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Inflammasome signaling and other factors implicated in atherosclerosis development and progression

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Abstract:

Chronic inflammation plays an extensive role in the onset and progression of metabolic disorders such as atherosclerosis, type 2 diabetes, gout and obesity. Atherosclerosis accounts for upwards of 70% mortality in patients with type 2 diabetes and is also a chronic condition that causes atrial stenosis due to a lipometabolism imbalance. The purpose of this article is to consider the inflammatory factors implicated in atherosclerosis and their role in the development and progression of this vascular disease. The inflammasome signaling pathway is an important inflammatory mechanism involved in the development of atherosclerosis. The most important inflammasome pathway in this respect is NLRP3 (Nucleotide-binding oligomerization domain (NOD)-like receptor with a pyrin domain 3), whose activation leads to the generation of important inflammatory cytokines including interleukins 1β and 18 (IL-1β and 18). The activities of these mature cytokines and inflammatory factors produced by other inflammatory pathways, lead to arterial inflammation and eventually arterial occlusion, which can result in life-threatening complications such as myocardial infarction and stroke. Therefore, it is essential to seek out more precise mechanisms for activation of inflammasomes and other inflammatory pathways for the development of therapeutic strategies for atherosclerosis.

Keywords: Atherosclerosis, NLRP3, Inflammasome, Inflammation, Cardiovascular disease,

1. INTRODUCTION

Cardiovascular diseases (CVDs) such as myocardial infarction and stroke are prevalent causes of mortality induced by atherothrombotic events in blood vessels. Dyslipidemia and arterial inflammation occur prior to the development of atherosclerotic plaques [1]. Different environmental, behavioral, and genetic risk factors are associated with CVDs and among them, high levels of blood cholesterol and particularly LDL-C (low-density lipoprotein cholesterol), are key to the pathogenesis of atherosclerosis [2].

Current treatment for atherosclerosis focuses on lowering blood cholesterol levels (mainly using a pharmacological regimen, such as statins), but this is not always adequate to reduce the risk of subsequent cardiovascular events in all patients. However, given that atherosclerosis is a chronic inflammatory disease, therapeutic approaches can be useful to treat arterial inflammation and clinical studies have reported the use of anti-inflammatory agents to be useful in the treatment of atherosclerosis [3].

One of the most important inflammatory pathways in the development of atherosclerosis is that involving the formation of an inflammasome, namely, the oligomeric protein complex NLRP3 (Nucleotide-binding oligomerization domain (NOD)-like receptor with a pyrin domain 3) belonging to the NOD-like receptor (NLR) family. Inflammatory cytokines such as the mature interleukins 1β and 18 (IL-1β and 18) are produced upon activation of this individual inflammasome complex. These mature cytokines play essential roles in arterial inflammation, atherosclerotic plaque formation, rupture and occlusion. In this context, the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) showed that use of the IL (interleukin)-1β neutralizing antibody, Canakinumab, reduced the risk of complications due to CVD in patients with a history of heart attack [4,5].

In this article, we first presented the role of monocytes, macrophages, and neutrophils in atherosclerosis, and then discussed the role of infectious agents in the development of atherosclerosis, and described the NLRP3 inflammasome, its activation and role in atherosclerosis.

2. ATHEROSCLEROSIS

Atherosclerosis is one of the leading causes of death in developed societies and the accumulation of lipids in areas of large arteries with a disturbed flow leads to the formation of atherosclerotic plaques. Rupture or erosion of these plaques can culminate in acute cardiovascular events such as myocardial infarction or stroke. It is highly noteworthy that inflammation plays an important role in both the progression of atherosclerotic disease and its complications [6,7]. Important risk factors for the incidence of atherosclerosis include age, gender, genetic disorders and family history, hyperlipidemia, hypertension, smoking, diabetes mellitus, homocystinuria, infections (herpes virus, chlamydia, pneumoniae,

cytomegalovirus), obesity, stress, lifestyle, and postmenopausal estrogen deficiency [6,8,9]. Atherosclerotic plaques mainly form in the elastic arteries (aorta, carotid and iliac artery) and medium and large muscular arteries (coronary and popliteal arteries). The abdominal aorta is involved much more frequently than the thoracic aorta. The symptomatic atherosclerotic disease mainly affects the blood vessels of the heart, brain, kidneys and lower extremities, the main complications of which are heart attack, stroke and leg gangrene [9,10].

