GSL Journal of Cardiovascular Diseases

Global Scientific Library

Short Communication

Regulatory Role of Non-canonical Inflammasomes in Atherosclerosis

Young-Su Yi*

Department of Pharmaceutical Engineering, Cheongju University, Cheongju-28503, South Korea.

Introduction

Inflammation is an innate immune response consisting of a series of complex biological processes to protect our body from the invading pathogens, such as bacteria, viruses, fungi, parasites and protozoan's and cellular danger signals and is characterized by redness, heat, swelling, pain and loss of functions [1,2]. Although inflammation is a host defense mechanism, the repeated and prolonged inflammation, known as chronic inflammation, has been considered as one of the major critical risks to cause a variety of human diseases, including inflammatory autoimmune diseases, cardiovascular diseases, neuronal diseases, degenerative diseases and even cancers [3]. Therefore, enormous efforts have been made to demonstrate the molecular and cellular mechanism of inflammatory responses in inflammatory cells and to develop various strategies modulating inflammatory responses to cure inflammation-mediated human diseases. Inflammatory response is initiated through recognizing Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs) by Pattern Recognition Receptors (PRRs) expressed on the cell surfaces or inside the cells [4]. Traditionally, researches regarding the recognition of PAMPs or DAMPs and the mechanisms of inflammatory responses has largely focused on extracellular PRRs, including toll-like receptors, scavenging receptors and c-type lectins [5]. Recent studies have demonstrated that inflammatory responses are induced by intracellular PRRs, such as nucleotide-binding oligomerization Domain-Like Receptors (NLRs) and Absent in Melanoma 2 (AIM2) inflammasomes as well as caspase-4, -5 and -11 by assembling inflammasomes, an intracellular protein complexes consisting of PRRs and inflammatory effector molecules, such as pro-caspase-1 and an bipartite adaptor molecule, ASC [6,7]. The activation of inflammasomes subsequently induces maturation and activation of pro-caspase-1, resulting in Gasdermin-D (GSDMD)-mediated pyroptosis, an inflammatory form of apoptotic cell death and the secretion of pro-inflammatory cytokines, such as IL-1β and IL-18 [6,7].

Atherosclerosis is a disease in which the inside of an artery narrows due to the buildup of lipid plaques and is known as an inflammatory diseases involving inflammatory responses in arteries. This review provides brief introduction to inflammasomes and discusses recent researches on the regulatory roles of non-canonical inflammasomes in atherosclerosis.

Structures and Activation of Inflammasomes

Canonical Inflammasomes

NLRP1 consists of Pyrin Domain (PYD), a nucleotide-binding and oligomerization domain (NACHT), Leucine-Rich Repeats (LRRs), A Functional-To-Find Domain (FIIND) and Caspase Recruit Domain (CARD) and NLRP1 inflammasome is a complex of NLPR1, ASC and pro-caspase-1 [6]. NLRP1 inflammasome is activated by *Bacillus anthracis* toxin [8]. NLRP3 consists of PYD, a NACHT and LRRs, and NLRP3 inflammasome is a complex of NLRP3, ASC and pro-caspase-1 [6]. NLRP3 inflammasomes is activated by various stimuli, including ATP, nucleic acid hybrids, pore-generating toxins, pathogens, uric acid, silica, alum, β-amyloids, and hyaluronan [6]. NLRC4 consists of CARD, a NACHT and LRRs and is similar in structure with NLRP3, which has a PYD instead of a CARD [6]. NLRC4 inflammasome is a complex of NLRC4 and pro-caspase-1 and is activated by bacterial components, including bacterial flagellin and bacterial needle subunits [9,10]. AIM2 consists of PYD and *hematopoietic* interferon-inducible nuclear protein 200 (HIN200) domain and AIM2 inflammasome is a complex of AIM2, ASC and pro-caspase-1 [6]. AIM2 inflammasome is activated by pathogen-derived double-stranded DNA [11].

Non-canonical Inflammasomes

Unlike canonical inflammasomes, caspase-11 was identified as a non-canonical inflammasome since it activates inflammasome pathway in a way independent on canonical inflammasomes [12]. Caspase-11 consists of CARD, p20 and p10 and caspase-11 inflammasome is a complex of caspase-11 and intracellular Lipopolysaccharide (LPS) derived from Gram-negative bacteria [7]. Caspase-11 was discovered in mice, and recent studies have demonstrated that caspase-4 and -5 are human counterparts of mouse caspase-11 due to their structural similarity to caspase-11 and their ability to interact directly with intracellular LPS [7]. The inflammasomes discussed are summarized in Table 1.

