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Review of Excessive Cytosolic DNA and Its Role in AIM2 and cGAS-STING Mediated Psoriasis Development

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Abstract: In psoriasis, keratinocytes are triggered by factors, such as infection or tissue damage, to release DNA, which thereby activates plasmacytoid dendritic cells and macrophages to induce inflammation, thickened epidermis, and parakeratosis. The recognition of double-stranded (ds)DNA facilitates the activation of cytoplasmic DNA sensors absent in melanoma 2 (AIM2) inflammasome assembly and cyclic guanosine monophosphate adenosine monophosphate (cGAMP) synthase (cGAS) - stimulator of interferon gene (STING) pathway, both of which play a pivotal role in mediating the inflammatory response and driving the progression of psoriasis. Additionally, secreted proinflammatory cytokines can stimulate further DNA release from keratinocytes. Notably, the activation of AIM2 and cGAS-STING signaling pathways also mediates programmed cell death, potentially enhancing DNA overproduction. As a result, excessive DNA can activate these pathways, amplifying persistent inflammatory responses that contribute to the maintenance of psoriasis. Several studies have validated that targeting DNA and its mediated activation of AIM2 and cGAS-STING offers promising therapeutic strategies for psoriasis. Here, we postulate a hypothesis that excessive cytosolic DNA can activate AIM2 and cGAS-STING, mediating inflammation and programmed cell death, ultimately fostering DNA accumulation and contributing to the development of psoriasis.

Keywords: DNA, AIM2, cGAS, STING, psoriasis

Introduction

Psoriasis is a chronic inflammatory skin disease that affects approximately 125 million people worldwide.[1] Studies have increasingly recognized psoriasis as a systemic disorder, for the multiple comorbidities such as cardiometabolic diseases, pulmonary inflammatory conditions and depression, collectively imposing a mounting healthcare burden.[1–3] The most characteristic lesion of psoriasis includes thickening of the epidermis, parakeratosis, and an inflammatory infiltrate of T cells in the dermis and epidermis.[4] Psoriatic inflammation can be triggered by factors such as infection, alcohol consumption, drugs, air pollution and obesity.[4,5]

It is now well accepted that tumor necrosis factor (TNF)-α, interleukin-23 (IL-23) and IL-17 produced by activated dendritic cells (DCs) and T cells are critical drivers of psoriasis pathogenesis.[6] However, keratinocytes (KCs) also play a crucial role in initiating and sustaining psoriasis. Current study has promoted a "key pathogenic loop" formed by DCs, helper T cells type 17 (Th17) and KCs.[7] In the initial stage of psoriasis, KCs activated by trigger factors prompt the release of self-DNA and antimicrobial peptides, which subsequently activate DCs to enhance production of interferon (IFN)- α and additionally promote the secretion of TNF-α, IL-6, IL-12, and IL-23.[4,7] DCs activate a diverse range of T cells, including IFN-γ-producing-Th1 cells and IL-17-producing-Th17 cells, sparking a cascade of T cell immune responses.[8] The infiltrating immune cells and overexpressed cytokines, including IL-17 and TNF-α, within psoriatic lesions induce a dose-dependent upregulation of psoriasis-associated genes in KCs, thereby amplifying inflammation, hyperproliferation, and impaired KC

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differentiation.[9–14] A recent study highlighted that in psoriatic skin, S100A9, a highly upregulated gene in KCs, triggers IL-23 production by dendritic cells, promoting IL-23/IL-17 axis activation, which in turn, reciprocally upregulates epidermal S100A9 expression, constituting an autoregulatory circuit that drives psoriasis progression.[15]

The innate immune system can detect invading microbial structures that do not exist in the host through pattern recognition receptor (PRR) systems and then initiate immune responses, which are called pathogen-associated molecular patterns (PAMPs).[16] Tissue or cell damage can also initiate a similar response in the absence of infection, named as damage associated molecular patterns (DAMPs), which is important in sterile inflammatory diseases.[17,18] The released endogenous molecules, such as self-DNA and RNA, can bind to PRRs, known as danger/damage-related molecular patterns. Some PRRs in the cytoplasm can specifically detect DNA, including absent in melanoma 2 (AIM2) and cyclic guanosine monophosphate adenosine monophosphate (cGAMP) synthase (cGAS). AIM2 and cGAS can mediate a series of inflammatory responses and cell death by recognizing endogenous dsDNA, thereby forming AIM2 inflammasomes and activating the cGAS- interferon gene stimulator (STING) pathway.[19,20] Toll-like receptors (TLRs) in DCs and KCs are taken as significant mediators in psoriasis initiation.[21] The enhanced endosomal self-RNA sensing of TLR7 in DCs, coupled with the production of IL-6, serves to amplify inflammatory circuits in psoriasis.[22] Furthermore, it is noteworthy that excessive DNA can be detected in psoriatic lesions, leading to the activation of AIM2 and STING, and the expression level of these molecules exhibits a strong correlation with the severity of psoriatic symptoms and inflammation, as evidenced by previous studies.[23,24] TNF-α prompts keratinocytes to discharge DNA into the cytosol, thereby intensifying inflammatory pathways associated with psoriasis.[24]

