Section A-Research paper

Brief overview about NLRP3 inflammasome and NLRP3- driven Diseases

Arwa Omar Ali Mohamed[1], Tarek Gaith[1], Noha M. Hammad[1], Hagar O. Nofal[2]

[1] Department of Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[2] Department of Dermatology, Venereology & Andrology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Email: Arwaomar080@gmail.com

Abstract

Background: A caspase-activating complex known as the inflammasome was discovered in 2002, according to Martinon and Kimberly. The inflammasome comprises caspase-1, caspase-5, Pycard/Asc, and NALP1, a protein with a Pyrin domain that is structurally similar to NODs. Infections brought on by bacteria, fungi, viruses, and protozoa may result in the host's demise. As a defender, the host immune system protects the body from pathogen attack. The destruction and removal of invasive microorganisms is facilitated by both innate and adaptive immune systems. Pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), respectively, are recognized by pattern recognition receptors (PRRs), which are part of the innate immune system. The innate immune system has a challenge when a pathogenic agent or tissue harm is present because it must integrate numerous signals in order to mount a good defence. Inflammasomes emerged in the last decade to constitute fundamental processing units contributing to PAMP and DAMP sensing, which actively participate in integration of their downstream signalling, in addition to Toll-like receptors (TLR), Lectin receptors, RIG-Ilike receptors, and oligoadenylate synthase (OAS)-like receptor. When dysregulated, the NLRP3 inflammasome has been linked to the pathogenesis of several inflammatory disorders, including cryopyrin-associated periodic syndromes (CAPS), Alzheimer's disease, diabetes, gout, autoinflammatory diseases, and atherosclerosis. The NLRP3 inflammasome is essential for host immune defences against bacterial, fungal, and viral infections.

Keywords: inflammasome, NLRP3

Introduction

A caspase-activating complex known as the inflammasome was discovered in 2002, according to Martinon and Kimberly. The inflammasome comprises caspase-1, caspase-5, Pycard/Asc, and NALP1, a protein with a Pyrin domain that is structurally similar to NODs **(1)**

Overview of Inflammosomes :

Infections brought on by bacteria, fungi, viruses, and protozoa may result in the host's demise. As a defender, the host immune system protects the body from pathogen attack. The destruction and removal of invasive microorganisms is facilitated by both innate and adaptive immune systems. Pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), respectively, are recognised by pattern recognition receptors (PRRs), which are part of the innate immune system **(2).**

Pathogen-associated molecular patterns (PAMPs), which are conserved components of infectious pathogens, and damage-associated molecular patterns (DAMPs), which are indicators of host cellular distress, are two categories of variables that cause an innate inflammatory response. An expanding range of

pattern recognition receptors (PRRs) and cells of innate and adaptive immunity detect PAMPs and DAMPs **(3).**

The innate immune system has a challenge when a pathogenic agent or tissue harm is present because it must integrate numerous signals in order to mount a good defence. Inflammasomes emerged in the last decade to constitute fundamental processing units contributing to PAMP and DAMP sensing, which actively participate in integration of their downstream signalling, in addition to Toll-like receptors (TLR), Lectin receptors, RIG-Ilike receptors, and oligoadenylate synthase (OAS)-like receptor **(4)**.

principles of inflammasome activation and assembly:

The inactive zymogen pro-caspase-1 is recruited using the canonical inflammasomes as a scaffold. Pro-caspase-1 proteins are auto-proteolytically cleaved into active caspase-1 when they oligomerize. A cysteine-dependent protease called active caspase-1 breaks down the precursor cytokines pro-IL-1 and pro-IL-18 to produce the physiologically active cytokines IL-1 and IL-18, respectively. Additionally, active caspase-1 has the capacity to cause pyroptosis, an inflammatory form of cell death **(5).**

