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Review

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Importance of NLRP3 Inflammasome in Abdominal Aortic Aneurysms

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Abdominal aortic aneurysm (AAA) is a chronic inflammatory degenerative aortic disease, which particularly affects older people. Nucleotide-binding oligomerization domain-like receptor family protein 3 (NLRP3) inflammasome is a multi-protein complex and mediates inflammatory responses by activating caspase 1 for processing premature interleukin (IL)-1β and IL-18. In this review, we first summarize the principle of NLRP3 inflammasome activation and the functionally distinct classes of small molecule NLRP3 inflammasome inhibitors. Next, we provide a comprehensive literature review on the expression of NLRP3 inflammasome effector mediators (IL-1β and IL-18) and components (caspase 1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and NLRP3) in clinical and experimental AAAs. Finally, we discuss the influence of genetic deficiency or pharmacological inhibition of individual effector mediators and components of NLRP3 inflammasome on experimental AAAs. Accumulating clinical and experimental evidence suggests that NLRP3 inflammasome may be a promise therapeutic target for developing pharmacological strategies for clinical AAA management.

Key words: **Abdominal aortic aneurysm, Inflammasome, NLRP3, Interleukin-1, Interleukin-18**

Introduction

Abdominal aortic aneurysm (AAA) is a life-threatening degenerative disease that is characterized by progressively localized dilatation of abdominal aorta, particularly infrarenal aorta. Advanced age, male sex, smoking, white race, hypertension, and hyperlipidemia increase the risk for AAAs, whereas female sex, black race, and diabetes reduce it[1-3]. There is a race difference in AAA prevalence, with high in Northern American and European and low in Asian[4, 5]. There is currently no effective pharmacological therapy available for AAAs, and patients are mainly treated with open or endovascular surgical repair as recommended by the Society for Vascular Surgery[6] and National Institute of Health and Care Excellence guideline for abdominal aortic aneurysm: diagnosis and management (https://www.nice.org.uk/ guidance/ ng156). Understanding of AAA pathogenesis will help establish nonsurgical pharmacological treatment for AAA disease.

Although AAA pathogenesis is not completely understood, inflammation has been shown to play a critical role. The major mechanisms include smooth muscle cell loss due to apoptosis[7, 8], accelerated extracellular matrix degradation resulting from imbalanced metalloproteinases and its tissue inhibitors[9-11], increased levels and activity of renin-angiotensin (Ang) system[12-16], augmented oxidative tissue damage[17], dysregulated immune cell-derived pro- and anti-inflammatory mediators[18-23], increased mural angiogenesis[24-30], altered hemodynamics and homeostasis[31-33], and increased genetic susceptibility[31-33].

Inflammasome is a multi-protein complex that is composed of an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), caspase 1, and nucleotide-binding oligomerization domain-like receptor family proteins (NLRPs) such as NLRP3 or HIN200 family proteins[34, 35]. Recognizing by pathogen-associated

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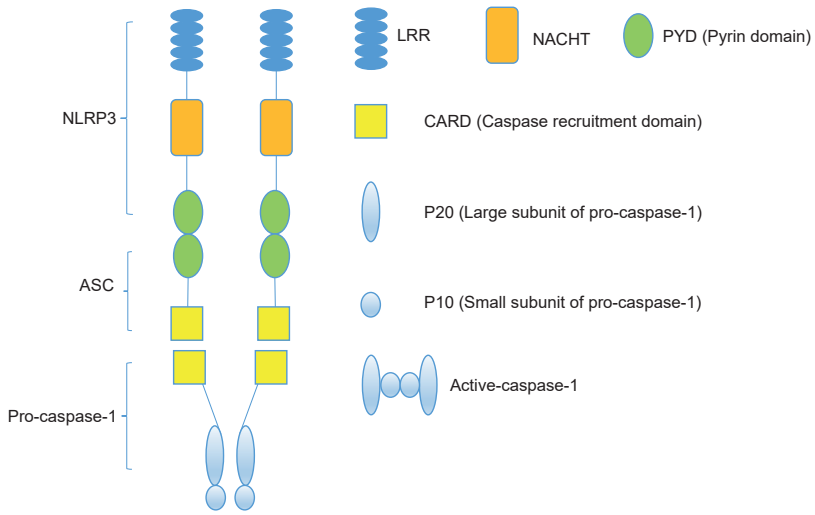

