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The Role of NLRP3 Inflammasome in Cardiovascular Diseases

Jasna Ajduković*

Independent researcher, Sinj, Croatia

***Corresponding author:** Jasna Ajduković, Fratarski prolaz 1, 21230 Sinj, Croatia, Tel: +385917983374; E-mail: jasna.ajdukovic@gmail.com

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Abstract

The inflammasome is a cytosolic protein complex involved in the pathogenesis of atherosclerosis. The NLRP3 inflammasome can be activated by a wide range of stimuli, including intracellular cholesterol crystals The NLRP3 inflammasome is up-regulated within the myocardium after myocardial infarction (MI), primarily in non-cardiomyocytes (i.e. fibroblasts). Its deficiency markedly improves myocardial function and reduces infarct size after *ex vivo* myocardial ischaemia-reperfusion injury I/R. NLRP3 inflammasome is up-regulated in myocardial fibroblasts after MI, potentially contributing to infarct size after myocardial I/R. NLRP3 inhibitors and mechanism of action, Glyburide, Apigenin, Parthenolide, Cysteinyl leukotriene receptor antagonist, Inhibitors of P2X7, Scropolioside B, Cyclooxygenase-2 (COX-2) inhibitors, Intravenous immunoglobulin, Resveratrol, C3a Pt and inhibitors of C3a receptor, Atorvastatin, Zinc, Umbelliferone (UMB), omega-3 fatty acids, Ethanol. Modulation of the inflammasome may represent a unique therapeutic strategy to limit cell death and prevent heart failure after AMI. Inflammasome inhibitors may improve current treatment approach.

Keywords: NLRP3; CAD

Introduction

NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome is a cytosolic protein complex involved in the pathogenesis of atherosclerosis [1,2]. After the endothelial NLRP3 inflammasome is activated by intracellular cholesterol crystals, it directly produces endothelial dysfunction and may initiate or exacerbate vascular injury during hypercholesterolemia [1-3]. In addition, an assembled inflammasome promotes the maturation and release of proinflammatory cytokines interleukin-1β (IL-1 β) and IL-18 [1,4].

IL-1β and IL-18 act as mediators that promote the cascade release of other cytokines. These interleukins have been previously implicated in the pathogenesis of atherosclerosis [5]. Wang et al. [5] found that NLRP3 and downstream cytokines are correlated with the severity of coronary artery disease (CAD).

The NLRP3 inflammasome is up-regulated within the myocardium after myocardial infarction (MI), primarily in non-cardiomyocytes (i.e. fibroblasts). Its deficiency markedly improves myocardial function and reduces infarct size after *ex vivo* myocardial ischaemia–reperfusion (I/R) injury [6]. It was Sandanger [6] who suggested that the NLRP3 inflammasome is up-regulated in myocardial fibroblasts after MI, potentially contributing to infarct size after myocardial I/R.

NLRP3 inhibitors

Glyburide belongs to the class of sulfonylurea agents, which are commonly used in the treatment of type 2 diabetes. Glyburide has a clear NLRP3 inhibitory activity *in vitro*, but to produce the same effect in vivo, it has to be administered in very high doses. As glyburide in high doses is associated with hypoglycemia, its use outside of type 2 diabetes is limited. An NLRP3 inhibitor, 16673-34-0, which is an intermediate substrate free of the cyclohexylurea moiety of glyburide, was shown effective in a model of acute MI not affecting glucose metabolism [4]. 16673-34-0 inhibits the NLRP3 inflammasome *in vitro* and limits NLRP3 inflammasome-mediated injury in a model of acute MI and acute peritonitis in the mouse [7].

Apigenin (4,5,7-trihydroxyflavone) is a non-toxic and non-mutagenic dietary flavonoid, which is abundantly present in common fruits and vegetables, such as oranges, grapefruits, parsley, onions, chamomile, wheat sprouts, and some seasonings. Apigenin specifically targets the oligomerization of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), which is necessary for NLRP3 inflammasome formation, and subsequently inhibits caspase-1 activation in macrophages [8].

Parthenolide is a naturally occurring plant sesquiterpene lactone with multiple anti-inflammatory properties. It has been used extensively as a herbal remedy for a variety of inflammatory diseases, with few and mild side effects. Once activated, the NLRP3 inflammasome causes the activation of caspase-1, which cleaves the precursor proforms of IL-1β and IL-18 into their mature forms. Parthenolide inhibits the activation of caspase-1 in response to NLRP3 [4]. It also directly inhibits NLRP3 by inhibiting its ATPase activity. Another NF-κB inhibitor, Bay 11-7082, which-similar to parthenolide-inhibits NF-κB by blocking IKKβ kinase activity, has also been shown to inhibit the ATPase activity of NLRP3.

