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A BRIEF REVIEW OF PYROPTOSIS BY NLRP3/CASPASE-1/GASDERMIN D IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis, a persistent autoimmune condition, results in inflammation that extends beyond the joints, causing damage to other organs in the body. Compared to men, women experience this twice or three times faster, with the disease affecting 1–2% of the global population. All of this joint degradation leads to deformities and bone degradation, which is the progressive disintegration or deterioration of bone structure, which often results in painful symptoms for the patient. RA commonly manifests as weight loss, fatigue, fever, rheumatoid nodules beneath the skin, and morning stiffness of the affected joints persisting for more than thirty minutes. This illness frequently shows symptoms in people aged 35 to 60. The pathogenesis of the disease involves many different pathways. This review is mainly focused on recently explored pathways such as pyroptosis of NLRP3/caspase-1/gasdermin-D, which results in inflammation in joints. Recent research indicates that RA may be aggravated by pyroptosis, a kind of regulated cell death that was just discovered. Interleukins such as IL-1β and IL-18 are two cytokines that are triggered during pyroptosis by NLRP3 inflammasome, which also activates caspase 1. Gasdermin D (GSDMD) can be split by caspase 1 and other caspases, and the GSDMD-N terminal opens pores in the plasma membrane that allow substances like lactate dehydrogenase (LDH) to flow out. The different immunohistochemistry methods support the increased activity of NLRP3/caspase-1/gasdermin D within the synovial fluid of RA patients.

KEYWORDS: Rheumatoid arthritis, pyroptosis, NLRP3/caspase-1/Gasdermin-D, inflammation.

INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disorder that predominantly targets the synovial membrane of joints, leading to rising disability, premature mortality, and economic difficulties.[1] Compared to men, women experience this twice or three times faster with the disease affecting 1-2% of the global population.[2] Chronic and inflammatory, RA is a complex disease that predominantly affects psychological and physical aspects of functioning. The most common causes of psychological distress and functional disability in rheumatoid arthritis include pain, exhaustion, length of disease, disease activity, and functional disability. All of this joint degradation leads to disabilities and bone erosion, which is generally extremely uncomfortable for the individual suffering from it. Common signs of RA include decreased appetite, weakness, fever, nodules under the skin, and aching in the morning of the bones involved, lasting for an extended period. The age interval from 35 to 60 is when this illness typically first appears, with intervals of improvement and worsening.[3]

The word "rheumatoid arthritis" originated from Greek words that meant inflamed and fluid joints. Augustin Jacob Landre-Beauvais, a French doctor, was the pioneer in identifying and detailing this significant illness in 1880.[4] The onset and course of RA are associated with some cytokines' faulty channels of signaling. Abnormal regulation of many signaling pathways at the local inflammatory site (the joint) led to the addition of pro-inflammatory mediators and abnormally high levels of inflammatory substances, which in turn caused abnormal proliferation of fibroblast-like synoviocytes (FLS).

Rheumatoid arthritis does not yet have a cure, and the treatments that are now available can only minimally relieve symptoms and somewhat prolong survival.[5] Several genetic as well as environmental variables, including smoking, microbes, and pathogenic organisms, have an impact on the cause of this condition. While traditional therapy approaches, which primarily involve glucocorticoids and disease-modifying antirheumatic drugs, remain the mainstay of care, new approaches, including biological DMARDs, are being researched and developed. Biologicals-based personalized methods that target specific pathways linked to the advancement of disease.[6]

Pro-inflammatory cytokines, including interleukin IL-1β and IL-18, are generated during pyroptosis. which is initiated by the NLRP3 inflammasome and caspase-1. Lactate dehydrogenase can flow out of plasma membrane openings that are created by the GSDMD-N-terminal, and caspases 1 and other caspases can break down gasdermin D (GSDMD).[7]

Since the pyroptotic pathways are essential to many disorders, they are valuable targets for drugs.[8]