Fig. 1. NLRP3 inflammasome structure

NLRP3 inflammasome is a protein complex composing of ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), pro-caspase-1, and NLRP3 protein. NLRP3 protein recruits ASC through the interaction of N-terminal PYD-PYD. ASC connects NLRP3 protein with pro-caspase-1 through PYD-PYD and CARD-CARD to form a pro-caspase-1 tetramer, which provides caspase 1 with enzyme cutting activity. LRR, leucine-rich repeat. NACHT/NOD, nucleotide-binding oligomerization domain.

molecular patterns or damage-associated molecular patterns, it activates caspase 1 for processing inactive interleukin (IL)-1β or IL-18 to its active form for innate immune response. NLRP3 inflammasome has been known to participate in many pathological conditions including cardiovascular diseases[36-39].

NLRP3 Inflammasome

NLRP3 inflammasome is one of the well-characterized inflammasomes, with three major components: NLRP3 receptor protein, ASC adapter protein, and caspase 1 effector protein **(Fig. 1)**[34, 35]. NLRP3 protein contains one leucine-rich repeat for ligand recognition, one nucleotide-binding oligomerization domain with ATPase activity for nucleic acid binding and self-oligomerization, and one pyrin domain for ASC binding. ASC protein composes of one pyrin domain and one caspase recruitment domain. Once NLRP3 inflammasome is activated, ASC binds to NLRP3 protein through the pyrin domain for recruiting and activating caspase 1 via caspase recruitment domain.

There are two signals required for NLRP3 inflammasome activation[34, 35] **(Fig. 2)**: Signal 1 (priming) activates NF-κB pathway through toll-like receptors, leading to the mRNA expression of IL-1β, IL-18, and NLRP3-related genes, and signal 2 (activation) such as damage- and pathogen-associated molecular patterns assembles NLRP3 inflammasome and activates caspase 1. Several potential mechanisms have been proposed for NLRP3 activation. In potassium efflux model, extracellular ATP activates purine-type membrane receptor P2X7, results in potassium efflux, and consequently reduces intracellular potassium levels, thus activating NLRP3 inflammasome[40]. Alternatively, certain crystalline or particulate matter enters cells and leads to lysosome rupture, which releases cathepsin B for NLRP3 inflammasome activation[41-43]. Interaction of mitochondria-derived reactive oxygen species (ROS) with thioredoxin-interacting protein is also able to trigger NLRP3 inflammasome activation. In addition, calcium influx also plays a role in NLRP3 inflammasome activation. All these mechanisms are not exclusive and may work together. For example, calcium influx results in mitochondrial ROS production, while lysosomal rupture promotes calcium influx[44, 45].

NLRP3 Inflammasome Inhibitors

Given the critical importance of NLRP3 inflammasome in a broad spectrum of inflammatory and degenerative diseases, to therapeutically target NLRP3 inflammasome, functionally distinct classes of NLRP3 inhibitors have been discovered. This has been the subject of several outstanding recent review articles[34, 46-49]. NLRP3 inflammasome inhibitors target either signal 1 or signal 2. As one of signal 1 inhibitors, Bay 11-7082 inhibits transcription of IL-1β and IL-18 by blocking IKKb kinase and NF-kB signaling pathway[47, 50]. JC124 suppresses the expression of IL-1β, NLRP3, ASC, and caspase 1[51].