There are a variety of hypotheses concerning the initiation or progression of atherogenesis. These include the idea that injury or oxidative stress could trigger the process, thrombogenic factors might be implicated, intimal cell proliferation can take place and infectious or an inflammatory-reparative reaction occurs as verified by the presence of inflammatory cells [11,12]. Thus, atherosclerosis arises as a chronic inflammatory response to endothelial injury in arterial walls. The progression of this damage can be mediated by actions and reactions in altered lipoproteins, monocyte-derived macrophages, T lymphocytes, and the components of cells in arterial walls [13,14]. Early lesions form in areas that contain healthy endothelial cells and this results in an increase in endothelial permeability and leukocyte adhesion, as well as changes in the formation of gene products of endothelial cells [15].

3. THE ROLE OF INFLAMMATION IN ATHEROSCLEROSIS

Under normal conditions, leukocytes present in the bloodstream do not bind to the endothelium. However, when the endothelium is injured by proinflammatory factors, endothelial cells induce an increase in adhesive molecules elevating leukocyte-endothelial adhesion [16].

Endothelial activation is the first stage of atherosclerotic lesion formation and under inflammatory conditions, endothelial cells secrete chemokines [17]. Once attached to the endothelium, monocytes migrate to the interior surface of blood vessels where they proliferate and are converted into active macrophages (monocytes and macrophages are known to be components of atheromatous plaques) [18]. This migration is facilitated by the formation of matrix metalloproteinases (MMPs), including MMP-9 [19].

As a result of increased plasma cholesterol, lipids penetrate the interior surface of blood vessels and foam cells are produced by absorption of these lipids by macrophages. Simultaneously, macrophages release a group of proinflammatory cytokines that lead to exacerbation of a local inflammatory response signifying the early stages of atherosclerosis. Additionally, adipocyte apoptosis evokes the release and accumulation of lipids on the interior surface of blood vessels [20].

Macrophages produce cytokines, such as IL-1 and TNF (tumor necrosis factor) to increase leukocyte binding as well as platelet aggregation and monocyte chemotactic proteins

(particularly MCP1 or monocyte chemoattractant protein-1) enhance the function of leukocytes in atheromatous plaques. In addition, oxidized LDL (low-density lipoprotein), a species of lipid laid down in vessels, can not only damage lysosomal membranes, but also induce macrophage nuclear cholesterol crystals within phagolysosomal compartments [21].

Chemotactic agents stimulate CD4 and CD8 lymphocyte entry into the intima and the cytokines IL-18, M-CSF (macrophage colony-stimulating factor), TNFx, TNFβ, IL-6, and CD-40 secreted from inflammatory cells in the local area produce mitogenetic, intracellular matrix-proliferating-, angiogenic- and foam cell-forming effects. Moreover, the interaction between T lymphocytes and macrophages also activates cellular and humoral immunity. Hence, T lymphocytes have a role in adjusting the atheroimmunological balance between pro-inflammatory and anti-inflammatory factors which may well determine whether an atherosclerotic lesion develops into a silent stable plaque or if fibrous cap rupture occurs [22].

The activated lymphocytes release a variety of fibrogenic polypeptide growth factors that cause the proliferation of smooth muscle cells and the production of a compressed extracellular matrix that is seen in advanced atherosclerosis. Various growth factors including PDGF (platelet-derived growth factor) 1, FGF (fibroblast growth factor), and TGFα (transforming growth factor alpha) are involved in the proliferation and differentiation of smooth muscle cells as well as matrix formation and migration of smooth muscle cells from the media layer to the intima, their proliferation, and formation of extracellular matrix causes the fatty streak to convert to fatty fibrous atheroma [21].

In addition, extracellular matrix molecules, specifically collagen secreted by smooth muscle cells, stabilize atherosclerotic plaques, but inflammatory and immune system cells activated in atheromatous plaques accelerate the death of smooth muscle cells through apoptosis [22].

