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# Association of different cell types and inflammation in early acne vulgaris

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Acne vulgaris, one of the most common skin diseases, is a chronic cutaneous inflammation of the upper pilosebaceous unit (PSU) with complex pathogenesis. Inflammation plays a central role in the pathogenesis of acne vulgaris. During the inflammatory process, the innate and adaptive immune systems are coordinately activated to induce immune responses. Understanding the infiltration and cytokine secretion of differential cells in acne lesions, especially in the early stages of inflammation, will provide an insight into the pathogenesis of acne. The purpose of this review is to synthesize the association of different cell types with inflammation in early acne vulgaris and provide a comprehensive understanding of skin inflammation and immune responses.

KEYWORDS

**acne vulgaris, inflammation, immune system, *Cutibacterium acnes*, cytokines**

## 1 Introduction

Acne vulgaris is a common inflammatory dermatosis, affecting approximately 650 million people worldwide (1, 2). Acne can negatively impact the quality of life of patients because of physical and psychosocial morbidities (3). Microcomedones and comedones are primary acne lesions that result from cystic formation in the infundibulum of the pilosebaceous unit (PSU) (4), and the majority of inflammatory lesions arise from comedones, including papule, pustule, nodule and cyst (5). The progression of acne vulgaris may not always occur in a linear manner from microcomedone to inflammatory lesions (6, 7). The etiology of acne is multifactorial and complex, mainly including hyperseborrhea and altered sebum composition, follicular hyperkeratinization, abnormalities of the microbial flora, inflammation and immune responses (8). These factors together can impair the PSU, leading to transformation of normal follicular canals into microcomedones and further progression into inflammatory lesions (9). It is now accepted that inflammation sets in early in the pathogenesis of acne (10).

*Cutibacterium acnes* (*C. acnes*; formerly known as *Propionibacterium acnes*) is a commensal microorganism that resides mainly in the anaerobic portions of the pilosebaceous follicles (11). Although *C. acnes* is observed in normal and acne skin, intense colonization likely causes inflammatory reactions and immune cell recruitment through dysbiosis of the skin microbiome and an imbalance of different *C. acnes* phylotypes (11–13). Based on the sequences of the recA and tly genes, *C. acnes* can be subdivided into phylotypes IA, IB, II and III (14, 15). Multilocus sequence typing (MLST) approaches further divide the type I strain into IA1, IA2, IB and IC clusters, some of which are acne-associated (IA1 and IC) (16, 17). Within microcomedones, which are usually barely visible clinically, *C. acnes* multiplies in the infra-infundibulum, resulting in bacterial colonization (18). *C. acnes* produces many enzymes and biologically active molecules to stimulate immune cells to secrete proinflammatory cytokines. The immune response to *C. acnes*, but not the bacteria itself, has a key role in the pathogenesis of acne (19).

The immune surveillance of the skin barrier is complex. Immune cells account for 7% of the cells in skin under normal conditions (20) and are involved in perceiving alarm signals and orchestrating immune responses when inflammation occurs. Because of the absence of the stratum corneum, the skin appendages become the points of entry for external pathogens, and skin commensal microbiota can extend within the dermis, establishing direct communication with the host immune system (21). The PSU is classified as a site of immune cell recruitment because alteration in microenvironments can impact skin immunobiology (22, 23). The anaerobic and lipophilic microenvironments of the PSU favor the growth of *C. acnes*, particularly in acne vulgaris.

# 2 Inflammation in early acne vulgaris

The early stage of acne is characterized by the subclinical microcomedones (5). The interior of microcomedones is mostly composed of lipids with clusters of bacteria, and their outer shell is made up of corneocyte layers (18). Due to increasing pressure from the expansion of the keratin layer in a confined space, hypoxia may facilitate the multiplication of *C. acnes* and lipid accumulation (24, 25). Increased sebum production supports *C. acnes* growth in the PSU. Moreover, the metabolites of bacteria can alter the sebum composition, which contributes to the inflammatory response (26). Eventually, the rupture of the follicular walls causes extrusion of the content and a rapid inflammatory response. Although both $CD4^+$ T lymphocytes and neutrophils infiltrate around acne inflammatory lesions (27), lymphocytes may play a more central role in early acne lesions than neutrophils, which are strongly attracted after the follicles have been disrupted (28). Additionally, other inflammatory cells, especially $CD4^+$ T cells and macrophages, are also observed in the perifollicular region and dermis in acne-uninvolved skin (10). This line of evidence suggests the involvement of innate and adaptive immune processes in the pathogenesis of acne vulgaris. Further studies indicate that acnes at early stage, 6-72 hours after the development of lesions, only show small papules with a minimal erythema, with neither rupture of the follicular walls nor neutrophilic infiltration. After 72 hours of the development of acne, neutrophils can be observed in 33% of lesions (28). This evidence indicates that acne vulgaris is featured by microcomedones and small papules in early stage, followed by neutrophilic infiltration. There is no agreed definition of the early stages of acne vulgaris. We defined microcomedones and small papules with no disruption of the follicle wall as the early stage of acne in our review (Figure 1).

