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What's New in Acne Pathogenesis

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ABSTRACT

In recent years, our knowledge on the classic pathogenic factors of acne, i.e., androgenic control of sebaceous gland, infundibular retention hyperkeratosis, *Propionibacterium acnes* and inflammatory events, attained a new depth. This article summarizes newer information, including the importance of altered lipid and oxidant/antioxidant ratio in sebum composition, the crucial role of *P. acnes* as the primary elicitor of host's innate and adaptive immune responses, and the likely involvement of matrix metalloproteinases in scar formation. Furthermore, polymorphisms of genes that function in the steroid hormone metabolism, innate immunity-related genes and fibroblast growth factor receptor 2 (FGFR2) found to be associated with acne are discussed. Emerging evidence demonstrates that dietary triggers, especially the high glycemic load diet and milk consumption, may aggravate acne vulgaris by raising insulin and insulin-like growth factor 1 (IGF-1) levels. Paradigm shifting data show that subclinical inflammation may be the initial driver of follicular hyperkeratinization and hyperproliferation, indicating that our understanding of acne pathogenesis will continue to evolve in the future.

INTRODUCTION

Acne, an exclusively human disease, is a very common skin condition which affects as many as 85% of teenagers and 3% of those aged 35–44 years.[1] Its pathogenesis is complex and multifactorial, with pubertal androgenic stimulation of the sebaceous gland playing a major role while follicular hyperkeratosis, increased colonization with *Propionibacterium acnes,* inflammatory events, and dietary and lifestyle factors contributing additionally in variable proportions in genetically susceptible

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individuals. The current body of evidence indicates that the relationship between sebum production, hyperkeratosis, *P. acnes* and inflammation is more complex than thought previously, with data even suggesting that inflammatory events may precede microcomedone formation and that the plug formation is at least partially influenced by inflammation produced by *P. acnes*.[2] It is clear that these processes are all interrelated since sebum is necessary for *P. acnes* colonization of the skin and *P. acnes* is essential in switching on the innate and adaptive immune system leading to the inflammation. Currently, acne is considered primarily an inflammatory skin disease of the pilosebaceous unit, and the precise mechanism by which *P. acnes* contributes to the pathogenesis of acne remains unknown.

Regarding the role of diet in acne, there is a general perception that non-Western populations have a lower incidence of acne, and that this incidence increases when a Western dietary pattern is adopted, implying that genetic predisposition is not the only relevant factor in the development of acne.[3] In this article, we provide a comprehensive review of these notable factors in the pathogenesis of acne.

PATHOGENIC FACTORS

Role of Sebaceous Gland and Androgens

Sebaceous Gland

The function of the sebaceous gland, a holocrine gland, is to excrete sebum and sebum excretion occurs in parallel with acne development. Sebum contains triglycerides (TGs) and fatty acid breakdown products, wax esters, squalene, cholesterol esters and cholesterol.[4] The sebaceous gland is a steroidogenic organ that possesses all the enzymes required for sex-hormone synthesis and metabolism. It can synthesize androgens *de novo* from cholesterol or by locally converting weaker circulating androgens to more potent ones.[5] Functional studies on sebocytes have been conducted mainly with cell culture models using mammalian sebocytes, human sebocyte-like cells (human, mouse, hamster and rat) and human sebaceous gland cell lines (SZ95, SEB-1, Seb-E6E7).[5,6] Identification of functional receptors for neuropeptides such as corticotropin-releasing hormone (CRH), melanocortins (MCs), β-endorphin, vasoactive intestinal polypeptide, calcitonin gene-related peptide and substance P[7,8] gave rise to the notion that human sebaceous gland is like the "brain of the skin".[9] Since CRH is expressed in human sebocytes, stress may affect inflammatory changes in early acne lesions.[10] In SZ95 cells that are not stressed, CRH promotes lipogenesis in autocrine fashion.[11] However in acne lesions, CRH expression was strongly enhanced, and this further stimulated the release of interleukin (IL)-6 and IL-8 from sebocytes by an IL-1β-independent manner.[7] Excessive sebum production is one of the major

