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Focus on the Function and Mechanism of Pyroptosis in Rheumatoid Arthritis

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ABSTRACT: The most important and basic processe that occurs inside of cells is cell death. There are several regulated cell death mechanisms, such as pyroptosis, necroptosis and apoptosis. Distinct sets of host proteins that contribute to biological outcomes regulate all such activities. Caspases regulate the execution of processes like pyroptosis and apoptosis. Inflammatory caspases trigger the process of pyroptosis, which results in necrotic, inflammatory cell death that causes inflammatory illness, even though it acts as a defense mechanism against a variety of microorganisms. The autoimmune, chronic inflammatory illness named as "rheumatoid arthritis (RA)"is characterized by inflammation in the joints caused by inflammatory- promoting cytokines such as tumor necrosis factor-alpha and interleukin-6. Rheumatoid arthritis is mainly characterized by synovitis, which is followed by clinical manifestation like stiffness, pain, swelling in several joints, malaise and fever as well as involvement of organ that are extra-articular like, interstitial pneumonia. Soon after the outset, joint damage advances, and once the impacted joints are distorted, irreversible physical impairment starts to manifest. Clarifying the role of pyroptosis in RA was the main goal of this review.

Keywords: Rheumatoid arthritis, Pyroptosis, Inflammasomes, Gasdermin D, Caspase 1

1. INTRODUCTION

The long-term autoimmune condition rheumatoid arthritis (RA) impacts many joints, it is typified by equilateral, joints inflammation resulting in bone loss, damage to cartilage and impairment (1). Although a small number of joints are impacted at first, numerous joints are eventually afflicted, and extraarticular symptoms are frequently experienced (2). Involvement of exocrine lacrimal and salivary gland may show up as extra-articular symptoms of the current illness. Reduced salivary flow and chemical alterations are signs of impaired salivary function in rheumatoid arthritis, which is thought to be directly linked to lymphocyte infiltration in afflicted glands (3,4). About 0.4% to 1.3% of the people affected by this disease based on factors like age (Compared to men, women are affected by RA two to three times more frequently, and first-time diagnoses for the disease peak in the sixth decade of person life) (5). Clinically, there are notable differences between the symptoms of RA in its early stages and those in its later stages when the illness is not adequately managed. RA in early-stage is distinguished by a widespread sickness with symptoms like swollen, morning stiffness and aching joints, it is also related with increased levels of (CRP) C-reactive protein and an increased (ESR) rate of erythrocyte sedimentation (6).

Anticitrullineated peptide antibodies (ACPAs), which are present in high serum concentrations, are indicative of rheumatoid arthritis (RA), albeit some individuals do not test positive for the illness. The pathophysiology of RA is not well known (7, 8). When it comes to the pathophysiology of RA, the main pro-inflammatory cytokines that promote osteoarthritis damage and an inflammatory response are interleukin-6 (IL-6), interleukin-1(IL-1), interleukin-18 (IL-18), and tumor necrosis factor (TNF) (9). A kind of planned cell death named pyroptosis was first recognized in 2000

(10) and is defined through the creation of pores in the plasma membrane, swelling, cell rupture, and the liberation of cytosolic components such high mobility group box 1 (HMGB1), IL-1ß, and IL-18. It is a form of death via necrosis that has become a significant part of the innate defense mechanism (11,12). Since then, pyroptosis research has expanded into entirely new areas. The nomenclature committee on cell death (NCCD) suggested in 2018 that the term "pyroptosis" be changed to refer to a controlled cell death that is frequently caused by inflammatory caspase activation and requires the GSDM protein family to create plasma membrane holes. (13). The aim of this review is to investigate the role of pyroptosis in rheumatoid arthritis, as this process is associated with the breakdown of the plasma membrane, which results in the release of several mediators, and an overabundance of these mediators is associated with rheumatoid arthritis. Additionally, pyroptosis may be a novel target in the management of rheumatoid arthritis.

2. MATERIAL AND METHOD

In order to perform this study, relevant publications were searched for using keywords such as "Rheumatoid arthritis, inflammasomes, pyroptosis, Gasdermin D, Caspase 1" in the academic databases, Web of Science, PubMed, Scopus and Google Scholar."

