Review Article

A narrative review of research progress on the role of *NLRP3* inflammasome in acne vulgaris

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Background and Objective: Acne vulgaris is a common skin disease around the world which affects the appearance of patients, as well as their physical and mental health. *Cutibacterium acnes* plays a vital role in the occurrence and development of acne vulgaris. Pattern recognition receptors (PRRs) are the first line of defense against external pathogens. The nucleotide oligomerization domain (NOD)-like receptor family pyrin containing 3 (*NLRP3*) inflammasome has recently been shown to contribute to the pathogenesis of acne vulgaris. The purpose of this review is to clarify the underlying mechanisms of *NLRP3* inflammasome in the pathogenesis of acne vulgaris, and its potential as a therapeutic target for the condition.

Methods: The PubMed database was searched for relevant articles published in English between January 2003 to December 2021 using keywords "acne vulgaris", "*NLRP3* inflammasome", and "*Cutibacterium acnes*". The reference lists of retrieved articles were also reviewed to identify relevant articles.

Key Content and Findings: *Cutibacterium acnes* infection can lead to a series of inflammatory reactions and the production of inflammatory factors such as interleukin (IL)-1β. *In vitro* and *in vivo* studies demonstrated that the *NLRP3* inflammasome plays essential roles in acne vulgaris. Further, innate immunity and adaptive immunity pervade the entire pathogenesis of acne vulgaris.

Conclusions: The *NLRP3* inflammasome may be a potential therapeutic target for acne vulgaris. Future studies are needed to investigate the potential therapeutic effects of *NLRP3* inhibitors on acne vulgaris.

Keywords: Acne vulgaris; *Cutibacterium acnes*; inflammation; *NLRP3*; pathogenesis

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Introduction

Acne vulgaris is a general chronic inflammatory disease of the sebaceous glands of the skin that is characterized by excessive papules, nodulocystic lesions, and inflammation of the pilosebaceous follicles (1,2). Non-inflammatory lesions of acne vulgaris are characterized as open comedones (blackheads) and closed comedones (whiteheads). Acne vulgaris has become a universal skin disease among adolescents and young adults with approximately 80% to 90% of adolescents experiencing moderate to strong acne vulgaris (3,4), and it can continue into older adulthood. The condition can seriously affect the appearance of patients, as well as their physical and mental health. It often causes discomfort that can lead to emotional disorders and disfigurement, and, in a large proportion of cases, results in scarring or hyperpigmentation (5,6). However, the pathogenesis of acne vulgaris has yet to be fully elucidated,

Table 1 The search strategy summary

Items	Specification
Date of search	March 1st, 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	"Acne vulgaris", "*NLRP3* inflammasome", and "*Cutibacterium acnes*"
Timeframe	January 2003 to December 2021
Inclusion criteria	English
Selection process	Wei Zhu and Hai-Lin Wang independently selected the included articles

NLRP3, nucleotide oligomerization domain-like receptor family pyrin containing 3.

and effective treatments are still lacking.

The nucleotide oligomerization domain (NOD)-like receptor family pyrin containing 3 (*NLRP3*) inflammasome, comprising *NLRP3*, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1, is involved in microbial infection, endogenous danger signals, and environmental stimuli (7-9). Increasing evidence indicates that the *NLRP3* inflammasome plays an important role in the pathogenesis of acne vulgaris. This review provides an update on research into the role of the *NLRP3* inflammasome in acne vulgaris. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5924/rc).

Methods

The PubMed database was searched to find relevant articles published in English between January 2003 to December 2021. The keywords used for the search included "acne vulgaris", "*NLRP3* inflammasome", and "*Cutibacterium acnes*" (*Table 1*).

Summary

Cutibacterium acnes in acne vulgaris

The pathogenesis of acne vulgaris may be induced by several factors, such as sex hormone levels, excess sebum production, *Cutibacterium acnes* infiltration, abnormal keratosis of sebaceous ducts in hair follicles, and inflammatory process. There are two inflammatory stages of acne vulgaris: scarring and hyperpigmentation (2,10). Research demonstrates that sebum production and secretion can be induced by androgen hormones (6,11). In particular, dihydrotestosterone (DHT) can greatly increase sebum secretion, triggering acne vulgaris. DHT can be converted from testosterone by two types of 5-α reductase, type I and type II, and inhibition of 5-α reductase activity can improve acne vulgaris by decreasing the level of DHT (12). Therefore, 5-α reductase could potentially be used as a target for the treatment of acne vulgaris.