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factors in the pathogenesis of acne. Among the MC receptors [melanocortin-1 receptor (MC-1R) and melanocortin-5 receptor (MC-5R)] that are expressed in human sebocytes, MC-1R is expressed in both undifferentiated and differentiated sebocytes, whereas MC-5R is expressed only in the differentiated lipid-containing cells at the center of sebaceous glands,[12] and is therefore associated with sebocyte differentiation and sebum production.[13] MC-1R expression was shown to be increased in the sebaceous glands of acne lesion *in vivo*.[14] Treatment of cultured sebocytes with substance P led to enhanced IL-1, IL-6, tumor necrosis factor alpha (TNF-α) and peroxisome proliferator-activated receptor gamma (PPARγ) gene and protein expression, further supporting the role of stress in acne development.[15]

The pilosebaceous unit is an immunocompetent organ, the infundibular keratinocytes and sebocytes being fully equipped with the capacity to elicit innate immune responses.[16] The keratinocytes and sebocytes may be activated by *P. acnes*, via toll-like receptors (TLRs) and cluster of differentiation (CD) 14, recognize altered lipid content in sebum, and produce inflammatory cytokines.[17]

Among the components of sebum, the TG fraction appears to be responsible for acne development;[18,19] bacteria can hydrolyze sebaceous TGs and liberate fatty acids which can penetrate the follicular wall and become incorporated into the surrounding epidermis.[20] The application of free fatty acids on rabbit ears or hairless mice was shown to induce hyperkeratinization and epidermal hyperplasia similar to the process of comedogenesis.[18,21] Research has shown that among the fatty acids only monounsaturated fatty acids (MUFAs) stimulate the morphological changes in comedo formation whereas TGs and saturated fatty acids (SFAs) have little effect.[18] Presumably, MUFAs of sebum interfere with the intracellular calcium dynamics of follicular keratinocytes and the intercellular lipid bilayer structure of epidermal barrier.[18] Sebum contains a high proportion of MUFAs, with a characteristic double bond at the Δ6 position[19] instead of the standard Δ9 position. Sebum itself is not a direct cause of acne since not everybody gets acne, rather, the compositional changes that occur with increasing sebum production seem to affect events involved in comedo formation.[22] Sebum alterations associated with acne include: (1) decrease in linoleic acid which affects the composition of sphingolipids, which may be involved in the follicular hyperkeratosis crucial in comedogenesis;[22] (2) incorrect activity of specific desaturase enzymes altering the ratio between Δ6 and Δ9 unsaturated fatty acids, with resultant compositional changes that can drive toward acne development;[23] and (3) lipid peroxidation byproducts, such as squalene peroxide, which lead to follicular hyperkeratinization, increased proliferation of sebaceous glands, and upregulation and release of inflammatory mediators such as IL-6.[23] When sebum was analyzed in individuals with and without acne, subjects with acne had more (59%) sebum than controls, and free fatty acids were reduced in the sebum of acne subjects whereas squalene was upregulated 2.2-fold in acne subjects,[24] suggesting

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potential utility of squalene amount as a lipid marker to diagnose acne-prone skin. Sebaceous gland lipids demonstrate direct proinflammatory and anti-inflammatory properties; specifically the induction of 5-lipoxygenase (5-LOX) and cycloxygenase-2 (COX2) pathways in sebocytes leads to the synthesis of proinflammatory lipids.[25] Conversely, the proinflammatory cytokine TNF-α can induce lipogenesis in SZ95 sebocytes through the Jun N-terminal kinase (JNK) and phosphoinositide-3-kinase/Akt (PI3K/Akt) pathways,[26] providing rationale for anecdotal reports of dramatic improvement in acne following administration of etanercept, a soluble TNF-α receptor antibody.

