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The interplay of type I interferon, NLRP3 inflammasome, and self-antigen clearance in systemic lupus erythematosus progression

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ARTICLE INFO

Article history:

Received Mar 20, 2026
Revised Mar 26, 2026
Accepted Apr 1, 2026

Keywords:

Autoimmune
Disease Progression
IFN-1
Inflammatory Pathway
NLRP3 Inflammasome
SLE

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease driven by impaired cellular debris clearance. While individual inflammatory pathways are well-documented, their synergistic interactions lack comprehensive synthesis, hindering the development of mechanism-based therapeutics. This literature review aims to elucidate the interconnected roles of specific cellular inflammatory pathways and their positive feedback loops in driving the clinical progression of SLE. A comprehensive literature review was conducted by analyzing 35 peer-reviewed scientific studies published between 2015 and 2025, sourced primarily from the PubMed database, focusing on SLE pathogenesis, cellular inflammation, and disease severity. SLE progression is propelled by a mutually reinforcing inflammatory cascade rather than isolated pathways. We identified three primary components establishing a pathological positive feedback loop: (1) Impaired self-antigen clearance, supplying a continuous source of Damage-Associated Molecular Patterns (DAMPs); (2) Type I Interferon (IFN-I) overactivation, acting as the systemic immune response conductor; and (3) The NLRP3 inflammasome, functioning as a local amplifier that induces direct tissue damage. The identification of this synergistic feedback loop demonstrates that single-target interventions may be insufficient. Comprehending this dynamic cascade necessitates a paradigm shift towards precision medicine. Future therapeutic strategies must prioritize multi-target combination therapies, stratifying patients based on their unique biological profiles to disrupt the pathogenic cycle effectively.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by dysregulation of the immune response, which ultimately triggers widespread systemic inflammation and damage to various organs and tissues (Arnaud et al., 2024). This disease can

manifest in all age groups and genders, although it predominantly affects women of reproductive age. Epidemiologically, the incidence rate of new SLE cases globally is estimated to reach 5.14 per 100,000 people each year, contributing to approximately 400,000 new cases annually. The global prevalence of SLE is estimated to be 43.7 per 100,000 individuals, affecting around 3.41 million people per year with a female-to-male ratio of approximately 9:1 (Justiz Vaillant et al., 2025). SLE involves a profound breakdown of immunological tolerance to nuclear nucleoproteins, initiated by the dysfunction of detection and clearance mechanisms for cellular debris (Arneth, 2019). This deficiency leads to the accumulation of self-antigens, subsequently generating an autoantibody response and the formation of immune complexes that deposit in target tissues, such as the kidneys and brain (Arneth, 2019; Justiz Vaillant et al., 2025; Lai et al., 2024).

Although the understanding of SLE immunopathogenesis continues to evolve, the development of highly effective, curative therapeutics remains elusive. Previous reviews have extensively detailed the isolated roles of distinct cellular mechanisms, identifying key pillars of inflammation: the unregulated activation of the Type I Interferon (IFN-I) pathway, chronic NLRP3 inflammasome activation, and impaired self-antigen clearance (Guan et al., 2025; Justiz Vaillant et al., 2025). However, what remains insufficiently explored in current literature is the precise synergistic crosstalk between these pathways. Much of the previous research treats these cellular mechanisms as independent variables, leaving a critical knowledge gap regarding how they continuously interact to accelerate clinical severity.

Unlike previous studies that focus on single-pathway pathology, this review uniquely conceptualizes SLE progression as a highly integrated, self-reinforcing inflammatory cascade. The primary objective of this review is to compile recent evidence to elucidate not only the individual inflammatory pathways but, more importantly, their intricate positive feedback loops. By refining the understanding of this dynamic immune dysregulation network, this study aims to facilitate a paradigm shift in SLE management, advocating for mechanism-based, precision therapeutic strategies that disrupt the entire pathological cycle rather than isolated targets.

RESEARCH METHOD

This comprehensive literature review adhered to the PRISMA guidelines to ensure a sensitive and specific search strategy. A meticulous search was conducted in the PubMed and Web of Science databases using Boolean operators and targeted keywords: ("SLE" OR "Systemic Lupus Erythematosus" OR "Lupus") AND ("cellular inflammatory" OR "inflammatory" OR "cellular inflammation") AND ("autoimmune disease*") AND ("disease progression" OR "disease severity"). To guarantee literature saturation, secondary citation searches were also performed. The initial search yielded 381 articles (PubMed=184; Web of Science=197). After removing 81 duplicates, 300 articles underwent a rigorous screening process conducted independently by two researchers to minimize selection bias. Initially, 274 articles were eliminated for being off-topic, general editorials, or not specifically focusing on cellular inflammatory pathways. Subsequently, the remaining 26 full texts were assessed for eligibility. Seven articles were excluded for lacking robust clinical translational context). This resulted in 19 highly pertinent articles from databases, supplemented by 14 rigorously assessed articles identified through secondary citation searching, culminating in a final synthesis of 33 articles.

