Innate and Adaptive Immunity in Acne Vulgaris

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Abbreviations

AIM2	Absent in melanoma 2
AP-1	Activator protein 1
C. acnes	*Cutibacterium acnes*
C. albicans	*Candida albicans*
CAMP (LL37)	Cathelicidin antimicrobial peptide
CAMP factor	Christie-Atkins-Munch Peterson factor
CXCL8	C-X-C motif chemokine ligand 8
GM-CSF	Granulocyte-macrophage colony-stimulating factor
hBD2	Human beta-defensin 2
IFNγ	Interferon-gamma
IGF-1	Insulin-like growth factor 1
IL-1, 6, 10, 12	Interleukin-1,6, 10, 12
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
MAPK	Mitogen-activated protein kinase
MMP1, 3, 9	Matrix metalloproteinase-1, 3, 9
NF-κB	Nuclear factor kappa B
NLRP1, 3	NLR Family Pyrin Domain Containing 1, 3
P. acnes	*Propionibacterium acnes*
PAPA syndrome	Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PAR2	Proteinase-activated receptor 2
PRR	Pattern recognition receptor
PSU	Pilosebaceous unit
ROS	Reactive oxygen species
SAPHO syndrome	Synovitis, acne, pustulosis, hyperostosis, and osteitis
SCFA	Short-chain fatty acids
TLR2, 4	Toll-like receptor 2, 4
TNFα	Tumor necrosis factor-alpha
TNIP1	TNFAIP3-interacting protein 1
VCAM1	Vascular cell adhesion molecule 1

Introduction

Acne vulgaris is a prevalent and clinically well-characterized skin disease. In the last three decades, the rapid advancement of experimental dermatology significantly improved our view, but there are still open questions regarding its exact molecular pathogenesis. This chapter aims to

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highlight the role of the skin immune system in the pathogenesis of acne.

Immune Events Are Crucial in All Stages of Acne Pathogenesis

According to the classical view, the most important pathogenic factors in the development of this skin condition includes a hormonal trigger, follicular epidermal hyperproliferation of the ductal keratinocytes within the pilosebaceous unit (PSU), excess and altered sebum production, presence and activity of the skin commensal *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes*, *P. acnes*), and inflammation [1–3]. Although the exact sequence of events and the primary cause is still not known, initial steps of acne pathogenesis may include microcomedo formations. These are clinically not yet visible precursor lesions that later often develop into comedones (open or closed), papules, pustules, nodules, or cysts [1].

Earlier it was thought that androgen imbalance, follicular hyperkeratinization, and reduced desquamation lead to the formation of a keratin plug at the infundibulum part of the PSU [4]. Below the obstruction, increasingly anaerobic conditions favor the growth of *C. acnes*, resulting in enhanced immune activation and more pronounced inflammation and the formation of inflammatory acne lesions. The severity of inflammation is also enhanced by the frequent rupturing of the follicle wall, the leakage of bacterial antigens, cellular debris, and immunogenic sebum components into the surrounding tissues, where these greatly enhance inflammation [5].

Results, however, of detailed clinical investigations started to challenge this concept (reviewed by Kircik et al.,) [6]. It became accepted that hyperproliferation and increased retention of infundibular keratinocytes were among the main initiators of microcomedo formation [7], and interleukin (IL)-1 appeared as an important molecule inducing keratinocyte hypercornification [8, 9]. More than one study described signs of inflammation and immune activation, which preceded or occurred parallel with the keratinization process during microcomedo formation, and researchers identified leukocytes, mostly CD4+ T cells, polymorphonuclear cells, and CD68+ macrophages in the immune infiltrate around these early structures [5, 10]. Later studies also detected a higher number of CD3+ and CD4+ T cells already in the clinically uninvolved skin of acne patients, where the levels of different molecules related to inflammation (e.g., IL-1, E-selectin, vascular adhesion molecule 1 – VCAM1) were also elevated [9]. Early in lesion formation, CD1+ dendritic cells were also identified around the PSUs, while neutrophils only appeared in increasing numbers in the more advanced states, around the forming pustules. Finally, CD8+ cells have also been recognized in the early infiltrate around the affected follicles [5, 10]. These data strongly argue that inflammation, and parallel with that immune activation, is already present even before lesion formation and throughout all the subsequent steps during lesion development [11]. What are the initial driving forces, however, is still a question that remains uncertain. Altogether, these results strongly argue that acne is a prototypic chronic inflammatory, rather than a hyperproliferative disorder [6, 12], and the classical distinction of non-inflammatory (microcomedos, comedones) and inflammatory (papules, pustules, nodules, cysts) lesions theory needs to be revised.