Fatty acids also act as ligands of nuclear hormone receptors such as the PPARs, which are transcription factors involved in lipid metabolism and energy homeostasis. Activation of PPARγ and PPARα by their respective specific ligands was found to stimulate lipid droplet accumulation in cultured immature sebocytes but not in keratinocytes, with 5α-dihydrotestosterone (DHT) exhibiting an additive effect only with combination of DHT and PPARγ. This demonstrates that PPARγ influences a step in sebocyte differentiation that is distinct from that influenced by androgen.[27] In another study, PPARβ/δ messenger ribonucleic acid (mRNA) was overexpressed in both inflammatory and noninflammatory acne *in vivo*.[28]

The sebaceous gland also expresses antimicrobial peptides such as human β-defensin 1 (hBD-1), hBD-2 and cathelicidin (LL-37).[29] Although hBD-2 has no direct antimicrobial effects on *P. acnes*,[30] it acts synergistically with cathelicidin.[31] Sebum free fatty acids have antibacterial activity against Gram-positive bacteria. When human sebocytes were incubated with free fatty acids, the expression of hBD-2 was dramatically enhanced, suggesting that free fatty acids may provide direct antibacterial activities against *P. acnes* and enhance the skin's innate antibacterial defense.[32]

SZ95 sebocytes express liver X receptor (LXR) α and LXRβ, which belong to the nuclear receptor superfamily and play a critical role in cholesterol homeostasis and lipid metabolism.[33] Among the two receptors, only LXRα expression was enhanced and lipid synthesis increased by LXR ligands. Furthermore, LXR ligands decreased lipopolysaccharide (LPS)-induced proinflammatory factors COX2 and inducible nitric oxide synthase (iNOS), suggesting the important roles of LXRα in differentiation and inflammatory signaling in the sebaceous gland.[34]

Acetylcholine receptors (AchR) are also expressed in sebocytes and infundibulum. Stimulation of the receptors by acetylcholine can promote infundibular epithelial hyperplasia and follicular plugging, possibly linking an etiological role of nicotine uptake from smoking in comedonal acne characteristic of smokers.[35]

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Androgens

Hormones are undeniably the initiating factor in the pathogenesis of acne. With the surge of androgens in puberty, sebaceous gland is known to mature and begin secreting sebum actively. Androgen receptors (ARs) are expressed in the basal layer of the sebaceous gland and in the outer root sheath keratinocytes of the hair follicle.[36] When free testosterone enters the cell, it is quickly reduced to DHT by the 5α-reductase enzyme, whose activity is increased in proportion to the size of the sebaceous gland.[37] In primary human sebocyte culture, androgens testosterone and DHT only stimulate sebocyte proliferation[38] through sterol-response element-binding proteins (SREBPs), whereas PPAR ligands are required for differentiation and lipogenic activity.[39] Exogenous administration of testosterone and dehydroepiandrosterone sulfate (DHEA-S) increases sebaceous gland size and sebum production.[40] Serum androgen levels, however, do not correlate with acne severity. Therefore androgens may only serve as a prerequisite for acne development.[17] Despite the clinical evidence that androgens stimulate sebaceous gland, the *in vitro* effect of androgens on the proliferation and differentiation of sebocytes vary in different experiments and cell types.[17] The mechanisms by which androgen/AR regulate sebocyte activity in acne vulgaris are still unclear. Androgens might cross talk with IGF-1 activities in controlling acne development.[41] At puberty, IGF-1 induces synthesis of androgens and enhances 5α-reductase activity in the skin.[42] In addition, IGF-1/PI3K/Akt activity stimulates phosphorylation of FoxO1, an AR corepressor. Upon phosphorylation, FoxO1 translocates from the nucleus to the cytosol and releases its inhibition on AR transactivation.[41] Recently, in human sebocyte culture, addition of DHT upregulated IL-6 and TNF-α gene and protein expression, suggesting that DHT may participate in inflammatory acne process as well.[43] In addition to affecting sebaceous gland activity, androgens also influence keratinization of follicular corneocytes.[44]