# 3 Adaptive immune cells

## 3.1 T helper 1 cells

Epidermal T cells, mainly $CD8^+$ T cells, are distributed in the stratum basale and stratum spinosum, while dermal T cells are often situated beneath the dermal-epidermal junction or adjacent to cutaneous appendages (29). The number of $CD4^+$ T cells in the epidermis is comparable to that in the dermis, and they are only found around hair follicles. Under physiological conditions, 98% of cutaneous lymphocyte-associated antigen $(CLA)^+$ effector memory T cells reside in the skin and can initiate and perpetuate immune reactions without recruiting T cells from the blood (30). $CD4^+$ T helper (Th) cells regulate adaptive immune responses by secreting cytokines and chemokines to activate and recruit effector cells (31).

Previous studies showed that a subpopulation of *C. acnes*-specific Th1 cells is present in early acne lesions, while *C. acnes* can stimulate T cell proliferation (32, 33). Acne lesions exhibit high expression levels of Th1 effector cytokine interferon-γ (IFN-γ), Th1 polarizing key transcription factor T-bet, and the pivotal Th1 activating cytokine interleukin 12 (IL-12), suggesting the role of Th1 cells in acne. (33, 34). *C. acnes* induces production of IL-12 by monocytes via Toll-like receptor-2 (TLR-2) signaling. The innate immune system recognizes *C. acnes* via TLR-2, increasing the levels of IL-8 and IL-12 (35). In turn, IL-12 activates the transcription factor signal transducer and activator of transcription 4 (STAT4), inducing the production of IFN-γ by Th1 cells (36), while IFN-γ promotes the differentiation of Th1 cells and induces chemokine secretion to recruit immune cells. IFN-γ–stimulated sebocytes seem to foster the migration of $CD45RO^+$ T cells with no influence on cytokine secretion (37).

## 3.2 T helper 17 cells

In comparison to the skin of healthy individuals, acne-involved skin displays a high number of $IL\text{-}17^+$ cells near the PSU (34, 38, 39). The dermal $IL\text{-}17^+$ cells are lymphocytes, which affect epidermal keratinocytes in a paracrine manner (40). There is a significant elevation in Th17 lineage signature cytokines, including IL-1β, IL-6 and transforming growth factor-β (TGF-β), in acne lesional vs. nonlesional skin (34). *C. acnes* increases expression levels of key Th17-related genes in human peripheral blood mononuclear cells (PBMCs) (38). Correspondingly, an integrated bioinformatics study demonstrates increased infiltration of Th17

cells and Th17-related cytokines in acne lesions (41). Moreover, the number of Th17 cells is increased in the closed comedone stage of acne, indicating that Th17 cells are involved in the pathogenesis of acne, at least in early stage (42).

Sebocytes can drive a Th17 immune response via the production of IL-6, TGF-β and IL-1β. Sebocytes can recruit various subsets of T cells, including $CD4^+CD45RO^+$ effector and $CD4^+CD45RA^+$ naive T cells in a CXCL8-dependent manner. Although sebocytes do not alter the effector T-cell phenotype, they affect the migration of naive T cells and alter their developmental trajectory towards Th17 cells via the secretion of IL-6, TGF-β and IL-1β (37). In addition to its effects on Th17 cells, *C. acnes* can also promote mixed Th17/Th1 cell and Th1-like cell responses *in vitro* by inducing concomitant secretion of IL-17A and IFN-γ (39). These mixed Th17/Th1 cytokines are most likely derived from Th17 subsets displaying a degree of plasticity and acquiring functional characteristics of Th1 cells (43). Acne-associated *C. acnes* strains provide a microbial microenvironment, regulating the programs responsible for the differentiation of Th17 cells into Th17/Th1 cells (44).