Hypercholesterolemia also plays an important role in the progression of atherosclerosis. The main component of serum total cholesterol is low-density lipoprotein (LDL) cholesterol, which is associated with an increased risk and plays an important role in transporting cholesterol to peripheral tissues [23]. Conversely, high density lipoprotein (HDL) cholesterol causes cholesterol to move from the forming atheroma and existing atheroma to the liver to be excreted in bile substances.

4. THE ROLE OF HUMORAL IMMUNITY AND ACQUIRED CELLULAR IMMUNITY IN THE PATHOGENESIS OF ATHEROSCLEROSIS

To date, countless published articles have addressed the mechanism and conditions of atherosclerosis, but the pathogenesis of this multifactorial disease even now remains to be fully elucidated [24]. Several studies have shown that, in addition to lipids, inflammatory and autoimmune processes account for an important pathogenetic component of

atherosclerosis and both acquired and humoral immunities contribute to its development and progression [25].

4.1. Humoral Immunity

The humoral immune system is mainly responsible for producing antibodies and studies have shown that they are generated to combat oxidized LDL (ox-LDL). These antibodies include the IgG (Immunoglobulin G) and IgM (Immunoglobulin M) classes, the former playing a prophylactic role and the latter, a protective role against antigenic epitopes arising from adducts between ox-LDL and other elements of atherosclerosis [26]. In addition, antibodies have been found to fight other atherosclerosis-associated antigens such as HSP 60/65, oxidized phospholipids, and beta-2 glycoproteins. In myocardial infarction patients, anti-endothelial protein C antibodies have also been detected. Furthermore, endothelial cells under stress express the HSP-60 protein and because of the similarity of this protein to bacterial HSPs, several antibodies may fight it [27].

4.2. Cellular Immune System

The cellular immune system is mainly based on T lymphocytes which, in turn, are divided into several subpopulations [31] (Table 1).

Table 1. T cell types, the cytokines produced and their roles.

References	Role	Cytokines produced	Different types of T cells
28-30	As the most commonly seen lymphocyte subtypes in atherosclerotic lesions, Th1 cells are active and proliferate at the lesion site. These cells themselves trigger the cascade of activities of other cells, leading ultimately to plaque instability and rupture	TNF, IL-2,	Th1
31-33	These cells play a dual role in the process of atherosclerosis, which depends on the cytokine produced. They have a protective role against atherosclerosis if they produce IL-5, but they can also play a progressive role by producing IL-4. These cells can even counteract the atherogenic effects of the Th1 subpopulation.	IL-4, IL-5	Th2
34-35	Regulatory T cells play an important role in the body's immune processes through silencing or suppressing cellular responses and they are key to inducing and maintaining the immune system. Unlike other types of inflammation, where the level of these cells reaches 25%, they do not exceed 5% in atherosclerotic lesions, and it has even been shown that the number of these cells in the circulatory system is lower in patients with atherosclerotic lesions than in healthy individuals.	TGFβ, IL-10	Regulatory T cells (Treg)

5. THE ROLE OF INFECTIOUS AGENTS AND MICROBES IN THE PATHOGENESIS OF ATHEROSCLEROSIS

One of the topics much discussed in the field of atherosclerosis is the role of microbes in developing or even preventing atherosclerosis. Emerging findings suggest that bacterial or viral infections can contribute to the pathogenesis of atherosclerosis [36] through direct infection of the arterial cells or by stimulating the release of cytokines and acute-phase proteins [37].

This has been reinforced by recent empirical studies that indicate a relationship between the risk of CVDs and their associated mortality with markers of infection. It is also corroborated by experimental studies indicating an accelerated development of atherosclerosis following infection in animal models of hyperlipidemia [38]. Currently, there are a number of different infectious agents associated with an increased risk of CVDs. They include Chlamydia pneumoniae, Porphyromonas gingivalis, Helicobacter pylori, influenza A virus, hepatitis C virus, cytomegalovirus and human immunodeficiency virus. Nevertheless, there are significant differences in the strength of the evidence regarding any association between microbial diversity and atherosclerosis [39]. In some cases, infectious agents have been detected inside plaques, suggesting a direct influence on the development of atherosclerosis [40].