Additionally, the AIM2 and cGAS-STING signaling pathways facilitate programmed cell death, ultimately leading to the liberation of DNA. Subsequently, this excessive DNA production can activate the AIM2 and cGAS-STING signaling, further exacerbating the inflammatory cycles implicated in psoriasis.

In this review, we delve into the intricacies of AIM2 and cGAS-STING signaling, highlighting their activation by excessive cytosolic DNA and the resulting inflammatory response and programmed cell death. Based on these, we further investigate the potential for DNA accumulation within lesions to activate AIM2 and cGAS-STING signaling, thereby accelerating the progression of psoriasis. This understanding underscores their potential as promising therapeutic targets in the management of this skin condition.

The Activation and Function of AIM2 and cGAS-STING

Aim2

AIM2 consists of one or two hematological, intermediate and nuclear (HIN) domains at the C-terminus and one Pyrin domain (PYD) at the N-terminus. HIN domains detect and bind to cytoplasmic dsDNA of which the length is more than 70 bp, and PYD binds to the PYD of adapter protein, typically apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD) (ASC).[25] The CARD of ASC binds to procaspase-1 and then the AIM2 inflammasome complex is formed.[26] After procaspase-1 activation, caspase-1 generated by cleavage cleaves proIL-1β and proIL-18, and thereby activate downstream IL-1β and IL-18.[26,27] IL-1β signaling can regulate IL-17-producing γδ T cells and stimulate keratinocytes to amplify inflammatory cascade.[28] IL-18 also participates in the activation of Th1, Th2, IL-17-producing γδ T cells to trigger inflammation.[27] The activated caspase-1 cleaves gasdermin-D (GSDMD) and forms a hole in the cell membrane that cytokines can be released through, ultimately leading to cell swelling and membrane rupture, which is defined as pyroptosis.[29]

AIM2 plays an important role in maintaining the stabilization of immune function. Activation of the AIM2 inflammasome triggers pyroptosis to remove genetically compromised cells, thus contributing to normal brain development.[30] Meanwhile, AIM2 can control the inflammation of microglia. AIM2 negatively regulates inflammation response in the central nervous system, and AIM2 deficiency enhanced neuroinflammation and demyelination during experimental autoimmune encephalomyelitis.[31] In chronic heart failure, systemic lupus erythematosus, and post-stroke cognitive impairment, the AIM2 inflammasome-mediated inflammation and pyroptosis facilitate disease progression, and the AIM2 deficiency or inhibition of AIM2 inflammasome can improve the symptoms.[32–34]

cGAS-STING Signaling

cGAS is another cytoplasmic DNA sensor. The binding of dsDNA to cGAS induces cGAMP production, with adenosine triphosphate and guanosine triphosphate as substrates.[35] The secondary messenger cGAMP activates interferon gene stimulator (STING).[36,37] Activated STING oligomerizes and recruits tank-binding kinase 1 (TBK1), which phosphorylates STING and interferon regulatory factor 3 (IRF3) to upregulate type-I IFNs and other cytokines.[38,39] In addition, STING–TBK1 association also activates nuclear factor kappa-B (NF-κB), and thus increases the inflammatory cytokines such as IL-6 and TNF-α.[40,41] cGAS can bind to dsDNA of any length, but the activation and stabilization are positively correlated with longer dsDNA, probably more than 39 bp, which allows two or more cGAS molecules to assemble in a "ladder-like" configuration along two arms of the same dsDNA.[42] Under these conditions, the surrounding cGAS dimers can strengthen each other to stabilize the cGAS.[38] At low cGAS concentrations, short dsDNA cannot strongly promote activation of cGAS. Only if cGAS is highly clustered can it be activated by dsDNA shorter than 20 bp to induce the catalytic activity in vitro.[43]

With the function of detecting cytoplasmic dsDNA and initiating innate immune responses, cGAS-STING is critical in preventing the invasion of microbial pathogens.[44,45] Meanwhile, the abnormal expression can also play an expanding role in immunity and inflammation.[46] The knockout of cGAS or STING could inhibit type-I IFNs and the tumor suppression of p53.[47] The agonists and antagonists of the cGAS-STING signaling can also affect the progression of cancer, neurodegeneration, metabolic diseases, and autoimmune or inflammatory diseases.[48] It has been found that STING deficiency correlates with the incidence of melanoma, colorectal adenocarcinoma, lung cancer, and other cancers. The application of STING agonists, such as cyclic dinucleotide, can promote tumor suppression through upregulating type I IFN expression and increasing lymph node-homing capability and spontaneous T cells.[49]