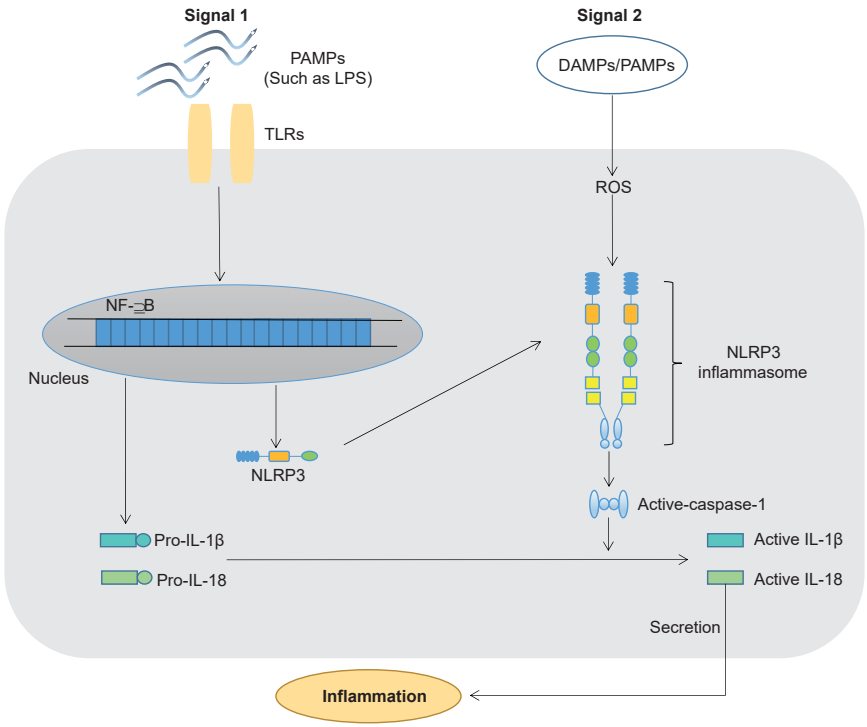

Fig. 2. Two signals are required for NLRP3 inflammasome activation

Signaling pathway. Signal 1: Toll-like receptors (TLRs) bind their cognate ligands such as lipopolysaccharides (LPS), trigger NF-κB signaling pathway, and ultimately lead to the expression of pro-IL-18, pro-IL-1β, and NLRP3 protein. Signal 2: DAMP (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) are recognized by NLRP3, causing NLRP3-ASC-pro-caspase-1 inflammasome assembly and activation, which convert inactive caspase 1 to active caspase 1 and subsequently cleaves pro-IL-18 or pro-IL-1β to corresponding active form.

Most inhibitors have however been designed to target signal 2, including upstream inducers (ion fluxes, mitochondrial ROS, nondegradable particles, and lysosomal proteinase cathepsin B), NLRP3 complex components (ASC and caspase 1), and NLRP3 per se[47, 48]. β-hydroxybutyrate inhibits NLRP3 inflammasome by blocking potassium efflux[52, 53], whereas both 5-nitro-2-(3-phenylpropylamino) benzoic acid, 4,4'-diisothiocyano-2,2'-disbenedisufonic acid, and IAA94 inhibit NLRP3 by disrupting chloride efflux[48]. Blockage of calcium mobilization by 2-APB, XeC, and U73122, the reduction of mitochondrial ROS by N-acetyl-L-cysteine and (2R,4R)-4-aminopyrro lidine-2,4-dicarboxylate, and the prevention of lysosomal rupture by a specific inhibitor to cathepsin, CA-074-Me, all inhibit NLRP3 inflammasome[48]. Inhibition of caspase 1 by VX-740 and VX-756 or the conversion of pro-caspase-1 to active caspase 1 by FC11A-2 also results in the inhibition of NLRP3 inflammasome[47, 48].

More important and specific inhibitors to NLRP3 inflammasome are those that directly inhibit NLRP3 activity, oligomerization, or interaction of NLRP3 with other complex components. For example, MCC950, CY-09, OLT1177/dapansutrile, MNS, and parthenolide inhibit NLRP3 by inhibiting its ATPase activity or modifying its ATPase domain[38, 48, 54-57]. Blocking NLRP3-MEK7 by oridonin via binding to NLRP3 cysteine 279 or NLRP3 oligomerization by tranilast specifically inhibits NLRP3 inflammasome[58]. Glyburide also inhibits NLRP3 inflammasome by inhibiting ATP-sensitive potassium channel and thus disturbs ASC aggregation[59]. Resveratrol inhibits the assembly of ASC and NLRP3[60]. Targeting molecules that interact with either NLRP3 or ACS represent alternative approaches for alternative inhibitor discovery[48].

Additional avenues for targeting inhibition of NLRP3 inflammasome activity are to specifically inhibit its effector mediators. These include IL-1β, IL-18, their receptors, or receptor antagonist as represented by two humanized anti-IL-1β monoclonal antibodies (canakinumab and gevokizumab) and two IL-1 receptor antagonists (anakinra and rilonacept)[36, 37].