Regulatory Roles of Non-canonical Inflammasomes in Atherosclerosis

Slocum et al. investigated the role of caspase-11 in *Porphyromonas gingivalis*-infected ApoE$^{(-/-)}$ mice and demonstrated that *Porphyromonas gingivalis* induced vascular inflammation and atherosclerosis progression in ApoE$^{(-/-)}$ mice in a caspase-11-dependent manner [13]. Patel et al. also reported that inflammasomes, including caspase-11 were activated during the progression of sterile inflammatory diseases, such as atherosclerosis [14]. Moreover, Suárez **a**nd Buelvas reported that canonical as well as non-canonical inflammasomes are activated during the pathogenesis of various inflammatory diseases, including atherosclerosis, type II diabetes, hyperhomocysteinemia, gout, malaria and hypertension [15]. Regulatory role of non-canonical inflammasome was also investigated in human caspase-4 and -5. Yang et al. demonstrated that Humic Acid (HA) induced atherosclerosis and Endoplasmic Reticulum (ER)-induced cell death by activating caspase-4 [16]. Dihlmann et al. investigated the role caspase-5 on the pathogenesis of Abdominal Aortic Aneurysm (AAA), a vascular disease characterized by apoptosis of vascular smooth muscle cells, increasing fibrosis, extracellular-matrix degeneration and chronic inflammation [17] in AAA patients. They demonstrated that caspase-5 was highly expressed in the sporadic infiltrating lymphoid cells and lymphoid aggregates of AAA patients and the expression level of caspase-5 positively correlated with the rupture risk [18]. Interestingly, inflammasome-positive cells were only found in the cholesterol plaque-associated areas of aortas, which is a hallmark of atherosclerosis [18]. Taken together, these studies strongly suggest that non-canonical inflammasomes play a critical role on the pathogenesis of atherosclerosis by increasing their expression and inducing their activation during inflammatory responses.

***Corresponding author:** Dr. Young-Su Yi, Department of Pharmaceutical Engineering, Cheongju University, Cheongju-28503, South Korea.

Received: February 21, 2018; **Accepted:** March 03, 2018; **Published:** March 07, 2018

Conclusions and Perspectives

Inflammasomes are intracellular protein complexes consisting of PRRs and inflammatory effector molecules and are activated during inflammatory responses and inflammatory diseases. Recent emerging studies have investigated the regulatory roles of non-canonical inflammasomes, such as mouse caspase-11 and human caspase-4 and -5 on the pathogenesis of atherosclerosis, an inflammatory vascular disease and reported that these non-canonical inflammasomes are critical players to induce atherosclerosis by inducing their expression and assembling caspase-4/5/11-LPS complex, as described in Figure 1. Given the strong evidences from these studies, non-canonical inflammasomes could be potential and promising targets to prevent and treat atherosclerosis and other inflammatory vascular diseases.

Categories	PRRs	PRR Domains	Inflammasome constituents	Inflammasome Stimuli
Canonical	NLRP1	PYD NACHT LRRs FIIND CARD	NLRP1 ASC Pro-caspase-1	*Bacillus anthracis* toxin
	NLRP3	PYD NACHT LRRs	NLRP3 ASC Pro-caspase-1	ATP, nucleic acid hybrids, pore-generating toxins, pathogens, uric acid, silica, alum, β-amyloids and hyaluronan
	NLRC4	CARD NACHT LRRs	NLRC4 Pro-caspase-1	*Bacterial flagellins*, needle subunits
	AIM2	PYD HIN200	AIM2 ASC Pro-caspase-1	Pathogen-derived double-stranded DNA
Non-canonical	Mouse caspase-11 Human caspase-4, -5	CARD p20 p10	Pro-caspase-4, -5, -11 LPS	Intracellular LPS

Table 1: Summary of Inflammasomes.