5. THE ROLE OF INFLAMMASOMES IN ATHEROSCLEROSIS

Inflammation is a supporting immune response that is triggered by the innate immune system in response to risk stimuli such as pathogens, dead cells, or stimuli. Insufficient inflammation can lead to persistent pathogenic infection while severe inflammation causes chronic inflammatory diseases. Intrinsic immunity function depends on the detection of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), which are mediated by pattern-recognition receptors (PRRs) and they are expressed by intrinsic immune system cells. Activation of PRRs by PAMPs and DAMPs trigger downstream cascades and the production of interferon type I (interferon alpha and beta) and proinflammatory cytokines [41].

PRRs act either individually or convergently in detecting harmful signals and are typically divided into four main families, including TLRs (toll-like receptors), RLRs (RIG-like receptors), CLRs (C-type lectin receptors) and NLRs (NOD-like receptors) [42-44].

Some members of the NLR protein family are involved in the formation of a macromolecular protein complex called an inflammasome [45-46]. The biochemical properties of one particular family, (NOD-like receptor, leucine-rich repeat and pyrin domain) NLRPs were delineated in the early studies of Tschopp et al. that prompted them to be referred to as inflammasomes, implying a role of the receptors in inflammation [47].

Activation of cytosolic inflammasome receptors stimulates protease caspase-1, which in turn converts pro-IL-1β and pro-IL-18 into mature secretory cytokines [45-49].

Active caspase-1 can also induce an inflammatory form of cell death called pyroptosis [50,51]. Inflammasomes are associated with autoimmune and auto-inflammatory diseases including neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. They also play an important role in inflammatory diseases such as atherosclerosis, type 2 diabetes and obesity [51].

Inflammasomes are NLRPs that structurally contain 3 domains, the first of which is often found at the C-terminus domain that is rich in amino acids of leucine-rich repeats (LRRs), involved in the regulation of NLRP3 activity, an interact with NLRP3 inducer and PAMP sensing. The second domain, called NACHT, is located at the center and causes oligomerization and the formation of the central structure of the NLR inflammasome. The third domain is an effector domain in the N-terminal region that is used to transmit the signal. This domain may include PYD (pyrin domain) [52]. The NLRs in host cells are housed in a guard-like complex where they are not only protected against proteasomal degradation but are also silent and inactive. Additionally, the chaperone-co-chaperone complex, SGT1–HSP90, contributes to the stabilization and maturation of NLR proteins and it is required for their function [53].

Most inflammasome complexes are composed of one or two members of the NLR family. In these complexes, the N-terminal domain of PYD binds to the PYD of the adaptor protein ASC (apoptosis-associated speck-like protein), and this binding ultimately results in the recruitment and binding of procaspase-1, leading to the formation of the inflammasome complex [54,55].

NLRP1, NLRP3, NLRP6, NLRP12 and NLRC4 inflammasomes are subsets of the NLR family. Each of them has a unique feature that is briefly mentioned: NLRP1 inflammasome was the first inflammasome identified. Although it was the first protein to be described in the inflammasome complex, the mechanism of its activation is poorly known [56]. NLRP6 inflammasome is associated with ASC and Caspase-1. The absence of NLRP6 inflammasome has been shown to cause qualitative changes in the microbial ecology of the gastrointestinal tract [57]. NLRP12 inflammasome with ASC and Caspase-1 forms the inflammasome that leads to IL_1β maturation [58]. NLRC4 inflammasome contains the CARD domain in N-terminal, a central NACTH domain and an LRR domain in C-terminal that is associated with the CARD domain of procaspase-1 by CARD-CARD interaction [59].

One type of inflammasome is NLRP3, which can create an inflammasome complex with ASC and caspase-1. This inflammasome responds to a range of stimuli such as the efflux of potassium from the cell, release of mitochondrial DNA or cardiolipin, and release of cathepsins after lysosomal destabilization [60-63].

