Inflammasome Dynamics in Psoriasis: AIM2, NLRP3, and NLRP1 at the Interface of Inflammation and Immunity

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Additional material is published online only. To view please visit the journal online.

Cite this as: Sharma S, Tanwar SS, Kaur I, Chavhan M and Tiwari N. Inflammasome Dynamics in Psoriasis: AIM2, NLRP3, and NLRP1 at the Interface of Inflammation and Immunity. Premier Journal of Science 2025;14:100182

DOI: https://doi.org/10.70389/PJS.100182

Peer Review

Received: 19 September 2025
Last revised: 18 November 2025
Accepted: 24 November 2025
Version accepted: 3
Published: 29 December 2025

Ethical approval: N/a
Consent: N/a
Funding: No external funding
Conflicts of interest: The authors declare no conflict of interest

ABSTRACT

Psoriasis, an incurable immune-mediated inflammatory skin illness, greatly affects patients' physical and emotional health. Genetics, epigenetics, environmental variables, and unbalanced immune cells such as T cells, dendritic cells (DCs), and keratinocytes cause psoriasis. The immune system plays a major role in psoriasis, yet it lacks well-defined antigens, autoimmune genetic risk factors, and particular antibodies. Psoriasis is an autoinflammatory illness due to molecular and cellular features like neutrophils in skin lesions and innate immune system stimulation. High-molecular-weight protein complexes known as autoinflammatory inflammasomes frequently occur in autoinflammatory diseases, genetic disorders characterized by recurring fever, higher acute-phase reactants, and organ inflammation. Immune cells organize these inflammasomes in their cytoplasm. They start inflammatory processes like making mature IL-1β, IL-18, caspase-1, and pyroptosis. Recent research has focused on immune response triggers rather than autoimmune psoriasis. Researchers have specifically linked NLRP1, NLRP3, and AIM2 inflammasomes to psoriasis. Identifying activators, inhibitors, genetic susceptibility regions, and inflammasome-related genes in psoriasis provides useful insights. This systematic review gathers recent and thorough research on inflammasomes and psoriasis to better understand this complex skin disorder's pathogenesis.

Keywords: AIM2, Inflammasome, NLRP1, NLRP3, Psoriasis, Autoinflammatory disorder

Introduction

Psoriasis, a diligent and fiery skin condition, is believed to result from a combination of inherited and natural factors.[1–2] Psoriasis manifests as textured reddish plaques due to intemperate growth and atypical separation of keratinocytes. Psoriasis affects approximately 2% to 4% of the population worldwide.[3–5] In addition to skin-related issues, persons with psoriasis may confront an expanded possibility of cardiovascular malady, diabetes, joint ache, sorrow, and indeed cancer.[6–10] These connected wellness difficulties collectively impact the physical and emotional well-being of individuals with psoriasis, leading to significant socioeconomic and psychological responsibilities (Figure 1).[11,12]

Methods

This review is based on a narrative search of the literature rather than a systematic or PRISMA-guided approach. Searches were conducted across PubMed, Scopus, Web of Science, EMBASE, and Google Scholar, focusing on publications from 2010 to 2024. Search terms included "psoriasis," "inflammasome," "AIM2," "NLRP3," "NLRP1," "keratinocyte inflammasome," and "myeloid inflammasome." Relevant peer-reviewed experimental studies, clinical studies, and mechanistic reviews were included based on thematic relevance to inflammasome biology and psoriasis pathogenesis. Non-English articles, non-peer-reviewed literature, and studies unrelated to inflammasome pathways were excluded. The goal of the narrative search was to summarize current mechanistic understanding of canonical and non-canonical inflammasome pathways in psoriasis, with emphasis on keratinocyte-driven AIM2 and NLRP1 activation and myeloid-driven NLRP3 signaling.

Psoriasis may be a complex condition characterized by dynamic interactions between keratinocytes, safe cells, and various skin cells, including endothelial cells.[13,14] When the growth and separation of keratinocytes don't happen properly, the epidermis gets bigger and resistant cells, especially dendritic cells (DCs) and T cells, obtain inside it deeply. Some of the most important things about psoriasis are thicker skin capillaries and numerous different chemokines and cytokines that cause it.[15–17] The crucial role in the progression of the disease lies in the interaction between resistant cells and keratinocytes, which is primarily mediated by interleukin (IL)-17. While IIL-17, IL-23, and tumor necrosis factor (TNF) are essential cytokines in the growth of psoriasis, the enactment of the multi-protein inflammasome complex plays a more prominent role in its pathogenesis. This actuation is connected with an increased generation of IL-1β and IL-18.[18–20]