Role of Follicular Epithelial Cells

The initial plugging of the pilosebaceous canal is thought to be from a mechanical effect[27] because electron microscopic findings show retention hyperkeratosis with increased number and size of keratohyaline granules and pressure-induced folding of retained squames on themselves.[27] Androgen stimulates ductal keratinocytes to multiply; the proliferating keratinocytes are propelled toward the center of the sebaceous duct, which expands to accommodate the increasing volume of lipid droplets until the inelastic "glassy membrane" that encloses the pilosebaceous duct can expand no further. Further accumulation of keratinocytes in this closed system causes an increase in intraluminal pressure, leading to hypoxia in the central part of the duct.[27] This produces an anoxic environment that favors intraductal *P. acnes*

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colony formation, which leads to rupture of the duct walls with release of luminal antigens and resultant inflammation. This was the classic theory of how acne develops. Recent studies using clinically normal follicles from uninvolved skin of acne patients show that vascular endothelial cell activation and inflammatory responses occur prior to and act as possible causal factors in the hyperproliferative changes of acne, as opposed to a secondary event, with increased IL-1 activity occurring prior to follicular hyperproliferation around uninvolved follicles, triggering the "keratinocyte activation cycle".[45]

Although the exact cause of follicular hyperkeratinization is still to be elucidated, IL-1α seems to play an important role since it was reported to induce infundibular hyperkeratinization *in vitro* and *in vivo*.[40] In addition to this change, dysregulated terminal differentiation with increased filaggrin expression[46] and follicular keratinocytic hyperproliferation with the hyperproliferative markers of keratin [K6 and K16] was observed.[47] Besides IL-1α, increased DHT,[44] relative deficiency of linoleic acid and peroxides in sebum,[48] and *P. acnes* extracts[46] may all contribute to abnormal hyperkeratinization of infundibular keratinocytes. To elucidate the pathogenesis of closed and open comedo formation, studies have been performed on nevus comedonicus, and the results show association of gain-of-function mutation of fibroblast growth factor receptor 2 (FGFR2), which is also the causative mutation of acne in Apert's syndrome.[49,50] This will be dealt with in more detail later in this article.

Role of *Propionibacterium Acnes*

Propionibacterium acnes is a normal commensal in the pilosebaceous units, found to be present in nearly 100% of adults.[51] Its population density rises in puberty with an increased sebum excretion rate, keeps increasing until the age of 25 years, and remains constant thereafter through middle age with a declining trend after age 70 years, regardless of race.[52] Not everyone gets acne, and there is no relationship between acne severity and follicular population density of *P. acnes*.[53] Therefore, a question rises as to whether *P. acnes* is a true etiological pathogen or not in acne. There is at present no definitive proof that microorganisms, particularly *P. acnes*, initiate either comedogenesis or inflammation in acne.[54] What exists is circumstantial evidence that a proportion of normal pilosebaceous follicles are colonized by *P. acnes*; a favorable microenvironment leads to increased colonization of microcomedone by *P. acnes* which may further aggravate comedogenesis; and an inflamed lesion may further provide an enriched environment for the colonization as well as proliferation of *P. acnes*. *P. acnes* can intensify the inflammatory process but is dispensable for its initiation. Nevertheless, we will overview the evidence of the role that *P. acnes* plays in comedogenesis and inflammation.

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Recently, acne was suggested to be an IGF-1-mediated disease.[55] IGF-1 and IGF-1 receptor (IGF-1R) were overexpressed in acne lesions, and *P. acnes* extracts elevated IGF-1 and IGF-1R expression in the epidermis and induced keratinocyte proliferation, demonstrating that *P. acnes* can help induce the formation of comedone by stimulating the IGF/IGF-1R system.[56] In addition, *P. acnes* extracts can directly modulate the differentiation of keratinocytes by inducing transglutaminase, K17, integrin (β1, α3, α6x and αVβ6) and filaggrin expression,[46] while decreasing K1 and K10 expression.[57] Also *P. acnes* was shown to increase the CRH expression in the epidermis, thereby modulating the differentiation of keratinocytes and increasing local inflammation, hence possibly playing a role in the formation of early microcomedo.[58] Furthermore, *P. acnes* has been shown to form biofilms, a biological glue, that may lead to the increased cohesiveness of corneocytes in acne, leading to comedone.[2] A biofilm is a complex aggregation of microorganisms within an extracellular polysaccharide lining, and it is secreted after adherence to a surface.[2] The biofilm confers *P. acnes* increased resistance to antimicrobial agents with enhanced production of virulence factors.[59] Indeed, the genome sequence of *P. acnes* revealed immunogenic and surface-associated genes, confirming the existence of the acne biofilm.[60]