3. RHEUMATOID ARTHRITIS: THE INFLAMMATORY RESPONSE

Rheumatoid arthritis is a common autoimmune illness that is typified by continuous joint inflammation and destruction caused by neutrophils, T and B lymphocytes, monocytes, and proliferating fibroblasts of synovial tissue (14). Furthermore, inflammation causes the synovium to swell, resulting in the pannus formation, which is abnormal tissue that attacks and destroys neighboring joints tissues. upregulation of cytokines that promote inflammation, chemokines, and matrix metalloproteinases by RA pannus cells causes cartilage and bone to gradually deteriorate (15).

Early in RA, innate immunity in the synovium being activated by Fc receptor interaction or Toll-like receptor agonists is a major pathogenic mechanism that triggers inflammation. Because the innate defense mechanism includes monocytes, dendritic cells, macrophages, and phagocytes, which are cells present antigen and produce cytokine (DCs) play a crucial role in innate immunity and contribute significantly to the onset and progression of disease. (16). Lymph nodes, which include inflammatory synovial tissue and can influence primed T cells to adopt the TH1 phenotype via chemokine receptors such as CCR5, are a potential target for dendritic cells in synovium activated by TLR ligands (17).

3.1 INFLAMMASOMES

An innate immune response, inflammation is mostly brought on by myeloid immune cells, Pattern recognition receptors (PRRs) and macrophages, are the first to notice it. Finding molecular patterns associated with pathogens (PAMPs) or dangers (DAMPs) caused by internal stress or infection (18). PRRs are made up of receptors on the membrane of the cell, like Toll-like receptors (TLRs), and the cytoplasm receptors, including inflammasomes and nucleotide-binding domain-like receptors (NLRs) in particular (19).

Procaspase-1, an adaptor, and a receptor protein form the protein complex known as an inflammasomes. These are the so-called "canonical" inflammasomes; they have NLRs and are lacking in the receptor protein apoptosis-associated speck-like protein (AIM2), which has an adapter protein called the caspase-recruitment domain (ASC) as in figure 1. Several triggers, including DAMPs from host injury and PAMPs from infection, can cause formation of inflammasomes (activation of inflammasome showed in figure 1), which ultimately can cause the development of cytokines that enhance host immunity, like interleukin (IL)-1β and IL-18(20). One important source of IL-1 and IL-18 is the NLRP3 inflammasome, and mounting data indicates that the inflammasome may be engaged in the process that causes rheumatic diseases (21). Upon cleavage, cytokines that are not active like pro-IL-1β and pro-IL-18 yield the active cytokines, IL-1β and IL-18, in that order (22). Peripheral blood leukocytes are the primary source of expression for the NLRP3 inflammasome. As a reaction to inflammatory triggers, An NLRP3 inflammatory complex quickly forms in conjunction with pro-caspase-1 and ASC. When the NLRP3 inflammatory complex forms, caspase-1 is activated, which lead to the maturation of IL-1β and IL-18, two cytokines that promote inflammation (23).