To ensure source validity, inclusion was strictly limited to peer-reviewed scientific literature published between 2015 and 2025. Although the 33 included articles comprised various designs ranging from *in vitro* mechanistic studies to clinical observations, all met a stringent high-quality threshold through critical appraisal of their methodological rigor, providing robust functional insights into SLE. During data extraction, specific parameters were systematically compared: the functional roles of distinct inflammatory pathways (IFN-I, NLRP3 inflammasome, and NETosis), involved DAMPs, target organ damage markers, and mechanisms of pathological feedback loops. Finally, this study's limitations include inherent publication bias due to reliance on

published data and the restriction to English-language literature published within the last decade, which may exclude relevant historical or non-English research.

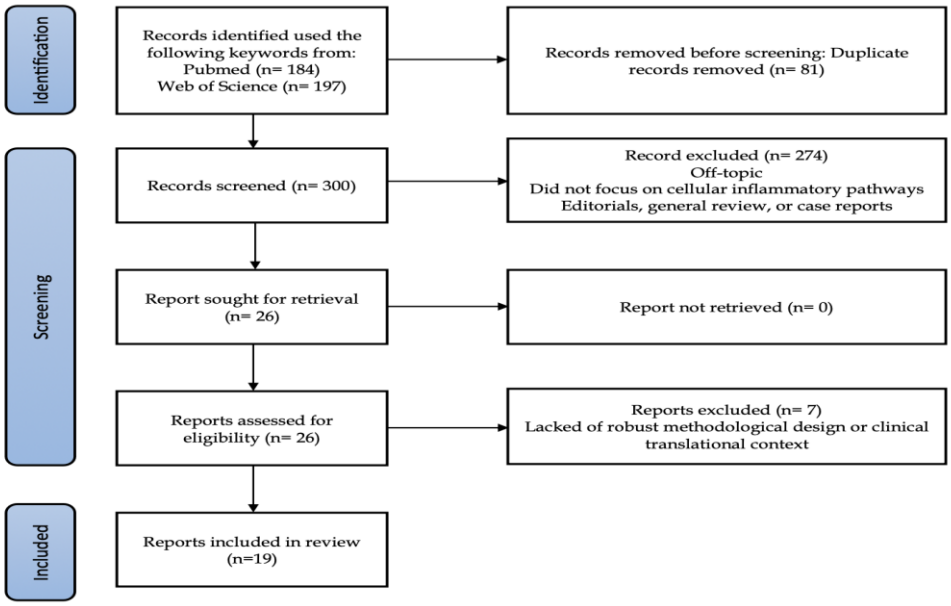

Figure 1. Flowchart for the literature search

RESULTS AND DISCUSSIONS

To provide a cohesive understanding of SLE pathogenesis, this section integrates the systematic findings from the literature with a comprehensive critical analysis. The first segment of this section outlines the core results extracted from the selected studies, specifically mapping the individual functional roles of the three primary inflammatory pillars: the Type I Interferon pathway, the NLRP3 inflammasome, and the disruption of self-antigen clearance. Building upon these findings, the subsequent segment transitions into a broader discussion. Here, we critically synthesize how these isolated pathways converge into a synergistic feedback loop, evaluate the methodological limitations of current literature, and outline the clinical implications for mechanism-based precision therapies.

Type I Interferon Pathway as the Main Conductor of Lupus Pathogenesis

The Type I Interferon (IFN-I) pathway is the main conductor and the most dominant pathogenic mechanism in Systemic Lupus Erythematosus (SLE) (Lai et al., 2024b). Almost all immune and non-immune cells in the bodies of SLE patients show signs of dysregulation triggered by IFN-I. This makes it a central signaling system that connects many aspects of the disease's pathogenesis. This strong IFN script is associated with disease activity, flare frequency, and specific organ manifestations, such as lupus nephritis, arthritis, and skin manifestations. High basal serum levels of IFN-α can even serve as a biomarker indicating poor renal outcomes in patients suffering from lupus nephritis (Gómez-Bañuelos et al., 2024; Londe et al., 2023; Rodríguez-Carrio et al., 2023; Wang et al., 2025).