P. acnes produces various exogenous proteases, and these proteases at least partially elicit cellular responses via proteinase-activated receptor 2 (PAR-2), a sensor for exogenous danger molecules. Increased protease activity and PAR-2 expression was demonstrated in acne lesions. *P. acnes* induced calcium signaling and stimulated IL-1α, IL-8, TNF-α, hBD-2, LL-37, and matrix metalloproteinase (MMP) 1, 2, 3, 9, and 13 in keratinocytes through PAR-2, indicating that PAR-2 plays an important role in acne pathogenesis by inducing inflammation, innate immune responses and matrix degradation.[61]

P. acnes is important in the induction and maintenance of the inflammatory phase of acne. The evolving concept of immune response includes microbial invasion, subsequent activation of innate immune system followed by recovery from the microbial infection, or in case this direct recovery is not feasible, secondary activation of adaptive immune system which results in recovery and immune memory with further activation of innate immune system. TLRs are the best studied transmembrane pattern recognition receptors (PRRs) that sense and bind with certain pathogen-associated molecular patterns (PAMPs) such as LPS and CpG DNA and activate the innate immune system. The intracellular portion of TLR has homology with the cytoplasmic domain of the IL-1 receptor; the intracellular portion may trigger a Myd88-dependent pathway that leads to the nuclear translocation of the transcription factor nuclear factor kappa B (NF-κB) and ultimate transcription of many immune response genes.[62] TLRs are mainly located in blood and tissue immune cells. Ten TLRs have been identified in humans so far.[63] TLR4 is highly specific for LPS from Gram-negative bacteria,

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while TLR2 mediates the recognition of lipopeptides from Gram-positive bacteria.[64] TLR2 was expressed on the surface of macrophages surrounding pilosebaceous follicles, and *P. acnes*, Gram-positive anaerobic bacilli, induced cytokine (IL-1β, IL-8, IL-12 and TNF-α) production in monocytes through a TLR2-dependent pathway.[65] The IL-8 produced by the activated monocytes is a potent T cell chemoattractant and neutrophil activator, and as a result, neutrophils release proteins including defensins. Among the six different α-defensins and two β-defensins identified in humans, human neutrophil proteins (HNP) 1-3,[66] and hBD 1 and 2[29] have been found in acne lesions. Interestingly HNPs were expressed only in inflammatory acne lesions suggesting that they may contribute to the development of inflammatory lesions.[66] Contrary to the earlier dogma, it has been shown that the initial infiltrating cells in developing inflammatory acne lesions are mononuclear cells which are predominantly CD4+ "memory/effector skin homing"T cells and that neutrophils appear later in the course of inflammation.[67,68] Inflammatory events, consisting of IL-1α and increased CD4+ T cells occur in the very earliest stages of acne development, before hyperproliferation or abnormal differentiation of follicular epithelium.[69] Once neutrophils infiltrate into the acne lesion, neutrophil α-defensins, in addition to their antimicrobial effects, induce selective chemotaxis of CD45RA/CD4 cells, CD8 T cells and immature dendritic cells at nanomolar concentrations,[70] amplifying chronic inflammatory responses.