Some studies indicate that intracellular Ca2+ signaling has the main role in NLRP3 inflammasome activation [64]. Several studies evidence that the release of Ca2+ from the ER (Endoplasmic Reticulum) to mitochondria is mediated by one product of phospholipase C (PLC), inositol-1, 4, 5-trisphosphate (InsP3), leading to mitochondrial Ca2+ overload and damage [65]. As a result of these events, the NLRP3 inflammasome activating factors are released from damaged mitochondria. The precise mechanism leading to the activity of PLC has not yet been identified. Recently, reports have shown that the NLRP3 inflammasome binds to mitochondria associated ER membranes (MAMs). The NLRP3 inflammasome for its full activity needs two other steps [66].

In most cell types, NLRP3 must be primed prior to activation, so activation involves two steps:

NF-κB activator stimuli: A prototypical example of these priming events is the binding of lipopolysaccharide (LPS) to TLR4 and priming is required to increase NLRP3 cell expression through NFκB signaling [67]. Deubiquitination must occur to activate NLRP3 and findings suggest that priming rapidly allows deubiquitination [68,69]. This ultimately results in the formation of the inflammasome complex and the ASC protein must be ubiquitinated and phosphorylated in readiness for inflammasome activation [70].

Stimulants known as NLRP3 agonists can induce the formation of the NLRP3 inflammasome complex. They include ATP, production of mitochondrial reactive oxygen species (ROS), pore-forming toxins, crystalline substances, nucleic acid, and hyaluronan as well as viral, bacterial, and fungal pathogens [60,71]. These stimuli can increase throughout infection or are released by the damaged cells [71].

After priming, activation of the inflammasome requires a secondary signal that leads to the formation of the NLRP3 inflammasome complex. The most important of these stimuli include the relocalization of NLRP3 to mitochondria, mitochondrial factors released into the cytosol (such as mitochondrial DNA or cardiolipin), the efflux of potassium from the cell through ion channels, and the release of cathepsin from lysosomal membranes [72-73].

The noncanonical inflammasome formed by caspase-11 in mice is interesting in the inflammasome field. Caspase-11 is needed for the activation of caspase-1 and caspase-3 [74]. It has been shown to develop NLRP3 inflammasome activation to indirectly augment the function of pro-IL-1β or pro-IL-18 [75]. Notably, caspase-11, independently of the LPS receptor TLR4, indicates intracellular LPS and some bacteria, and mediates cell death and IL-1α secretion [76]. Caspase-4 and caspase-5, in human cells, play a similar role [77] that leads to the activation of the NLRP3 inflammasome in the absence of stimulus needed for a canonical NLRP3 activation [78].

6. THE MECHANISM OF NLRP3 INFLAMMASOME ACTIVATION IN ATHEROSCLEROSIS

The accumulation of cholesterol and white blood cells in the arterial wall restricts oxygen-rich blood flow to the organs [79]. Atherosclerosis acts as a hardener on arterioles and can lead to life threatening complications such as stroke and myocardial infarction [79].

Based on various observations, it has been shown that IL-18, a product of inflammasome activation, can play a key role in the onset and progression of atherosclerosis [80-81].

Human atherosclerotic plaques have also been shown to contain high densities of IL-18 and IL-18 receptors compared to healthy arteriole tissues. Apo lipoprotein E (Apo E) is essential for cholesterol metabolism and a lack of Apo E in mice has been shown to increase atherosclerotic lesions and IL-18 levels. This may explain arterial inflammation and the increased instability of atherosclerotic plaques, whereas, in the absence of IL-18, the size of atherosclerotic lesions decreases [82-84]. Augmentation of LDL and free fatty acids (FFAs) in the blood leads to an imbalance in lipid metabolism that can induce the production of pro-IL-1β by TLRs providing an early signal for inflammasome activation [85].

In vitro studies have shown that macrophages can secrete large amounts of IL-1β in response to cholesterol crystals derived from the inflammasome NLRP3-dependent pathway [86]. In light of this, it has been demonstrated that the CD36 cell surface receptor facilitates the internalization of oxidized LDL (ox-LDL) and its conversion into cholesterol crystals inside the cell [87]. Cholesterol crystals formed within cells activate the NLRP3 inflammasome through phagolysosomal damage, which is a cathepsin B- and cathepsin L dependent mechanism [80]. Mice lacking the LDL receptor are susceptible to the development of atherosclerotic plaques and when fed a cholesterol-rich diet, a marked decrease in lesion size ensues if their bone marrow cells lack NLRP3, ASC, IL-1α, and IL-1β [80].