Discovery of the Immune Properties of Keratinocytes

As opposed to vertebrates, where immune recognition is provided by the organized efforts of the two arms of their immune system, the innate and the acquired ones, in less evolved organisms, their protection relies only on the former type. Research efforts toward the end of the twentieth century led to the discovery of Toll, a protein in fruitfly (*Drosophila melanogaster*), which plays a role not only early in develop-

ment in a process called embryonic segmentation [13] but also in antifungal responses in adults [14]. Soon after that, members of this protein family were also discovered in humans (Toll-like receptors, TLRs), and their importance in vertebrate immune recognition was proposed [15].

During the 1980s, epidermal keratinocytes have been considered passive building blocks of the human skin, which serves as the very first line of defense and an essential delimiter between the outside world and our body. However, studies beginning in these years started to question this static view and suggested for the first time that our epithelial cells can actively identify sources of danger in the external environment and initiate active defense processes. The discovery that human keratinocytes not only recognize the presence of *Candida albicans* (*C. albicans*) in their culture but also actively kill this fungus opened a new path for subsequent research studies. These results suggested that keratinocytes, although does not belong to professional immune cells, still possess some functional properties allowing them to identify and respond to the presence of harmful foreign invaders [16–19].

Around the turning of the century, different research laboratories reported the presence of TLRs in epidermal keratinocytes, and it was also proved that these receptors are functional in this epithelial cell type. Challenge with microbial ligand resulted in the activation of the known, downstream signaling cascades in these cells, too, resulting in innate immune and inflammation activation due to the organized expression changes of pro-inflammatory cytokines, chemokines, antimicrobial peptides, and other factors [20–22]. It also became clear that not only pathogenic microbes but different members of the commensal microflora or their conserved structural molecules (e.g., *C. acnes*, *C. albicans*, lipopolysaccharide (LPS), lipoteichoic acid (LTA)) are recognized by these pattern recognition receptors (PRRs); thus it may contribute to the molecular pathogenesis of different chronic inflammatory diseases [22].

Innate Immune Events

The Role of Keratinocytes in Acne Pathogenesis

Immune activation and inflammation are central events in acne pathogenesis. Nevertheless, what are the exact driving forces of these reactions during the different phases in lesion development is still not clear. Etiopathogenic role of *C. acnes* in these processes was suggested for the first time more than 100 years ago, but since its first mention, a long-standing scientific debate formed about the exact role the bacterium plays in the disease [23, 24], reviewed by Dessinioti and Katsambas [25]. In the early 2000s, studies, investigating the keratinocyte – *C. acnes* interaction identified TLR2 as the major receptor playing indispensable roles in bacterial recognition. TLR4 has also been implicated in these processes [20–22], and the expression of both receptors was found to be increased in acne lesions [26]. Studies showed that receptor activation led to innate immune and inflammation activation, and the central mediator of these events was MAPK, NF-kB, and AP-1 transcription factor-dependent [21, 27]. As a result, coordinated expression changes of different pro-inflammatory mediators, among them cytokines (IL-1α, IL-6, IL-10, IL-12, GM-CSF, TNFα), chemokines (CXCL8), antimicrobial peptides (hBD2, CAMP(LL37)), matrix remodeling proteins (MMP-1, MMP-3, MMP-9), and other factors were detected [9, 20–22, 28–32]. Apart from these molecules, PRR activation also leads to the generation and elevated expression of factors (e.g., TNIP1) exhibiting negative regulatory effects on innate immune activation [33].

PRR activation is not restricted to keratinocytes, but monocytes and freshly isolated peripheral blood mononuclear cells from healthy controls and acne patients also reacted very similarly to the bacterium [20, 34–36].

The question that remains is how and exactly at which steps are these processes play a role in acne pathogenesis? The presence of IL-1α-like activity in the comedonal extracts [37], together

with the fact that the same cytokine may cause hyperkeratinization of infundibular keratinocytes, suggests that IL-1α may be one of the initiators or early factors in microcomedo formation [8, 38]. The source of the cytokine is not clear, but in vitro data suggests the role of keratinocytes, which are close to *C. acnes* in the still intact PSU [36, 39].

Parallel with TLR activation, another system capable of inflammation activation may also play a role in acne pathogenesis, the inflammasomes. Immunohistochemical studies around the turning of the century revealed the presence of lymphocytes and macrophages around the healthy-looking follicles of acne patients and in early acne lesions [9, 10]. Later, Qin and colleagues detected mature caspase-1 and NLRP3 molecules in the proteasome of macrophages. These data suggest a role of the NLRP3 inflammasome pathway and IL-1β in disease pathogenesis, particularly in shaping the innate receptors-induced immune and inflammatory reactions [35]. At this point, essential sources of secreted IL-1β are the monocytes, which may also play a role in the induction of neutrophilic inflammatory responses [36, 40]. Different inflammasomes (NLRP1, NLRP3, and AIM2) are also present in keratinocytes [41, 42], but whether and how they contribute to acne pathogenesis and if they react to the presence of *C. acnes* are not clear. It is a rather interesting fact that in various autoinflammatory diseases (e.g., PAPA, SAPHO syndrome), skin involvement often includes severe acne [42].