Names of inflammasomes refer to the scaffold-forming protein. NLRC4 needs to connect with an NLR member of the NAIP subfamily of proteins in order to create most inflammasomes, which are composed of one or two NLR family members**.** Inflammasomes can also be formed by non-NLR proteins such pyrin and AIM2, however. Through CARD-CARD interactions, NLRC4 can join directly with caspase-1. Pro-caspase-1 is attracted to the inflammasome by NLRs with an amino-terminal pyrin domain (PYD), which also associates with an ASC protein called an apoptosis-associated speck-like protein **(6).**

Nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing proteins, (NLR) family members NLRP1, NLRP3, and NLRC4, absent-in-melanoma 2 (AIM2), and pyrin are the five PRRs members that have been proven to form inflammasomes. Inflammasome formation has also been linked to various PRRs, including NLRP2, NLRP6, NLRP7, NLRP12, and IFI16. A bipartite adaptor protein known as apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) enhances the recruitment of pro-caspase-1 to the inflammasome complex in the case of some of these PRRs, including NLRP1, NLRP3, AIM2, and pyrin **(7**).

A wide range of PAMPs, including bacteria-associated signals, which have been the subject of the most research, are essential in starting the activation of different inflammasomes. Salmonella, Legionella, Shigella, and Pseudomonas spp. are some examples of the Gram-negative bacteria that produce pathogenic activators of the NLRC4 inflammasome **(4)**.

The Bacillus anthracis lethal toxin is discovered in the cytoplasm by the murine NLRP1b inflammasome. Numerous Gram-positive and Gram-negative bacteria, such as Staphylococcus aureus, Streptococcus pneumoniae, enterohemorrhagic Escherichia coli, and others, have the ability to activate the NLRP3 inflammasome **(2).**

Lipoteichoic acid produced by Gram-positive bacteria like Listeria monocytogenes is detectable by the NLRP6 inflammasome. The NLRP7 inflammasome in human macrophages detects acylated lipopeptides, a component of microbial cell walls. To activate the inflammasome-forming DNA sensor AIM2, free cytosolic DNA released by a range of bacterial species, such as Francisella novicida, is necessary **(4)**.

The Pyrin inflammasome is dependent on the modification and inactivation of the Rho GTPases by bacterial toxins, such as the Clostridium difficile cytotoxin TcdB and the Clostridium botulinum ADP-ribosylating C3 toxin**.** In addition, it has been demonstrated that human or mouse caspase-4/5 may identify the intracellular lipopolysaccharide (LPS) produced by Gram-negative bacteria and activate non-canonical inflammasomes **(8).**

NLP3 Inflammosome:

When dysregulated, the NLRP3 inflammasome has been linked to the pathogenesis of several inflammatory disorders, including cryopyrin-associated periodic syndromes (CAPS), Alzheimer's disease, diabetes, gout, autoinflammatory diseases, and atherosclerosis. The NLRP3 inflammasome is essential for host immune defences against bacterial, fungal, and viral infections **(6).**

An amino-terminal pyrin domain (PYD), a central nucleotide-binding and oligomerization domain (NOD; also known as the NACHT domain), and a C-terminal leucine-rich repeat (LRR) domain make up the tripartite structure of NLRP3 **(9**).

To start the inflammasome assembly process, the pyrin domains of NLRP3 and ASC engage. NLRP3 oligomerization after activation is dependent on the ATPase activity of the NOD domain **(7**).

NLRP3 GENE :

The NLRP3 gene, which codes for the production of the NLR protein family member cryopyrin, which is required for the development of inflammasomes, is found at position 44 of the long (q) arm of chromosome 1 (1q44) **(10)**

Mechanisms of NLP3 inflammosome activation :

1-Priming the NLP3 inflammosome :

For inflammosome activation, a priming signal (signal 1) is necessary. Toll-like receptor (TLR) ligands, NLRs (such as NOD1 and NOD2), or cytokine receptors, which activate the transcription factor NF-B, must first be presented to macrophages. NLRP3, pro-IL-1, and other molecules whose expression is not constitutively present in dormant macrophages are upregulated by NF-B. **(11).**

Inhibition of NLP3 Inflammosome:

The significance of the successful integration of the priming elements is paralleled by the negative regulation of NLRP3 inflammasome priming. When their primary function has been achieved, powerful inflammatory reactions must stop, or else they carry the risk of doing more harm to the host than the initial injury. By increasing the anti-inflammatory cytokine IL-10, type I IFNs acting through IFNAR suppress the production of pro-IL-1 **(12).**

Nitric oxide (NO) is produced by the inducible nitric oxide synthase (iNOS) by type I IFNs and IFN-alpha, which inhibits NLRP3 and causes it to be nitrosylated **(13)**

The NLRP3 inflammasome is inhibited when mature or memory T cells engage with macrophages via CD40-CD40L. Additionally, increased cellular cAMP levels decrease NLRP3 activity. The microRNA miR-223 controls NLRP3 expression via regulating the quantity of NLRP3 mRNA **(14).**

Non canonical inflammosome pathway:

For pathogens that have evolved to avoid cell surface TLR4, this non-canonical inflammasome is important. Instead of caspase-1, the non-canonical inflammasome uses caspases 4/5 in humans and caspase-11 in mice **(15).**

These caspases directly bind to intracellular LPS to recognise it without the need of TLR4. Pent-acylated and hexa-acylated lipid A, but not tetra-acylated lipid A, is the LPS component that is detected by these noncanonical caspases **(16).**

For non-canonical inflammasome activation in human cells that express large amounts of caspase-4, priming is not required. Through the processing of GSDMD and pannexin-1, a protein channel that transfers ATP from the cell, caspases-4/5/11 cause pyroptosis. The P2X7 receptor (P2X7R), an ATP-gated cation selective channel, is activated by extracellular ATP and opens a pore that causes K+ outflow. In macrophages, oxidised phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (oxPAPC), which competes with LPS binding, directly binds to caspase-4 or caspase-11 to suppress LPS-induced pyroptosis **(7**).

The Alternative Inflammasome Pathway:

It was shown that a different pathway operated in contrast to both the canonical and non-canonical pathways. Caspase-1 activation and IL-1 maturation and release are induced by LPS stimulation in human monocytes without the need for additional stimuli**.** The alternate inflammasome pathway does not necessitate K+ efflux, cause the creation of ASC specks, or result in pyroptosis afterward **(17).**

Long-term LPS treatment in the absence of additional activating signals caused P2X7 independent NLRP3-mediated IL-1 processing and release in murine dendritic cells.In this alternate route, TLR4-TRIF-RIPK1-FADD-CASP8 signaling is involved **(7**).

Mechanisms of inflammasome spreading:

ASC has long been known to relocate from the nucleus to the cytoplasm following inflammasome activation and create a large perinuclear aggregation in living cells. ASC specks were recently discovered to be released by dying cells, causing extracellular pro-IL-1 to be cleaved and activating caspase-1 in macrophages that internalize the specks. Importantly, data shows that inflammasome activation propagates inflammation from cell to cell because activation of all main inflammasomes is linked to the creation of specks. Since purified ASC speck injection into mice in vivo was proven to promote inflammation, the accumulation of specks in sites of inflammation has major implications for inflammatory disorders **(6).**

Furthermore, it has recently been discovered that phosphorylation of ASC is a crucial stage in the development of ASC specks. When the NLRP3 inflammasome is activated, the kinases Syk and JNK become active and cause the phosphorylation of numerous downstream targets, including ASC. By inhibiting these kinases, ASC speck formation and caspase-1 activation were avoided **(18).**

Importantly, phosphorylation was not necessary for the oligomerization of NLRP3 and ASC. This implies that ASC's conversion to its prion form and formation of self-replicating filaments may require phosphorylation. This also implies that, in the absence of more specific inhibitors, kinase inhibition may have potential therapeutic value against inflammatory disorders **(6).**

The NLRP3/IL-1 axis and its roles in the immune system:

The primary mechanism by which the NLRP3 inflammasome is activated includes the conversion of the physiologically active versions of IL-1 and IL-18 from their inactive precursors **(18).** The IL-1 family, which also consists of IL-1, IL-1ra, IL-33, and IL-37, comprises IL-1 and IL-18. Members of the IL-1 family are essential for host defense, immunological control, and inflammatory responses **(19).**

The immune system's powerful pro-inflammatory cytokine IL-1 is mainly expressed on monocytes, macrophages, and dendritic cells (DCs). In order to attract leukocytes and increase the lifespan of neutrophils and macrophages, IL-1 stimulates the overexpression of adhesion molecules and chemokines. This enhances the functions of these cells. Thus, inflammation and tissue damage are caused by the proinflammatory mediators that activated leukocytes create, such as prostaglandin-E2 and cyclooxygenase type 2. Additionally, IL-1 promotes systemic inflammation by causing fever, the acute phase response, vasodilatation, angiogenesis, and leukocyte activation **(3**). Effective DC activation by IL-1 stimulates the production of IL-12, which in turn causes T cells to produce interferon (IFN-**) (20).**

IL-1β, also known as lymphocyte activating factor, was initially a co-stimulatory factor for T cells that offers potent pro-survival and proliferative signals. Later, scientists discovered that IL-1 can promote T cell polarization and differentiation, particularly towards Th17 cells. Naive CD4+ T cell development into Th17 cells and the production of IL-17 are induced by the activity of IL-1 with IL-6, IL-21, and IL-23 **(21).**

IL-1β and IL-4 effectively promote the development of CD4+ (Th9) cells that produce IL-9. Particularly, Th17 and Th9 cells have a substantial correlation with autoimmune disease **(22).**

Additionally, IL-1β directly promotes naive CD8+ T cell migration, differentiation, and proliferation, which is a crucial component of an efficient immune defense. Additionally, IL-1β promotes the growth and synthesis of antibodies from B cells. IL-1β is a crucial element in the process of turning innate immunity into adaptive immunity **(20).**

IL-18 was first identified as an IFN-inducing factor in 1989. Later research has revealed that IL-18 can stimulate Th1 responses in conjunction with IL12, causing T helper cells to produce IFN-γ. However, in the absence of IL12, IL-18 triggers Th2 responses. Additionally, IL-18 stimulates the production of IFN-γ and IL-8 and activates natural killer (NK) cells. Together, NK cells and Th1 responses support the presentation of antigens as well as antiviral and anticancer activities. Alternatively, epithelial-derived IL-18 controls Foxp3+ Treg cell activity and Th17 cell development **(23).**

It has been shown that the imbalance between Th17 and Treg contributes to the pathophysiology of autoimmune diseases. Together, IL-1 and IL-18, which are byproducts of NLRP3 inflammasome activation, are essential for both innate and adaptive immunity **(20).**

The NLRP3/IL-1 axis stimulates naive T cell differentiation, enhances T and B cell responses, and leads to inflammation and target organ damage. As a result, the immune system, which controls autoimmunity, depends heavily on the NLRP3 inflammasome. The malfunctioning of the NLRP3 inflammasome may be a factor in autoimmune disorders **(20).**

NLRP3- driven Diseases:

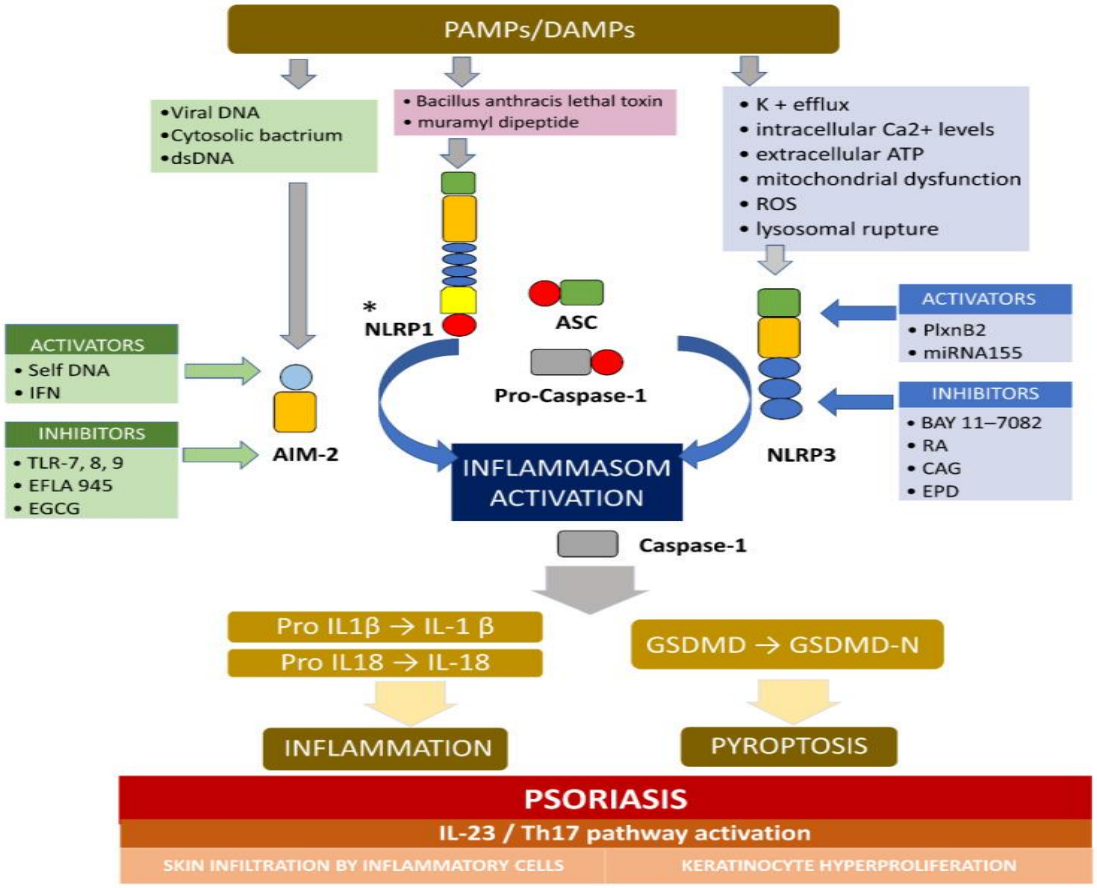
1- Psoriasis:

Caspase-1, which is activated by NLRP3 activation, splices pro-IL-1 and pro-IL-18 to create active versions of IL-18 and IL-1. Additionally, new research has discovered that NLRP3 splits caspase-1 into two pieces in order to normalize the splicing of gasdermin D (GSDMD) (the C and N domains). In order to cause pyroptosis, the N-terminal fragment (GSDMD-N) then collects and creates pores on the plasma membrane. Consequently, it is hypothesized that GSDMD is also a key protein part of NLRP3. Additionally, by cleaving the pore-forming GSDMD, caspase-11 promotes pyroptosis directly and indicates that the canonical NLRP3 is activated for the release of cytokines **(22).**

The development of psoriasis depends on an abnormally increased immune response, hence the function of NLRP3 inflammasome activation in psoriasis has drawn considerable interest. It is established that the NLRP3 inflammasome development may influence the inflammatory response in psoriasis. NLRP3 was expressed four times more in the psoriasis samples than it was in the normal skin biopsy samples. Furthermore, Su et al findings 's show that IL-1 expression levels are higher in abnormal skin biopsy samples than in normal skin biopsy samples. . The expression of IL-1 was roughly three to four times higher in psoriasis samples compared to normal skin biopsy specimens, and caspase-1 expression was also significantly elevated. In comparison to normal skin biopsy specimens, Caspase-1 gene expression was 2-3 times greater **(24**).