The recognition of Damage-Associated Molecular Patterns (DAMPs) by Pattern Recognition Receptors (PRRs) triggers an excessive IFN-1 production mechanism in SLE. The main source of DAMPs is self-nucleotides, primarily DNA and RNA, which originate from dead cells (apoptosis) or are released by neutrophils during the NETosis process. The main receptors that recognize these self-nucleotides are located in the endosome and cytoplasm. Toll-like Receptor 7 (TLR7) recognizes single-stranded RNA (ssRNA) within the endosome, and TLR9 recognizes CpG-

rich DNA (unmethylated DNA). These two receptors are often bound in immune complexes that are internalized by plasmacytoid dendritic cells (pDCs) (Justiz Vaillant et al., 2025; Londe et al., 2023; Tian et al., 2025).

pDCs are producers of IFN-I and are responsible for the significant production of IFN-α in SLE. Additionally, cytoplasmic sensors such as RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs) can also detect viral RNA or self-RNA. The most relevant cytoplasmic DNA sensor is cGAS (cyclic GMP-AMP synthase), which detects cytoplasmic DNA, including mitochondrial DNA (mtDNA) released by cellular stress or DNA from NETs. Activation of cGAS produces the secondary molecule cGAMP, which then activates STING (stimulator of interferon genes) and, together with TLR, triggers transcription factors such as IRF3 and IRF7, responsible for IFN-I production. The main genetic risk factors for SLE are genetic variations in genes encoding parts of this pathway, such as IRF5, IRF7, STAT4, and TYK2, which support the role of the IFN-I pathway in the pathogenesis of the disease (Chang, 2024; Gu et al., 2024; Ji et al., 2023; Luo et al., 2025).

Chronic IFN-I has several effects that directly enhance tissue development and damage in SLE. First, IFN-I significantly alters the adaptive immune system, lowering the activation threshold of B cells, promoting extrafollicular differentiation, and producing autoreactive antibodies, including anti-dsDNA. Additionally, IFN-I stimulates the differentiation of CD4+ T cells into pro-inflammatory subpopulations such as Th1, Th17, and T follicular helper (Tfh). The presence of these cells will increase inflammation and trigger antibody production by B cells (Arnaud et al., 2024; Tian et al., 2025). Second, IFN-I has cytotoxic properties that cause direct organ damage. IFN-I receptors (IFNAR) are widely expressed in all types of cells, including cells in target tissues such as the kidneys, skin, and joints. In the kidneys, IFN-I interacts with resident cells such as podocytes, mesangial cells, tubular epithelial cells, and endothelial cells, leading to interstitial fibrosis, impaired filtration function, apoptosis, mesangial proliferation, and the production of chemokines (CXCL9/10/11) that recruit infiltrating immune cells (Chyuan et al., 2019; Lai et al., 2024). In a single-cell analysis study, the IFN score in renal tubular epithelial cells strongly correlated with fibrosis and poor therapeutic response, even more so than the IFN score in infiltrating immune cells. This shows the important role of IFN-I in local tissue damage. Third, IFN-I functions to control cellular metabolism and homeostasis. For example, it has the ability to promote the formation of NETs in neutrophils, which then provide more fuel (DNA) for IFN-I production, resulting in a feedback loop (Gupta & Kaplan, 2021; Ji et al., 2023a; Lai et al., 2024b).

There is pathobiological heterogeneity in the SLE patient population eventhough the primary role of IFN-1 in SLE is quite clear. The IFN-independent endotype is a normal IFN script found in approximately 36% of SLE patients. This endotype may explain clinical variations and the failure of several anti-IFN clinical trials to achieve universal efficacy, as patients without a high IFN script may not respond to such therapy. To improve the success of future clinical trials, patient stratification should be based on biological profiles, such as IFN signature status (Gómez-Bañuelos et al., 2024; Jones & Morand, 2024). Despite these differences, IFN-1 remains a highly promising therapeutic target. Drugs that work by inhibiting this pathway have shown clinical efficacy. The monoclonal antibody Anifrolumab, which targets the IFNAR1 subunit, has been approved by the FDA and EMA as a treatment for moderate to severe SLE (Dai et al., 2025; Jones & Morand, 2024; Wang et al., 2025). Litif Litifilimab also showed positive results in phase II trials (Dai et al., 2025; Tian et al., 2025). Litifilimab targets BDCA2 on pDCs to inhibit IFN-I production. Current drug developments include JAK inhibitors (Baricitinib) and TYK2 inhibitors (Deucravacitinib) that inhibit downstream signaling of IFNAR. In practice, clinical trial results are not always consistent. The phase III trial of anifrolumab (TULIP-1) did not achieve the primary therapeutic goal in some patients. This indicates the complexity of the IFN pathway and the possibility of other alternative pathways supporting the disease (Jones & Morand, 2024; Wang et al., 2025).

Overall, the IFN-I pathway is an important part of SLE development as it acts as a conductor regulating both innate and adaptive immune responses, causing organ damage, and serving as a major therapeutic target in contemporary SLE treatment.