PYROPTOSIS

Pyro and ptosis are combined to form the phrase "pyroptosis." "Pyro" means fire and refers to the inflammatory characteristics of pyroptosis, whereas "ptosis" denotes declining similar to other kinds of intentional destruction of cells. Interestingly, pyroptotic cells undergo swelling, accompanied by the appearance of numerous projections on the cell surface that resemble foam before they burst. However, the distinctive morphological traits of pyroptosis noticeably differ from the ones related to apoptosis.[9] Pyroptosis is characterized as a harmful mechanism of cell death that is regulated by the enzymatic activity of caspases-family inflammatory proteases. The enzyme caspase depends on aspartate-specific protease and cysteine.[10] Phagocytes such as keratinocytes, dendritic cells, neutrophils, macrophages, and T cells are more likely to undergo the process of pyroptosis. Higher concentrations of inflammatory caspases, which cause pyroptosis, are the cause of the process.[11]

The two different processes that lead to pyroptosis are the caspases-1 dependent and caspases-1 independent pathways.[12,13] Human caspases 5 and 4, as well as mice caspases 11, perform caspase-1-independent pyroptosis. Pyroptosis is a process that is initiated by caspase-1, which causes the cell membrane to burst quickly and generates a large number of pro-inflammatory chemicals. The traits shared by both are chromatin condensation, cell enlargement, and lack of DNA laddering.[14] The mitochondria within these cells trigger a weakening of the membrane's integrity, leading to its rupture. The contents of the cell come out as a result of this break, primarily consisting of cytokines, endogenous ligands, and alarmins, which can have significant adverse effects.[14,15]

Cytokine maturation by proteolysis occurs when caspases-1 is activated through either the non-canonical or canonical pathway. The IL-1β and IL-18 signaling occur via separate pathways; IL-1β predominantly interferes through the IL-1 receptor, primarily type 1, which acts as apyrogenic role, responsible for fever and causing immune cell stimulation.[16] ATP, high mobility group box 1 and S100A9 proteins are among the highly inflammatory danger-associated molecular patterns that are uncontrolled released during pyroptosis, together with the active types of IL-1β and IL-8.[17]

NLRP3 INFLAMMASOMES

Cellular complexes known as inflammasomes are made up of three main components: apoptosis-associated speck-like protein, an adaptor with a caspase recruitment domain, the enzyme caspase 1, and a sensor molecule that has distinct functions in the cell.[18] The pattern recognition receptors NLRP1, NLRC4, NLRP3, pyrin, and AIM2 are the five different members that make up an inflammatory complex. The protein families that contain leucine-rich repeats and nucleotide-binding oligomerization domains include these receptors.[14] One of the NLR proteins NLRP3 has at least 34 members in mice and 22 members in humans.[19]

NLRP3 was first connected to a set of inherited autoinflammatory illnesses called cryopyrin-associated periodic syndromes, which are linked with recurrent fevers and skin rashes.[20] An NLR is involved in the production of inflammasomes, numerous internal and external stimuli are interpreted by NLRP3, which is implicated in the development of autoinflammatory illnesses, such as gout, diabetes, and Alzheimer's disease.[21] Important roles for the innate immune system and inflammation are played by the cytoplasmic NLRP3 inflammasome. After formation, it causes caspase-1 to become activated, which then processes and delivers proinflammatory cytokines.[22]

NLRP3 inflammasome activation

NLRP3 is thought to recognize a common cellular event triggered by its stimulus instead of directly binding to many different types of stimuli that are physically and chemically different. NLRP3 inflammasome activation is currently characterized as a two-signal process. In this approach, extracellular ATP, pore-forming toxins, or particulate matter supply a second signal that primes the NLRP3 inflammasome, which is then triggered. The initial signal is supplied by microbial elements.[23] Compared to individuals with osteoarthritis, rheumatoid arthritis patients had significantly greater levels of NLRP3 mRNA in their synovial fluid.[24] In Rheumatoid arthritis, pentaxin 3 in monocytes and complement C1q work together to stimulate pyroptosis and NLRP3 inflammasome amplification.[25]