The two developed caspase 1 inhibitors are pralnacasan (VX-740) and VX-765 [4].

A cysteinyl leukotriene receptor antagonist developed by Bayer Pharmaceuticals (Bayer AG, Leverkusen, Germany) (Härter et al., US Patent 7,498,460, 200974) was found to inhibit NLRP3 inflammasome-induced IL-1β processing by preventing ASC oligomerization, which is essential for the NLRP3 inflammasome formation [4].

NLRP3 can be activated in response to potassium ion efflux through the ATP-gated P2X7 channel [4]. Inhibitors of P2X7 have been developed and tested in humans. AZD9056, a P2X7 inhibitor, led to a

significant clinical improvement in joint inflammation in patients with rheumatoid arthritis, but oral inhibitors of P2X7 did not seem to be effective in diminishing the disease symptoms [4].

Scropolioside B, isolated from a Tibetan medicine (Scrophularia dentata Royle ex Benth.), and catalpol, a substance similar to scropolioside B, decreased the expression of NLRP3 and cardiolipin synthetase at both the mRNA and protein levels [9].

Cyclooxygenase-2 (COX-2) mediates increase in NLRP3 inflammasome levels. The inhibition of COX-2 in mice *in vivo* with celecoxib reduced IL-1β serum levels and caspase-1 activity in the spleen and liver in response to lipopolysaccharide (LPS) challenge [10].

Levels of NLRP1 and NLRP3 inflammasome proteins, IL-1β and IL-18 were elevated in ipsilateral brain tissues of cerebral I/R mice and stroke patients.

Intravenous immunoglobulin treatment protected brain cells in experimental stroke models by a mechanism involving suppression of NLRP3 inflammasome activity [11].

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is a natural non-flavonoid polyphenolic compound found in the skin of red grapes. Resveratrol is an activator of SIRT1, an enzyme that deacetylates proteins that contribute to cellular regulation. Its activation inhibits the transactivation activity of NF-κB, which suppresses NLRP3 transcription and subsequent IL-1β production. Fu et al. [12] concluded that SIRT1 can effectively regulate the NLRP3 inflammasome.

Complement is activated not only by pathogen associated molecular patterns (PAMPs), but also by damage associated molecular patterns (DAMPs). Proinflammatory complement activation fragments, such as C3a participate in the induction of IL-1 β production because the activation C3a-receptor (C3aR) expressed on monocytes increases ATP efflux, NLRP3 inflammasome activation, and IL-1 β secretion in human monocytes [13]. C3aR inhibition or C3a neutralisation will probably suppress NLRP3 inflammasome activity.

A randomized clinical trial has shown that atorvastatin markedly diminished NLRP3 inflammasome levels, whereas rosuvastatin had no impact on its levels. Atorvastatin down-regulates NLRP3 inflammasome expression in CAD, possibly contributing to the inhibitory effects of atorvastatin on chronic inflammation and atherogenic progression in this disorder [14].

Zinc depletion damages the integrity of lysosomes and this event is important for NLRP3 activation [15].

Korean red ginseng extracts (RGE) inhibited IL-1β maturation resulting from NLRP3 inflammasome activation in both *in vitro* and *in vivo* models. In addition, RGE strongly attenuated IL-1β secretion via pyroptotic cell death by macrophages through inhibition of AIM2 (absent in melanoma 2) inflammasome activation [16].

Wang investigated the effects of coumarin derivate umbelliferone (UMB) in a rat model of focal cerebral ischemia induced by middle cerebral artery occlusion/reperfusion (MCAO/R) and found that UMB treatment suppressed NLRP3 inflammasome [17].

Stimulation of macrophages with omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and other family members, abolished NLRP3 inflammasome activation and inhibited subsequent caspase-1 activation and IL-1 β secretion [1].

In cultured human macrophages, ethanol inhibits NLRP3 inflammasome activation and it may represent a biological pathway underlying the protective effect of moderate alcohol consumption on coronary heart disease [18].

Conclusion

Summary, an inflammasome may initiate or exacerbate vascular injury during atherogenesis in coronary artery disease, where risk factors such as hypercholesterolemia are present [3].

Recent study of one-hundred and twenty-three (123) subjects proved that there is a positive correlation of NLRP3 level with severity of coronary atherosclerosis. NLRP3 showed good predictive value for major adverse cardiac events [19].

Expression of NLRP3 in subcutaneous adipose tissue correlated positively with the severity of coronary atherosclerosis and remains as an independent predictors for the severity of coronary atherosclerosis [20].

Modulation of the inflammasome may represent a unique therapeutic strategy to limit cell death and prevent heart failure after AMI [21]. Some of above mentioned inflammasome inhibitors may improve current treatment approach for patients with cardiovascular diseases.

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