Among NLRP3 inflammasome inhibitors, some are currently used for treating certain medical

conditions with proved safety. For example, glyburide and its analogs are used to treat type 2 diabetes, while tranilast is an approved drug for treating allergic diseases in China, Korea, and Japan. Resveratrol is commercially available as a nutritional supplement. A large number of clinical trials have been registered to test the safety and efficacy of functionally distinct classes of NLRP3 inflammasome inhibitors for various inflammatory diseases through https://clinicaltrials.gov or alternative clinical organizations. In one open-label, dose-adaptive, proof-of-concept phase II trial, dapansutrile has been shown to safely and effectively reduce joint pain in patients with goat flare[61]. In another trial, dapansutrile will be tested for treatment of moderate COVID-19 symptoms and early cytokine syndrome (https://clinicaltrials.gov). Several clinical trials have also completed or are undergoing to test the therapeutic efficacy of canakinumab, gevokizumab, anakinra, and rilonacept for treating several cardiovascular diseases such as certain type of heart failure and acute myocardial infraction[36].

Expression of NLRP3 Inflammasome Effector Mediators (IL-1β and IL-18) in AAAs

In clinical AAAs, it has been reported that serum IL-1β levels were elevated in AAA patients as compared to healthy controls and patients with coronary heart disease[62]. High plasma levels of IL-1β were observed in participants who had homozygous for common C allele of NLRP3 rs35829419 but not polymorphisms of any IL-1 gene cluster[63, 64]. However, Batra *et al.* reported detectable levels of serum IL-1β in non-aneurysmal patients, but not aneurysmal patients. In aortic tissues from aneurysmal patients, most studies have shown that IL-1β mRNA and protein levels were higher in aneurysmal patients than those in non-aneurysmal patients[65-71]. The mRNA and protein levels of IL-18, another NLRP3 inflammasome effector mediator, were also increased in the aortae of patients with AAAs as compared to non-aneurysmal controls[72, 73].

Consistent with the findings in clinical AAAs, IL-1β mRNA and protein levels were markedly increased in aneurysmal mice created by intra-aortic elastase infusion or adventitial calcium painting in normolipidemic mice, subcutaneous Ang II infusion, or alternative technique[65, 74-77]. Elevated aortic IL-1β protein levels were also noted in hyperhomocysteinemia-accelerated experimental AAAs[78]. Both aortic macrophages and smooth muscle cells have been identified as major sources for increased expression of IL-1β[74, 78]. IL-1β levels were also significantly higher in aneurysmal mice than those in non-aneurysmal mice in Ang II-induced AAAs[74]. In addition, increased aortic IL-18 mRNA and protein abundance have been shown in AAAs induced by combined use of Ang II and β-aminopropionitrile[79]. In summary, both clinical and experimental data support elevated levels of NLRP3 inflammasome effector mediators in AAA disease.

Expression of NLRP3 Inflammasome Components in AAAs

ASC, caspase 1, and NLRP3 are key elements in NLRP3 inflammasome complex. Analysis of 100 patients with vascular diseases, including 34 AAA patients, revealed high mRNA expression levels of ASC, caspase 1, and NLRP3 in peripheral mononuclear cells from male patients as compared to female patients; it was however unknown whether this difference was associated with increased risk for AAAs in males[68]. The mRNA levels for caspase 1 and NLRP3 were higher in male AAA patients than those in non-AAA patients, but reduced protein levels were only noted for NLRP3 [68]. In another study, both NLRP3 and ASC protein levels, as assessed by flow cytometric analysis, were higher in circulating granulocytes and monocytes in AAA patients than those in non-AAA controls, but the differences did not reach statistical significance[80].

In aneurysmal aortae, an early study by Schonbeck *et al.* showed increased aortic protein levels of caspase 1 in AAA patients as compared to non-AAA patient controls. NLRP3 mRNA levels were increased in the aortae of aneurysmal patients as compared to occlusive aortic disease and healthy controls[81]. In another study analyzing aortae from 46 aneurysmal patients and 40 healthy organ donors[82], more NLRP3-positive staining was noted in the aortae from aneurysmal patients as compared to non-AAA patient controls, with no difference in ASC and caspase 1 staining between two patient groups. However, NLRP3 expression levels were inversely associated with inflammation pathological grade, implying that NLRP3 inflammasome may be an early event in AAA pathogenesis[82]. In addition, smooth muscle cells from AAA patients had an increased ability to express NLRP3 and caspase 1 in response to necrotic cell debris[83].