As for autoimmune disease, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are mainly concerned. Increased levels of cGAMP and dsDNA in some SLE patients induce subsequent cGAS-STING activation, displaying a positive correlation with type I IFN production.[50] Further research demonstrated that dsDNA is contained in apoptosis-derived membrane vesicles in the serum of SLE patients, which can effectively prevent against extracellular nuclease degradation, sustaining the activation of the cGAS-STING signaling cascade, thereby augmenting the production of IFN-I.[51] A contrary opinion has proposed that deficiency of cGAS and STING exacerbates autoimmune responses in mouse models of SLE,[52] suggesting the need for further investigation into the precise roles of these molecules.

In RA patients, the expression of dsDNA within the cytoplasm of fibroblast-like synovial cells is elevated, and this upregulation of dsDNA and cGAS correlates positively with the severity of rheumatoid synovitis.[53] Furthermore, knocking out cGAS or STING decreases the expression of cytokines in RA patients.[54] An other study found that TNF elicits alterations in mitochondrial function and an increase in cytosolic mtDNA levels, subsequently facilitating the binding of cytosolic mtDNA to cGAS, thereby triggering a cGAS-STING-mediated interferon response in inflammatory arthritis mouse models.[55]

Excessive DNA-Mediated AIM2 and cGAS-STING Activation in Psoriasis Development

Caused by increased production or deficiency in degradation, DNA can accumulate in PRR-competent compartments, and when DNA exceeds the "immunostimulatory threshold", PRRs are activated, including AIM2 and cGAS.[18] In the pathogenesis of psoriasis, factors such as infection and damage not only produce pathogen-derived DNA but also trigger the KCs in the epidermis and subsequent self-DNA release.[56] These exogenous and endogenous DNA fragments could accumulate in KCs, accompanying high levels of TNF-α, and IFN-β in psoriatic lesions.[57] During this inflammatory process, the role of AIM2 inflammasome and STING signaling seems to be critical. A study has validated that cytosolic DNA in KCs could prompt inflammasome assembly in psoriatic lesions, including AIM2, the excessive DNA and the mediated-AIM2 activation are involved in acute and chronic psoriatic inflammation.[23,58] Furthermore, recent studies have shown that highly expressed cytosolic DNA participates in progression of psoriasis in a STING-dependent manner, deficiency of STING could alleviate the psoriatic symptoms in mice, while STING agonist could induce amplification of psoriatic symptoms, epidermal thickening, and inflammation, especially in conditions with prior systemic inflammation.[24,59] Inflammatory cytokines TNF-α and IL-1β

could break down tolerance for DNA in KCs and induce IFN-inducible protein 16 (IFI16) -STING signaling in response to DNA, thus contributing to inflammation in psoriasis.[60]

In addition to KCs, some immune cells can also be activated by DNA to innate inflammatory response. Plasmacytoid DCs (pDCs) can sense DNA to produce type I IFNs and mediate initial inflammation of psoriasis.[4,22,61,62] It has been reported that cGAS-STING can be activated by DNA in pDCs, and the knockdown of cGAS or STING contributes to reducing this IFN response and suppressing IL-17A production.[63–65] Meanwhile, activated by excessive DNA, the AIM2 inflammasome and STING signaling could mediate macrophages to release TNF-α, IL-6, IL-12, IFN-β, and reactive oxygen species, thus resulting in hyperproliferation of KCs and inflammation.[66–68]

Defective degradation of DNA during terminal differentiation of KCs may also lead to DNA accumulation. In psoriatic lesions, deoxyribonuclease 1-like 2 (DNase1L2) expression was downregulated, which suppressed nuclear DNA degradation and caused parakeratosis.[69,70] Furthermore, lower expression of mesotrypsin and caspase-14 are also involved in impaired DNA degradation during KC terminal differentiation and contribute to parakeratosis, as well as barrier disruption of psoriasis and atopic dermatitis.[71] Due to the imbalance in the supply and degradation of DNA, accumulated DNA leaks into the cytoplasm and activates the cGAS-STING pathway, which in turn intensifies chronic inflammation and aggravates symptoms such as epidermal thickening and parakeratosis, ultimately fueling the progression of psoriasis.[72–74]

However, DNA degradation in psoriatic lesions remains controversial. Three prime repair exonuclease 2 (TREX2) has been reported to repress cGAS-STING signaling by degrading cytosolic dsDNA in mouse tumor models.[75] A high level of TREX2 has also been found in the nucleus of psoriatic KCs, which promotes DNA degradation and cell death to initiate inflammatory response,[76,77] which is contrary to the decreased DNA degradation induced by low expression of DNase1L2 in psoriasis. It can be speculated that the upregulated TREX2 and downregulated DNase1L2 in psoriatic lesions might limit the accumulation of DNA to a certain range, thus preventing an excessive immune response.