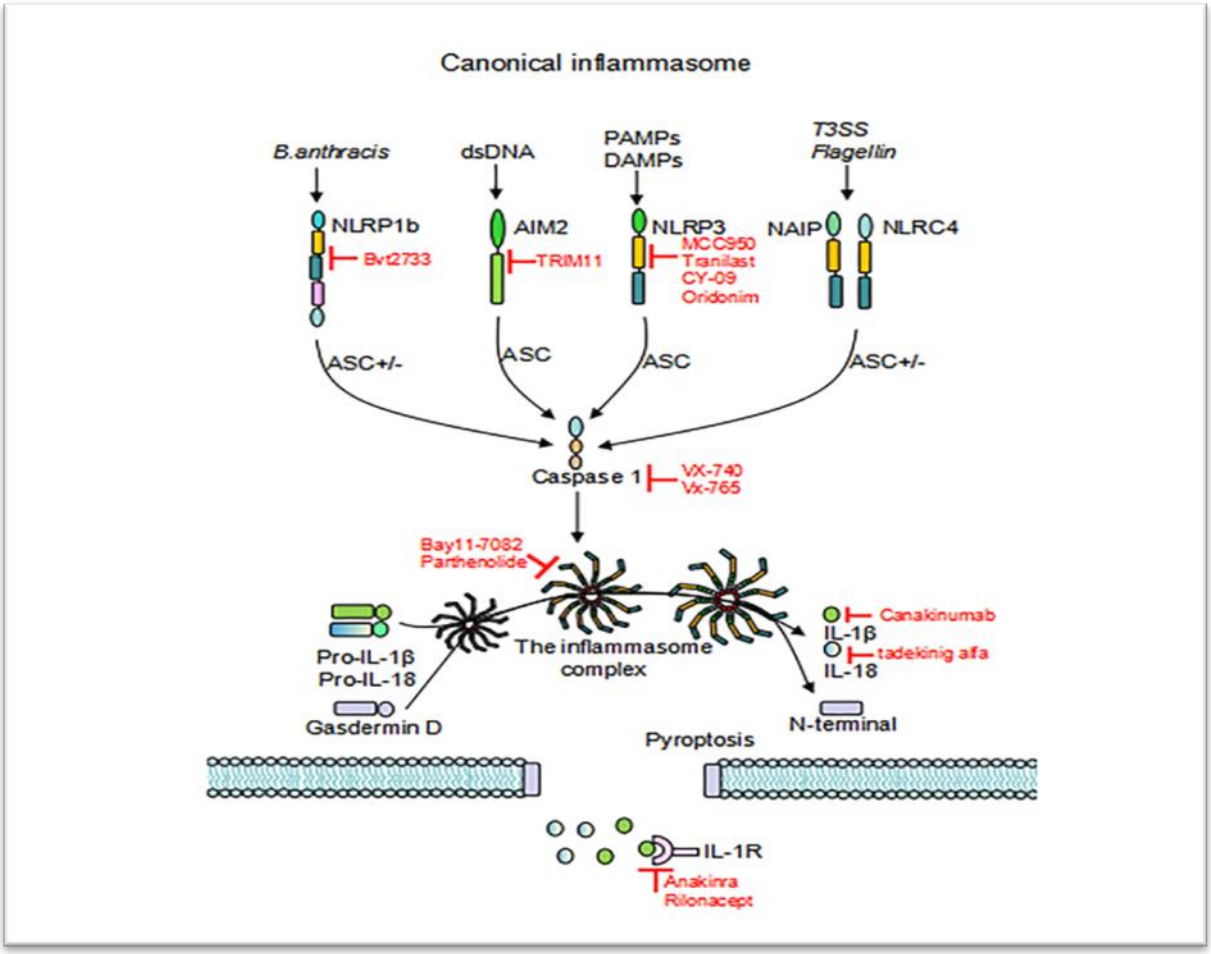

FIGURE 1. - Activation of inflammasomes (Jiang et al., 2022)

3.2 CASPASE-1

A family of proteolytic enzymes named caspases triggers and relays signals that ultimately cause death of cell. They can be separated pyroptosis-mediated caspases that cause inflammation (caspase-1, 4, 5, and 11) and apoptotic caspases (caspase-8, 9, 10, 3, 6, and 7) that induce apoptosis (24). Inflammation is brought on by caspase-1, also named interleukin-1b converting enzyme (ICE), which interferes with preinterleukin maturation. The sequences of caspase-1 and other inflammatory caspases, like caspase-4, 5 and 11, have the closest sequence identity (25). GSDMD can be used as a direct substrate to cause pyroptosis in both the caspase-1 intervening canonical route, and the caspase-4/11 or caspase-5 intervening noncanonical route (26).

The well-known inflammatory mediated caspase, the development of cytokines that are pro inflammatory (proIL-1β and IL-18) into IL-1β and IL-18 depends on caspase-1 (27). In order to overcome the stimulatory materials, caspases that are participated in inflammation and death are known as inflammatory mediated caspases (28). Inflammasome assembly, which is triggered by a number of molecules that are small, resulting from tissue injury, infections, or metabolic dysfunctions, activates pro-caspase-1 (29). As a result, macrophages, dendritic cells, and epithelial cells frequently exhibit caspase-1 activation as an immunological defense mechanism (30).

3.2.1 THE ROLE OF CASPASE-1 IN PYROPTOSIS

A type of planned necrosis that is different from apoptosis is called pyroptosis. Numerous cell types in the body undergo pyroptosis, which is caused to release inflammatory cytokines that remove pathogen-infected cells and encourage monocyte reassembly at the site of injury (24). Cytoplasmic content flows out of the cells as the cytoplasmic membrane ruptures, causing pyroptotic cells to swell and have numerous vesicular protrusions. It differs from apoptosis, which lead to apoptotic bodies formation also the cytoplasmic membrane preservation (31). An important aspect of pyroptosis for a long period has been reliance on caspase-1 (32). The role of GSDMD; the primary substrate and principal executor of pyroptosis. After that, activated caspase 1 cleaves GsdmD to release its N-terminus, which creates the transmembrane pore and acts as the pyroptosis executor as in figure 2(33). In recent times, the role of additional inflammatory caspases has been discovered, offering valuable understanding into the process of pyroptosis (34, 35).