Table 1. The effect of IFN-I pathway in SLE progression

Components of IFN-I Pathway	Role in the Pathogenesis of SLE	Effect on Disease Progression
Plasmacytoid dendritic cells (pDCs)	Massive production of IFN-α (up to 1000 times more than other cells) when activated by self-nucleotide	Causing an increase in IFN script, enhancing B and T cell activation, and worsening systemic inflammation (Tian et al., 2025; Wang et al., 2025)
TLR 7/9	Identifying ssRNA and unmethylated DNA in endosomes	Encouraging the production of IFN-α that triggers the inflammatory process (Justiz Vaillant et al., 2025; Kalliolias et al., 2024; Londe et al., 2023)
Cytoplasm censor (cGAS/STING)	Detecting cytoplasmic DNA (e.g., mtDNA, NETs) and producing cGAMP to activate STING	Producing IFN-1 from TLR independently facilitates an alternative pathway for persistent IFN-1 activation (Chang, 2024; Luo et al., 2025; Tian et al., 2025)
Transcription factors (IRF5, IRF7, STAT4)	The main transcriptional regulator that triggers IFN-1 gene expression. Genetic variations can increase the risk of SLE	Increasing cell sensitivity to IFN induction signals and modulating adaptive immune responses (Dai et al., 2025; Londe et al., 2023; Wang et al., 2025)
IFNAR receptors (IFNAR1/IFNAR2)	Ubiquitous receptor for all IFN-1 subtypes, signaling to immune and non-immune cells	Causes organ damage (e.g., kidney podocytes), gathers immune cells, and increases disease activity (Chyuan et al., 2019; Jones & Morand, 2024; Lai et al., 2024)

NLRP3 Inflammasome as a Local Amplifier and Cause of Organ Damage

The NLRP3 inflammasome functions as a trigger for intense local inflammation and directly causes tissue necrosis and organ damage, especially in the manifestation of lupus nephritis (LN). This is different from the IFN-1 pathway, which is systemic and involves a broad immune response (Chen et al., 2023; Neamţu et al., 2024).

Inflammasome is an intracellular multi-protein complex that acts as the primary sensor for various cellular stresses and pathogenic stimuli. The NLRP3 inflammasome is assembled through two distinct steps, namely priming and activation. The priming step is usually triggered by pro-inflammatory signals such as cytokines TNF-α or IL-1β, or signals from the IFN-I pathway, which increase the transcriptional expression of the NLRP3 gene and pro-IL-1β via the NF-κB pathway. After priming, the cells are ready for activation. The activation of the NLRP3 inflammasome can be triggered by various DAMPs prevalent in the inflammatory environment of SLE, including urate crystals, reactive oxygen species (ROS), potassium ion (K+) efflux, and lysosomal rupture caused by immune aggregates or NETs. In SLE cases, the main triggers that are consistently replicated are immune aggregates, dsDNA, and the NETs themselves. After being assembled, the NLRP3 inflammasome recruits the ASC adaptor (apoptosis-associated speck-like protein containing CARD) and the proform of the caspase-1 enzyme. Caspase-1 then becomes active and performs its two main catalytic tasks. First, it converts the active forms of the pro-cytokines IL-1β and IL-18 into secreted forms. IL-1β, a potent inflammatory mediator, enhances the Th17 response, attracts neutrophils, and causes kidney damage (Tian et al., 2025; Xu et al., 2023; Y. Zhang et al., 2021). Conversely, IL-18 stimulates the production of IFN-γ and promotes the formation of additional NETs, creating a feedback loop that exacerbates inflammation. The second function of caspase-1 is to cleave the Gasdermin D (GSDMD) protein. This protein then forms pores in the cell membrane, leading to a process called pyroptosis. Pyroptosis is a type of rapid inflammatory cell death that causes the release of cytoplasmic contents such as DAMP, inflammatory cytokines, and alarmins. This infects neighboring cells and increases the area of inflammation (Fetter et al., 2023; Mittal et al., 2025; Y. Zhang et al., 2021).

Activation of the NLRP3 inflammasome and the progression of LN are associated with very strong evidence. Histopathological studies show increased expression of NLRP3 inflammasome components, ASC, and caspase-1 in the glomeruli and tubulo-interstitium of LN patients compared to healthy controls. The SLEDAI disease activity score and the renal pathology activity index are positively correlated with the expression levels of the NLRP3, ASC, and caspase-1 inflammasomes. This indicates that the level of inflammasome activation is proportional to the severity of inflammation and organ damage (Chen et al., 2023). Functional studies show that the NLRP3 inflammasome can damage podocytes, crucial cells in the kidney filaments, leading to proteinuria. IL-18 produced by the inflammasome has the ability to enhance NETosis, resulting in a feedback loop that increases inflammation and vascular damage. Additionally, inflammasome activation occurs in other tissues, such as the skin in cutaneous lupus erythematosus (CLE), where IL-1β and IL-18 are locally induced and contribute to inflammatory lesions (Fetter et al., 2023; Mähönen et al., 2022; Y. Zhang et al., 2021).