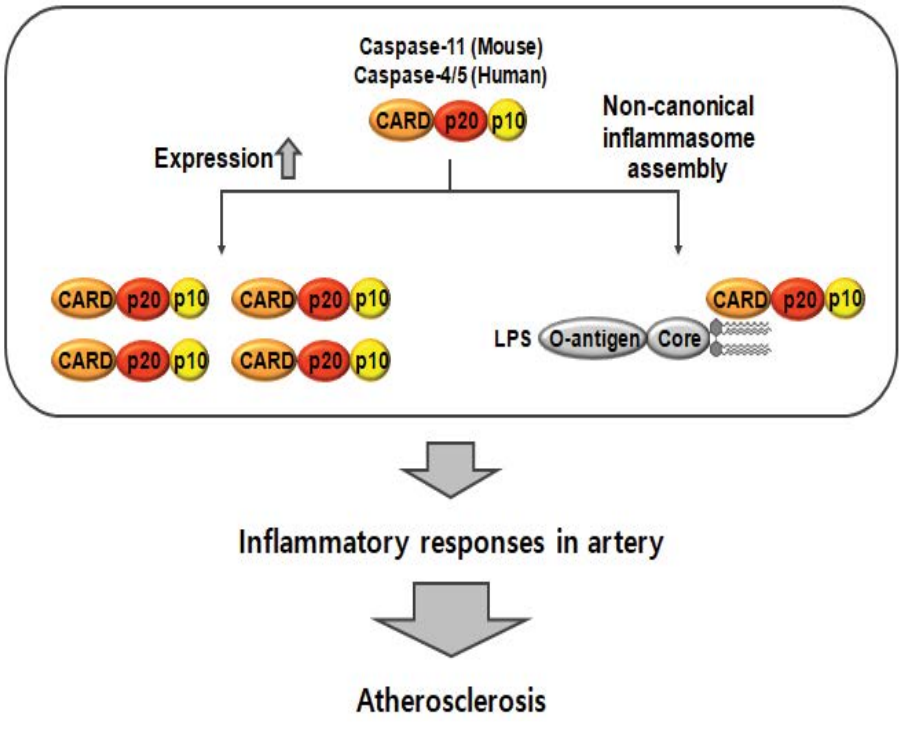

Figure 1. Schematic summary for the activation of non-canonical inflammasomes in the pathogenesis of atherosclerosis.

References

1. Janeway CA, Jr., Medzhitov R. Innate immune recognition. Annu Rev Immunol. 2002; 20: 197-216.
2. Yi YS. Folate Receptor-Targeted Diagnostics and Therapeutics for Inflammatory Diseases. Immune Netw. 2016; 16: 337-343.
3. Kramer CD, Genco CA. Microbiota, Immune Subversion, and Chronic Inflammation. Front Immunol. 2017; 8: 255.
4. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010; 140: 805-820.
5. Pluddemann A, Mukhopadhyay S, Gordon S. Innate immunity to intracellular pathogens: macrophage receptors and responses to microbial entry. Immunol Rev. 2011; 240: 11-24.
6. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol. 2016; 16: 407-420.
7. Yi YS. Caspase-11 non-canonical inflammasome: a critical sensor of intracellular lipopolysaccharide in macrophage-mediated inflammatory responses. Immunology. 2017; 152: 207-217.
8. Boyden ED, Dietrich WF. Nalp1b controls mouse macrophage susceptibility to anthrax lethal toxin. Nat Genet. 2006; 38: 240-244.
9. Miao EA, Alpuche-Aranda CM, Dors M, Clark AE, Bader MW, Miller SI, Aderem A. Cytoplasmic flagellin activates caspase-1 and secretion of interleukin 1beta via Ipaf. Nat Immunol. 2006; 7: 569-575.
10. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, Roose-Girma M, Erickson S, Dixit VM. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature. 2004; 430: 213-218.
11. Lugrin J, Martinon F. The AIM2 inflammasome: Sensor of pathogens and cellular perturbations. Immunol Rev. 2018; 281: 99-114.
12. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, Newton K, Qu Y, Liu J, Heldens S, Zhang J, Lee WP, Roose-Girma M, Dixit VM. Non-canonical inflammasome activation targets caspase-11. Nature. 2011; 479: 117-21.
13. Slocum C, Coats SR, Hua N, Kramer C, Papadopoulos G, Weinberg EO, Gudino CV, Hamilton JA, Darveau RP, Genco CA. Distinct lipid a moieties contribute to pathogen-induced site-specific vascular inflammation. PLoS Pathog. 2014; 10: e1004215.
14. Patel MN, Carroll RG, Galvan-Pena S, Mills EL, Olden R, Triantafilou M, Wolf AI, Bryant CE, Triantafilou K, Masters SL. Inflammasome Priming in Sterile Inflammatory Disease. Trends Mol Med. 2017; 23: 165-180.
15. Suarez R, Buelvas N. [Inflammasome: activation mechanisms]. Invest Clin. 2015; 56: 74-99.
16. Yang HL, Huang PJ, Chen SC, Cho HJ, Kumar KJ, Lu FJ, Chen CS, Chang CT, Hseu YC. Induction of macrophage cell-cycle arrest and apoptosis by humic acid. Environ Mol Mutagen. 2014; 55: 741-750.
17. Michel JB, Martin-Ventura JL, Egido J, Sakalihasan N, Treska V, Lindholt J, Allaire E, Thorsteinsdottir U, Cockerill G, Swedenborg J. Novel aspects of the pathogenesis of aneurysms of the abdominal aorta in humans. Cardiovasc Res. 2011; 90: 18-27.
18. Dihlmann S, Erhart P, Mehrabi A, Nickkholgh A, Lasitschka F, Bockler D, Hakimi M. Increased expression and activation of absent in melanoma 2 inflammasome components in lymphocytic infiltrates of abdominal aortic aneurysms. Mol Med. 2014; 20: 230-237.

Citation: Young-Su Yi. Regulatory Role of Non-canonical Inflammasomes in Atherosclerosis. GSL Cardiovasc Dis 2018; 1:104.