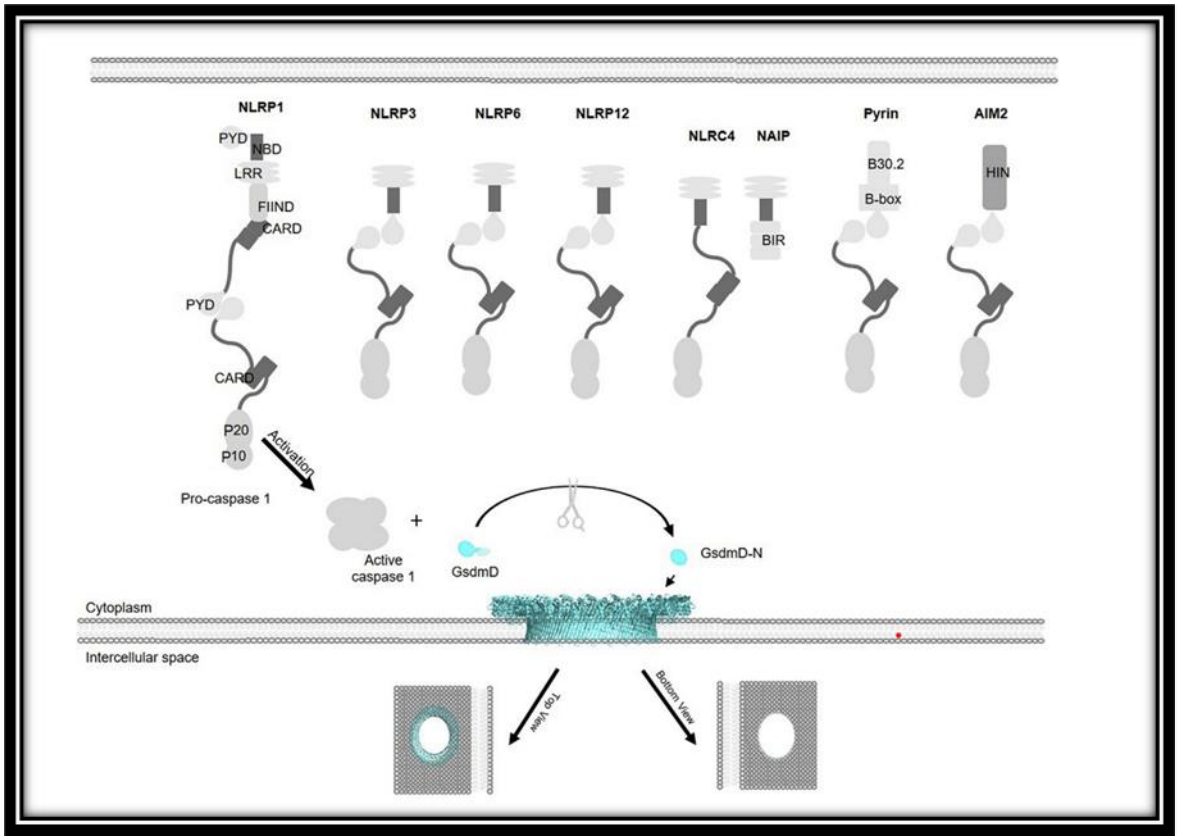

FIGURE 2. - The role of caspase 1 in pyroptosis (Burdette et al., 2020)

4. GASDERMIN D (GSDMD)

The pore-forming protein family known as gasdermins is becoming one of the most important controller of autoinflammation, infection and anticancer immunity. Their involvement in causing pyroptosis, a pro-inflammatory, lytic kind of cell death, are crucial, as several recent investigations have demonstrated. Furthermore, Gasdermins are quite important in NETosis, secondary necrosis, and apoptosis (36)

Human GSDMD is present in the cytoplasm as an inactive pro-protein while the body is at rest. The two domains that make up GSDMD are the NT-GSDMD and the C-terminal domain (CT-GSDMD), which are joined by a flexible interdomain linker. When CT-GSDMD binds to NT-GSDMD, the protein remains auto-inhibited and unable to create membrane holes. The human GSDMD linker domain's Asp275 proteolytic cleavage site is where pore-forming activity is obtained. The primary cause of proteolytic activation of GSDMD is a class of proteases called inflammatory caspases, which in humans includes caspase-1, caspase-4, and caspase-5(37).