Th17 cells are characterized by the production of IL-17A and IL-17F and potent inducers of tissue inflammation. IL-17 and IL-22, effector cytokines of Th17 cells, enhance the expression of antimicrobial peptides (AMPs), including cathelicidins and β-defensins (45). Human β-defensin-2 (hBD)-2 is elevated in acne. AMPs suppress excess cytokine release after minor epidermal injury to maintain inflammatory homeostasis. Other studies also showed that AMPs promote additional inflammatory responses in addition to their antibacterial activity (46, 47). Although Th17 cells can strengthen the body's defense against extracellular pathogens, the excessive Th17 responses can drive chronic inflammation, likely contributing to the development of acne (48). The role of Th17 response in acne cannot be dissociated from the local microenvironment, i.e., dysseborrhea and loss of *C. acnes* phylotype diversity.

While Th17-cell-derived IL-26 exerts direct antimicrobial activity against extracellular bacteria, it lacks antimicrobial potency against *C. acnes* (44, 49). *C. acnes* phylotypes directly influence the Th17 cytokine profile and differentially modulate the $CD4^+$ T cell responses involving the generation of Th17 cells. *C. acnes* phylotypes IA2, IB, and IC are increased in acne patients. The acne-related *C. acnes* subtypes increase secretion of IFN-γ and IL-17, while decreasing levels of IL-10 in PBMCs. In contrast, healthy skin-related *C. acnes* subtypes increase IL-10 levels (50). IL-10 can repress proinflammatory responses by downregulating IFN-γ and IL-17 (51). IL-10-producing Th17 cells are protective and exhibit microbicidal activity against *C. acnes*, whereas IFN-γ-producing Th17 cells are pathogenic without microbicidal activity (44). Acne-associated *C. acnes* strains promote the differentiation of a non-antimicrobial Th17 subpopulation ($n\text{-}_{AM}Th17$). Healthy skin-related *C. acnes* strains can specifically stimulate antimicrobial subpopulation of Th17 cells ($_{AM}Th17$) to secrete antimicrobial proteins and generate T-cell extracellular traps (TETs) capable of capturing and killing *C. acnes*. *C. acnes* is entangled in TETs in proximity to Th17 cells in acne lesional skin (52). Although TETs are involved in antimicrobial responses, whether TETs exacerbate inflammation is unclear.

### 3.3 Regulatory T cells

In inflammatory disorders, Th17 cells have intimate links with Foxp3-expressing regulatory T (Treg) cells in immune balance. Tissue-resident Treg cells are predominantly distributed near the hair bulge area in the steady state (53). Tregs are efficient suppressors of both innate and adaptive immune responses, which are well known to be involved in preservation of cutaneous homeostasis and in the regulation of skin immune response (54). Significantly high numbers of $Foxp3^+$ cells are observed in the papillary dermis in early acne lesions (34, 40). Treg cells in acne patients may have functional deficiency to suppress the abnormality persistent immune response in acne lesions. Treg cells lose their suppressive function and become IL-17-expressing cells under inflammatory conditions. The dysfunction of Treg cells might be a underlying mechanism accounting for chronic skin inflammation (55–57). Moreover, the number of Tregs is lower in acne lesions than in nonlesional skin of acne patients (41). However, whether an increase in the number of Treg cells alone can benefit acne remains to be determined.

Immunopathogenesis of acne vulgaris may be related to deviations of the Th17/Treg balance (41). Increases in the Th17/Treg ratio may contribute to the initiation of inflammatory processes and can negatively affect Treg-controlled homeostasis and integrity of hair follicles (58). Retinoids exert beneficial effects on acne, via inhibition of IL-17 and increase in Foxp3 expression, whereby regulating the balance between Treg and Th17 cell differentiation (59, 60). The effective drugs treatment should not only attenuate Th17/IL-17 signaling, but also improve Treg function in order to stabilize the hair follicles. Comparison of the ratio of Th17/Treg cells between acne lesional skin and healthy skin and clarification of Treg-related disturbances of homeostasis of hair follicle would be helpful to elucidate the pathogenesis of acne vulgaris.