As mentioned above, pDCs, KCs, and macrophages are stimulated by exogenous and endogenous DNA in lesions, and thereby contribute to psoriasis symptoms and inflammation. In this process, self-DNA could be overproduced but deficient in degradation, which leads to excessive DNA in lesions. The excessive cytosolic DNA can be recognized by AIM2 and cGAS, thereby activating the AIM2 inflammasome and cGAS-STING pathway to induce the release of proinflammatory cytokines such as TNF-α, which promotes DNA release, and results in cGAS-STING activation.[24,55] Thus, the activated AIM2 inflammasome and cGAS-STING pathway by DNA could amplify persistent inflammatory responses and psoriatic symptoms and histopathology, such as erythema, scaling, thickened epidermis and parakeratosis epidermal, as shown in Figure 1.

Interestingly, as cGAMP produced by activated cGAS can induce inflammasome formation and enhancement of DNA-induced inflammasomes,[78] and type I IFN induced by STING can increase the expression of AIM2 in human cells,[79] there seems to be a certain subsequence in activation of AIM2 and cGAS. Murthy et al proposed that the activation of different DNA sensors could be determined by DNA concentration.[80] They assumed that cGAS–STING signaling could be activated by a low level of cytoplasmic DNA to increase type I IFN expression and mediate inflammatory responses, and AIM2 inflammasome assembly could be promoted in a high level of cytoplasmic DNA to initiate the immune reactions via IL-1β and IL-18 release and induce pyroptosis by caspase-1 and GSDMD.[80] During DNA accumulation in psoriasis, dsDNA of lower concentration in the initial stage could activate cGAS and then induce AIM2 inflammasome formation. As the disease progresses, further accumulated dsDNA could activate both cGAS and AIM2, which in turn promote the development of psoriasis. However, the "thresholds" of cGAS and AIM2 activation remain unclear, which makes the subsequence of activation fail in persuasiveness.

AIM2- and cGAS-Mediated Programmed Cell Death in Psoriasis Development

Abnormal programmed cell death plays a critical role in psoriasis development. There are complex interactions between cGAS–STING pathway and different forms of programmed cell death.[80] AIM2 is also found to participate in some other pathways of cell death, in addition to pyroptosis. Programmed cell death could be important in DNA over-production and thereby activate AIM2 and cGAS-STING,[18] which provides a possible mechanism for maintaining psoriasis.