C. acnes also enhances the production of reactive oxygen species (ROS), in particular, superoxide anions (O_2^-) by keratinocytes, and these functions depend on the scavenger receptor, CD36. This pathway may also function as an important modulator of bacterially induced TLR signaling events in several different levels; among others, O_2^- itself can induce inflammation, modulates the production of the CXCL8 chemokine, and directly inhibits *C. acnes* bacterial growth [30].

Bacterially secreted enzymes, including lipases, proteases, and hyaluronidases [32, 43–46], may also exert different biologic functions that contribute to acne inflammation and lesion development. *C. acnes*-produced proteases can generate tissue injury, by weakening and subsequently rupturing the follicular epithelium. However, the same enzymes may also be recognized by PAR-2 (protease-activated receptor-2), and these events can modulate the production of inflammatory mediators [32].

These results argue for the role of microbes, especially *C. acnes* itself and/or bacterially secreted metabolic products in innate immune and inflammation induction in acne vulgaris pathogenesis. Opposers question its role because this bacterium is one of the most prominent commensal microbes, especially in the sebum-rich skin regions. Thus it is rather difficult to consider the same microbe as a prototypic pathogen [47]. Ongoing research still aims to find a definite answer and explain a seemingly dual role this bacterium plays in skin physiology.

Sebocytes Are Active Players in Acne Immunity Too

The fact that acne mostly present in skin regions (face, shoulders, upper chest, and back), which are sebaceous gland rich [31], already suggests that besides keratinocytes, another cell type that may play a key role in disease pathogenesis is the sebocytes. Hyperseborrhea and altered sebum composition have long been considered as important factors in the pathophysiology of this disease. The cause of enhanced sebum secretion, however, may be complex; hormonal and genetic factors, together with dietary habits, may influence it [48].

Earlier, sebum was considered as a substance playing important roles in the moisturization of the skin surface. It is also an important food source for the *C. acnes* bacterium, which uses sebaceous triglycerides for its growth [49]. It is clear now that sebum composition and secretion rate rapidly change together with the changing environment, and specific lipids may exert antimicrobial and pro- or anti-inflammatory properties. Through their sebum production, sebocytes may also act as important modifiers of the inflammatory processes [48, 50, 51].

Nevertheless, sebocyte functions are not restricted to sebum production [52, 53]. These cells are also immunocompetent, actively respond to different external signals, and produce inflammatory cytokines and other mediators, similarly to keratinocytes [20, 54–56]. *C. acnes* recognition in sebocytes, similarly to keratinocytes, takes place through the activation of, among others, TLR2, CD14 and CD1, and inflammasomes. As a result, this cell type also plays an essential role in immune and inflammation activation in the PSU [54, 57–59]. On the other hand, through these signaling pathways, the bacterium also influences sebocyte viability and differentiation [54] and directly enhances lipogenesis, and sebum secretion rates tend to correlate with the severity of skin symptoms [60, 61].

These data suggest that this cell type may act as an important regulator of a complex equilibrium. By regulating the amount and composition of sebum, sebocytes may promote the growth and metabolism of the skin commensals. They, on the other hand, may also limit bacterial viability during bacterial dysbiosis and pathogenic events and enhance microbial clearance by contributing to innate immune and inflammation activation.

This cell type is regulated by many factors (reviewed by Makrantonaki et al., [48]), among them, sex hormones. Pubertal hormonal changes, especially local androgen synthesis, are markedly higher in acne patients, which results in increased sebocyte activity and hyperseborrhea [48, 62, 63]. Recently, another hormone has emerged with complex roles in acne, the insulin-like growth factor 1 (IGF-1). In sebocytes, it induces increased lipid synthesis, while in keratinocytes, it also acts as a mitogen [64, 65], and in in vivo studies, IGF-1 levels were elevated in acne patients [66, 67]. The levels of this hormone are also increased in individuals following a Westernized lifestyle and diet (decreased physical activity, consuming high glycemic index food and milk products), which would explain how diet and acne may be linked [68].

One crucial point that should be mentioned is that it is still not clear whether and how sebocyte-*C. acnes* interaction takes place in the skin. Sebaceous glands usually are free from bacteria [69], so direct interaction in intact PSU may not happen. It is possible, though, that bacterially derived structural proteins, enzymes, and other secreted molecules and metabolic products reach the sebaceous glands and the sebocytes in the distance. In this way, the bacterium may still exert a biologic function on these cells [70].