Cathepsin in combination with ROS activates the NLRP3 inflammasome, thus cleaving and maturing caspase-1. Caspase-1 then produces mature IL-1β, which upon release from the cell, enhances inflammasome components within the same cell and surrounding cells. It also induces inflammatory responses that result in the production of immune system cells and progression of the atherosclerotic plaque [88].

Overall, in atherosclerosis, FFAs can initiate the NLRP3 inflammasome by TLR2 and TLR4 signaling. In addition, ox-LDL can trigger the NLRP3 inflammasome via CD36-TLR4-TLR6 complex signaling. However, the CD36 receptor can also facilitate the internalization of ox-LDL and its conversion into cholesterol crystals intracellularly. Furthermore, phagolysosome degradation can release cathepsin, resulting in the activation of the inflammasome, while phagocytosis of extracellular cholesterol is also an inflammasome trigger. Notwithstanding this, the inhibition of cathepsin prevents the inflammasome from being activated by cholesterol crystals [88, 89]. (Fig. 1)[90].

One of the other mechanisms in atherosclerotic progression is the effect of autophagy on inflammasome activation [91]. Autophagy is the natural regulated mechanism of the cell that removes damaged organelles or useless components. It allows the necessary cellular components to recycle [91,92]. In many diseases, such as cancers, atherosclerosis, heart failure and neurodegenerative diseases, defects in autophagy have been observed [92]. Studies show autophagic markers found in most cells of atherosclerotic plaques [82,92]. A study indicates that the disorder of macrophage autophagy enhances atherosclerotic plaque formation. The process that makes this happen is the high activity of macrophage inflammasome and the production of IL-1b. Therefore, defenses of autophagy are intense stimuli for inflammasome activation [93].

It has been reported that oxidative stress stemming from the generation of excessive amounts of free radicals and a weakening of the antioxidant system can contribute to the development and progression of atherosclerosis. Clinical and epidemiological studies have also shown that LDL cholesterol has a positive effect on the development of atherosclerosis. However, according to the hypothesis of oxidative changes in biological systems, LDL is not inherently atherogenic in nature itself, but becomes atherogenic after conversion to ox-LDL [94].

Principal sources of oxidative stress in arterial walls include NADPH oxidase activity, nitric oxide synthase, myeloperoxidase, xanthine oxidase, lipoxygenase, and cyclooxygenase. Likewise, the cellular mitochondrial respiratory chain that, along with the weakening of the antioxidant defense system in pathological conditions, predisposes these vascular walls to more serious damage [95].

Besides, some studies have demonstrated that the oxidative stress-responsive transcription factor NF-E2-related 2 (Nrf2) is necessary for inflammasome activation and vascular inflammation is mediated through IL-1. The study has shown that an endogenous disastrous activator signal of Nrf2 and the NLRP3 inflammasome are an accumulation of cholesterol crystals in atherosclerotic plaques. These findings indicate that between oxidative stress and inflammasome activity a common pathway of chronic vascular inflammation exists which leads to atherosclerosis [96].

Antioxidants may be partly effective in reducing oxidative stress [97]. In this connection, it has also been shown that strengthening the antioxidant system by improving lifestyle and consuming plant sources rich in antioxidants and phenolic compounds, can also decrease oxidative stress [97].