In contrast, studies on the expression of NLRP3 inflammasome components are limited for experimental AAAs. In Ang II-induced AAAs, ASC was highly expressed in adventitial macrophages[74]. Increased active caspase 1 was also elevated in Ang II-induced aneurysmal aorta[84]. Furthermore, NLRP3 and active caspase 1 were also detected in aneurysmal aorta in calcium chloride AAA model and further augmented by hyperhomocysteinemia[78]. Although

evidence from experimental AAAs is limited, a large body of evidence from clinical AAA studies has demonstrated increased expression of NLRP3 inflammasome components in aneurysmal lesion or immune cells.

Influence of Inflammasome Effector Mediators on Experimental AAAs

Several studies have been conducted to investigate the role of two NLRP3 inflammasome effector cytokines, IL-1β and IL-18, in AAA pathogenesis using rodents deficient for IL-1β, IL-18 or its cognate receptor, or pharmacological inhibitors **(Table 1)**. In mice deficient for IL-1β or IL-1 receptor, or treated with IL-1 receptor blocker anakinra, Johnston *et al.* reported attenuation of aneurysmal aortic enlargement and accumulation of macrophages and neutrophils following intra-aortic elastase infusion[65]. In these experimental settings, AAA suppression was associated with reduced expression levels or activity of CC-motif chemokine ligand 2, IL-6, complement C5a, and matrix metalloproteinase (MMP) 9. A recent study by Meker *et al.* reported that IL-1β mediated AAA disease by promoting neutrophil extracellular trap formation[69]. In a special form of AAAs associated with Kawasaki disease induced by *Lactobacillus casei* cell wall extract injection, AAAs were suppressed in mice deficient for IL-1α, IL-1β, or IL-1 receptor or treated with an antibody against IL-1α, IL-1β, or IL-1 receptor[77]. Conversely, Ang II-induced AAAs were accelerated in high fat diet fed mice deficient for IL-1 receptor antagonist and counteracted following IL-1β antibody injection[85].

Two recent studies have further demonstrated the significance of IL-18 in experimental AAAs. In Ang II/β-aminopropionitrile (lysyl oxidase inhibitor)-induced AAA model[79], genetic deficiency of IL-18 suppressed aneurysmal aortic expansion and lowered AAA incidence in association with reduced aortic CD68-positive macrophage infiltration, pro- and active MMP levels, and osteopontin. IL-18 deficiency also resulted in a switch from proinflammatory M1 macrophage activation toward anti-inflammatory M2 macrophage activation as indicated by reduced ratio of CD11c-positive to CD206-positive macrophages in aneurysmal aorta. Similarly, deficiency of either receptor for IL-18, IL-18 receptor or Na-Cl cotransporter, also suppressed Ang II-induced AAAs in ApoE-deficient hyperlipidemic mice as evidenced by reduced aortic diameter expansion and active MMP2 and MMP9[73]. In these experimental settings, adipocytes have been shown to promote IL-18 function by inducing the expression of leptin and fatty acid-binding protein 4. Together, accumulating evidence from recently published studies supports the importance of both mediators in AAA disease using various AAA modeling systems.

Two studies, however, have failed to demonstrate the contribution of IL-1 to experimental AAAs. In an early study, treatment with anti-IL-1 receptor antagonist was not effective in suppressing elastase-induced AAAs in rats[86]. In experimental AAAs created by topical application of calcium chloride, deficiency of IL-1β or IL-1 receptor had no remarkable impact on AAA formation, although it decreased MMP expression levels[75].

Influence of Genetic NLRP3 Inflammasome Component Deficiency on Experimental AAAs

Processing pro-IL-1β and pro-IL-18 to their active forms can also be mediated by other inflammasomes rather than NLRP3. As shown in **Table 2**, mice with genetic deficiency of individual NLRP3 inflammasome components have contributed to our understanding of NLRP3 inflammasome in AAA pathogenesis. In Ang II infusion/ApoE-deficient AAA model, whole-body ablation of NLRP3, ASC, or caspase 1 reduced aneurysm incidence, attenuated aneurysmal aortic enlargement, and preserved medial elastin and smooth muscle cells[74]. Similarly, AAA suppression has also been confirmed in high fat diet fed NLRP3- or caspase 1-deficient mice following chronic Ang II infusion[87]. In Kawasaki disease-associated AAAs, deficiency of NLRP3 or caspase 1 also led to AAA suppression[77]. In addition, topical application of lentivirus siRNA to aortic wall abrogated AAAs in alternative calcium AAA model[78]. Altogether, these genetic studies provide solid evidence for NLRP3 inflammasome in AAA pathogenesis.