Following proteolytic activation, NT-GSDMD reveals many regions of basic amino acids that function as binding sites for acidic phospholipids, including cardiolipin, phosphatidylserine, phosphoinositide phosphates, and phosphatidic acid (38). This interaction makes it easier for NT-GSDMD to be recruited to lipid-containing cellular membranes, such as the plasma membrane's inner leaflet, where it oligomerizes and creates multimeric holes (39). Much research has been done on the biophysical processes that turn NT-GSDMD monomers into multimeric pores.

4.1 ROLE OF GSDMD IN RHEUMATOID ARTHRITIS

GSDMD is the well-researched of gasdermin family member, is found at chromosome 8q24.2. At first, it was discovered that the stomach and oesophagus' epithelial cells exhibited GSDMD. According to recent research, GSDMD is additionally abundantly expressed in T cells, B cells, neutrophils, macrophages, and monocytes, where it functions a crucial job in inflammatory cell death. The N-terminal domain and the C-terminal repressor domain of GSDMD are joined by a linker region that contains a variety of location of cleavage for various caspases or granzymes (40, 41).

It was unknown how GSDMs cause cell death up till 2015, when two investigations defined GSDMD as the agent responsible for the lysis of cells process (pyroptosis). Initially, it was demonstrated that upon LPS transfection, cells lacking GSDMD had decreased lysis of cells and liberate of IL-1β. While caspase-11 cannot break pro-IL-1β, it is necessary for pyroptosis and release of IL-1β following different pyroptotic triggers. Additionally, the same site where

caspase-11 cleaves GSDMD can also be used by caspases-1/4/5. Following aspartic acid in its linker region at position 276, which causes pyroptosis, murine caspase-11 directly breaks GSDMD. This cleavage event is followed by processing of pro-IL-1β by caspase-1 following further NLRP3 inflammasome turning on (42). A third study that appeared a few months later made use of highly sensitive quantitative mass spectrometry analysis to reach the same conclusions (43) All things considered, these investigations demonstrated that pyroptosis requires N-terminal domain liberation via GSDMD processing in the linker region (GSDMDNT) from the autoinhibition of the C-terminal domain (GSDMDCT). Remarkably, an exosite that binds to GSDMDCT is present in caspases-1/4/11, increasing the propensity for binding to GSDMD (44, 45). Numerous labs throughout the world became interested in GSDMD's identification as A pyroptotic manager and how caspases that induce inflammation-1/4/5/11 activated it, as seen by the rise of work published during the years that followed. Four investigations published important discoveries in 2016 already about the methods by which GSDMD causes pyroptosis (46, 47). These investigations, which used a variety of techniques, including atomic force microscopy, fluorophore-filled liposomes, and electron microscopy, showed that GSDMDNT attaches to acidic phospholipids and cardiolipin following the linker region's GSDMD cleavage, creating perforations on liposomes. These huge, thermodynamically stable ring-shaped oligomers are called pores (48). According to a recent study, GSDMD pores are dynamic systems that possess open-closed conditions. that are controlled by local phosphoinositide metabolism rather than being constitutively open (49). GSDMD pores have the ability to release tiny intracellular compounds such cleaved IL-1β. Larger proteins (>50 kDa) can only be found in the supernatant following lysis of cell. Examples of these proteins are lactate dehydrogenase (LDH, a common label to quantify cell lysis) and complexes involving high mobility group protein-1 (HMGB1) (50). Not just is the cargo's molecular size a factor in controlling the release of chemicals via GSDMD perforations, but also the cargo's electric charge (51, 52). The revealed structure of GSDMD pore, which appeared that the pore conduit in liposomes is negatively charged with an inner diameter of 21.5 nm, and a 31–34-fold symmetry, revealed that compared to negatively charged payloads, positively charged and neutral cargoes are released with faster kinetics. with similar size of molecules. When pro-IL-1β is processed by polybasic charged patch caspase-1 is revealed, which encourages membrane targeting and release (51).