Autoinflammation

It is considered an immune system reaction, developing from the over-the-top enactment of the safe framework and presenting a clinical phenotype imprinted by substituting phases of compounding and abatement.[21–24] It is well-established that there is a close connection between intrinsic and versatile resistive responses, and any disarray in this environment stems from an awkwardness between these two components.[25–28]

The fundamental qualifications for the dysregulation of these immune system compartments are found within the incorporated components and cells. As expected, autoimmune pathogenesis comprises a glitch in flexible insusceptibility, driving the creation of autoantibodies with the cooperation of T and B cells.[29–31] In contrast, autoinflammation fundamentally locks in the intrinsic immune system and presents fiery scenes without the nearness of autoreactive T cells and towering autoantibody levels.[32]

Author contribution:
Seema Sharma, Sampat Singh Tanwar, Inderpreet Kaur, Mranali Chavhan and Nishant Tiwari – Conceptualization, Writing – original draft, review and editing

Guarantor: Seema Sharma

Provenance and peer-review: Unsolicited and externally peer-reviewed

Data availability statement: N/a

In particular, cells of the natural resistant framework, like epithelial and dendritic cells, polymorphonuclear leukocytes, and macrophages, play two roles when the immune system is sick. They not only operated as a rapid barrier to the fiery process however additionally worked as effectors within the movement of the fiery reaction. This audit focuses fundamentally on the potential role of the inflammasome in the pathophysiology of psoriasis.[33]

Inflammasomes

The inflammasome could be a high-molecular-weight protein complex that massively amasses within the cytoplasm of stimulated resistant cells. Upon actuation, it sets off a cascade of provoking occasions, leading to the age of dynamic caspase-1.[34–38] This dynamic caspase-1, in turn, supports the formation of pro-inflammatory cytokines such as Interleukin-1β (InL-1β) and IL-18, and starts a shape of modified cell passing known as pyroptosis. Recognized as a critical component of the intrinsic resistant framework, the inflammasome can notice components of irresistible specialists or tissue injury.[39–42] Various examines have uncovered the association of distinct inflammasomes with both innate and acquired autoinflammatory disorders. Over the past decades, extensive evidence has enlightened the part of the inflammasome and its constituents inside the etiology of numerous skin disorders.[43] Examinations reveal that the connect between the inflammasome and psoriasis essentially derives from its association with pro-inflammatory cytokines.[44–46] An inflammasome is an integral part of the intrinsic safety framework; it forms an intracellular complex that binds to pathogens and sets off a chain reaction to destroy them.[47–49]

Different kinds of inflammasomes incorporate.[50,51]

- The nucleotide-binding oligomerisation space (NOD)-like receptor (NLR) P3 inflammasome.
- The absent in melanoma 2 (AIM2) inflammasome
- The NLRC4 inflammasome.
- An atomic design acknowledgment receptor (PRR).

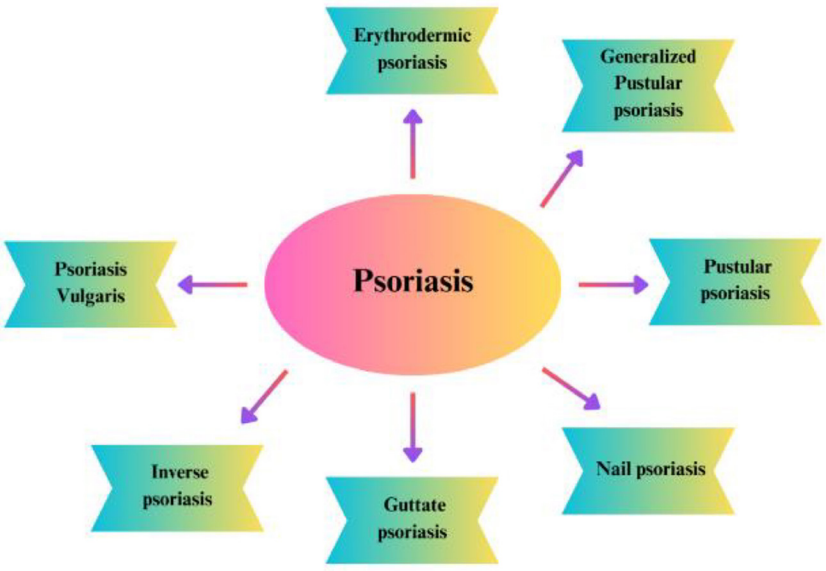

Fig 1 | Types of psoriasis

The ASC connector protein and caspase-1 chemical synthesize up the apoptosis-associated speck-like protein.[27,52,53] Inflammasome action is linked to chronic fiery clutters, and growing evidence in blocked tissues implies a role in psoriasis progression.[54,55] In the first study, psoriatic injuries had a 20-fold increase in caspase-5 mRNA and a clear increase in caspase-1 and other inflammasome-related transcripts.[56–58]