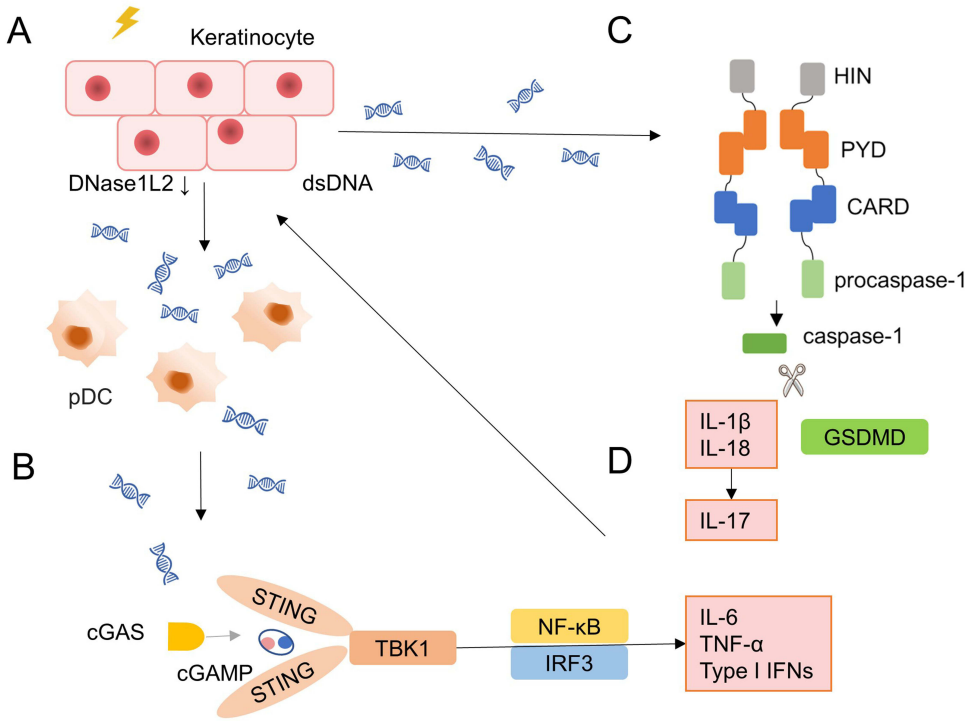

Figure 1 AIM2 and cGAS in psoriasis inflammation. (**A**). Some factors such as bacteria and virus not only produce pathogen-derived dsDNA but also trigger keratinocytes to release self-dsDNA, which subsequently activate DCs. The downregulated DNase1L2 results in a deficiency in DNA degradation. (**B**). Activated by dsDNA from keratinocytes and pDCs, cGAS enhances cGAMP production and STING activation. STING oligomerizes and recruits TBK1, which phosphorylates STING and IRF3 to induce type-I IFNs. In addition, STING–TBK1 association also activates NF-κB which induces upregulation of IL-6 and TNF-α. Both type-I IFNs and TNF-α contribute to psoriasis development. (**C**). AIM2 consists of one or two HIN domains at the C-terminus to detect and bind to cytoplasmic dsDNA, and one PYD at the N-terminus to bind to the PYD of ASC. The CARD of ASC binds to procaspase-1 and fulfills the AIM2 inflammasome complex assembly. Caspase-1 cleaves GSDMD and proIL-1 β, proIL-18.IL-1β and IL-18 can upregulate IL-17 expression to promote the progression of psoriasis. (**D**). Proinflammatory cytokines such as TNF-α and IL-17 facilitate further release of dsDNA from keratinocytes.

cGAS, AIM2, and Autophagy

Autophagy induction is a primordial function of cGAS-STING signaling.[81] Activated by cGAMP, STING transfers to the endoplasmic reticulum-Golgi intermediate compartment, which thereby acts as a membrane source for microtubule-associated protein 1A/1B-light chain 3 lipidation to drive autophagosome formation, and induce canonical and non-canonical autophagy.[81,82] Drp1 overexpression in esophageal squamous cell carcinoma(ESCC) can induce cytosolic mtDNA release, which subsequently activates the cGAS-STING pathway and autophagy to promote ESCC progression.[83] It is also found that DNase I–induced mtDNA degradation and STING depletion can abate autophagy in ESCC.[84]

Meanwhile, autophagy can restrict cGAS-STING signaling. Autophagy proteins can down-modulate STING activity and induce attenuation of cGAS-STING signaling through both canonical and non-canonical pathways.[85] Furthermore, the cGAS- and STING-dependent type I IFN response can be suppressed by autophagy-mediated limitation of cytosolic mtDNA accumulation in breast cancer cells,[86] while impairing mitophagy can activate cGAS-STING pathway by enhancing mtDNA release in acute liver injury.[87]

There might be a negative correlation between autophagy and AIM2 inflammasome. Autophagy and AIM2 inflammasome can both be induced by the high-mobility group box 1-DNA complex, thus autophagy can negatively regulate AIM2 inflammasome activation via the commonly dependent receptor for advanced glycation endproducts.[88] In addition, autophagy protein-beclin 2 can direct AIM2 to lysosomes for degradation through non-classical autophagy to negatively regulate inflammasome activation.[89] While caspase-1, as a component of the inflammasome, can suppress mitophagy to trigger mitochondrial damage via cleavage of the key mitophagy regulator Parkin after assembly of AIM2 inflammasome.[90] Under conditions of AIM2 reduction, autophagy activation is discovered to be advanced.[91]

In Aurora kinase A-mediated psoriatic inflammation, the function of inhibited autophagy in promoting AIM2 inflammasome activation has been demonstrated.[92] And inducement of autophagy could help alleviate inflammation in psoriasis.[93]

cGAS, AIM2, and Apoptosis

During apoptosis, activated pro-apoptotic proteins, Bax and Bak, cause mitochondrial outer membrane permeabilization and lead to cytochrome c and mtDNA release.[94] Cytochrome c actuates the apoptosome assembly to drive caspase-3 and caspase-7 activation.[95] mtDNA released from mitochondria via mitochondrial outer membrane pores formed by Bax and Bak can activate cGAS-STING signaling and thereby upregulate type-I IFNs and other cytokines to drive immune responses,[96] and trigger AIM2 inflammation activation, leading to tissue inflammation.[97] On the other hand, increased apoptosis can down-regulate this pathway by activating caspase-3-mediated cleavage of cGAS or IRF3 and inhibiting STING.[98,99]