Recent research indicates that RA may be exacerbated by pyroptosis, a recently identified kind of controlled cell death. The NLRP3 inflammasome triggers caspase-1 during pyroptosis (53, 54), which in turn triggers pro-inflammatory cytokines such IL-18 and interleukin (IL)-1β. Gasdermin D (GSDMD) can be cleaved by caspase-1 and other caspases, and the GSDMD-N-terminal (GSDMD-N) opens pores in the plasma membrane that allow substances like lactate dehydrogenase (LDH) to flow out (55,56). In a model of collagen-induced arthritis in mice, NLRP3 knockout reduced inflammatory response and improved joint damage (57). In a mouse model of chronic arthritis, removing caspase-1 reduced cartilage degradation and joint inflammation (58), and T lymphocytes that live in RA patients' lymph nodes seem to frequently activate caspase-1 (59). Monocyte cultures were exposed to the serum of patients, which caused GSDMD-dependent pyroptosis that was linked with disease activity (60).

The effectiveness of Chinese medicine in treating RA is good. According to recent research, many Chinese medications can prevent and treat RA by acting through the pyroptosis pathway. Therefore, if researchers can examine the mechanism of Chinese medicine against RA from the standpoint of pyroptosis, it can offer some new targets for the clinical medication development of RA. From the standpoint of pyroptosis, research into novel RA mechanisms may offer a target for RA treatment and the creation of novel medications for use in clinical settings (61).

4.2 GSDMD INDUCE PYROPTOSIS VIA INFLAMMATORY CASPASES.

A kind of planned cell death called as pyroptosis was first identified in 2000 (62). It is typified by the production of hole forms in the membrane of the plasma, enlargement, cell rupture, and the liberation of cytosolic substances like IL-1ß, IL-18, and high mobility group box 1 (HMGB1). This kind of necrotic cell death has become a crucial innate immune response against intracellular infections such as Burkholderia thailandensis, Salmonella typhimurium, Escherichia coli, and Shigella flexneri. (63, 64).

Even though pyroptosis plays a crucial biological role, its activation mechanism was unknown until recently. Three research groups independently and concurrently showed in 2015 that inflammatory caspase-1 and caspase-11 (caspase-4/5 in humans) break GSDM-D between pore-forming, pyroptotic-inducing region and autoinhibitory domain, in response to either canonical or noncanonical activation of inflammasome. GSDM-D is a novel substrate of both caspases. They did this by employing distinct methodologies (such as CRISPR/Cas-9 nuclease screening, ENU-forward mice genetic screening, and highly sensitive quantitative mass spectrometry) (figure 3a and b) (65, 66). After inflammasome activation, caspase-1/4/11, which are auto-processed, identify and incorpated into a hydrophobic groove created by Leu306, Leu310, Val367, and Leu370 of the GSDMD-C domain, eventually breaking GSDMD, according to recent structural insights into formation of caspase-1/4/11–GSDM-D complex (44). It is interesting to note that GSDMD's N terminal domain (GSDMDNT) selectively attaches to phosphatidylinositol phosphates (PIPs), phosphatidylserine (PS), phosphoinositide (PI; present in the inner leaflet of the mammalian cell membrane), and cardiolipin (located in the outer and inner leaflets of membranes of bacteria). This cytotoxic fragment has an molecular weight approximation of 30 Kd (p30), and it is emitted following caspase-1/4/11 processing (67, 68).

Following GSDM-D cleavage, GSDMDNT is able to attach to these fats, oligomerise, and create ring-shaped holes in the membrane of the plasma, with an estimated inner diameter of 10–16 nm (67). Mulvihill et al. used to better understand the mechanism of GSDMDNT-mediated membrane pore creation, high resolution atomic force microscopy (AFM) will be used. The delay in time GSDMDNT has the ability to construct transmembrane oligomers with slit, arc and ring shapes which fit into membranes containing PIP, PS or PI according to AFM pictures. These transmembrane oligomers with arc, slit, and ring shapes have the ability to absorb more oligomers over time to produce big, stable ring-shaped oligomers. Whole transmembrane pore systems are finally produced by the progressive reduction in membrane lipid on the inside of these circles-shaped formations (69). Furthermore, they did not notice any appreciable variations in the height of GSDMDNT oligomers throughout the development of GSDMDNT pores, indicating that prepore-to-pore transitions are not necessary because the process of pore-forming of GSDMDNT is began directly in lipid membranes (70). Current structural analysis also shows that the GSDMDNT's a1 helix and b1–b2 loop are necessary for the capacity of lipid binding (71).