Mitochondrial reactive oxygen species (mtROS), which are produced in response to stress, injury, or malfunction of the mitochondria, are among the first recognized activators of this inflammasome. The inhibition of ATP-induced caspase-1 stimulation and IL-1β generation in macrophages is due to NADPH oxidase-dependent mtROS. This is due to the preliminary research showing mtROS's involvement in NLRP3 activation.[26] There is a proposal that ion fluxes involving potassium (K+), calcium (Ca2+), sodium (Na+), and chloride (Cl−) are

important processes that start the NLRP3 inflammasome's activation. Many inflammasome activators can cause the efflux of potassium ions, which is an essential signal for the activation of NLRP3. These include extracellular ATP, particulate materials like silica, calcium pyrophosphate crystals, and nigericin, an ionophore.[27] Cell swelling is caused by water influx from monosodium urate (MSU) crystals, which decreases internal K+ and triggers the NLRP3 inflammasome.[28]

Particles including silica, amyloid-β, alum, cholesterol crystals, asbestos, and calcium crystals can trigger the activation of the NLRP3 inflammasome in macrophages. This activation is brought on by lysosomes losing their effectiveness following phagocytosis, which permits lysosomal contents to leak into the cytoplasm. Lysosome disruption is one of the critical steps in the cascade that results in particulate matter-induced NLRP3 inflammasome activation.[23] The ubiquitous mechanism of protein phosphorylation is fundamental to the activation of multiple signaling pathways, including the NLRP3 inflammasomes.[29]

Regulators of NLRP3 inflammasome activation

Guanylate binding protein 5 is a human protein that is not NLR/ALR but instead promotes the assembly of inflammasomes. GBP5 aids in triggering NLRP3 inflammasome responses when exposed to soluble substances that prime inflammation but not those that are crystalline, in reaction to pathogenic bacteria. After producing Gbp5(-/-) mice, *in vitro* experiments revealed notable deficiencies in the cleavage of caspase-1 and IL-1β or IL-18. Furthermore, in live organisms, deficiencies were observed in host defense mechanisms and NLRP3-dependent inflammatory responses.[30,31]

Apart from its function in mitosis, NEK7 is also important for triggering NLRP3 inflammasomes. To control the NLRP3 inflammasome's assembly and caspase-1's triggering, which is mediated by K+ efflux and reactive oxygen species, NEK7 interacts with the NLRP3 LRR domain. A possible target for medicine is the NLRP3 inflammasome since it is connected to inflammation caused by autoimmune diseases like rheumatoid arthritis. Regarding the host's defense against bacteria, fungi, and viruses, NLRP3-mediated immune systems have a pivotal role. The balance between NLRP3 inflammasome activators and inactivators is therefore necessary for immunological homeostasis. The NLRP3 inflammasome is more susceptible to direct targeting of molecules than to cytokine-mediated inhibition.[32]

CASPASE-1

A special class of cysteine proteases called caspases is implicated in both death and inflammation. They are primarily apoptotic or inflammatory, and they belong to two highly conserved categories. The IL-1β-converting enzyme, initially recognized as the archetypal cysteine protease caspase-1, was subsequently cloned and acknowledged as a member of the cysteine protease family. The activation mechanism of caspase-1 is initiated by autoproteolysis of caspase-1 precursor molecules by proximity, which is induced by a large multiprotein complex known as the inflammasome.[33] Caspases contain a caspase domain at the tail end, which helps break down target proteins. Additionally, they have other parts like the caspase activation and recruitment domain or death effector domain located at the front end in different caspases.[34]

Caspase-1, an enzyme central to inflammation, has been extensively investigated for its role in converting precursor forms of pro-inflammatory cytokines like pro IL-1β and IL-18 into their active states. It's termed an inflammatory caspase because it participates in processes related to cellular death and inflammatory conditions. Inflammasomes, responsible for activating pro-caspase-1, can form in response to different triggers like infections, tissue injury, or metabolic imbalances. This activation of caspase-1 typically occurs in immune cells such as macrophages, epithelial cells, and dendritic cells acting as an essential defense mechanism against invading pathogens.[35]

