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

Received date: Jul 29, 2015; Accepted date: Sep 7 2015; Published date: Sept 17, 2015

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 Pr 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-1β) 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-kB inhibitor, Bay 11-7082, which similar to parthenolide-inhibits NF-kB 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].

Scopolioside B, isolated from a Tibetan medicine (Scrophularia dentata Royle ex Benth.), and catapul, a substance similar to scopolioside B, decreased the expression of NLRP3 and cardioprotin 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-1β production because the activation C3a-receptor (C3aR) expressed on monocytes increases ATP efflux, NLRP3 inflammasome activation, and IL-1β 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-1β 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.

References

1. Yan Y, Jiang W, Spinetti T, Tardivel A, Castillo R, et al. (2013) Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. Immunity 38: 1154-1163.
2. Peng K, Liu L, Wei D, Lv Y, Wang G, et al. (2015) P2X7R is involved in the progression of atherosclerosis by promoting NLRP3 inflammasome activation. Int J Mol Med 35: 1179-1188.
3. Zhang Y, Li X, Pitzer AL, Chen Y, Wang L, et al. (2015) Coronary Endothelial Dysfunction Induced by Nucleotide Oligomerization Domain-Like Receptor Protein with Pyrin Domain Containing 3 Inflammasome Activation During Hypercholesterolemia: Beyond Inflammation. Antioxid Redox Signal 22:1084-1096.
4. Ozaki E, Campbell M, Doyle SL (2015) Targeting the NLRP3 inflammasome in chronic inflammatory diseases: current perspectives. J Inflamm Res 8: 15-27.
5. Wang L, Qu F, Zhao J, Chang Y (2014) NLRP3 and downstream cytokine expression elevated in the monocytes of patients with coronary artery disease. Arch Med Sci 10: 791-800.
6. Sandander Ø, Ranheim T, Yngre LE, Blikse M, Aifnes K, et al. (2013) The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury. Cardiovasc Res 99: 164-174.
7. Marchetti C, Chojnacki J, Toldo S, Mezzaroma E, Tranchida N, et al. (2014) A novel pharmacologic inhibitor of the NLRP3 inflammasome limits myocardial injury after ischemia-reperfusion in the mouse. J Cardiovasc Pharmacol 63: 316-322.
8. Zhang X, Wang G, Gurlcy EC, Zhou H (2014) Flavonoid apigenin inhibits lipopolysaccharide-induced inflammatory response through multiple mechanisms in macrophages. PLoS One 9: e107072.
9. Zhu T, Zhang L, Ling S, Duan J, Qian F, et al. (2014) Scopolioside B inhibits IL-1β and cytokines expression through NF-κB and inflammasome NLRP3 pathways. Mediators Inflamm 2014: 819053.
10. Hua KE, Chou JC, Ka SM, Tasi YL, Chen A, et al. (2015) Cyclooxygenase-2 regulates NLRP3 inflammasome-derived IL-1β production. J Cell Physiol 230: 863-874.
11. Fann DY, Lee SY, Manzenero S, Tang SC, Gelderblom M, et al. (2013) Intravenous immunoglobulin suppresses NLRP1 and NLRP3
inflammasome-mediated neuronal death in ischemic stroke. Cell Death Dis 4: e790.

12. Fu Y, Wang Y, Du L, Xu C, Cao J, et al. (2013) Resveratrol inhibits ionising irradiation-induced inflammation in MSCs by activating SIRT1 and limiting NLRP-3 inflammasome activation. Int J Mol Sci 14: 14105-14118.

13. Asgari E, Le Friec G, Yamamoto H, Perucha E, Sacks SS, et al. (2013) C3a modulates IL-1β secretion in human monocytes by regulating ATP efflux and subsequent NLRP3 inflammasome activation. Blood 122: 3473-3481.

14. Satoh M, Tabuchi T, Itoh T, Nakamura M (2014) NLRP3 inflammasome activation in coronary artery disease: results from prospective and randomized study of treatment with atorvastatin or rosuvastatin. Clin Sci (Lond) 126: 233-241.

15. Summersgill H, England H, Lopez-Castejon G, Lawrence CB, Luheshi NM, et al. (2014) Zinc depletion regulates the processing and secretion of IL-1β. Cell Death Dis 5: e1040.

16. Kim J, Ahn H, Han BC, Lee SH, Cho YW, et al. (2014) Korean red ginseng extracts inhibit NLRP3 and AIM2 inflammasome activation. Immunol Lett 158: 143-150.

17. Wang X, Li R, Wang X, Fu Q, Ma S (2015) Umbelliferone ameliorates cerebral ischemia-reperfusion injury via upregulating the PPAR gamma expression and suppressing TXNIP/NLRP3 inflammasome. Neurosci Lett 600: 182-187.

18. Nurmi K, Virkanen J, Rajamäki K, Niemi K, Kovanen PT, et al. (2013) Ethanol inhibits activation of NLRP3 and AIM2 inflammasomes in human macrophages—a novel anti-inflammatory action of alcohol. PLoS One 8: e78537.

19. Afrasyab A, Qu P, Zhao Y, Peng K, Wang H, et al. (2015) Correlation of NLRP3 with severity and prognosis of coronary atherosclerosis in acute coronary syndrome patients. Heart Vessels.

20. Bando S, Fukuda D, Soeki T, Nishimoto S, Uematsu E, et al. (2015) Expression of NLRP3 in subcutaneous adipose tissue is associated with coronary atherosclerosis. Atherosclerosis 242: 407-414.

21. Mezzaroma E, Toldo S, Farkas D, Seropian IM, Van Tassell BW, et al. (2011) The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. Proc Natl Acad Sci U S A 108: 19725-19730.