Table 2. The effect of NLRP3 pathway in SLE progression

Components of IFN-I Pathway	Role in the Pathogenesis of SLE	Effect on Disease Progression
NLRP3 censor	Recognizing DAMPs such as ROS, ATP, dsDNA, and immune aggregates	Triggering intense local inflammation in target tissues, especially the kidneys and skin (Chen et al., 2023; Xu et al., 2023)
ASC adaptor	Connecting NLRP3 with caspase-1 via the PYD-CARD domain. Important for energy transfer and caspase activation	Improving the efficiency of caspase-1 activation, enhancing the production of IL-1β/IL-18, and pyroptosis (Chen et al., 2023; Xu et al., 2023; Y. Zhang et al., 2021)
Caspase 1	Processing pro-IL-1β and pro-IL-18 into their active forms; cleaving Gasdermin D to trigger pyroptosis	Producing strong inflammatory mediators (IL-1β, IL-18) and causing pyroptosis, leading to direct tissue damage (Chen et al., 2023; Xu et al., 2023; Y. Zhang et al., 2021)
Cytokine effectors (IL-1β and IL-18)	L-1β: Strengthens Th17, attracts neutrophils IL-18: Induces IFN-γ, promotes NETosis	Encouraging pro-inflammatory T cell subpopulations, attracting infiltrative immune cells, and creating feedback loops with other pathways (Fetter et al., 2023; Tian et al., 2025; Y. Zhang et al., 2021)
Pyroptosis	Release of cytoplasmic contents (DAMPs, cytokines) due to pore formation by Gasdermin D	Infect neighboring cells, expand the area of inflammation, and cause direct tissue damage (Mittal et al., 2025; Y. Zhang et al., 2021)

However, there is an intriguing contradiction in the research data regarding the NLRP3 inflammasome in SLE. In several studies, it was found that although the catalytic enzyme (caspase-1) and effector cytokines (IL-1β, IL-18) were higher in active SLE patients, the mRNA of inflammasome components (NLRP3, NEK7, ASC) was lower. This suggests that, rather than just gene expression, the issue may lie in post-translational regulation or primary activation (Ma et al., 2018). On the other hand, other studies show that there is a positive correlation between the expression of inflammasome components and SLE disease activity. This discrepancy may be due to the complex biological dynamics and the fact that SLE patients are heterogeneous. However, there is a consensus that IL-1β and IL-18, which are the end products of inflammasome activation, are important pathogenic mediators. Therapeutic targets focusing on the NLRP3 inflammasome are currently being developed. In other inflammatory conditions, drugs such as Anakinra, an IL-1 receptor antagonist, and Canakinumab, an anti-IL-1β monoclonal antibody, have been used. These drugs also show potential in preclinical SLE models (Chen et al., 2023; Mittal et al., 2025). Phytochemical compounds such as curcumin and baicalein have been shown to inhibit NLRP3 and

have renoprotective effects in mouse LN models. Direct NLRP3 inhibitors, such as Dapansutrile, are also being developed. The success of inflammasome therapy, like anti-IFN therapy, depends on the ability to identify patients with a dominant inflammasome profile, which may not apply to all SLE patients (Mittal et al., 2025; Neamţu et al., 2024).

Disruption of Self-Antigen Recognition and Clearance as a Fuel Resource for Inflammation

Inflammation in SLE would not occur without the role of self-antigens. In SLE, a significant defect in the mechanisms of recognition and clearance of cellular debris becomes a crucial starting point that triggers interconnected inflammatory pathways. This process is called the clearance of apoptotic cells and cellular debris, which is an important physiological mechanism to ensure that dead cells are normally cleared by macrophages without triggering an immune response (Arnaud et al., 2024). This process is disrupted, leading to the accumulation of cellular debris containing nuclear proteins. This debris then becomes a major source of strong DAMP molecules, such as dsDNA and RNA, which activate PRRs on innate immune cells, triggering IFN-I production and inflammasome activation (Arneth, 2019; Tian et al., 2025).

One of the most significant defects associated with SLE is the deficiency of complement components, particularly C1q and C4. C1q deficiency is the strongest genetic risk factor for SLE, found in 90-95% of cases, while C4 deficiency is found in about 75% of cases. Complement, especially C1q, functions as an opsonin that helps macrophages recognize and clear dead cellular debris. Without adequate C1q function, these debris persist in tissues and circulation, increasing continuous exposure to the immune system and causing DAMP accumulation. Additionally, C3 deficiency is also closely associated with SLE disease activity, as C3 is required for mediating tissue damage in LN. Clinical biomarkers such as the decrease in serum levels of C3 and C4 are routinely used to monitor SLE disease activity, as complement depletion indicates intense activation of the complement pathway due to immune complex deposition (Arnaud et al., 2024; Dai et al., 2025; Holers, 2025; Justiz Vaillant et al., 2025).