Both the cGAS-STING pathway and AIM2 inflammasome can positively regulate apoptosis. cGAS-STING-IRF3 signaling can induce Endoplasmic Reticulum Stress-mediated-apoptosis via Bax activation.[100] AIM2 inflammasome can activate caspase-8 and caspase-3 to induce apoptosis,[101] and AIM2 inhibition can reduce pulmonary alveolar cell apoptosis in mouse models of emphysema.[102] Activated by cell-free DNA after tissue injury, AIM2 inflammasome can thereby induce IL-1β secretion to drive extrinsic T cell apoptosis mediated by FasL.[103]

In psoriatic lesions, KC resistance to apoptosis is positively correlated with severity, and inducement of apoptosis can relieve the symptoms.[104] Impaired mitophagy can induce apoptosis by causing mtDNA escape and subsequent cGAS-STING activation in ultraviolet B-irradiated human KCs,[105,106] which could probably illustrate the effect of ultraviolet radiation on psoriasis via apoptosis.[4]

cGAS, AIM2, and Necroptosis

In conditions of apoptosis or caspase suppression, another mode of regulated cell death named necroptosis can be promoted to initiate immune response.[107] The activated cGAS-STING pathway can upregulate the expression of TNF-α and type-I IFN, and the binding of IFN to type 1 IFN receptor 1 and TNF to TNF receptor 1 can result in Receptor-Interacting Protein 1 (RIPK1)–RIPK3 and then mixed lineage kinase domain-like protein(MLKL) activation to execute necroptosis.[108] In addition, IFN and inflammation can upregulate MLKL expression in cancer cells,[109] suggesting a positive effect of cGAS-STING signaling on necroptosis. The cytoplasmic DNA accumulation induced by Z-DNA-binding protein 1(ZBP1)-MLKL mediated necroptosis in irradiated tumor cells can enhance necroptosis via activated cGAS-STING pathway, thus driving persistent inflammation.[110] When infected by S. aureus, AIM2-mediated necroptosis and AIM2 inflammasome formation can be induced within macrophages by intracellular bacteriolysis, which enables S. aureus to establish infection.[111]

However, the function of necroptosis in psoriasis development remains unclear. Convallatoxin can ameliorate psoriasis-like lesions in mouse models via the inducement of KC necroptosis.[112] Saracatinib ameliorates psoriatic inflammation via inhibiting necroptosis.[113] Meanwhile, there is a contrary opinion. Duan et al discovered a positive relationship between necroptosis and psoriasis, and inhibition of RIPK1/RIPK3/MLKL mediated necroptosis could mitigate psoriatic inflammation.[114] Further research is demanded to clarify the function of necroptosis in the development of psoriasis, and the role of the cGAS-STING pathway and AIM2 in this process.

cGAS and AIM2 and Pyroptosis

As detailed above, pyroptosis is initiated by inflammasomes such as AIM2. Meanwhile, the cGAS signaling can activate inflammasomes and subsequent pyroptosis. cGAMP can induce inflammasome formation and enhancement of DNA-induced inflammasomes and engage STING to amplify IFN-I signaling,[78] and type I IFN induced by STING can increase the expression of AIM2 in human cells.[79] cGAS-STING signaling activated by dsDNA in the cytoplasm can draw forth the inflammatory response and induce inflammasome and pyroptosis-pertinent components in cerebral venous sinus thrombosis, while cGAS inhibitor RU.521 can decrease the levels of cGAMP, STING, and proinflammatory cytokines to diminish the neuroinflammatory, as well as suppress microglia pyroptosis.[115] However, caspase-1 triggered by the AIM2 inflammasome can cleave cGAS to downregulate the downstream inflammatory response,[116] and GSDMD activated by the AIM2 inflammasome can promote intracellular potassium efflux via membrane pores to control cGAS-dependent

IFN-β response.[117] Inhibition of inflammasome activation and pyroptosis in macrophages can reduce inflammation in psoriasis-like lesions of mouse models.[118] GSDMD-mediated pyroptosis in KC contributes to the hyperproliferation and poor differentiation of psoriatic KC.[119] Gasdermin-E (GSDME), another member of the gasdermin family, has also been found to be cleaved by caspase-3 to induce KC pyroptosis and exacerbate the severity of psoriatic inflammation, which is mediated by TNF-α in vitro.[120] It has been established that exposure to cadmium triggers the activation of the AIM2 inflammasome, subsequently upregulating GSDMD and GSDME, ultimately resulting in pyroptosis within testicular tissue.[121] Given the involvement of GSDME in psoriasis, this study advances our comprehension of AIM2-mediated pyroptosis in psoriasis, though further direct research is required.