Recent research has shown that patients with psoriasis who were compared to healthy controls had considerably higher expression of the IL-18 and ASC proteins. By measuring the quantities of inflammasome components in human serum, the protein level was detected. The authors also discovered a statistical correlation between the levels of ASC protein expression and IL-18 expression. According to their research, inflammasome signaling pathway proteins including IL-18 and ASC are essential for the inflammatory reactions connected to the pathogenesis of psoriasis. These proteins may one day serve as important biomarkers in this patient population, aiding in the diagnosis of psoriasis**.** Additionally, according to new research, BAY 11-7082 is thought to be an antagonist of causes, including the activation of NF-kB, and it can relieve dermatitis that resembles psoriasis by blocking the NLRP3 inflammasome and the NF-kB pathway **(25**).

Additionally, imiquimod-induced psoriasis-like dermatitis can be greatly improved by MCC950, a well-known NLRP3 inflammasome inhibitor**.** These findings supported the idea that this skin disease's pathophysiology involves NLRP3 activation. In the Asian population, the involvement of NLRP3 in psoriasis susceptibility was also seen. The scientists there indicated that NLRP3 polymorphisms rs10754557 and rs3806265 can be a causal genetic or important genetic marker factor in the development of psoriasis **(24).**



The NLRP3 and AIM2 inflammasomes' activation and inhibition in psoriasis **(24).**

2-the Cryopyrin-Associated Periodic Syndromes (CAPS):

CAPS is one of the so-called rare diseases, orphan diseases. Similar to other rare diseases, its true incidence is unclear due to underdiagnosis, underreporting, and selection bias. However, because CAPS is still not well-known and is frequently misdiagnosed, the prevalence is believed to be between 2.7 and 5.5 per million people, however it could be greater **(26).**

Cryopyrin-associated periodic syndromes (CAPS), a clinical spectrum of various autoinflammatory phenotypes with variable disease activity and phenotype-related risk for morbidity and mortality, are typically caused by mutations in the NLP3 gene **(27).**

Mild, moderate, and severe phenotypes are included in the CAPS spectrum. The moderate phenotype is also known as Muckle-Wells syndrome (MWS, OMIM 191900), the severe phenotype is known as neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA), and the mild phenotype is also known as familial cold autoinflammatory syndrome (FCAS, OMIM 120100). It was recently suggested to refer to the CAPS spectrum as NLRP3-associated autoinflammatory disorders (NLRP3-AID) in a consensus proposal for a new taxonomy for monogenetic AID **(28).**

CAPS is a multi-system inflammatory illness that affects the eyes, skin, muscles, joints, bones, kidneys, and central nervous system, much like other AID. Neutrophilic dermatitis, the typical dermatological manifestation of CAPS, can present clinically as "urticaria-like" lesions or as erythematous and edematous papules or plaques. Rarely irritating, the rashes are frequently unpleasant and sensitive to touch. In addition to the face, upper arms, thighs, and abdomen, the rashes are typically found on the trunk and limbs **(26).**

The rashes in moderate CAPS variants, like FCAS, are typically not brought on by direct contact with cold objects or water, but instead frequently emerge 1-4 hours after cold exposure in places that were not necessarily directly exposed to cold. Furthermore, painful extremities swelling has been noted. A skin sample can histologically reveal perivascular neutrophilic infiltrations with leucocytoclasia without

vasculitis and eosinophilic infiltrations**.** Treatment with IL-1 inhibitors has proven to be extremely effective **(29).**

3-Gout :

Gout is an inflammatory condition marked by hyperuricemia and the deposition of MSU crystals in the tissues surrounding the joints. Patients with hyperuricemia may go years without showing any clinical symptoms, but they occasionally experience acute inflammatory flares marked by erythema, severe pain, and swelling of the affected joints. These flares develop very quickly, peaking 6–24 hours after onset, and then spontaneously resolve within 4–14 days. Chronic erosive inflammatory joint disease can develop from acute gout if elevated uric acid levels are not managed for years **(30).**

Large numbers of neutrophils entering the synovium and synovial fluid in gout enhance inflammation, and IL-1 has been shown to be a significant mediator in this process. Despite the fact that MSU crystals experimentally and in vitro cause the generation of inflammatory mediators from monocytes and macrophages when injected into the peritoneum of mice. Accumulated crystals ingested by inflammatory cells operate as metabolic triggers to activate the NLRP3 inflammasome in tissue macrophages and cause an IL-1β mediated inflammatory response, demonstrating that MSU inflammation is inflammasome dependent **(31**).