In addition to complement deficiency, defects in enzymes responsible for breaking down self-nucleotides also significantly contribute to the pathogenesis of SLE. Enzymes such as DNASE1, TREX1, DNASE1L3, and RNase H2 are the main protectors of the cytoplasm and extracellular space from self DNA and RNA. DNASE1 breaks down extracellular DNA, while TREX1 and DNASE III (DNASE1L3) clear cytoplasmic DNA and microparticles. Mutations in these genes, such as TREX1, are known to cause autoinflammatory disorders similar to lupus (Arneth, 2019; Chang, 2024b). In SLE, DNASE1 levels are often reduced, and the function of this enzyme can be disrupted by antibodies or altered redox conditions. As a result, self DNA and RNA are not degraded and can accumulate in the cytoplasm, potentially activating sensors such as cGAS and RLRs. This process can trigger the production of IFN-I (Chang, 2024; Luo et al., 2025; Tian et al., 2025).

Neutrophil extracellular traps (NETs) are a unique phenomenon that connects intrinsic pathophysiology (cell death) with the activation of inflammatory pathways. NETosis is an inflammatory cell death process in which neutrophils release long DNA structures coated with proteolytic enzymes such as elastase and myeloperoxidase (Guan et al., 2025; Justiz Vaillant et al., 2025). In SLE, neutrophils tend to abnormally form NETs (aberrant NETosis), which is caused by various factors such as IFN-I, pro-inflammatory cytokines, and oxidative stress. Additionally, SLE patients often have defects in NET clearance, caused by a lack of active DNASE1 or the presence of anti-NET antibodies that inhibit the degradation process. As a result, NETs are excessively formed and cannot be cleared, becoming their own antigen reservoir (Guan et al., 2025; Gupta & Kaplan, 2021; Tian et al., 2025). The molecules within NETs are highly immunogenic, particularly DNA and histones. The DNA in NETs, especially the oxidized ones, is very stable and strongly activates TLR9 on pDCs, triggering massive production of IFN-α (Gupta & Kaplan, 2021; Tian et al., 2025). The compromised identification and clearance of cellular debris from apoptosis and NETosis, beyond merely undermining immunological tolerance, serve as a continual source of DAMPs that activate central inflammatory pathways. This deficiency initiates a self-sustaining pathogenic cycle:

initial cellular damage results in debris accumulation, which activates PRRs to stimulate IFN-I production and inflammasome activation. The intensified inflammation then induces further cellular damage, so perpetuating the cycle. Therefore, it is essential to discover therapeutic ways to address these clearance deficiencies to interrupt this cascade and prevent disease progression.

Discussion: The Synergistic Inflammation Cascade and Feedback Loops

The progression of SLE is not caused by the activation of independent inflammatory pathways, but by a strong inflammation cascade where these pathways reinforce each other through an inherent positive feedback cycle (Gupta & Kaplan, 2021; Mittal et al., 2025). The three main pillars of inflammation, namely IFN-I, the NLRP3 Inflammasome, and NETs, work in pathological synergy, where the activation of one triggers or enhances the others, creating progressive and damaging inflammation. Understanding these pathways is key to elucidating the relationship between cellular mechanisms and the clinical progression of the disease. A crucial meeting point in this network is the NET, which serves as a medium connecting intrinsic events (cell death) with the activation of the external inflammatory pathway (Guan et al., 2025; Justiz Vaillant et al., 2025).

The positive feedback between IFN-I and the NLRP3 inflammasome is one of the strongest mechanisms of inflammation amplification in SLE. IFN-I not only acts as a systemic conductor but can also prepare cells to be more responsive to inflammasome stimuli. IFN-I can enhance the expression of inflammasome components and make cells more susceptible to activation, creating a stronger "priming" condition (Fetter et al., 2023). On the other side, the end products of inflammasome activation, namely the cytokines IL-1β and IL-18, can also modulate the IFN-I response. The pyroptosis process induced by the inflammasome causes the death of inflammatory cells, triggering the release of cytoplasmic contents, including DAMPs (Mittal et al., 2025; Y. Zhang et al., 2021). DAMPs such as oxidized mitochondrial DNA (mtDNA), which can then be released into the extracellular environment. DAMPs are then taken up by pDCs and internalized, where the DNA can activate TLR9 to trigger IFN-I, or taken up by other cells to activate cytoplasmic sensors like cGAS, which also triggers IFN-I (Mittal et al., 2025). This inflammasome-mediated inflammatory cascade not only causes local damage but also provides additional fuel for IFN-I production, which in turn reinforces the inflammasome, creating a sustained feedback loop.