cGAS and AIM2 and PANoptosis

Moreover, the co-regulation and crosstalk between these pyroptosis, apoptosis, and necroptosis complexes has been confirmed. Therefore, a new form of programmed cell death is defined as PANoptosis, which refers to the simultaneous occurrence of pyroptosis, apoptosis, and necroptosis, and is controlled by a molecular complex called the PANoptosome.[122,123] AIM2 can drive PANoptosis by forming AIM2 PANoptosome with innate immune sensors pyrin and ZBP1, as well as ASC, caspase-1, caspase-8, RIPK1, and RIPK3.[124] The application of STING agonists in the airway can induce DNA release, PANoptosis, and acute lung inflammation mediated by type I IFN.[125] The leakage of self-DNA can subsequently induce AIM2 inflammasome formation and hyper-activation of the cGAS-STING pathway and following inflammation mediated by IFN-I, TNF-α, and IL-6.[125] Meanwhile, based on the aforementioned functions of the AIM2 and cGAS-STING pathways in cell death, it could be speculated that during PANoptosis, activated caspase-1, caspase-3, and GSDMD might suppress the cGAS-STING signaling and thereby AIM2 inflammasome assembly to avoid over immune response. A recent study has definitively established that the heightened PANoptosis signaling in psoriatic lesions fuels a robust immune response, while disulfiram mitigates psoriatic manifestations such as erythema, induration, and desquamation of the plaques by suppressing pyroptosis-mediated inflammation and bolstering apoptotic processes.[126] However, necroptosis expression in psoriasis remains uncertain. An in-depth understanding of the complex relationship between different pathways of cell death and psoriasis is required.

Targeting DNA and the Mediated AIM2 and cGAS-STING Activation Serve as Potential Therapeutic Methods for Psoriasis

Excessive cytosolic DNA and cfDNA are causative factors in the development of psoriasis, suggesting that the elimination or scavenging of these DNA fragments could potentially offer a protective effect against the disease. Topical cationic hairy particles can effectively scavenge cfDNA in dermis to downregulate the expression of TNF-α, IL-6, IL-17 and IL-23, alleviate the lesion severity, and improve epidermal proliferation, parakeratosis, and hyperkeratosis in mice.[127] In a recent study, a new treatment named as biguanide chitosan microneedles (BGC-MNs) has been developed, which can remove cfDNA from the dermis to reduce the production of inflammatory factors (such as TNF-α, IL-1β, IL-6, IL-17 and IL-23) and alleviate psoriatic symptoms, such as erythema, scaling and epidermal thickening in mice.[128]

Inhibition of AIM2 activation is taken as a potential therapy for psoriasis. EFLA 945, a product of red grape vine leaf extracts, can interfere with the entry of dsDNA into the cytoplasm to inhibit AIM2 inflammasome assembly, and thereby caspase-1 activation and IL-1β and IL-18 release, thus attenuating inflammatory responses and controlling the symptoms of psoriasis.[129] The application of Cornus officinalis Seed Extract can decrease the formation of AIM2 inflammasome by reducing the components, including AIM2, ASC, and caspase-1 in lesions, and also serum IL-17A, therefore alleviating psoriasis-like symptoms in imiquimod-treated mice.[130]

Targeting cGAS-STING pathway also provides a protective effect for psoriasis. cGAS deficiency can decrease IFN responses and inflammation in inflammatory arthritis and stroke mouse models.[55,131] The inhibitors of the cGAS–dsDNA complex formation, such as antimalarial drugs, suramin, and suppressive oligodeoxynucleotides, are also supposed to be available for the treatment of dsDNA-mediated autoimmune diseases.[46] The mechanism could be assumed that inhibition of cGAS can downregulate the expression of cGAMP and STING, which therefore alleviates inflammation. A recent study has revealed that a platinum-doped positively charged carbon dot nanoinhibitor is capable of scavenging cf-DNA

and reactive oxygen species, thereby inhibiting the activation of the cGAS-STING pathway and the subsequent secretion of TNF-α, CCL20, and CXCL10, which effectively reverses skin homeostatic imbalance and alleviates the symptoms of psoriasis.[132]

STING agonist has been found to induce skin inflammation, and suppression of AIM2 or STING activation could protect psoriasis.[59] Topical administration of STING antagonist H-151 can suppress macrophage infiltration and IL-23, IL-17, and IL-6 expression by inhibition of STING/NF-κB signaling, thereby relieving the psoriatic dermatitis.[133] In psoriasis with diabetes mellitus, STING inhibitor C-176 can decrease the activation of STING-IRF3 signaling and expression of IFN-β, TNF-α, IL-17A, and IL-23 in the skin of mice models to protect against psoriasis development.[48]

