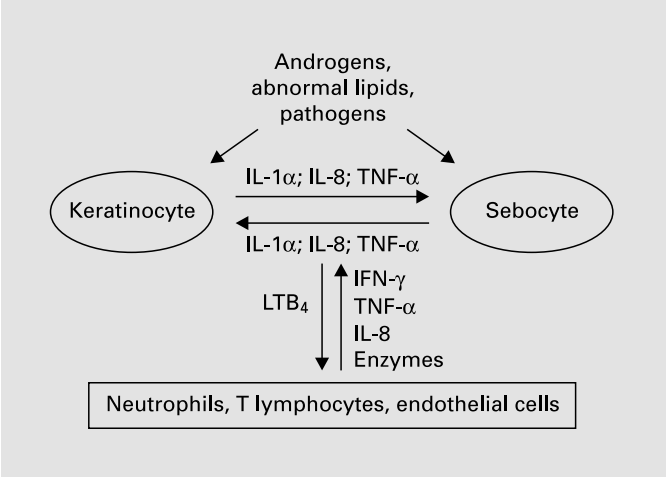

Fig. 1. Factors affecting cytokine release in the pilosebaceous unit of acne. TNF-α = Tumor necrosis factor α; IFN-γ = γ-interferon; LTB_4 = leukotriene B_4.

Role of Innate Immunity in the Pathogenesis of Acne

The two major cell types involved in the initiation of acne are the keratinocytes and the sebocytes. Since both cell types can participate in innate immunity, if *P. acnes* colonization occurs in the pilosebaceous unit, there is an increased possibility that PAMPs from *P. acnes* can stimulate the immune activity of these cells.

Expression of the LPS receptor CD14 was demonstrated in keratinocytes and sebocytes [66]. Hornemann et al. [89] showed that LPS can stimulate IL-8 secretion by human sebocytes but do not influence IL-1α expression at the mRNA and protein level. Interestingly, linoleic acid reduced the IL-8 secretion of sebocytes [90]. These results implicated the expression of CD14 molecules in human sebocytes and a competition of the proinflammatory activity of LPS by linoleic acid. CD14 expression was reduced in sebocytes by LPS and phorbol myristate acetate (PMA). Interestingly, both LPS and PMA enhanced IL-8 expression, while linoleic acid was unable to inhibit the stimulatory LPS effect. IL-1α expression in SZ95 sebocytes was barely affected by LPS, PMA or linoleic acid. PMA, but not LPS and linoleic acid, stimulated total sebaceous lipids. Therefore, LPS and PMA are likely to serve as proinflammatory signals in human sebocytes inducing CD14-dependent and independent IL-8 expression, respectively. Linoleic acid was unable to antagonize the proinflammatory activity of LPS [66, 91].

It was demonstrated that *Staphylococcus aureus* induces the production and release of IL-8 by keratinocytes in a TLR_2 -dependent manner. It was also shown that LPS induced IL-8 expression and release by keratinocytes in a TLR_4-dependent manner [63]. The expressions of TLR_2 and TLR_4 in cultured human sebocytes were demonstrated by Oeff et al. [65]. Upon ligand binding, TLRs activate NF-κB, which promotes the transcription of proinflammatory cytokines, inducible enzymes, adhesion molecules and antimicrobial peptides. The effect of LPS on TLR expression was also examined in sebocytes; LPS increased TLR_2 expression and was without significant effect on TLR_4 [92].

Recent investigations on the recognition of *P. acnes* have shown that this pathogen induces expression of IL-8 in a TLR_2- and NF-κB-dependent manner [27, 67]. CD14 is also involved in the *P.-acnes*-induced upregulation of IL-8 expression. Confirmation of the presence of receptors and signaling pathways involved for the recognition of *P. acnes* in cells of the pilosebaceous unit supports the widely accepted view that inflammation in acne vulgaris may be induced or at least sustained by an immunological reaction to extracellular products of *P. acnes.*

The mechanisms by which *P. acnes* induces immune responses in keratinocytes and sebocytes are possibly similar to those of other gram-positive bacteria. Two major components of the gram-positive cell wall that had been described to induce immune responses are peptidoglycan and lipoteichoic acid. The former induces the production of IL-8 in a TLR_2-dependent manner in keratinocytes, while the effect of the latter on keratinocytes is mediated by TLR_4 [63, 64]. In sebocytes lipoteichoic acid suppressed the expression of TLR_2 and TLR_4 [92].

Keratinocytes are biochemically very active cells, which are able to produce various kinds of cytokines, growth factors and antimicrobial compounds. They contain a significant amount of intracellular IL-1α, which is released after physical stress. IL-1α is known to amplify the immune response. Guy and Kealey [93] have investigated whether IL-1α could be responsible for the induction of hypercornification of the infundibulum in a cultivated human pilosebaceous model system. They found that addition of 1 ng/ml IL-1α to the pilosebaceous infundibulum maintained in keratinocytes serum-free media resulted in hypercornification of the infundibulum similar to that seen in comedones [93].

Walters et al. [94] have investigated the ability of skin commensal microorganisms to modulate IL-1α release in cultured human keratinocytes. According to their results, low levels of IL-1α are released constitutively by cultured

keratinocytes, but the release of a biologically active form of this cytokine was not increased by microorganisms. They also found that there were individual differences in sensitivity to microbes between individuals [94]. Similarly to keratinocytes, cultured human sebocytes were also shown to produce IL-1α, but its expression was barely influenced by LPS [89].

Increased IL-8 release could initiate increased antigen presentation since IL-8 is known to upregulate the expression of HLA-DR in cultured human keratinocytes [95]. IL-1α has no effect on the expression of intercellular adhesion molecules 1 and 3 or HLA-DR in infundibular keratinocytes [13].

The finding of Vega et al. [96] that adapalene, a synthetic retinoid used for the topical treatment of acne, exerts its beneficial effects at least partially through downregulation of the expression of TLR_2, one of the main receptors involved in the recognition of *P. acnes*, may suggest that microorganisms present in acne lesions could make a significant contribution to the promotion and sustainment of inflammation in acne. Adapalene has no effect on the expression of other myeloid markers such as CD14, which is also involved in the recognition of *P. acnes* and on the expression of HLA-DR.

Beside *P. acnes*, abnormal lipids may also affect the activity of keratinocytes and sebocytes. These lipids could directly influence the proliferation and differentiation status of these cells and the release of various cytokines [10]. Keratinocytes and sebocytes may function as non-professional antigen-presenting cells. CD1d, which is expressed by both types of cells [77, 86] may present abnormal lipids from the pilosebaceous unit and stimulate NKT cells. After activation these cells are capable of secreting cytokines, which further activate conventional T cells and cells of the innate immune system [79]. These cytokines could also stimulate keratinocytes and sebocytes contributing to their abnormal proliferation and differentiation (fig. 1).

Conclusion

The SIS plays an important role in the pathogenesis of acne. Beside the implication of immune mechanisms in the induction and maintenance of inflammatory lesions, the SIS may have a role in the development of early, non-inflammatory lesions of acne. New aspects of the immune functions of keratinocytes and sebocytes, such as pathogen recognition performed by PRRs and lipid antigen presentation by CD1d molecules, should be considered as possible pathogenetic factors in the development of acne lesions.

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