Studies demonstrate greater NLRP3, NLRP1, and AIM2 levels in psoriatic skin.[55,59–61] Hereditary information links NLRP1, NLRP3, and AIM2 polymorphisms are associated with psoriasis, while inflammasome-related polymorphisms are linked to joint pain.[59–64] Psoriatic epidermal samples and full-thickness skin exhibit a higher expression of NLR signature genes.[65–69] A later study demonstrated greater peripheral blood inflammasome activity in psoriasis patients, suggesting systemic irritation.[70–73] Researchers found that people with psoriasis had higher amounts of IL-1β, IL-18, and the inflammasome sensors NLRP3, NLRP1, and AIM2 in their peripheral blood cells. Their caspase-1 activity was higher. IL-1 stimulated human and model Tcells to produce IL-17. TNF-α regulates NLRP3 inflammasome component translation in mouse models.[74,75] TNF-α exposure dramatically boosts NLRP3 and pro-IL-1β expression. Research indicates that TNF-α can activate the NLRP3 inflammasome without a flag. TNF-blocking medications normalize IL-1, IL-18, and caspase 173 activity (Figure 2).

Although the specific etiology is unknown, incendiary reactions and aberrant safe cell activation are thought to produce psoriasis.[76,77] When intracellular signaling pathways and inflammatory substances are overactive, safe cells synthesize more cytokines. These cytokines boost translation factors and synthesize epidermis and psoriasis worse. Psoriasis advances as a result of TLRs, particularly TLR7/8, inhibiting the start of the response. TLR signaling recruits connector proteins and MyD88. A pathway dependent on MyD88 creates nuclear factor-κB, which triggers inflammatory cytokines and boosts TLR7/8-MyD88-NF-κB signaling, leading to long-lasting inflammation. Because of NLRP3, caspase-1, and an ASC, the NLRP3 inflammasome is vital to TLRs. Cytoplasmic macromolecular complex.[78,79] During activation of the NLRP3 inflammasome, IL-1β is produced, and ASC and caspase-1 are activated. Psoriasis improves with inflammation. TLR7/8-My88-NF-κB and NLRP3 pathways contribute to psoriasis onset and progression.[63,80] Psoriasis therapies today include topicals, systemics, and phototherapy. These procedures often lead to relapses and pharmaceutical side effects. The compulsive components of psoriasis remain poorly understood, necessitating safe, effective, and globally approved treatments. Therefore, it is crucial to find psoriasis specialists who can minimize side effects.

DOI: https://doi.org/10.70389/PJS.100182 | Premier Journal of Science 2025;14:100182

Narrative of Inflammasomes

Dr. Jurg Tschopp and colleagues[27] initially used the "inflammasome," formerly known as NLRP1, to describe a "caspase-activating complex" that included caspase-1, caspase-5, Pycard (the caspase interaction domain), and NALP1.[81–84] It was later discovered that this NLRP1 inflammasome has a role in the creation of IL-1β. Two years down the road, the identical group of researchers found the NLRP3 inflammasome; since then, it has risen to the position of most-studied inflammasome thanks to its roles in innate and adaptive immunity. There are many things that can activate NLRP3, such as infectious agents like fungi, bacteria, and viruses, as well as endogenous substances like fibrillar amyloid-β (Aβ) peptide, extracellular ATP, and glucose.[85–90] Poyet et al. discovered another inflammasome, initially known as IPAF however later renamed NLRC4 due to structural similarities to other NLR proteins.