In acne vulgaris, the sebaceous duct narrows and becomes blocked due to hyperkeratosis of the follicle. This phenomenon leads to abnormal discharge of epithelial cells and secretion of sebum from the hair follicle, eventually contributing to acne vulgaris (13). Inflammatory reactions in the early stage of micro acne vulgaris have also been found to lead to skin lesions. Research has found that the expression levels of $CD4^+$ T cells, macrophages and interleukin-1α (IL-1α) increase significantly in the normal hair follicles of patients with acne vulgaris (14).

Microbial *Cutibacterium acnes* infection is another important factor in acne vulgaris. *Cutibacterium acnes* is a gram-positive anaerobic pathogen which is widespread on human skin (15). It can attack the host tissue by producing neuraminidases, lipases, sialidases and other toxic factors. *Cutibacterium acnes* can also produce endogenous porphyrin to oxidize squalene and promote the formation of acne vulgaris in keratinocytes (16). There is evidence that Cutibacterium acnes lipase enzyme can hydrolyze sebum into glycerol and free fatty acids, which in turn stimulates hair follicles, leading to acne vulgaris (17). Cutibacterium acnes can stimulate immune cells to release IL-1β and because different individuals have different immune responses to pathogens, not all individuals develop acne vulgaris (18,19). These studies suggest that topical antibiotic

and oral therapeutic strategies can be used to target *Cutibacterium acnes* and thus to treat acne vulgaris.

NLRP3 inflammasome

Pattern recognition receptors (PRRs), as a critical innate immune defense system, are the first line of defense against external pathogens (20). PRRs contain NOD-like receptors (NLRs), which are belong to cytoplasmic recognition receptor and toll-like receptors (TLRs) (19,21). PRRs are expressed on macrophages, monocytes, neutrophils, epithelial cells and other immune cells. They have been demonstrated to play a critical role in the secretion of IL-1β. PRRs can be induced by pathogen-associated molecular patterns (PAMPs), which are external pathological signals (22,23).

Under the stimulation by *Cutibacterium acnes*, activated *NLRP3* inflammasome prompts the activation of caspase-1, which subsequently promotes the secretion and maturation of the important proinflammatory cytokines IL-1β and IL-18, leading to pyroptosis (24). It indicates that pyroptosis plays an essential role in the inflammatory reaction process.

The *NLRP3* inflammasome can be activated by bacterial toxins, fungus, viruses, some environmental stimuli, endogenous adenosine triphosphate (ATP), hyaluronic acid, amyloid protein, PAMPs, and damage-associated molecular pattern molecules (DAMPs) (25). Activation of the *NLRP3* inflammasome can be induced by factors such as stimulation of ionic flux (K^+ efflux, Ca^+ mobilization, Na^+ influx, and Cl^- efflux), mitochondrial dysfunction, reactive oxygen species (ROS) production and lysosomal disruption. Among these factors, K^+ efflux is the most important for the activation of the *NLRP3* inflammasome (26,27). There are two signals for the activation of the *NLRP3* inflammasome. The first signal is the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which can promote the expression and release of pro-IL-1β, NLRP3 and other pro-inflammatory cytokines. The second signal is the initiation of *NLRP3* inflammasome formation, which can lead to the activation of caspase-1, which converts pro-IL-1β and pro-18 into active forms (25-27). It is worth mentioning that phagocyte activation leads to lysosomal acidification, which activates the *NLRP3* inflammasome and promotes the maturation and secretion of caspase-1 and IL-1β (28). Some studies have proven that post-transcriptional modifications can regulate *NLRP3* inflammasome activation. Furthermore, caspase-11, another analeptic, can induce pyroptosis via the inflammasome (23,28). A recent study found that cell death, such as pyroptosis, apoptosis, necroptosis and ferroptosis has a close relationship with the *NLRP3* inflammasome. These connections may provide us with a new strategy for the treatment of *NLRP3* inflammasome-associated diseases (9).