Inflammasomes have a role in the development of the disease, as shown by the clinical response of acute gout to therapy with IL-1β blocking drugs, as measured by prolonged pain alleviation, normalisation of inflammation markers, and enhanced remission rates. In fact, calcium pyrophosphate dihydrate and basic calcium phosphate mycrocrystals, which are perceived as danger signals by the innate system, activate inflammasome. Inflammasome, which produces IL-1b, IL-18, and matrix-degrading enzymes, is thus one of the primary causes of cartilage degeneration and synovitis in the osteoarthritic joint **(32).**

4-Systemic sclerosis:

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by skin and internal organ fibrosis. Currently, the disease's various pathogenic mechanisms—including vasculopathy, immunological activation, and uncontrolled extracellular matrix production—are all grouped under the umbrella term of dysregulation of tissue repair, which leads to intractable scar formation in the skin and internal organs.There is growing proof that toll-like receptors, which are part of the innate immune system, play a critical role in beginning and maintaining the fibrotic response in SSc. Numerous investigations have shown that inflammasome overexpression causes elevated IL-1β and IL-8 production in the skin and lungs of SSc people in both early and later phases**.** According to earlier findings, this group also exhibits increased caspace-1 activity, which has been associated with scar formation and myofibroblast differentiation. Inflammasome complex-forming protein genes and SSc show connections, according to genome-wide association studies, further demonstrating the involvement of innate immune systems in disease development**.** For instance, a rare functional polymorphism (Pro631His) in the toll-like receptor-2 gene was linked to both pulmonary arterial hypertension and SSc that was positive for anti-topoisomerase antibodies **(33**).

5-Systemic lupus erythematosous:

SLE is an autoimmune disorder that is often characterised by immunological reactions against self-antigens, especially to nucleic acids and their binding proteins, which partly results from improper clearance of dead cells. Despite the fact that SLE patients have been found to have impaired B- and T-cell tolerance, new insights points to aberrant TLR signalling as a significant factor in the development of the illness**.** In that regard, it has been demonstrated that immunological complexes including necrotic or apoptotic cells combined with IgG antibodies specific for SLE stimulate the manufacture of type-I interferon through TRL-dependent pathways. Additionally, apoptotic materials can potentially initiate innate immune responses and cause the release of cytokines that promote inflammation **(34).**

6-Rheumatoid arthritis:

RA is characterised by chronic inflammation and the gradual loss of articular cartilage and bone as a result of inflammatory cell infiltration and fibroblast proliferation in the synovial joint. TNF-a, IL-6, and IL-1 are just a few of the cytokines that are upregulated as a result of abnormal innate and adaptive immune responses in the pathophysiology of RA. These cytokines all have a role in mediating inflammatory processes in the affected joints **(35).**

An essential role in cartilage damage and bone resorption in RA may be played by the NLRP3-inflammasome activation following stimulation from damage-associated molecular pathogens and subsequent production of IL-1 and IL-18 **(34).** Increasing evidence suggests that increased TLR expression in the RA synovium causes the release of cytokines and matrix metalloproteases into joint tissue. For instance, hypoxia, a crucial component of the inflammatory process in RA that is active, is a significant trigger for the activation of the NLRP3-inflammasome**.** The widely used antimalarial drug hydroxychloroquine, which is also used to treat RA, is thought to have anti-inflammatory effects through inhibiting endosomal TLRs**.** Increased expression of NLRP3-related genes and lower expression of CARD8 were both associated with active RA. Studies revealed that SNPs in two distinct NLPR3-inflammasome components (NLRP3 and CARD8) can influence both illness susceptibility and response to treatment **(34).**

Conflicts of Interest: The authors declare no conflict of interest.

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