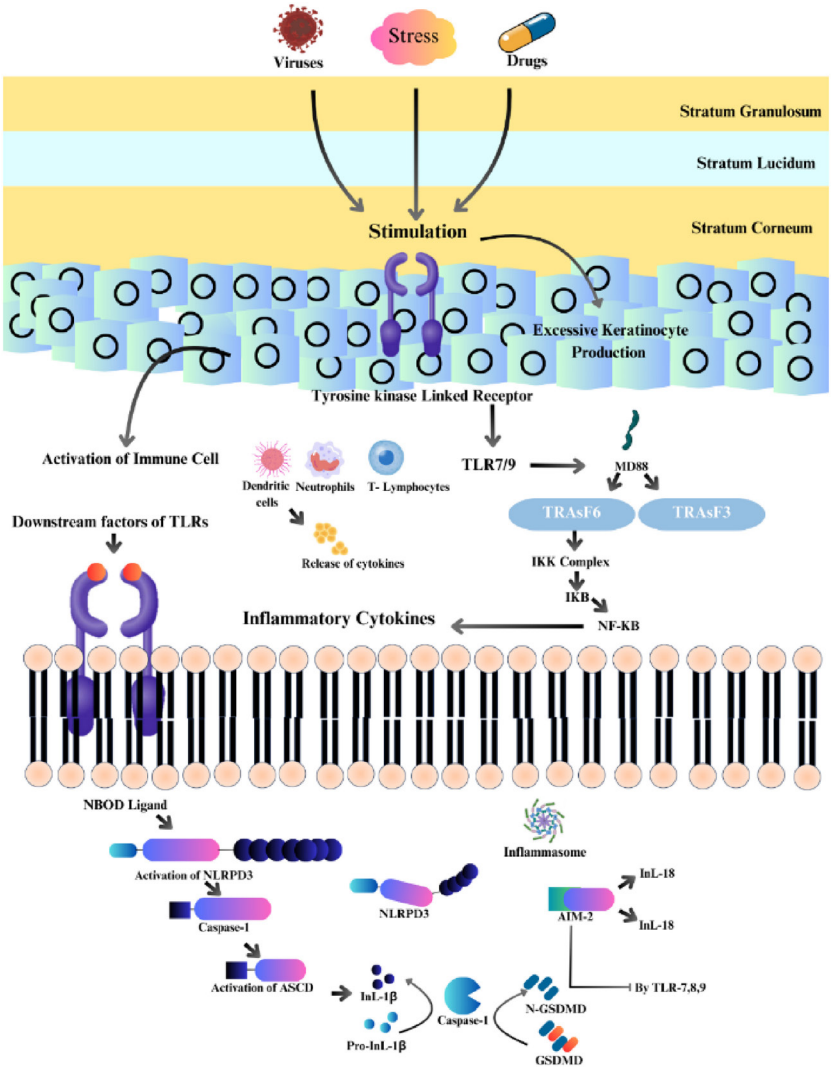

Fig 2 | The TLR7/8–MyD88–NF-κB pathway promotes NLRP3 and AIM2 inflammasome activation by inducing transcription of pro-IL-1β, pro-IL-18, and inflammasome components. TLR7/8 stimulation activates MyD88, leading to NF-κB signaling and priming of the inflammasome ("signal 1"). Subsequent cellular stress or pathogen DNA provides the activation signal ("signal 2") that triggers NLRP3 or AIM2 assembly, caspase-1 activation, and release of IL-1β and IL-18. Thus, TLR7/8-MyD88-NF-κB signaling primes, while NLRP3 and AIM2 pathways execute, the inflammatory response

Different research groups used different methods to independently identify the AIM2 inflammasome. Different techniques were used to find AIM2, which is controlled by IFN-β and linked to DNA. These included mass spectrometry, electromobility shift tests, and genome screens. Our results show that the HIN-200 family member AIM2 can activate caspase-1 and caspase-3. We highlighted the ability of the therefore-called "canonical inflammasomes," which include AIM2, NLRP1, NLRP3, and NLRC4, to trigger caspase-1 action.[86–90]

The "noncanonical" inflammasome, only recently discovered, activates caspase-11 in mice and caspase-4 and caspase-5 in humans in response to LPS.[91] One key difference between canonical and noncanonical inflammasomes is that the latter do not trigger caspase-1 activation. The GSDMD is broken, and pyroptosis begins by creating holes in the cell membrane, which is accomplished by activating caspase-11 in mice and caspase-4/5 in humans (Table 1).[92–95]

In conclusion, the discovery and study of new complexes has expanded our knowledge of inflammasomes. All of them have contributed to our understanding of innate immune responses and their role in inflammatory processes.

The extensively researched inflammasome complex, additionally known as the nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain-containing receptor 3 (NLRP3), consists of NLRs, an apoptosis-associated speck-like protein that includes a caspase recruitment domain (ASC), and caspase-195,100. Many extracellular inflammatory stimuli, such as bacteria, viruses, pathogen-associated molecular patterns (PAMP), and damage-associated molecular patterns (DAMP), can indirectly activate NLRP3. However, the precise molecular pathways beginning NLRP3 activation remain insufficiently understood. Several stress factors, such as K+ efflux, intracellular Ca2+, extracellular ATP, mitochondrial malfunction, reactive oxygen species (ROS), and lysosomal rupture, control the activation of the protein complex.[123–128]