## 4 Innate immune cells

### 4.1 Dendritic cells

Dendritic cells (DCs) are a family of antigen-sensing and antigen-presenting cells that link the innate and adaptive immune systems (61). Skin DCs can be classified into four types: epidermal Langerhans cells (LCs), conventional DCs (cDCs), plasmacytoid DCs (pDCs) and monocyte-derived DCs (62). DC subsets are developmentally imprinted and modulated by local microenvironmental and inflammatory state (63). LCs are the main DC subsets in the epidermis, taking up and processing antigens for presentation to skin resident memory T cells or effector T cells (64, 65).

Skin immunohistochemistry revealed that $CD1^+$cells (considered to be LCs) and $CD83^+$ dendritic cells were significantly higher in early acne stage than in nonlesional skin (10, 27, 28, 34). An analysis of skin biopsy samples also noted a clear increase in the number of LCs and DCs in the closed comedone stage. Interestingly, cDC2s are associated with perilesional $CD4^+$T cells (42). Bacterial peptidoglycan (PGN)-activated DCs selectively

produce IL-1 and IL-23, which efficiently activate protective Th17 cells (66, 67). It has been postulated that changes in the follicular microenvironment may increase the production of immunogenic *C. acnes* proteins. LCs process antigens and migrate to the local lymph node, where antigens are presented to $CD4^+$T cells (68).

## 4.2 Macrophages

Macrophages are usually regarded as terminally differentiated monocytic phagocytes. Monocytes are recruited to the tissue where they differentiate into macrophages. Macrophages are activated by different stimuli and exert heterogeneous effects in healthy and inflamed skin, and based on these effects, they can be classified into classically (M1) and alternatively (M2) activated subsets (69, 70).

Number of $CD68^+$ macrophages is significantly higher both in early acne lesions and uninvolved follicles in acne patients compared with healthy subject (10, 34, 42). *C. acnes* triggers inflammatory cytokine expression through the activation of TLR2 on macrophages, followed by the activation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, Nuclear factor kappa-B (NF- κB) as well as mitogen-activated protein kinase (MAPK) signaling cascade (71–74). $TLR2^+$ macrophages are present in acne lesions and increased during the evolution of the disease (35). *C. acnes* can also stimulate type I interferon (IFN-I) synthesis via the wiring of a TLR2- TIR-domain-containing adapter-inducing interferon-β (TRIF) pathway in human macrophages (75). In addition, IFN-I stimulates and amplifies the secretion of chemokines and other immune mediators, contributing to inflammatory responses (76).

Under normal conditions, M1 macrophages, also termed as skin-resident macrophages, surround the sebaceous glands (77, 78). Both M1 and M2 subsets can be found in acne lesions (79), and M1-like macrophages mount an antimicrobial response against *C. acnes* (80). Sebum can affect the polarization of macrophages favoring the generation of M2 macrophages (81). Lipids that accumulate in the PSU are oxidized by *C. acnes* lipase, and macrophages can phagocytose oxidized lipids, consequently becoming foam cells (82). These foam cells express TREM2 and infiltrate in acne lesions. The sebum of acne patients has a higher content of squalene (83), which can increase TREM2 expression on macrophages. TREM2 expression enhances the phagocytic capacity of the macrophages to uptake lipids and bacteria, but these macrophages are unable to kill the bacteria. Squalene-induced TREM2 macrophages contribute to inflammation by up-regulating expression of proinflammatory chemokines, cytokines, MMPs, and S100 proteins to recruit and activate immune cells (79). Accumulation of intracellular lipids and lipid metabolic products trigger the production of proinflammatory cytokines in macrophages, contributing to the immunopathology of early acne vulgaris. Notably, TREM2 macrophages are not typically present in other inflammatory skin diseases, such as psoriasis (84) and atopic dermatitis (85). However, the pathogenic role of macrophages in acne has not been fully elucidated yet and more studies are needed to characterize the functional of macrophage in acne.

## 4.3 Mast cells

Mast cells (MCs) are most abundant in the upper dermis and are located near blood vessels and nerve endings under physiological conditions. The MC number is not affected by age or sex (86). MCs are key effector cells that respond to allergic inflammation and innate immune responses against bacteria. A number of factors can activate MCs to release granule-stored mediators and synthesize other types of mediators, leading to the development of inflammatory dermatoses (87).