Normal keratinocytes express TLR1, 2, 4 and 5.[71,72] When keratinocytes from acne patients are exposed to *P. acnes* extract *ex vivo*, the expressions of TLR2, TLR4 and MMP9 are increased.[73] Only certain strains of *P. acnes* were found to induce selective IL-8 and hBD-2 expression in human keratinocytes via TLR2 and TLR4 and induce keratinocyte growth *in vitro*.[74] *P. acnes* GroEL (a heat-shock protein) is able to upregulate the proinflammatory cytokine production of keratinocytes.[75] In inflammatory acne, the early interaction between keratinocytes and bacteria appears crucial since keratinocytes produce reactive oxygen species (ROS) and proinflammatory cytokines in response to the bacteria.[76] SZ95 sebocytes also constitutively express TLR2, TLR4, CD14, IL-1α, IL-1β, IL-6 and IL-8. When exposed to LPS of Gram-negative bacteria and lipoteichoic acid of Gram-positive bacteria,[30] SZ95 sebocytes increase the production of IL-6 and IL-8, in addition to antimicrobial lipids[48] and antimicrobial peptides (hBD-2, psoriasin and cathelicidin).[30,31,77] Therefore, innate immunity can be induced directly in keratinocytes and sebocytes without involving the inflammatory cells, and recruitment of inflammatory cells to the involved sites amplifies the inflammatory process in acne.[78] Once the adaptive immune response takes over the innate immunity, the inflammatory reaction is augmented dramatically. However, the magnitude of this response is not related to the amount of bacteria.[76] Rather, acne severity is related to the capacity of various *P. acnes* strains to induce inflammation, and to the host's genetic capacity to respond to *P. acnes* immunologically.[76]

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Colonization of pilosebaceous unit by *P. acnes* is the main event that leads to inflammation. Recently a higher prevalence of follicular *P. acnes* colonization was actually visualized, with greater number of follicles containing *P. acnes* and the greater numbers of bacteria in macrocolonies/biofilms than in controls.[79] *P. acnes* also directly augments intracellular lipid formation in hamster sebocytes by increasing the *de novo* synthesis of triacylglycerols.[80] LPS directly increases inflammation in sebaceous glands *in vivo* by augmenting COX2, $PGF_{2\alpha}$ and $PGF_{2\alpha}$-mediated pro-MMP2 productions.[81] The production of pro-MMP2 was augmented by *P. acnes*-derived factors in hamster sebocytes and dermal fibroblasts, suggesting that the bacteria may participate directly in acne scar formation.[82]

In summary, *P. acnes* is capable of inducing inflammation by: (1) releasing lytic enzymes and lipases that trigger the rupture of follicular epithelium and inflammatory reaction; (2) producing chemotactic factors that recruit neutrophils through the epithelial wall;[83,84] (3) activating the innate immune system through the TLR2 and TLR4 mentioned above; (4) stimulating the formation of C5a by activation of the classical and alternative complement pathways;[85] and (5) triggering the adaptive immune response evidenced by the presence of activated T helper 1 (Th1) cells in early inflamed acne lesions.[86] In acne vulgaris patients, high serum antibody titers[87] directed to several putative surface proteins[88] of *P. acnes* were detected. Infiltrating neutrophils destroy the *P. acnes*, but the bacteriolysis results in the production of hydrolases that add to further disruption of follicular epithelium and enhanced inflammation. Recently *P. acnes* was shown to secrete Christie Atkins Munch-Petersen (CAMP) factor, a virulence factor that was cytotoxic to keratinocytes and macrophages in a synergistic manner with the host acid sphingomyelinase. Such observation has led to the possibility of applying vaccine technology that targets both the secreted *P. acnes* CAMP factor and host acid sphingomyelinase to locally suppress inflammatory acne.[89]

Gene array expression profiling in acne lesions was conducted for the first time in 2006 and revealed marked upregulation of genes involved in inflammation and matrix remodeling, including MMP1 and 3, IL-8, hBD4, and granzyme B.[90] An emerging picture is the chronic inflammatory nature of acne triggered by a pathogen, *P. acnes*.