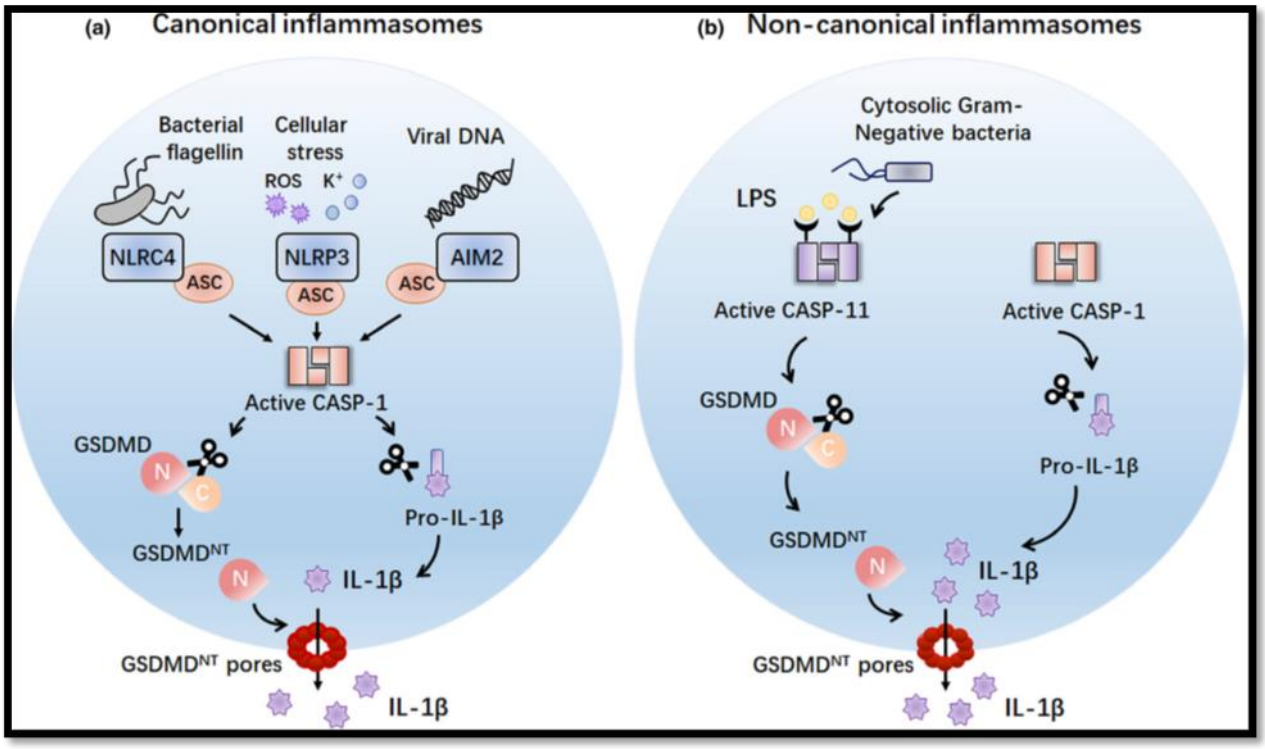

FIGURE 3. - Inflammatory caspases cause pyroptosis that is dependent on GSDMDNT(Lipeng et al., 2020)

5. CONCLUSION

There exist many distinct kinds of cell death, comprising apoptosis and pyroptosis , which are mediated by the inflammasome. When these inflammasomes are released in excess, they have two main purposes: one is protective and the other is pathogenic. Pro-inflammatory mediators, such as IL-18, are released during the process of cell death that depend on caspase-1, also named as pyroptosis. Pyroptosis define as a process that contributes to the pathophysiology of RA and is not just confined to defensive effects. It may also be connected to the release of cytokines that induce the inflammation through the caspase-1-dependent route. The primary activators of caspase-1 are Nlrp3, Nlrp4, and PPRs. Pro-inflammatory mediators are released during activation, and this further promotes the release of additional cytokines and chemokines that cause inflammation in the synovial joint and ultimately lead to the progression of RA.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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