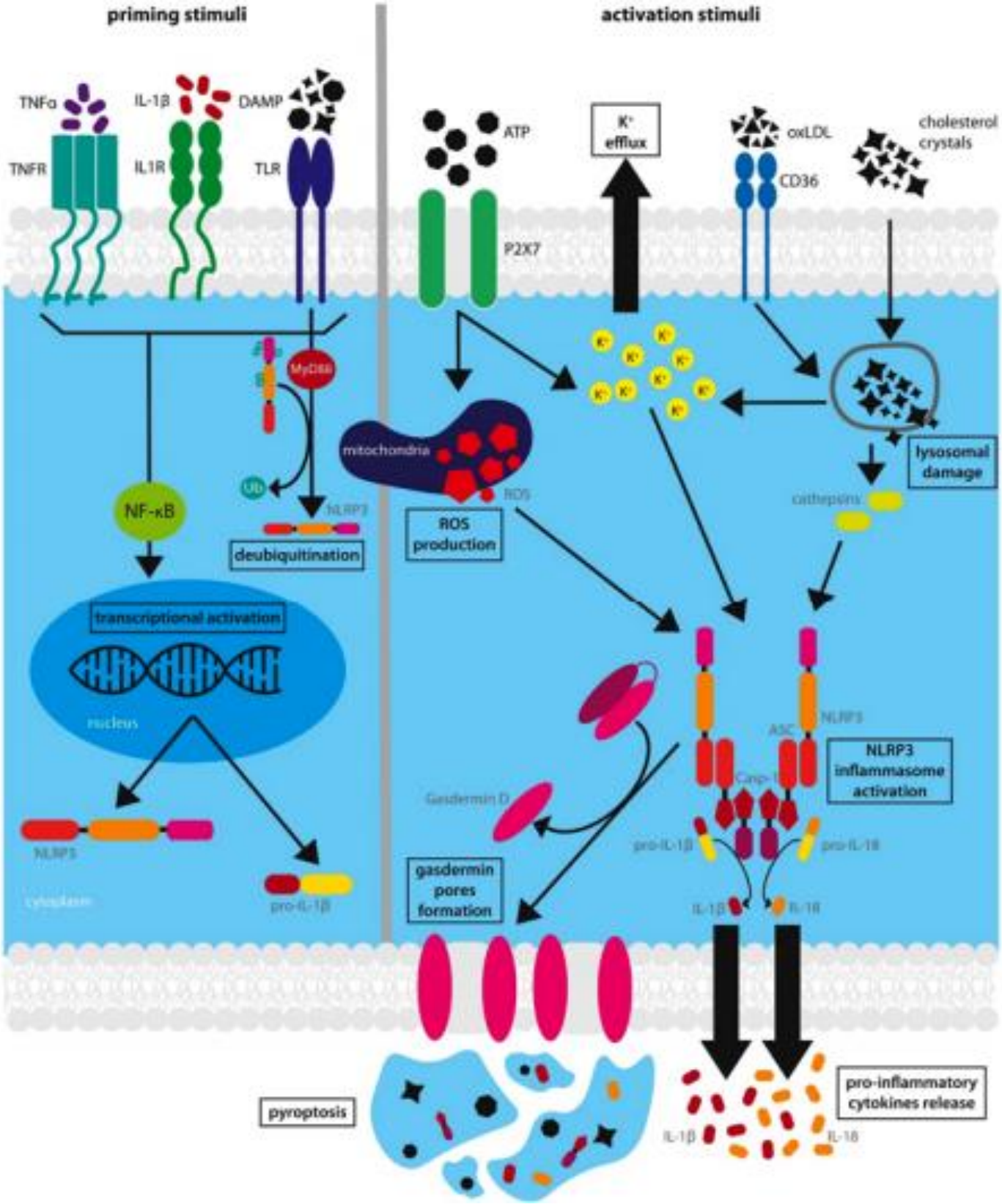

Fig. (1). Mechanism of inflammasome activation in atherosclerosis [90].

CONCLUSION

Considerable evidence emphasizes the importance of the NLRP3 inflammasome in the pathophysiology of inflammatory disease and atherosclerosis. During the development and progression of atherosclerosis, cholesterol and cholesterol crystals activate NLRP3 and other inflammatory pathways consequently leading to arterial inflammation and obstruction by producing IL-1β and IL18.

To achieve effective therapeutic strategies based on inflammasome mediators, numerous as yet unknown mechanisms of NLRP3 inflammasome activation, as well as its relationship to other inflammatory pathways involved in the development of atherosclerosis, require elucidation. Accordingly, mechanistic and genetic studies are needed to ascertain any additional upstream and downstream molecules and signals involved in activating inflammasomes and other inflammatory pathways associated with atherosclerosis. A variety of risk factors for CVD such as type 2 diabetes, chronic kidney disease, and clonal hematopoiesis may also be related to atherosclerosis through the inflammasome pathway activation and this also warrants further investigation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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