Role of Immune Mediators

Clearly, inflammatory cytokines, chemokines and other proteins including IL-1, IL-8 and certain MMPs mediate acne.[91] In normal unstressed sebocyte culture, cytokines such as IL-1α, TNF-α, IL-6 and IL-8 are present.[25] Treatment of cultured sebocytes with *P. acnes* and LPS significantly upregulates the expression of proinflammatory cytokines, with *P. acnes* stimulating IL-8 and TNF-α and LPS stimulating IL-8, TNF-α and IL-1α.[30]

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P. acnes-stimulated keratinocytes also play an important role in the inflammatory reaction, producing a number of proinflammatory cytokines and chemokines such as IL-1α, IL-1β, IL-8, GM-CSF, TNF-α and hBD-2 through the TLR2 and TLR4 signaling pathways *in vitro*.[65,73] *P. acnes* activates NF-κB and mitogen-activated protein kinase (MAPK) pathways[92] and recruits macrophages and immune cells to the site of infection.

When stimulated by *P. acnes* surface proteins, keratinocytes were shown to rapidly produce ROS, and especially superoxide anions[93] by NAD(P)H (nicotinamide adenine dinucleotide phosphate hydrogen) oxidase (NOX) pathway through activation of the scavenger receptor CD36. The superoxide anions combine with nitric oxide to form peroxynitrites which in turn, activate p38 and extracellular signal-regulated kinase (ERK), MAPKs, leading to IL-8 production. IL-8 production is also activated through *P. acnes*-induced TLR2 signaling pathway.[93] Furthermore, *P. acnes*-induced superoxide anions abrogated *P. acnes* growth and were involved in the lysis of keratinocytes through formation of peroxynitrites. Retinoic acid derivatives prevent superoxide anion production, IL-8 release and keratinocyte apoptosis, demonstrating the relevance of this pathway *in vivo*.

Leukotriene B4 (LTB4), a proinflammatory mediator synthesized from arachidonic acid by 5-LOX, is also implicated in the pathogenesis of acne because systemic treatment with a specific LOX inhibitor resulted in 60% decrease in acne severity index within 3 weeks and 70% reduction in inflammatory lesions at 3 months, with 65% reduction in sebum total lipids.[94] LTB4 is also a natural ligand for PPARα; therefore, PPAR regulation can modulate the tissue inflammation in acne lesions by inhibiting the expression of proinflammatory genes.[95] On the other hand, COX-2 expression and PGE_2 production are increased by PPARγ agonists.[81]

A decrease in the body's antioxidant activity may also play a role in the pathogenesis of acne. The superoxide dismutase (SOD) levels were significantly lower in leukocytes from acne patients[96] in a dose-dependent manner; the more severe the acne, the lower the SOD activity in tissues and blood. Other parameters of oxidative stress such as serum malondialdehyde (MDA) level and xanthine oxidase activity were higher, and serum catalase and SOD activity was lower in acne patients.[26] MDA is an end-product of lipid peroxidation induced by oxygen free radicals and is well correlated with the degree of lipid peroxidation.[12] When stratum corneum samples from involved and normal skin of acne patients and healthy controls were compared for quantity of glutathione, a component of endogenous antioxidant system, both samples from acne patients contained a significantly lower amount.[97] Whether the oxidative stress is the cause or outcome of the inflammatory events is yet to be determined. All these data suggest that *P. acnes* could modulate host genes, which might in turn influence the inflammatory reaction.

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Genetic Factors

Genetic factors, which play a role in the pathogenesis of acne, were initially demonstrated by twin studies and community-based studies.[36,98-101] In these studies, the occurrence and severity of acne symptoms showed a strong concordance in identical twins and a familial tendency. In a large British female twin study of 458 monozygotic and 1,099 dizygotic pairs, 47% of acne twins had a family history of at least one non-twin sibling affected with acne compared with 15% in non-acne twins; acne in either parent was reported in 25% of acne twins and 4% of non-acne twins; 41% of acne twins had at least one child affected with acne, in contrast to 17% of controls.[99] The authors of this study showed that acne is one of the most heritable skin disorders with 81% of the variance in acne liability attributed to additive genetic factors and only 19% to environmental factors.[99]