Adaptive Immune Regulation in Acne

Microscopic identification of different adaptive immune cells around the affected follicles suggested that this arm of our immune system is also involved in acne pathogenesis. The findings that higher number of CD3+ and CD4+ T cells are present in the uninvolved skin of acne patients supported this idea, but what is the main initiator of such T cell infiltration remains to be unknown [5, 9, 10].

Another line of evidence suggested that *C. acnes* exhibited a potent immunostimulatory activity and the induction of T helper 1 immune responses in animal models [71, 72]. Finally, these data led to the identification of a T cell subpopulation in early inflamed acne lesions that exhibited increased cell proliferation in response to *C. acnes* extract, possibly as a result of the recognition of bacterial antigens. These T cells also exhibited a characteristic Th1 cytokine pattern and expressed IFNγ in high whereas IL-4 in low quantities [73]. Further studies also identified essential roles for Th17 activation in acne pathogenesis, and IL-1β, IL-6, and TGF-β appeared as key activators of this arm of the adaptive immune responses, similar to other systems. As proof of this concept, IL-17 expressing lymphoid cells were found around inflamed follicles by immunohistochemical analysis [74, 75]. Finally, CD4+ T cells expressing IL-17 together with IFNγ were also identified, characteristic of mixed Th1/Th17 differentiation [40].

Based on these results, *C. acnes* appears as one factor playing important roles in the initiation of the above adaptive immune responses. Nevertheless, apart from the bacterium, sebocytes may also act as critical factors, as the super-

natant of these cells induces Th17 differentiation of naïve T cells. The resulting cell population is suggested to exhibit a dual function; it not only mediates host defense but can also actively participate in disease pathogenesis [56].

These data altogether clearly indicate that Th1, Th17, and mixed Th1/Th17-type adaptive immune responses play important roles in the cutaneous response to *C. acnes* and through that in acne pathogenesis [40, 73, 74]. However, there are still many open questions remains. Why acne vulgaris mostly affect the adolescent population? Why is it a self-limiting condition? What happens before, during, and after puberty? According to the current view, acne may be viewed as a transient arrest of homeostatic host-microbial dialogue between two phases of microbial tolerance [76]. This is a novel and intriguing concept, which suggests the crucial role of adaptive immune regulation in the maintenance of skin homeostasis in child- and adulthood and the lack or disturbance of these events as a critical pathogenic factor in puberty.

Not All *C. acnes* Strains Are Created to Be Equal?

Within the *C. acnes* species, different subtypes have long been identified, and currently, six major phylotypes are recognized: IA1, IA2, IB, IC, II, and III [77, 78]. A hot topic of the recent investigations is whether various *C. acnes* strains differ in their microbiological, metabolical, genetic, pathogenic, and other properties. The origin of these investigations comes from early findings, suggesting that various strains may differ in their innate immune induction properties in keratinocytes and sebocytes [22, 54], and differences in the internalization rates were also noted [79]. Selected strains might have different growth properties. They also exhibit variations in their metabolic traits, among them the production of short-chain fatty acids (SCFA), including acetic, propionic, and butyric acid, some of which exhibiting potent immunomodulatory properties [80–82].

According to the current knowledge, one of the most significant, differentially expressed molecules by the *C. acnes* strains are the CAMP (Christie-Atkins-Munch-Peterson) factors, cohemolytic enzymes involved in pore formation processes [83]. These are secretory virulence factors, and genomic analysis revealed five different genes belonging to this family in *C. acnes* [80]. Recent studies indicate that TLR2 may directly recognize CAMP-1 [84], which would suggest that strains producing more virulence factors also are more potent innate immune activators.

Recently, it was identified that selected strains (IA, IC), and within that specific ribotypes (IB-1, IB-2, IC-2, IC-3), were frequently associated with acne [77, 85, 86], and variations in the ability of selected strains to induce adaptive immune responses have been described [87].

Acne Has a Complex Pathogenesis

Inflammation is vital in all stages of acne pathogenesis, in which *C. acnes* plays essential roles. What is still not clear is the initiator, the first step that pushes the delicate balance between the bacterium and the cutaneous cells to microbial dysbiosis. Or in other words, why and how exactly an important member of the skin microbiota turns into a microbe exhibiting opportunistic pathogen features? One idea is that loss of microbial diversity plays essential roles. Whether this means the loss of various species that were part of the cutaneous microbiota during human evolution [33] or the loss of the diversity of various *C. acnes* phylotypes [88] requires further investigations. One thing is clear; acne is an intriguingly interesting and complex skin disease. By uncovering its exact pathogenesis, we will not only gain more in-depth knowledge on the pathogenesis of the most common prototypic inflammatory skin disease but may also have more excellent knowledge on how the human body and our microbes interact to generate a healthy ecosystem.

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