The high-affinity IgE receptor (FcεRI) and CD69 are strongly expressed in acne lesions (42). MC number and CD69 expression peaked in the closed comedone stage, indicating that activated MCs are involved in early acne lesions. The increase in the number of MCs depends on keratinocyte-produced stem cell factor (SCF). Lipoteichoic acid (LTA), a gram-positive cell wall component, stimulates an increase in the production of SCF in keratinocytes, indirectly influencing the recruitment and maturation of MCs (88). A colocalization experiment showed that most $IL\text{-}17A^+$ cells are positive for tryptase (a MC marker) and negative for CD3 and CD4, markers of T cells. Thus, MCs are possibly the cellular source of IL-17A rather than $CD4^+$ T cells in closed comedone (42). Activated Th cells drive IL-17A production in MCs via cell-cell contact. Neither classical MC stimuli nor Th cell cytokines induce IL-17 production in MCs, which means the mechanism underlying IL-17 production by MCs is tightly regulated (42, 89). IL-17A, a proinflammatory cytokine, increases CXC ligand (CXCL)8 production in epithelial cells and activates fibroblasts to recruit neutrophils (90), while neutrophils generate reactive oxygen species (ROS) that irritate and destroy follicular integrity, causing inflammatory progression of acne lesions, which are then classified as pustules (91, 92). Moreover, IL-17A synergizes with other inflammatory cytokines, leading to increased production of IL-6 and IL-8 (93). IL-17 is not a typical mast cell cytokine, but it is increasingly appreciated that innate immune cells can produce IL-17 during an inflammatory response (94). However, the underlying mechanisms by which mast cells secrete IL-17 are not clear. To understand the complex pathophysiology of acne vulgaris, it is imperative to define the mechanisms mediating IL-17 release.

## 4.4 Innate lymphoid cells

Innate lymphoid cells (ILCs) exhibit a lymphoid morphology; they do not express rearranged antigen-specific receptors but do have important functions in innate immunity and tissue remodeling. ILCs are subdivided into 3 subsets, ILC1s, ILC2s and ILC3s. ILC2s are the predominant tissue-resident skin ILC subset under steady state and during inflammation (95, 96). Lack of ILCs causes sebaceous hyperplasia and alters the equilibrium of skin commensal bacteria by modulating the production of palmitoleic acid, a component of sebum with antimicrobial properties, and inhibiting the growth of several species of gram-positive cocci (97). Sebaceous hyperplasia and dyshomeostasis of skin commensal bacteria induce inflammation in the pathogenesis of acne vulgaris,

which means that ILCs may be involved in the early stage of inflammation in acne. A large number of ILC3s are present in the non-lesional skin in hidradenitis suppurativa (HS) (98). Both IL-1β and IL-23 can activate ILC3s to produce IL-22 and IL-17 (99, 100). With expression of multiple Th17- and Th1-derived cytokines, ILCs are subsequently replaced by adaptive Th mediated response. It remains to be seen whether ILCs operate in the same way in humans as they do in experimental animal models. Future study is needed to investigate ILC subsets in skin of patients with acne and characterize the functional capacity of ILC to contribute to immune responses.

# 5 Skin cells involved in acne inflammation

## 5.1 Keratinocytes

As the major cell type in the epidermis, keratinocytes not only form a physical barrier but also secrete cytokines to modulate the immune response and inflammation (101). Keratinocytes express different types of pattern recognition receptors (PRRs), recognizing various pathogens and secreting cytokines, chemokines, and AMPs (102). Keratinocytes constitutively synthesize IL-1α and IL-1β (103). Excessive skin colonization of *C. acnes* can activate TLR-2 and TLR-4 on keratinocytes, resulting in the production of a panel of inflammatory mediators, including IL-8, IL-6, IL-1α, TNF-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), matrix metalloproteinase (MMP)-9 and hBD-2 (74, 104–107). These mediators activate tissue-resident immune cells to induce and perpetuate an inflammatory response. *C. acnes* is also recognized by CD36, a scavenger receptor expressed on keratinocytes, inducing a rapid production of ROS by keratinocytes, consequently leading to inhibition of bacterial growth and production of inflammation (108). Moreover, keratinocytes in hair follicles express squalene epoxidase, which converts squalene to squalene epoxide (79). Lipid peroxides, in particular squalene peroxides, have been shown to activate lipoxygenases and increase the production of IL-6 in keratinocytes in a dose-dependent manner (109). In addition, hypoxia due to increasing intraductal pressure may induce hypoxia inducible factor (HIF)-1 production, stimulating keratinocytes to produce proinflammatory cytokines (24, 110). Thus, keratinocytes can contribute at least in part to the inflammation in acne vulgaris.