Conclusion

The pathogenesis of psoriasis has been explored in genetic and immunological studies, and pDCs, KCs, and macrophages have been proven to be critical in the mechanism of psoriasis inflammation.[134] The released inflammatory cytokines decrease the tolerance of KCs to DNA and afterward induce disease development.[60] Excessive DNA and high expression of AIM2 and STING have been discovered in psoriatic lesions, and the activated inflammatory response has been proven to lead to DNA release and the progression of psoriasis.[57,133,135] AIM2 and cGAS-STING could also mediate different modes of programmed cell death, such as autophagy, pyroptosis, apoptosis, necroptosis, and PANoptosis, which might induce DNA oversupply. Meanwhile, downregulated DNase1L2 causes deficient degradation of nuclear DNA in the stratum corneum of psoriasis.[69] Due to increased production and defective degradation, accumulated DNA could promote hyperactivation of AIM2 and cGAS-STING to amplify inflammatory response. In this review, the cycle of "recognition of DNA-activation of DNA sensors-excessive DNA accumulation" is implicated as a key participant in the inflammatory process and characteristic skin lesions observed in psoriasis, as shown in Figure 2.

Perspectives

As previously discussed, the degradation of DNA within psoriatic lesions may be impaired, yet the intricate mechanism is compounded by the elevated presence of TREX2 and diminished levels of DNase1L2 in psoriasis. Consequently, further in-depth research is imperative to elucidate the precise role of DNA degradation in the accumulation of DNA within psoriatic lesions. The activation of different DNA sensors could be determined by DNA concentration.[80] In our hypothesis, activated by DNA of lower concentration, cGAS facilitates further DNA accumulation and subsequently AIM2 activation. Therefore, in addition to observations of DNA concentration required for AIM2 and cGAS activation, the impact of cGAS deficiency on the activation of AIM2 deserves attention. Meanwhile, while the accumulation of DNA fragments in psoriatic lesions is considered a significant risk factor for disease progression, the precise correlation

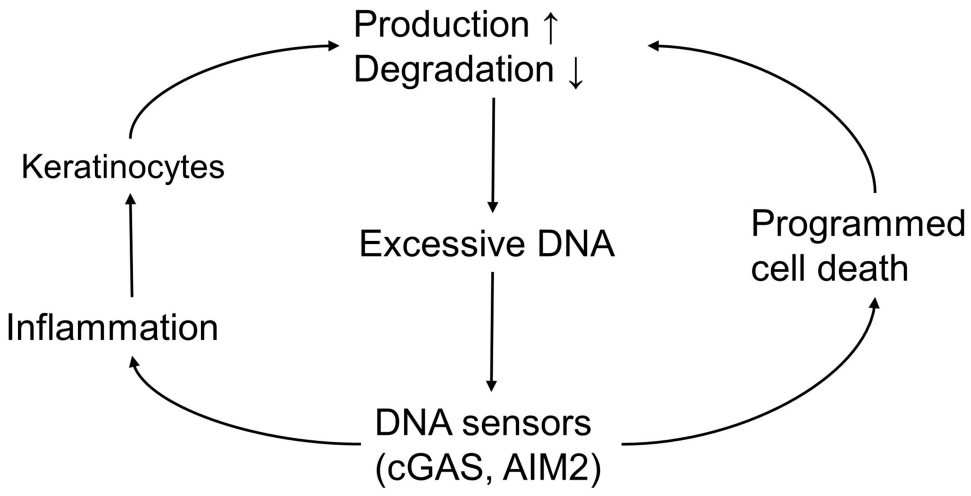

Figure 2 The "recognition of DNA-DNA sensors activation-excessive DNA accumulation" cycle.

remains ambiguous. Thus, longitudinal studies are essential to monitor the evolution of psoriasis in relation to cytosolic DNA alterations over time.

Another noteworthy subject is the influence of cell death, particularly necroptosis, on the development of psoriasis. Programmed cell death has the potential to serve as a source of self-DNA, potentially contributing to the activation of cGAS and AIM2 pathways. However, the precise connection between these processes remains elusive, necessitating further research.

Abbreviations

IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; Th1, helper T cells type 1; Th17, helper T cells type 17; PRR, pattern recognition receptor; AIM2, absent in melanoma 2; HIN, hematological, intermediate and nuclear; PYD, Pyrin domain; CARD, caspase recruitment domain; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin-D; NF-κB, nuclear factor kappa-B; cGAMP, cyclic guanosine monophosphate adenosine monophosphate; cGAS, cGAMP synthase; STING, stimulator of interferon gene; TBK1, tank-binding kinase 1; IRF3, interferon regulatory factor 3; DNase1L2, deoxyribonuclease 1-like 2; ESCC, esophageal squamous cell carcinoma; RIPK, receptor-interacting protein; MLKL, mixed lineage kinase domain-like protein; ZBP1, Z-DNA-binding protein 1; TREX2, three prime repair exonuclease 2.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests associated with the manuscript.

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