Influence of Pharmacological NLRP3 Inflammasome Inhibition on Experimental AAAs

Table 3 summarizes published studies on the influence of various NLRP3 inflammasome inhibitors on experimental AAAs. Yamanouchi D *et al.* have shown that treatment with Q-Vd-OPh, a pan-caspase inhibitor, inhibited Ang II infusion-induced aneurysmal aortic enlargement and reduced AAA incidence in ApoE-deficient mice. The AAA suppression was accompanied by attenuation of aortic macrophage infiltration, smooth muscle cell apoptosis, and CCL2-mediated macrophage migration[88]. Administration of tranilast has been shown to suppress calcium chloride-induced AAAs in association with preservation of medial elastin, attenuation of mural mast cells and lymphocytes, reduced neoangiogenesis, and reduced MMP9 activity[89]. Treatment with

Table 1. Influence of genetic deficiency or pharmacological inhibition of inflammasome effector mediators on experimental AAAs

Mouse strain	AAA model	Gene knockout or pharmacological inhibitor	Influence on experimental AAAs	References
C57BL/6	Elastase infusion	IL-1$\beta^{-/-}$, IL-1R$^{-/-}$ or anakinra treatment	•Attenuated AAA formation and reduced aortic macrophages and neutrophils	[65] Johnston WF *et al.* Arterioscler Thromb Vasc Biol 33: 294-304, 2013.
C57BL/6	Lactobacillus casei cell-wall extracts	IL-1$\alpha^{-/-}$, IL-1$\beta^{-/-}$, or treatment with an antibody to IL-1α IL-1β	•Protected AAA formation	[77] Wakita D *et al.* Arterioscler Thromb Vasc Biol 36: 886-897, 2016.
C57BL/6	Calcium chloride	IL-1$\beta^{-/-}$, IL-1R$^{-/-}$	•No influence on AAA formation and proinflammatory macrophage polarization	[75] Batra R *et al.* Arterioscler Thromb Vasc Biol 38: 457-463, 2018.
C57BL/6	Elastase infusion	IL-1$\beta^{-/-}$	•Reduced elastase-induced aortic diameter enlargement and aortic neutrophil infiltration •Transferring wild type neutrophils restored aneurysmal aortic expansion in IL-1β knockout mice	[69] Meher AK *et al.* Arterioslcer Thromb Vasc Biol 38: 843-853, 2018.
C57BL/6	Ang II infusion	IL-1Ra$^{-/-}$	•Increased aneurysmal aortic diameter and aneurysm rupture •Elevated inflammatory cytokines (IL-6 and TNF-α) and matrix metalloproteinases (MMP2 and MMP9) production •Promoted smooth muscle degradation and macrophage infiltration •Anti-IL-1β antibody treatment inhibited aortic dilation and inflammation in Ang II-infused IL-1Ra$^{-/-}$mice	[85] Isoda K *et al.* Int J Cardiol 270: 221-227, 2018.
C57BL/6	Ang II infusion and treatment with β -aminopropionitrile	IL-18$^{-/-}$	•Reduced aneurysm diameter and rupture •Reduced macrophage infiltration and phenotype switch towards anti-inflammatory macrophages •Inhibited OPN-induced inflammation and matrix metalloproteinases activation	[79] Suehiro C *et al.* Atherosclerosis 289: 14-20, 2019.
ApoE$^{-/-}$	Ang II infusion	NCC$^{-/-}$ or IL-18R$^{-/-}$	•Attenuated aneurysmal aortic dilation and reduced aneurysm rupture •Reduced inflammatory cell infiltration and the levels of MMP2, MMP9, IL-6, IFN-γ and TNF-α	[73] Liu CL *et al.* Eur J Heart 41: 2456-2468, 2020.