To prevent pyroptotic cell death or excessive IL-1β production, the host must tightly regulate caspase-1 activation. Thus, two signaling checkpoints regulate the assembly of inflammasomes. At the cell surface, transmembrane binding Toll-like receptors (TLR) identify extracellular PAMPs (pathogen-associated molecular patterns) or DAMPs (danger-associated molecular patterns). This signal causes NF-κB to become activated, which subsequently primes the inflammasome and enhances the transcription of pro-inflammatory target genes. Posttranslational changes like deubiquitination and transcriptional activation are both involved in inflammatory pore priming. But before the inflammasome can assemble and activate caspase-1, another signal must activate the intracellular sensor, which initiates the inflammasome.[33]

During joint inflammation, caspase-1 or serine proteinases like PR3 are not necessary for the production of bioactive IL-1β, but when these processing systems are inhibited, IL-1β activation is nearly entirely inhibited, and significant articular cartilage degradation is

prevented.[36] The activation of caspase-1 is triggered by many inputs that are recognized by different inflammasomes. T3SS rod proteins or cytosolic flagellin bind to NLRC4, muriatic AIM2 reacts to cytosolic DNA, NLRP3 to a range of agonists, including crystals and NLRP1b to the deadly toxin of anthrax. These sensors all cause pyroptosis to occur.[37]

GASDERMIN-D (GSDMD)

In host reactions, GSDMD activation could be a double-edged sword. The host's defense may be harmed by overactivation which causes gasdermin activation to kill inflammatory cells. In line with this, numerous investigations have demonstrated that the gasdermin family is linked to autoimmune diseases like rheumatoid arthritis (RA).[38] Gasdermin D is a protein consisting of two segments, GSDMD-N and GSDMD-C, with molecular weights of approximately two kilodaltons each. Peptide linkers bind these segments together and the gene responsible for encoding GSDMD is located on chromosome 8 (8q24.3) when activated, the linker is cleaved, releasing GSDMD-N from its autoinhibitory domain. Besides releasing cytokines like interleukin IL-1β and IL-18 and disrupting water and ion balance, GSDMD-N creates an opening in the cell membrane, which results in pyroptosis.[8] The pore-forming and repressor domains at both ends of GSDMD consist of a linker region containing different cleavage sites specific to various caspases or granzymes. By examining the crystal structure of GSDMD, we gain insight into how these two domains interact with each other.[39]

During inflammasome activation triggered by external stimuli or internal damage, GSDMD becomes a direct target of inflammatory caspases like caspase 1/4/5 and murine caspase 11. These caspases cleave GSDMD, producing an active N-terminal domain known as GSDMD-NT. Pyroptosis is primarily regulated by the inflammatory response-mediated cleavage of GSDMD and subsequent lysis of cells.[40,41] Developing novel molecules that target GSDMD and other gasdermin family proteins is gaining attention due to their essential role in pore formation, which is implicated in conditions such as sepsis and numerous autoinflammatory disorders.[38] Pyroptosis associated with GSDMD is a major factor in the immunological and pathological outcomes.[34]