When NLRP3 is activated, it starts caspase-1, which cuts pro-IL-1β and pro-IL-18 into active IL-18 and IL-1β. New research demonstrates that NLRP3 controls the splicing of gasdermin D (GSDMD) by turning on caspase-1, which splits the protein into two pieces called the C and N domains. The N-terminal segment (GSDMD-N) assembles to generate pores on the plasma membrane, triggering pyroptosis. Hence, GSDMD is considered a critical component of NLRP3. In addition, caspase-11 directly contributes to pyroptosis by cutting the GSDMD membrane-forming protein, which then activates the canonical NLRP3 and releases cytokines.[124,125]

A major factor in the development of psoriasis is an abnormal activation of the immune system. This has led to more research being done on the role of NLRP3 inflammasome activation. Studies confirm that the development of the NLRP3 inflammasome contributes to

Table1 | Inflammasomes detect danger signals via specific ligands to trigger inflammation. NLRP3 responds to ATP, nigericin, and crystals; AIM2 to cytosolic DNA; NLRC4 to bacterial flagellin; NLRP1 to anthrax toxin; NLRP6 to microbial metabolites; NLRP12 to bacterial lipoproteins; and IFI16 to viral DNA. These activations lead to caspase-1 activation, IL-1β/IL-18 release, and pyroptosis, crucial for immune defense

Types of Cells	Functions of Inflammasome in Immune cells			References
	NLRP3	NLRP1	AIM2	
CD4+Tcells	It releases IL-1β, and promote IFN-γ	NLRP1 serves as an inhibitory modulator of Th17 cell development in both mice and humans experiencing autoimmune diabetes.	It shows CD4+Tcells in mouse as well as human and it is managed by TCR Activation, In Th-cell differentiation no Specific effect.	96–101
CD8+Tcells	Initiates the NLRP3 inflammasome in antigen-presenting cells (APCs) through an antigen-dependent process to facilitate the maturation of IL-1β. The involvement of perforin released by antigen-specific cytotoxic T lymphocytes (CTLs) is essential for activating the NLRP3 inflammasome in APCs.	NLRP1 functions as an inhibitory modulator of Th17 cell development in both mice and humans experiencing autoimmune diabetes.	AIM2 identifies damage-associated molecular patterns (DAMPs), generates inflammatory cytokines, and enhances the proliferation and activity of CD8+ cells.	101, 105–107
B cells	It releases IL-1β, Production of IgM	–	IFN-γ and CD28+ B cells can activate AIM2, as evidenced by the release of IL-1β secretion in primary B cells stimulated with synthetic dsDNA, along with the production of caspase-1 at reduced activity levels.	104, 109–110
Keratinocytes	BAY 11-7082 alleviates the NLRP3 and dual NF-kB, and release of IL-1β, IL-18	Release of IL-1β, IL-18 in NLRP1 inflammasome and activated isostearic acid in cultured keratinocytes.	NETs – activated AIM2 in keratinocytes not only it promotes IL-β release through the inflammasome pathway but also promotes IFN- γ production by X-Linked inhibitor of apoptosis protein (XIAP).	111–113
Dendritic cell	CAG markedly diminished the imiquimod-induced NLRP3 release of IL-1β and initiated gasdermin D (GSMD)-mediated pyroptosis.	–	In psoriasis, AIM2 initiates caspase-1-dependent inflammasome signaling, leading to the release of IL-18 and IL-1β. The inflammatory response of AIM2 can synergize with the IFN-γ produced by plasmacytoid dendritic cells.	111–114
Macrophages	Activation of NLRP3 signaling in macrophages induces the development of CD4+ T cells into tumor-promoting T helper type 2 cell (Th2 cell), Th17 cell, and regulatory T cell populations, concurrently inhibiting Th1 cell polarization and activation of cytotoxic CD8+ T cells. The inhibitory impacts of NLRP3 signaling are contingent on the presence of IL-10	NLRP1 undergoes N-terminal proteolysis, triggering pyroptosis in macrophages and eliciting a pro-inflammatory cytokine response.	Organelle, pathogen respond to AIM2, efficient macrophage to release IL-18 and IL-1β inducing Th adaptive immune system.	115–118
Neutrophils	Activation of NLRP3 in neutrophils triggers the production of pro-inflammatory cytokines and chemokines in the liver. This activation also results in the infiltration of neutrophils and macrophages into the liver, along with an elevated incidence of cell death.	Improving neurological function and decreasing NLRP1-induced neuronal death are achieved through the depletion of neutrophils	Elevated levels of ASC, AIM2, and caspase-1 in neutrophils can induce GSMD-mediated pyroptosis. The AIM2 inflammasome signaling pathway, triggered by infection, releases IL-1β from infected cells and enhances IL-17 release by Th cells. This, in turn, stimulates the production of chemokines and recruits additional neutrophils into the inflammatory microenvironment.	119–122

the inflammatory response in psoriasis. In psoriasis samples, NLRP3 expression was four times higher than in normal skin biopsies. Additionally, psoriasis samples had IL-1 expression levels approximately 3–4 times higher than normal skin biopsy specimens, and caspase-1 expression significantly increased, reaching 2–3 times higher levels than normal skin biopsies.[126–127]