NET serves as a crucial intersection point that connects all pillars of inflammation. NETs are DNA structures coated with proteolytic enzymes released by neutrophils as an immune response. In SLE, NETs are formed excessively and cannot be cleared (Guan et al., 2025). This structure acts as a dual stimulator for the inflammatory pathway. First, NETs are a major source of strong self-nucleotides. DNA and histones in oxidized NETs are highly immunogenic and strongly activate TLR9 on pDCs, triggering massive production of IFN-α (Gupta & Kaplan, 2021). The persistence of IFN-I signaling establishes a potent, self-reinforcing feedback loop, as IFN-I inherently stimulates further NETosis, which in turn perpetuates IFN-I production (Gupta & Kaplan, 2021; Ji et al., 2023). This inflammatory milieu is compounded by the activities of macrophages; upon the phagocytosis of immune aggregates contained within NETs, these cells often undergo lysosomal rupture. This mechanical and biochemical stress serves as a primary catalyst for the activation of the NLRP3 inflammasome (Y. Zhang et al., 2021). The resulting secretome of the inflammasome, particularly IL-18, acts as an additional trigger for NET formation, thereby instituting a secondary reciprocal cycle where immune aggregates and NETs drive NLRP3 activation, subsequently fueling further NETosis via IL-18. Beyond these localized cycles, the systemic implications of NETs are profound; their capacity to compromise the integrity of the blood-brain barrier and induce vascular injury significantly contributes to the pathogenesis of Neuropsychiatric SLE (NPSLE) and the acceleration of atherosclerosis (Guan et al., 2025; Gupta & Kaplan, 2021).

The cGAS-STING pathway is also an integral part of this cascade, often serving as an alternative or additional pathway for IFN-I production. The cytoplasmic sensor cGAS detects

cytoplasmic DNA, which can originate from various sources, including mtDNA released due to cellular stress or DNA from NETs that cannot be cleared (Chang, 2024; Gu et al., 2024; Luo et al., 2025). Aktivas The activation of the cGAS-STING pathway directly triggers the production of IFN-I via TBK1 and IRF3 (Ji et al., 2023a; Luo et al., 2025). This pathway can be activated independently of TLR, providing a redundant pathway to maintain chronic IFN-I production in SLE. This interaction becomes more complex due to the cross-talk between pathways. For example, IFN-I can inhibit STING degradation through the NF-κB pathway, extending the duration of the IFN-I signal. Similarly, activation of the NF-κB pathway by TLR or pro-inflammatory cytokines can trigger the transcription of IFN-I and other inflammatory cytokine genes, as well as inhibit STING degradation and create strong signal integration (L. Zhang et al., 2023; Zhong et al., 2024). NF-κB also participates in the activation of the NLRP3 inflammasome, thus becoming a central hub for integrating inflammatory signals that connect the TLR, IFN, and inflammasome pathways (Xu et al., 2023; Zhong et al., 2024). The progression of SLE is driven by a mutually reinforcing inflammatory cascade rather than isolated pathways. A major limitation of previous research is the tendency to study these mechanisms, such as the IFN-I pathway or the NLRP3 inflammasome in isolation. In reality, they are highly interconnected. Impaired clearance of cellular debris provides a constant supply of DAMPs. This accumulation fuels the IFN-I pathway, which then primes the NLRP3 inflammasome. The inflammasome subsequently triggers inflammatory cell death (pyroptosis) and NETosis, releasing even more DAMPs and restarting the vicious cycle.

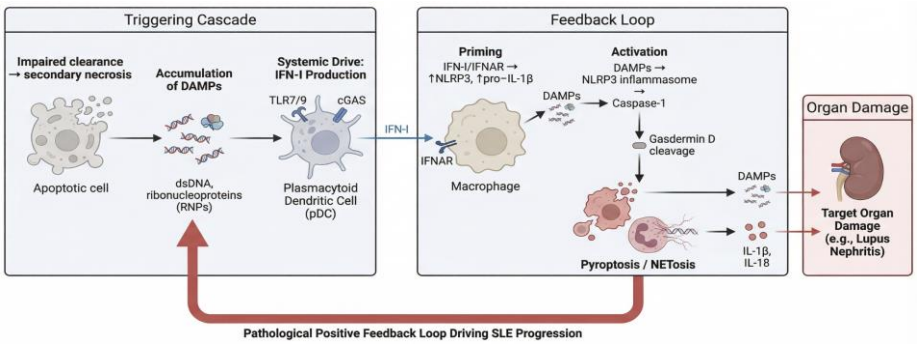

Figure 2. The positive feedback loop of cellular inflammatory cascades in SLE

Clinical Implications and Direction of Therapy Based on Inflammatory Pathways

A deep understanding of the cellular inflammatory pathway cascade in SLE has led to a paradigm shift from traditional symptomatic treatment to more targeted and cell biology-based therapeutic strategies (Arnaud et al., 2024; Dai et al., 2025). This literature not only deepens our understanding of disease progression but also opens the door for the development of prognostic biomarkers and targeted therapies. The clinical implications include patient stratification based on biological profiles, identification of dominant pathogenic pathways, and the development of interventions that specifically disrupt the inflammatory feedback loop.