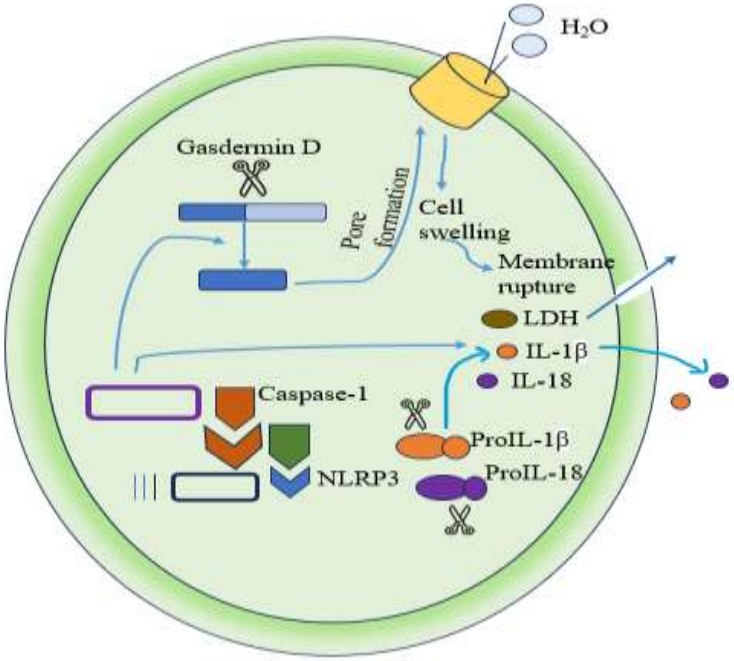

Fig 1: Diagram illustrating how pyroptosis could be involved in the rheumatoid arthritis pathogenesis.

HOW PYROPTOSIS OF NLRP3/CASPASE-1/GASDERMIN-D PATHWAY AFFECTS IN RA

The possibility of a connection between pyroptosis, a kind of regulated cell death connected to inflammation, and rheumatoid arthritis (RA) was examined by Xue Zhang et al. A comparison was made between samples of blood, synovial fluid, and/or tissues from thirty healthy individuals, thirty individuals had RA and forty-six patients had osteoarthritis (OA). The tissues were subjected to measurements of lactate dehydrogenase (LDH), IL-18 and IL-1β. Furthermore, the amounts of NLRP3-caspase-1, and cleaved gasdermin-D in synovial tissue were assessed using multiplex immunohistochemistry and immunohistochemical techniques.

Using these methods, it was possible to compare RA patient synovium to similar tissue from OA patients and find that RA patients showed higher levels of NLRP3, caspase-1, and GSDMD-N. This increase was seen in different synovial cells, including macrophages, which were identified using the CD68 marker. In line with the findings, multiple studies have identified higher concentrations of IL-1β and IL-18 in the synovial fluid of RA patients compared to OA patients. IL-1β activates macrophages and monocytes to stimulate fibroblast proliferation, which results in synovial hyperplasia, contributing to the pathophysiology of RA.[7] Although IL-18 plays a role in the pathogenesis of RA by inducing the production of

osteoclasts, IL-1β stimulates macrophages and monocytes to boost fibroblast proliferation, which results in synovial hyperplasia. The accumulation of inflammatory cytokines in joint areas caused by pyroptosis may accelerate the disease's severity.[7,42] In the synovium of mice treated with collagen-induced arthritis, there was an important association between the expression of NLRP3 and the degree of arthritis.[43] Mice with arthritis caused by antigens exhibited severe joint inflammation along with elevated NLRP3 inflammasome and IL-1β expression in the synovium.[44] The involvement of pyroptosis driven by caspase-1, GSDMD, and the NLRP3 inflammasome in RA is confirmed by investigations.[7]

CONCLUSION

Rheumatoid arthritis is a condition that affects 1-2% of persons globally. It can result in joint swelling in the hands and/or feet as well as systemic inflammation. Joint deterioration and severe disability may arise from untreated rheumatoid arthritis. The majority of recent research has been on the several pathways connected to RA. A kind of cell death called pyroptosis is present in numerous inflammatory illnesses, including RA. Interleukin IL-1β and IL-18, two pro-inflammatory cytokines, are activated through pyroptosis. The review focuses on the function of NLRP3/caspase-1/gasdermin D pyroptosis in rheumatoid arthritis. Rheumatoid arthritis may worsen due to pyroptosis, a recently identified type of controlled cellular death. The NLRP3 inflammasome, in conjunction with caspase-1, is responsible for the activation of pro-inflammatory cytokines, including interleukin IL-1β and IL-18. After GSDMD is cleaved by Caspase-1, GSDMD-N-terminal is produced. This leaks chemicals such lactate dehydrogenase (LDH) through holes in the cellular membrane. Since the pyroptotic pathways are involved in many diseases, they act as excellent therapeutic targets.

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