A year earlier, researchers found similar data in an experimental mouse model of imiquimod-induced psoriasis-like dermatitis, where skin samples showed NLRP3 activation and higher levels of pNF-B expression.[1]

Recent research has shown that IL-18 and ASC proteins are much more abundant in people with psoriasis than in healthy controls. This suggests that they may be important biomarkers for diagnosing psoriasis. The fact that IL-18 and ASC proteins are linked to each other demonstrates how important they are in the inflammatory responses that lead to psoriasis.[108,129]

NLRP1 in Psoriasis

Another NLRPD family member, NLRP1, is in charge of forming an individual's inflammasomes. The atomic mechanisms behind its activation and the events that followed are still not fully known, despite the fact that it was the most investigated inflammasome.[109,129,130] The changes found in NLRP1 in people with different skin diseases show how complexly NLRP1 activation is controlled. This highlights the skin's important role and vulnerability to chronic inflammatory conditions.[131,132] We used single nucleotide polymorphism analysis to find genetic variants in the NLRP1 inflammasome complex that are linked to a higher risk of getting psoriasis. These variants are rs878329, rs12150220, rs8079034, and rs6502867. They found

DOI: https://doi.org/10.70389/PJS.100182 | Premier Journal of Science 2025;14:100182

that psoriasis is associated with over transmission of the NLRP1 rs878329C and rs8079034C genotypes. Additionally, research found a high correlation between psoriasis and polymorphisms in the NLRP1 gene. An earlier diagnosis of psoriasis was associated with homozygosity for the rs878329C variation. In the peripheral blood of psoriasis patients, researchers detected increased levels of circulating IL-18 and NLRP1 mRNA expression. They additionally discovered a correlation between the rs878329C allele and higher levels of circulating IL-18. These findings clearly suggest that the NLRP1 inflammasome has a role in the development and course of psoriasis.[132,133] The authors of another paper talked about how important the NLRP1 inflammasome is for human keratinocytes' ability to recognize UVB and then synthesize IL-1β and IL-18. According to their findings, NLRP3 is the main inflammasome in myeloid cells, while NLRP1 is the main inflammasome in keratinocytes. Researchers linked psoriatic arthritis (PsA) patients to a genetic variation in the inflammasome-related gene CARD8-C10X (rs2043211). Researchers linked different PsA symptoms to different inflammasome gene variations, however not to NLRP1 or NLRP3.

AIM2 in Psoriasis

It is part of a group of cytosolic innate immune receptors that can find cytosolic double-stranded DNA (dsDNA) from bacteria, viruses, and even its own DNA. When AIM2 finds dsDNA, it speeds up the formation of the inflammasome, which releases the cytokines IL-1β and IL-18, which cause inflammation. AIM2 plays a vital function in host defense against numerous pathogens and may contribute to immune system or autoinflammatory diseases. Melanocytes and Langerhans cells in healthy epidermis normally express AIM2. However, inflammatory disorders such as atopic dermatitis, allergic contact dermatitis, and psoriasis dramatically enhance AIM2 expression in keratinocytes. A study by Dombrowski et al. discovered that in psoriatic lesions, cytosolic DNA activates AIM2 inflammasomes only in keratinocytes, which makes proinflammatory cytokines. They observed no such phenomenon in healthy lesions. Psoriasis triggers the activation and suppression of AIM2 and the NLRP3 inflammasome. We still don't know the source of cytosolic DNA in psoriatic keratinocytes, however one hypothesis suggests that cytosolic AIM2 may recognize extracellular DNA from dying cells, leading to sterile inflammatory skin disorders.[134] Extracellular self-DNA, which is usually removed by deoxyribonuclease (DNase), may combine with the germ-killing peptide cathelicidin LL-37 in psoriasis, which could lead to the disease. Dombrowski et al. studied the role of LL-37 in DNA-induced inflammation and postulated that the interaction between LL-37, abundantly expressed in psoriatic skin, and cytosolic DNA might contribute to AIM2-dependent inflammasome activation.[134]