One of the most significant clinical implications is the use of biomarkers to monitor disease activity and predict prognosis. Based on the literature, IFN-I and serum IFN-α levels consistently correlate with disease activity, flare frequency, and the risk of LN (Londe et al., 2023; Rodríguez-Carrio et al., 2023; Wang et al., 2025). Therefore, measuring IFN-script can be used as a prognostic tool to identify high-risk patients who may require intensive or new therapy (Wang et al., 2025). The same applies to biomarkers in the inflammasome pathway, such as IL-1β and IL-18, as well as tissue damage products like Interferon-inducible protein 16 (IFI16) in the kidneys, which show a strong correlation with pathological activity and clinical prognosis (Ma et al., 2018; Wang et al., 2023). For example, IFI16 shows high expression in the kidneys of LN patients and positively correlates with the pathological activity index and negatively with eGFR, making it an

independent prognostic biomarker (Wang et al., 2023). The integration of these biomarkers into clinical practice will enable an individualized approach, where therapy can be selected based on the dominant inflammatory pathway in individual patients, and is expected to enhance the success of future clinical trials (Jones & Morand, 2024).

Inflammatory pathway-based therapies have been applied in the treatment of SLE. Drugs that inhibit the IFN-I pathway have shown significant clinical efficacy. Anifrolumab, a monoclonal antibody that inhibits the IFNAR1 subunit, is the first drug to directly target the IFN pathway and has been approved for the treatment of moderate to severe SLE. It is crucial to critically appraise the strength of the evidence supporting these pathways. The evidence for the IFN-I pathway is robust and directly translatable, supported by extensive human genetic data and successful Phase III clinical trials of anifrolumab. Conversely, the strength of evidence for the NLRP3 inflammasome is currently limited; while it shows promising targeted efficacy in murine lupus nephritis models and *in vitro* macrophage assays, it lacks definitive validation in large-scale human clinical trials. This discrepancy highlights a significant translational gap in the literature that future research must address (Dai et al., 2025; Jones & Morand, 2024; Wang et al., 2025). Litifilimab, which targets BDCA2 on pDCs to inhibit IFN-I production, also showed positive results in phase II trials for reducing joint inflammation (Dai et al., 2025; Tian et al., 2025). Additionally, kinase inhibitors within the IFN-I signaling pathway, such as JAK inhibitors (Baricitinib) and TYK2 inhibitors (Deucravacitinib), have also shown efficacy in phase III clinical trials (Jones & Morand, 2024; Wang et al., 2025).

Therapies targeting the inflammasome pathway are also under development. Drugs such as Anakinra (IL-1 receptor antagonist) and Canakinumab (anti-IL-1β antibody) have been used for other inflammatory conditions and show potential in preclinical SLE models. Direct NLRP3 inhibitors are in the early stages of clinical development, and phytochemical compounds that inhibit the inflammasome have demonstrated renoprotective effects in murine LN models (Mittal et al., 2025; Neamțu et al., 2024). Therapies targeting NETosis, such as antimalarials (hydroxychloroquine) that inhibit nucleotide internalization and reduce NETosis, remain part of the standard therapy, while new agents like dual TLR7/8 antagonists (e.g., E6742) are undergoing clinical trials (Kalliolias et al., 2024; Tian et al., 2025).

Overall, the relationship between cellular inflammatory pathways and the progression of autoimmune diseases, particularly SLE, can be explained as a dynamic and interconnected network. The root of the problem lies in the defect in clearing cellular debris, which provides a constant source of DAMPs. This fuel is then mobilized by the main inflammatory pathways, namely IFN-I, the NLRP3 inflammasome, and NETosis, which reinforce each other by a strong positive feedback loop. IFN-I functions as the central conductor coordinating the systemic immune response, while the inflammasome acts as a local amplifier causing direct tissue damage. The synergy between these pathways creates persistent and progressive inflammation that is difficult to stop. The implications of this understanding are very broad. On one hand, it explains the clinical heterogeneity of SLE and the failure of single, non-targeted therapies. On the other hand, it paves the way for an era of more individualized treatment, where patients can be categorized based on their biological profiles (for example, "high IFN signature" vs. "high inflammasome activity"). The future direction of SLE treatment is likely to involve combinations of drugs targeting multiple inflammatory pathways simultaneously, especially in patients with clear biological profiles, to effectively break the pathological cycle and halt disease progression.

CONCLUSION

The progression of SLE is propelled by a self-reinforcing inflammatory cascade, rather than isolated pathways. This cycle is initiated by impaired cellular debris clearance, which perpetually supplies DAMPs to fuel a pathological synergy between the Type I Interferon (IFN-I) pathway, the NLRP3 inflammasome, and NETosis. The primary practical implication of this feedback loop is the

urgent need for a paradigm shift toward precision medicine. Clinicians must stratify patients using molecular biomarkers to implement multi-target combination therapies tailored to individual biological profiles to effectively disrupt this persistent cycle.

However, this synthesis is limited by inherent publication bias and a reliance on preclinical models that may not fully capture human SLE heterogeneity. To address these gaps, future research must prioritize longitudinal human studies to validate the *in vivo* crosstalk between these inflammatory pathways. Furthermore, future clinical trials should focus on evaluating the efficacy of combination therapeutics designed to simultaneously disrupt multiple components of this complex pathological cycle to successfully halt disease progression.

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