## 5.2 Sebocytes

Sebocytes form the sebaceous gland acini belonging to the upper PSU (111, 112). Matured sebocytes secrete their contents in a holocrine manner, leading to DNase2-mediated programmed cell death (113), which affects skin barrier function (114). Human sebum is a lipid mixture, and wax esters and squalene are characteristic of sebocytes (115, 116). Sebocytes may act as immune-active cells, recognizing microorganisms and then producing AMPs and cytokines. Sebocytes are not only a target of inflammation, but also modulate of immunity (117, 118). Increased activity of androgen hormones and insulin-like growth factor 1 (IGF-1) stimulates the proliferation and differentiation of sebocytes, resulting in hyperseborrhea (119). Clinical research has demonstrated a positive correlation between serum IGF-1 levels and disease severity, especially in female acne patients (120). IGF-1 induces the expression of proinflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α, in sebocytes via the NF-κB signaling pathway (121). Sebocytes express PRRs, such as TLR2, TLR4, TLR6 and CD14, to recognize *C. acnes* and produce IL-1β, IL-6 and TGF-β *in vitro*, which drives a Th17 immune response (37, 122–125). GATA6 expressed in differentiating sebocytes can induce the expression of IL-10 and negatively regulates acne-driven IL-8 and IL-17 cytokines. Expression levels of GATA6 are reduced in early acne lesions, resulting in increased acne-driven cytokines (126).

Bacterial lipases hydrolyze some of the triglycerides in the sebum to free fatty acids (FFAs), which have a proinflammatory effect and antibacterial activity (127, 128). Proteases produced by *C. acnes* activate protease-activated receptor-2 (PAR-2) on sebocytes can also induce the production of inflammatory cytokines and antimicrobial peptides (129). FFAs and *C. acnes* upregulate the expression of hBD-2 in human sebocytes to enhance innate immune defense (47, 130). The development of more anaerobic conditions in hair follicles can lead to outgrowth of *C. acnes* and buildup of short-chain fatty acids (SCFAs) (131, 132). SCFAs have been shown to amplify TLR-driven cytokine responses from sebocytes through inhibition of histone deacetylase activity and the activation of fatty acid receptors (132).

Moreover, sebocytes secrete biologically active lipids to regulate inflammation. Sebum from acne patients contains lower levels of linoleic acid and higher levels of squalene, lipoperoxides, and monounsaturated fatty acids (MUFAs), particularly palmitoleic acid (C16:1) and oleic acid (C18:1) (83, 133–135). Stearoyl-CoA desaturase (SCD) and fatty acid desaturase (FADS)-2, two enzymes responsible for the biosynthesis of MUFAs in sebocytes, are upregulated by the TLR-2 ligand macrophage-activating lipopeptide-2 (MALP2) (122, 136). Excessive generation of squalene and MUFAs increases the rate of lipid peroxidation, and their oxidation products create a proinflammatory environment and induce comedogenesis (135, 137). Palmitic acid activates the NLRP3 inflammasome to induce release of IL-1β (138) and inflammatory response in sebocytes via TLR2 and TLR4 signaling (128). Epidermal growth factor together with palmitic acid may augment the inflammatory properties of sebocytes (139). In contrast, linoleic acid has an anti-inflammatory effect via inhibition of IL-1β production in *C. acnes*-activated macrophages (81). It is qualitative changes, not quantitative changes, in sebum composition that play a central role in the development of acne (26). Finally, sebocytes can release leptin after being triggered by TLR-2 and TLR-4 or mTORC1 pathway (118, 140). Sebocyte-derived leptin induces the expression of proinflammatory lipids, such as cyclooxygenase 2 (COX-2) and 5-lipoxygenase (5-LOX), and augments the expression of IL-6 and IL-8 (141, 142). Leptin also plays a pivotal role in Th17 cell differentiation (143). Sebocytes expressing leptin receptor (LEPR) may perpetuate inflammation in an autocrine manner (144). Collectively, sebocytes can provoke inflammation in acne via multiple mechanisms.