Genes Involved in Steroid Metabolism

Serious search for specific genetic susceptibility factors only began in the 1990s.[102-104] At that time studies involved genes affecting steroid hormone metabolism, including human cytochrome P-450 1A1 gene (CYP1A1),[102] steroid 21-hydroxylase gene (CYP21)[103] and AR gene polymorphisms.[104] Since cytochrome P-450 enzymes are involved in the metabolism of a wide range of endogenous and foreign compounds and CYP1A1 is involved in vitamin A and endogenous retinoid metabolism, polymorphisms in the regulatory sites of CYP1A1 may impair the biological efficacy of natural retinoids due to their rapid metabolism to inactive compounds, with resultant abnormal sebocyte differentiation and hyperkeratinization of follicular canal, initiating acne in some patients.[102] Several years later, two Chinese studies investigated CYP17-34 (T > C) single nucleotide polymorphisms (SNPs) and found that CC homozygote Chinese male patients were at a significantly increased risk of developing severe acne[105] and that this mutation increased the risk of postadolescent acne in Chinese female patients with increased androgen levels.[106] CYP17 encodes cytochrome P-450c17α which is a key enzyme in androgen biosynthesis, mediating both steroid 17α-hydroxylase and 17,20-lyase activity.[107] Therefore, this SNP may result in a higher level of androgen in serum, followed by enhanced sebum production and follicular keratosis. An inadequate activity of steroid 21-hydroxylase, as well as CYP21 mutation, is the most common defect in late-onset congenital adrenal hyperplasia which presents with symptoms of androgenicity including acne. Although a CYP21 mutation was more common in acne patients, there was a poor correlation between the mutation and either elevated steroids or acne, suggesting other factors for the variable phenotype of hyperandrogenism.[103]

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Androgen works by binding to nuclear ARs which are localized in the basal layer of sebaceous gland and outer root.[108] When androgen activates the receptor, the ligand-receptor complex is translocated to the nucleus and transactivation of androgen-regulated genes occurs. The modulatory domain of AR gene includes a polymorphic CAG triplet repeat coding for a polyglutamine tract whose number is inversely correlated with AR's transcriptional activity.[109] AR polymorphism of CAG repeat length did not exhibit a correlation with acne in Caucasians,[104] but in Chinese Han population the CAG repeat length was significantly shorter in male acne subjects,[110] suggesting this variable number of tandem repeat (VNTR) polymorphism as a candidate genetic marker for male acne susceptibility and hinting at genetic differences in each ethnic group.

Since elevated levels of serum IGF-1 correlate with overproduction of sebum and acne[55,111] and functional relationship between IGF-1 (CA) 19 polymorphism and circulating IGF-1 levels is known,[112] IGF-1 (CA) 19 polymorphism was investigated in Turkish acne patients and a significant association was found between this polymorphism and acne severity regardless of gender.[113] The varying frequency of IGF-1 (CA) 19 among different populations, with the highest frequency in Caucasian (65.5%) followed by Asian (33.3%) and African-American (15.6%) population,[114] may offer a partial explanation for different susceptibility to acne in each race.

Innate Immunity Genes

More recently, a handful of reports on genetic polymorphisms in the innate immunity genes were added.[102,103,105,106,110,113,115-123] In the innate immune system, external danger signals including microbes activate pathogen recognition receptors such as TLRs, which leads to the release of early response cytokines including IL-1α and TNF-α. The resultant increased expression of various downstream target genes such as those of adhesion molecules, secondary cytokines and chemokines, and infiltration of professional immune cells, can lead to uncontrolled inflammation.[124]

Two mutations in the TLR2 gene, Arg677Trp and Arg753Gln, and two SNPs causing Asp299Gly and Thr399Ile changes in the TLR4 gene were investigated in 101 Central European subjects, but no association was found between these mutations and acne, suggesting that carriage of TLR2 or TLR4 SNP allele may not affect susceptibility of patients for acne vulgaris.[125] More recently, the carriage of the above SNPs of TLR4 was shown to be protective against the development of acne conglobata in Greek subjects, implying the possibility of modulating TLR4 for therapeutic purposes.[115]

The gene IL1A encoding IL-1α, a central molecule in cutaneous inflammatory reactions, was also investigated for a relevant mutation in Central Europeans, and

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