AAA: Abdominal aortic aneurysm. Ang II: Angiotensin II. ApoE: Apolipoprotein E. IFN: Interferon. IL: Interleukin. IL-1Ra: IL-1 receptor antagonist. MMP: Matrix metalloproteinase. R: Receptor. TNF: Tumor necrosis factor. NCC: Na-Cl co-transporter. OPN: Osteopontin. -/-: Deficient mice

MCC950 also inhibited the development of aortic aneurysms at various aortic segments, including abdominal aorta, in conjunction with reduced expression levels of NLRP3, caspase 1, and MMPs and preserved contractible proteins of smooth muscle cells[84]. Treatment with glyburide also reduced AAA formation induced by Ang II[87], potentially associated with AAA inhibition in diabetic patients[90-92]. Treatment with glucagon-like peptide receptor agonist suppressed elastase infusion-induced AAAs in rats by reducing ROS production and aortic inflammatory response[93]. Sitagliptin, a dipeptidyl peptidase-4

Table 2. Effect of genetic deficiency of individual NLRP3 inflammasome components on experimental AAAs

Mouse strain	AAA model	Gene knockout	Influence on experimental AAAs	References
ApoE$^{-/-}$	Ang II infusion	NLRP3$^{-/-}$, ASC$^{-/-}$, or caspase-1–/–	•Reduce AAA severity, aortic inflammatory cell infiltration and the serum levels of IL-1β, MMP2, MMP9	[74] Usui F *et al.* Arterioscler Thromb Vasc Biol 35: 127-136, 2015.
ApoE$^{-/-}$	Ang II infusion and homocysteine diet	Lentivirus-mediated NLRP3 silencing	•Reduced aneurysmal aortic diameter and severity •Downregulated the expression levels of aortic inducible nitric oxide synthase and myofibroblast markers •Reduced aortic MMP9 activity	[78] Sun W *et al.* J Mole Cell Cardiol 81: 96-106, 2015.
C57BL/6	Lactobacillus casei cell-wall extract injection	Caspase-1$^{-/-}$ or NLRP3$^{-/-}$	•Prevented AAA formation	[77] Wakita D *et al.* Arterioscler Thromb Vasc Biol 36: 886-897, 2016.
C57BL/6	Ang II infusion and high fat diet	Caspase-1$^{-/-}$ or NLRP3$^{-/-}$	•Reduced aneurysm incidence and maximal diameter •Degraded aortic contractile proteins	[87] Wu D *et al.* Arterioscler Thromb Vasc Biol 37: 694-706, 2017.

AAA: Abdominal aortic aneurysm. Ang II: Angiotensin II. ApoE: Apolipoprotein E. ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain. IL: Interleukin. MMP: Matrix metalloproteinase. -/-: Deficient mice

inhibitor, prevented the formation and progression of AAAs by increasing glucagon-like peptide[94-97]. Resveratrol has also been reported to suppress AAA formation in Ang II, elastase, and/or calcium models[98-100].

All published studies were to evaluate the preventive effect of pharmacological NLRP3 inhibitor on AAAs by administering inhibitors prior to AAA induction. It has not been investigated whether NLRP3 inhibition is effective in limiting the progression of existing small experimental AAAs, which is more clinically relevant. In addition, most studies have also been performed in Ang II-induced AAAs in hyperlipidemic animals, which is primarily initiated and driven by aortic dissection. Thus, it warrants more validating studies in non-dissection AAA models such as intra-aortic elastase infusion model or alternatives.

Conclusions

In summary, clinical and experimental evidence supports the critical importance of NLRP3 inflammasome in AAA pathogenesis. Thus, pharmacologically targeting NLRP3 inflammasome activity may provide a novel translational application for clinically treating small AAA disease.

Conflicts of Interest

All authors declare no conflicts of interest to this work.

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Author Contributions

SJY performed PubMed search and literature review and wrote manuscript draft. ZDL performed literature review and drafted manuscript. JG, XBH and MM designed the work and finalized manuscript. All authors approved manuscript contents for final submission.

Abbreviations

AAA: Abdominal aortic aneurysm
Ang: Angiotensin
ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain
IL: Interleukin
NF-kB: Nuclear factor kappa B
NLRP: Nucleotide-binding oligomerization domain-like receptor family protein
ROS: Reactive oxygen species
COVID: Coronavirus disease

Table 3. Influence of pharmacological NLRP3 inflammasome inhibition on experimental AAAs