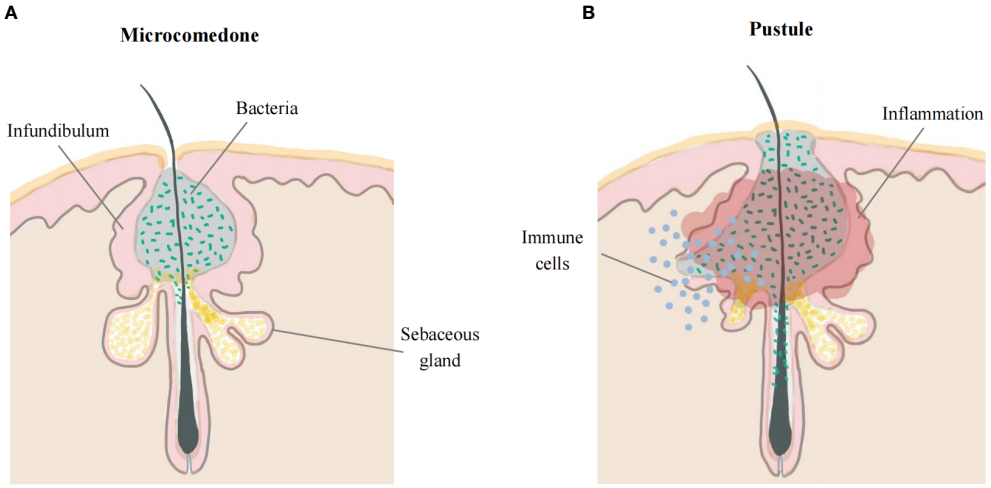


FIGURE 1
Early acne lesions and late acne lesions. **(A)** The early stage of acne occurs in the hair follicle infundibulum. Microcomedone is mostly composed of lipids with clusters of bacteria, and the outer shell is made up of corneocyte layers. **(B)** The walls of the follicles rupture, leading to extrusion of the content and causing a rapid inflammatory response.