In any case, researchers discovered that when the LL-37-DNA complex internalizes into the cytosol, it loses its ability to perform the AIM2 inflammasome. In psoriatic injuries that haven't been treated, the AIM2 inflammasome was still activated, even though LL-37 levels were higher. This suggests that the levels of LL-37 in untreated psoriasis may not be enough to control AIM2 inflammasome activity. Treatments such as UVB radiation or neighborhood vitamin D analogs, which are known to enhance cutaneous vitamin D amalgamation, stimulated the expression of cathelicidin in damaged skin, thereby reducing skin aggravation. These studies not only show how well UVB and vitamin D therapy work, however they additionally suggest that anti-psoriatic drugs that affect inflammasomes, especially AIM2, could be used to treat cathelicidin LL-37.

Certainly, the pro-inflammatory cytokine IL-1β plays a major role in the genesis of numerous scorching skin ailments, including psoriasis. In general, keratinocytes from murine models don't synthesize IL-1β. Instead, they synthesize the cytokine IL-18, which can be changed into its active form by inflammasomes in these cells. The fact that cathelicidin LL-37 interacts with DNA and is more abundant in people with psoriasis suggests that LL-37–DNA intelligence may assist turn on AIM2-dependent inflammasomes.[123] Elicidin mRNA expression in skin damage significantly increased in psoriasis patients compared to healthy individuals, suggesting a possible role in the pathogenesis of psoriasis.[124]

Dermal cathelicidin LL-37 binds to self-DNA and activates dermal plasmacytoid dendritic cells, which leads to inflammation of the skin. Conversely, epidermal LL-37 in keratinocytes binds with cytosolic DNA, potentially inhibiting its pro-inflammatory activities.[134] This distinction may explicate the efficiency of vitamin D3, a major inducer of cathelicidin production in keratinocytes and monocytes, in treating psoriasis and lowering inflammation in psoriatic lesions.[131] Members of the Toll-like receptor (TLR) superfamily, critical in both innate and adaptive immune responses, contribute to the pathogenesis of psoriasis. In animal models, injections cause symptoms similar to psoriasis, and treatment with TLR-7, −8, and −9 antagonists lessens skin lesions related to psoriasis, lowers the expression of NLRP3 and AIM2 in the dermis, and lowers the production of Th1 and Th17 cytokines in both the skin and serum. This highlights the potential of inflammasomes as therapeutic targets for psoriasis treatment.[19] Focusing on stopping the activation of AIM2 inflammasomes in psoriasis, researchers showed in 2020 that red vine leaf extract (EFLA 945) may stop the activation of AIM2 and other inflammasomes, highlighting its potential as a psoriasis treatment (Table 2).[134]

The Vital Role of NF-κB and TNF-α in Psoriasis

NF-κB and TNF-α are key drivers of the inflammation seen in psoriasis. These molecules play important roles in starting and maintaining the disease by triggering a chain reaction of immune responses. NF-κB is a protein that acts like a switch, turning on genes involved in inflammation and immune activity. It gets activated when the body detects stress, harmful microbes, or inflammatory signals like TNF-α. When NF-κB is turned

Table 2 | Various types of regulators, activator, inhibitor and inducer of inflammasome

Inflammasome	Regulator	Activator	Inhibitor	Inducer	References
AIM2	PK2	Cytoplasmic DNA Poly(dA-dT)	EGCG	-	131
	CARD18	IFN-α, IFN-γ	EFLA945	-	112
	AURKA	-	Obovatol	-	127
	TLR7,8,9	-	WFA	-	128
	Fra-1	-	RGFP966	-	129
NLRP3	-	CD100-PIXnB2	Rosmarinic Acid Poly(I:C)	IMQ AC-YVAD-CMK	130
	-	miR-155	EPD	IMQ	131
	-	IL-17, IL-22	CAG	ATP, βzATP, POM1, A438079	132
	-	-	IMQ BAY11-7082	-	108
NLPR1		Isostearic Acid		-	128

on, it moves into the cell nucleus and tells other molecules to synthesize substances that cause inflammation, like TNF-α, IL-1β, and IL-6. This leads to the buildup of immune cells in the skin, fueling ongoing inflammation.

In psoriasis, this system becomes overactive. In skin cells (keratinocytes), NF-κB drives excessive growth and abnormal behavior, creating the thick, scaly patches typical of psoriasis. In immune cells like T cells and dendritic cells, NF-κB controls the release of inflammatory molecules like IL-23 and IL-17, which are central to the disease's chronic nature.