Roles of the NLRP3 inflammasome in acne vulgaris

The main pathological changes in acne vulgaris are the destruction of hair follicle epithelium and bacterial infection. *Cutibacterium acnes* has been evidenced to play a crucial role in the development of acne vulgaris. It can induce IL-1β secretion via the activation of the *NLRP3* inflammasome in human monocytes leading to acne vulgaris (29). Porphyrins produced by *Cutibacterium acnes* strains can interact with the cell membrane of keratinocytes to promote the activation of *NLRP3* inflammasome and IL-1β by inducing K^+ leakage (30). The *Cutibacterium acnes-NLRP3* inflammasome-IL-1β symbiont is thought to stimulate the innate immune response in the skin (29,30). Sebaceous glands play a crucial role in the progression of acne vulgaris. *Cutibacterium acnes* activates *NLRP3* inflammasome expression which in turn leads to increased expression of IL-1β and caspase-1 in human sebocytes (31). IL-1β, which is abundant in the inflammatory lesions of acne vulgaris, participates in the process of follicular hyperkeratosis and acne vulgaris lesions (32). Clinical research demonstrates that the IL-1β monoclonal antibody gevokizumab and the IL-1α monoclonal antibody MABp1 can significantly reduce the inflammatory response of acne vulgaris (33). *Cutibacterium acnes* has been reported to show a weak performance in *NLRP3*-deficient mice. Therefore, the *NLRP3* inflammasome and IL-1β may be potential therapeutic targets for acne vulgaris. Moreover, macrophages are not the only cells that secrete IL-1β, human sebocytes can also express inflammasome proteins and IL-1β (23,34).

Genetic factors have also been shown to be related to acne vulgaris. For instance, a close relationship has been found between the rs10754558 C/G polymorphism of the *NLRP3* gene and acne vulgaris in the Chinese Han population which proves that *NLRP3* plays a critical role in the pathogenesis of acne vulgaris (21). Based on this finding, the mutant *NLRP3* gene might be a target for the therapy of acne vulgaris.

Baicalin inhibits the activation of the *NLRP3* inflammasome via the NF-κB and mitogen-activated protein (MAPK) pathways, thereby reducing the inflammasome induced by *Cutibacterium acnes* (25). Polyphyllin I inhibits

ROS production, *NLRP3* activation and IL-8 secretion induced by *Cutibacterium acnes* and also suppresses the proliferation and migration of UVB-irradiated keratinocytes (HaCaT cells) (35). Schisandrin A, B and C inhibit the secretion of IL-1β and pyroptosis in human acute leukemia-derived monocytes (THP-1) infected with *Cutibacterium acnes* (19). The possible mechanisms of this inhibitory effects are that Schisandrin A, B and C decrease the levels of *NLRP3* and caspase-1 by inhibiting the production of mtROS, K^+ efflux and ATP release. Caspase-1 that is produced by *NLRP3* can induce pyroptosis (19,23). A recent study showed that the inflammatory reactions induced by palmitic acid in sebocytes occurred through *NLRP3* inflammasome activation, while *NLRP3* knockdown attenuated IL-1β production by sebocytes stimulated with palmitic acid (36). There is evidence that licochalcone A suppresses the activation of the *NLRP3* inflammasome induced by *Cutibacterium acnes* via blocking mtROS production, thereby relieving the symptoms of acne vulgaris (18). Eucalyptol extracted by *Laurus nobilis* can attenuate the activation of the *NLRP3* inflammasome to protect against acne vulgaris (37). One study found that superoxide dismutases (SODs) could reduce the occurrence of acne vulgaris by inhibiting the activation of the *NLRP3* inflammasome in experimental mice (16). Auranofin, an anti-rheumatic gold compound, can attenuate the activation of *NLRP3* inflammasome in macrophages, sebocytes and animals. Using auranofin may therefore be a potential pharmacological therapeutic strategy to treat acne vulgaris via attenuating *NLRP3* inflammasome activation (8).

Therefore, *NLRP3* plays a crucial role in the pathogenesis of acne vulgaris, and it is a potential therapeutic target for this disease.

Progress of research in immunological pathogenesis in acne vulgaris

Acne vulgaris, a common inflammatory disorder, is caused by multiple factors. Abnormal ductal keratinization, inflammation, increased sebaceous gland secretion, and abnormal microbial flora have been identified as the most important causes of acne vulgaris (38). Innate immunity and adaptive immunity are involved in the occurrence and development of the condition.