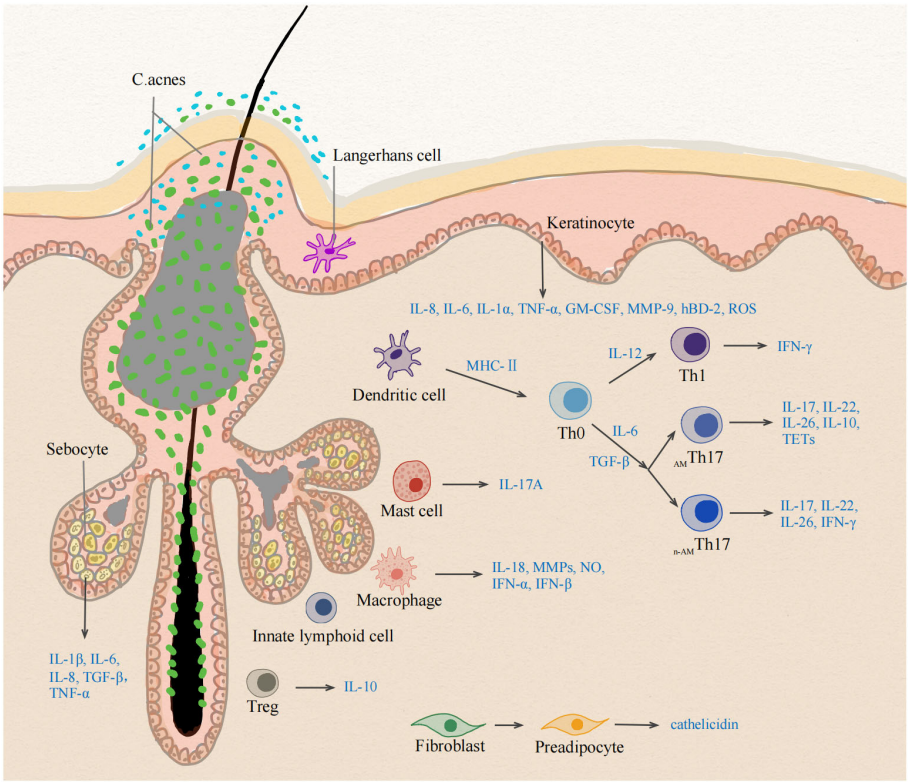


FIGURE 2
Different cell types at the early stage of inflammation in acne vulgaris. The early stage of acne vulgaris manifests microcomedones and small papules, which has no disruption of the follicle wall. The change of follicle microenvironment in acne initiate the immune activation of skin cells. Activated sebocytes, keratinocytes and skin-resident APCs upregulate the production of pro-inflammatory mediators, such as IL-1β, IL-6, IL-12 and TGF-β. IL-6 and TGF-β induce the differentiation into Th17 cells, whereas IL-12 drives a Th1 differentiation program. Healthy-related *C. acnes* induce IL-10-producing $_{AM}$Th17 cells, whereas acne-associated strains promote the development of n-$_{AM}$Th17 cells. $_{AM}$Th17 cells release IL-17, IL-22, IL-26, IL-10 and TETs, n-$_{AM}$Th17 cells induce IFN-γ. Treg lose their suppressive function for deviations of the Th17/Treg balance. MCs are the cellular source of IL-17A in early acne. Lack of ILCs leads to sebaceous hyperplasia and alters the equilibrium of skin commensal bacteria. Accumulation of intracellular lipids and lipid metabolic products induce the production of proinflammatory cytokines in macrophages. *C. acnes* triggers dermal fibroblast differentiation and enhances cathelicidin expression. APC, Antigen presenting cell; TGF-β, Transforming growth factor- Beta; IFN-γ, Interferon gamma; MC, mast cell; TETs, T-cell extracellular traps; ILCs, innate lymphoid cells. $_{AM}$Th17 cells, antimicrobial Th17 cells; n-$_{AM}$Th17 cells, non-antimicrobial Th17 cells.

### 5.3 Fibroblasts

Dermal fibroblasts are essential cells that support the structural integrity of tissues. Dermal white adipose tissue (dWAT) is a unique tissue layer made up of adipocytes mainly concentrated around the PSUs (145). Intradermal infection with *Staphylococcus aureus* induces proliferation and differentiation of fibroblasts into the preadipocyte lineage, leading to rapid expansion of the dWAT layer and triggering the production of antimicrobial peptides, a process dubbed reactive adipogenesis (146). Recent studies have shown that reactive adipogenesis occurs in the perifollicular stroma of acne. *C. acnes* triggers dermal fibroblast differentiation and enhances cathelicidin expression, which is partially dependent on TLR2 activity (147). Hence, dermal perifollicular fibroblasts are involved in the pathogenesis of acne and represent a potential target for acne therapy.

## 6 Conclusions

Acne lesions begin with the formation of microcomedones. Follicular epidermal hyperproliferation, increased sebum production and the growth of *C. acnes* in PSUs contribute to microcomedone formation.

The alteration of the follicle microenvironment stimulates skin-resident antigen presenting cells (APCs), sebocytes, and keratinocytes to produce proinflammatory cytokines, such as IL-1β, IL-6, and TGF-β. Macrophages phagocytose oxidized lipids and produce proinflammatory cytokines. MCs appeared as pioneer cells to produce IL-17, followed by the appearance of ILCs and Th cells. With the expression of multiple Th17- and Th1-derived cytokines, adaptive Th-mediated response plays a pivotal role in the early stage of acne. Deviations of the Th17/Treg balance may contribute to the initiation of inflammatory processes and negatively affect PSU homeostasis destabilizing the hair follicle infundibulum (Figure 2). The follicle walls eventually rupture, and neutrophils take over, increasing the latter stage of IL-17 production and triggering a rapid inflammatory response. The crosstalk of different skin cells in the early stage of acne remains to be revealed. Understanding these skin immune cells in the pathogenesis of early acne can facilitate the identification of biomarkers as well as the development of targeted therapies for acne vulgaris. Because of immune overactivation in acne, anti-inflammatory treatments should be employed in the management of acne.

## Author contributions

LH: Writing – original draft, Writing – review & editing. SY: Writing – original draft, Writing – review & editing. XY: Writing – review & editing. FF: Writing – review & editing. LZ: Writing – review & editing. LW: Writing – review & editing. XZ: Writing – review & editing. CY: Writing – review & editing. QQ: Writing – review & editing. TZ: Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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