TNF-α, a key protein influenced by NF-κB, makes this problem worse. It is overproduced in psoriatic skin and blood, creating a vicious cycle: TNF-α activates NF-κB, and NF-κB increases the production of TNF-α. This cycle causes skin cells to grow too quickly, attracts more immune cells to the area, and keeps the inflammation going. TNF-α additionally spreads inflammation to other parts of the body, which can lead to related conditions like heart disease, diabetes, and arthritis.

This connection between NF-κB and TNF-α explains why they are major targets for treating psoriasis. Blocking these molecules can interrupt the cycle of inflammation, reduce skin symptoms, and lower the risk of other health problems linked to the disease.[133,134]

Discussion

Inflammasomes, particularly the NLRP3 inflammasome, are important contributors to the development of plaque psoriasis. These complexes trigger the production of inflammatory proteins such as IL-1β and IL-18, which are responsible for the inflammation that is observed in this illness. The overactive NLRP3 inflammasome causes plaque psoriasis by increasing inflammation. This accelerates the growth of skin cells and attracts immune cells to the area, exacerbating the condition. This mechanism additionally increases the activity of other inflammatory pathways, such as the Th17 response, which plays a significant role in the development of psoriatic plaques. Treatments that focus on inflammasome activity have shown potential in lowering inflammation and relieving symptoms. This emphasizes the significance of inflammasomes in plaque psoriasis and lends credence to the notion of targeting them as a component of therapeutic treatments.

Conclusion

In conclusion, the inappropriate functioning of specific inflammasomes, such as AIM2, NLRP3, and NLRP1, is a major factor in the development and aggravation of psoriasis. These inflammasomes are protein complexes that enhance inflammation in the skin by generating chemicals such as IL-1β and IL-18. They additionally interact with other key pathways, such as NF-κB and TNF-α, which further contribute to the inflammation. NF-κB is responsible for the production of more inflammatory chemicals, while TNF-α not only activates the inflammasome however is additionally increased by it, resulting in a cycle of continuous inflammation. There is still a lot to learn about how these inflammasomes function in psoriasis, particularly in terms of how they interact with one another and with pathways such as NF-κB and TNF-α. Our understanding of these relationships may assist us develop more effective and personalized psoriasis treatments. We are getting closer to discovering novel and innovative treatments for psoriasis and improving the lives of those who have it by investigating the role of inflammasomes in this chronic skin condition.

Abbreviation

PsA - Psoriasis arthritis
DCs - Dendritic cells
Caspase-1 - Cysteinyl aspartate specific proteinase - 1
IL-1β - Interleukin -1β
IL-18 -Interleukin -18
IL-23 - Interleukin -23
NOD - Nucleotide binding oligomerization domain
NLRP1 - Nucleotide binding oligomerization domain (NOD) likereceptor family pyrin domain containing 3
NLRP3 - Nucleotide binding oligomerization domain (NOD) like receptor family pyrin domain containing 1
AIM2 - Absent in Melanoma 2
TNF - Tumor necrosis factor
TRAF3 - Tumor necrosis factor receptor like associated factor 3
TRAF6 - Tumor necrosis factor receptor like associated factor 6
PPP - Psoriasis pustulosa palmoplantaris
ASC - Apoptosis associated speck like protein contained a caspase recruitment domain
TLR 7/8 - Toll like receptor 7/8
MyD88 - Myeloid differentiation primary response gene 88
IKK - Inhibitor of nuclear factor-κβ(Iκβ) kinase
NF-κB - Nuclear factor κβ
IKB - Inhibitor of nuclear factor-κβ
GSDMD - Gasdermin-D
GSDMD-N - Gasdermin-D N-terminal fragment
Aβ - Amyloid β peptide
IPAF - Ice protease-activating factor
IFN-β - Interferon-β
HIN-200 - hematopoietic expression, interferon-inducible nature, and nuclear localization

DOI: https://doi.org/10.70389/PJS.100182 | Premier Journal of Science 2025;14:100182

LPS - Lipopolysacride
APCs - Antigen-presenting cells
CTLs - Cytotoxic T lymphocytes
IgM - Immunoglobulin M
Th1 Cell - Type 1 T helper cells
Th2 cell - Type 2 T helper cells
Th17 cell - Type 17 T helper cells
pDcs - Plasmacytoid dendritic cells
DAMP - Damage-associated molecular patterns
PAMP - Pathogen-associated molecular patterns
PK2 - Prokinetic 2
CARD-18 - Caspase recruitment domain family member 18
EGCG - Epigallatechin gallate
CD4 - Cluster of differentiation 4
CD8 - Cluster of differentiation 8

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