Animal species and strain	AAA model	Intervention	Influence on experimental AAAs	References
Wild type Sprague-Dawley rats	Calcium chloride	NLRP3 inhibitor (Tranilast)	•Reduced aneurysmal aortic dilation and preserved medial elastin •Attenuated aortic infiltration of mast cells and T cells •Reduced aortic MMP activity	[89] Tsuruda T *et al.* Circ Res 102: 1368-1377, 2008.
ApoE$^{-/-}$ mice	Ang II infusion	Pan-caspase inhibitor (Quinoline-Val-Asp difluorophenoxymethylketone)	•Reduced aneurysm diameter and incidence •Inhibited cell apoptosis and reduced macrophage infiltration	[88] Yamanouchi D *et al.* Arterioscler Thromb Vasc Biol 30: 702-707, 2010.
Wild type C57BL/6 mice	Calcium chloride	ROS scavenger (Resveratrol)	•Inhibited AAA formation •Reduced inflammatory cell infiltration and aortic expression of MMPs, MCP-1 and TNF-α	[99] Kaneko H *et al.* Atherosclerosis 217: 350-367, 2011.
Wild type Sprague-Dawley rats	Elastase infusion	ROS scavenger (Resveratrol)	•Reduced aneurysmal size •Reduced systemic and aortic levels of TNF-α and MMP9 •Reduced circulating L-selectin-expressing monocytes and aortic macrophages	[100] Palmieri D *et al.* J Surg Res 171: e237-e246, 2011.
ApoE$^{-/-}$ mice	Ang II infusion	Dipeptidyl peptidase-4 inhibitor (sitagliptin)	•Inhibited AAA formation, reduced aortic inflammation and preserved elastin lamina	[94] Lu HY *et al.* Plos One 10: e0121077, 2015.
ApoE$^{-/-}$ mice	Ang II infusion and high fat diet	Dipeptidyl peptidase-4 inhibitor (MK0626)	•Reduced aneurysm diameter and incidence •Reduced aortic IL-1β mRNA levels but increased aortic TIMP-2 mRNA levels	[96] Kohashi K *et al.* J Atheroscler Thromb 23: 441-454, 2016.
Wild type Sprague-Dawley rats	Intra-aortic Elastase infusion and abluminal calcium chloride application	Glucagon-like peptide 1 receptor analog (lixisenatide)	•Attenuated aneurysmal aortic dilation and macrophage infiltration but increased aortic elastin contents •Reduced aortic ROS production, oxidative DNA damage and ERK phosphorylation •Reduced the aortic mRNA levels of MMP9 and TNF-α	[93] Yu J *et al.* Surgery Today 46: 1099-1107, 2016.
Wild type C57BL/6 mice	Ang II infusion and high fat diet	NLRP3 inhibitor (Glyburide)	•Reduce aneurysmal aortic diameter, aneurysm incidence and elastin destruction	[87] Wu D *et al.* Arterioscler Thromb Vasc Biol 37: 694-706, 2017.
ApoE$^{-/-}$ mice	Ang II infusion and high fat diet	ROS scavenger (Resveratrol)	•Reduced aneurysmal aortic diameter •Increased the expression levels of aortic ACE2 and SIRT1 •Reduced the phosphorylation of AKT1 and ERK1/2 as well as the expression levels of Ang II type-1 receptor, MMP2 and MMP9	[98] Moran CS *et al.* Arterioscler Thromb Vasc Biol 37: 2195-2203, 2017.
ApoE$^{-/-}$ mice	Ang II infusion and high fat diet	Dipeptidyl peptidase-4 inhibitor (teneligliptin)	•Suppressed aneurysmal aortic expansion, reduced aneurysm severity, and lowered aneurysm incidence •Attenuated medial elastin degradation and macrophage infiltration •Reduced MMP activity, the phosphorylation of AKT and ERK and IL-6 mRNA levels in aneurysmal aorta	[97] Takahara Y *et al.* J Atheriosclerosis Thromb 25: 698-708, 2018.
Wild type C57BL/6 mice	Ang II infusion and high fat diet	NLRP3 inhibitor (MCC950)	•Reduced aortic diameter, aneurysm/dissection rate and macrophage accumulation •Reduced aortic expression of active IL-1β and caspase 1 as well as MMP activity	[84] Ren P *et al.* J am Heart Assoc 9: e014044, 2020.

AAA: Abdominal aortic aneurysm. ACE2: Angiotensin-converting enzyme 2. AKT1: Rac-alpha serine/threonine-protein kinase or protein kinase B. Ang II: Angiotensin II. ApoE: Apolipoprotein E. ERK: Extracellular-signal-regulated kinase. IL: Interleukin. MMPs: Matrix metalloproteinases. MCP: Monocyte chemotactic protein. ROS: Reactive oxygen species. SIRT1: Silent mating type information regulation 2 homolog 1. TNF: Tumor necrosis factor. -/-: Deficient mice

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