Innate immunity responses occur rapidly and they are the first line of defense against pathogens. The pathogenesis of acne vulgaris involves multiple innate immunity pathways. Acne vulgaris inflammation can be induced through a variety of innate immune pathways, such as changes in skin barrier function, inflammation of pathogen recognition pathways, and the expression of inflammatory molecules and antimicrobial peptides (AMPs) (39). The skin's physical barrier function includes skin microbiota and the stratum corneum. Destruction of the ecological balance of the skin microbiota may lead to the occurrence of acne vulgaris. Damage to the stratum corneum increases the ability of pathogens to cause infection, but some substances secreted by the skin, such as lipid layers, can prevent the growth of some bacteria (40). *Cutibacterium acnes* is abundant in normal healthy skin, but it can cause inflammation under certain conditions (41). Different *Cutibacterium acnes* strains modulate different cutaneous innate immune targeting markers and cause different inflammatory responses, resulting in acne vulgaris lesions and scars of varying severity (15). Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine, whereas transforming growth factor-beta (TGF-β) is an anti-inflammatory cytokine. Different *Cutibacterium acne* strains have different effects on acne vulgaris depending on the ratio of TNF-α to TGF-β (15). One found that TNF-α polymorphisms, especially TNF-α-863, increase the risk of acne vulgaris (42). Another study demonstrated that an increased in insulin-like growth factor type 1 receptor (IGF-1R) leads to hypertrophic scar formation through inhibiting fibroblast apoptosis (43). It is worth mentioning that zinc gluconate can down-regulate the expression of inflammatory molecule such as protease-activated receptor 2 (PAR-2), TNF-α, and TGF-β (15,44). Matrix metalloproteinases (MMPs) in the innate immune pathway may be involved in acne vulgaris scar formation with different types of acne vulgaris inducing different levels of MMP (45). Research has found that MMPs and tissue inhibitors of metalloproteinases (TIMPs) play crucial roles in acne vulgaris by remodeling of sebaceous glands. *MMP-1* and *TIMP-1* gene polymorphisms are involved in the development of acne vulgaris (46). Furthermore, in the Chinese Han population, the combination of MMP-2 polymorphism and TIMP-2 polymorphism contributes to acne vulgaris susceptibility (45).

Cutibacterium acnes promotes inflammation via TLRs which has able to leading inflammation via cJUN transcription factors (47,48). TLR signals can induce the NF-κB-dependent expression of genes encoding *NLRP3*, pro-IL-18, and pro-IL-1β (25). Some *Cutibacterium acnes* strains promote inflammation via TLR2 and TLR4, which induces the secretion of IL-8, IL-12, AMP hBD2 and MMP-9 (49). AMP S100 A7, AMP hBD-2 and human

neutrophil peptide (HNP) 1–3 have been found to be expressed in acne vulgaris lesions. The reproduction of *Cutibacterium acnes* is restricted in AMP molecules such as IL-37, hBD-2, RNase 7 and Psoriasin (40). TNFAIP3 interacting protein 1 (TNIP1) has been found to negatively regulate the inflammatory response induced by *Cutibacterium acnes* through c-Jun N-terminal kinase (JNK), NF-κB, and P38, and to activate the MAPK signaling pathways in keratinocytes (50). All-trans retinoic acid (ATRA) negatively affects the inflammatory response induced by *Cutibacterium acnes* through the regulation of TNIP1 expression (50).

Macrophages, neutrophils and epithelial cells play a vital role in the innate immune system. Innate immune system cells recognize PAMPs produced by microbes via PRRs, including TLRs, retinoic acid-inducible gene (RIG)-like receptors, and NLRs (51). These PRRs may initiate during innate pathogen recognition. AMPs can be found at high levels in the lesions of patients with acne vulgaris, which suggests that they may have a protective role in infection (52). The responses of AMPs that triggered by *Cutibacterium acnes* in sebocytes depend on TLRs (52). In conclusion, acne vulgaris can progress through a variety of innate immune pathways.

The inflammatory signals produced by innate immune pathways can trigger the activation of T and B cells to regulate the adaptive immune response. *Cutibacterium acnes* can stimulate B lymphocytes to produce antibodies such as IgG and IgM, which play an important role in the process of acne vulgaris (53). The early infiltrating cells in acne vulgaris lesions are mainly $CD4^+$ T cells, and naïve $CD4^+$ T cells differentiate to Th1, Th2, Th17 and pTregs following stimulation by pathogen (54). The phenomena of cytokine secretion and proliferation in Th1 and Th2 cells *in vitro* and *in vivo* are universal in adaptive immunity. In addition to Th1 and Th2 cells, Th17 cells can complement the function of $CD4^+$ T cells family lineages (14). During inflammatory processes, $CD4^+$ T cells play an essential role in balancing adaptive immunity. *Cutibacterium acnes* can promote mixed Th17/Th1 responses by inducing $CD4^+$ T cells secreting IL-17A and interferon-gamma (IFN-γ). IL-17 and IL-22, the main Th17 effector cytokines, promote antimicrobial responses by inducing a series of AMPs (55,56). Sebocytes stimulated by *Cutibacterium acnes* promote the activation of Th17 cell types via the secretion of IL-6, IL-1β, and growth factor-β (57). A recent study showed that $CD4^+$Th17 clones with the same antibacterial properties as cytotoxic T cells and granulocytes killed bacteria in the IL-26-independent pathway (14). These $CD4^+$Th17 clones were produced by monocyte culture of acne strains in healthy skin, which was not related to acne. These findings suggest that the antibacterial mechanism of the Th17 subgroup involves a unique relationship between innate immunity and adaptive immunity (14). Proinflammatory IL-17-generating cells and anti-inflammatory $FOXP3^+$ Treg cells are the main factors for $CD4^+$ T cells to play a crucial role in inflammatory diseases. In acne vulgaris, the expression levels of IL-17 and FOXP3 are increased in epidermal keratinocytes and lymphocytes (58). *Cutibacterium acnes* can induce the activation of IL-17, with one study finding that the expression of serum IL-17 was increased in patients with acne vulgaris scarring compared to those without (59).

Further research proves that IL-17 expression in peripheral blood mononuclear cells is significantly increased in the skin of acne vulgaris patients with *Cutibacterium acnes* strains compared to healthy skin with *Cutibacterium acnes* strains (55,57). IL-17A plays an important role in acne vulgaris in a paracrine manner involving interaction between dermal lymphocytes and epidermal keratinocytes (60). IL-17, TNF-α, and IL-1 play synergistic roles in acne vulgaris by inducing the production of several metalloproteinases (58). Platelets may play a role in adaptive immunity in acne vulgaris by up-regulating lymphocytes (61). Therefore, Th1, Th17 and Th17/Th1 cells may play significant roles in the pathogenesis of acne vulgaris.

Conclusions and perspectives

Acne vulgaris is a chronic inflammatory disease characterized by abnormal ductal keratinization, increased sebaceous gland secretion, inflammation and abnormal microbial flora. This review has focused on the relationship between the *NLRP3* inflammasome and acne vulgaris in the pathogenesis of acne vulgaris. *Cutibacterium acnes* plays a key role in the pathogenesis of acne vulgaris. *Cutibacterium acnes* infection can lead to a series of inflammatory reactions and the production of inflammatory factors such as IL-1β. Increasing evidence has proven that the *NLRP3* inflammasome plays essential roles in acne vulgaris. Further, innate immunity and adaptive immunity pervade the entire pathogenesis of acne vulgaris. The major developments regarding this issue were summarized in *Table 2*. Thus, the inflammatory response process in acne vulgaris is complex. The *NLRP3* inflammasome may be a potential therapeutic target for acne vulgaris. In the future, further investigations are needed to determine whether the *NLRP3* inflammasome

Table 2 Summary of the major developments regarding the role of *NLRP3* inflammasome in acne vulgaris

Items	References
NLRP3 inflammasome participates in the pathogenesis of acne vulgaris	(18,19,21,23-25,37)
NLRP3 inflammasome is a potential therapeutic target for acne vulgaris	(8,16,18,19,21,25,35-37)
A variety of innate immune pathways are involved in the pathogenesis of acne vulgaris	(15,39,40,42-50,52)
Adaptive immune responses in the development of acne vulgaris	(14,55-61)

NLRP3, nucleotide oligomerization domain-like receptor family pyrin containing 3.

is the core mechanism in the pathogenesis of acne vulgaris. Moreover, the effectiveness of using *NLRP*3 inflammasome inhibitors as an intervention for acne vulgaris also needs to be further assessed.

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Footnote

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