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Review

NLRP3 inflammasome as a treatment target in atherosclerosis: A focus on statin therapy

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ABSTRACT

Activation of NOD-like receptor (NLR) family and pyrin domain containing 3 (NLRP3) inflammasome contributes to inflammation and may lead to atherosclerosis. The NLRP3 inflammasome as a molecular platform regulates the activation of ATP signaling, K^+ efflux, cathepsin-B activity, lysosomal function and pro-inflammatory cytokines (i.e. IL-1β and IL-18). Statins has been widely prescribed for the treatment of hyperlipidemia and cardiovascular diseases. In addition to lipid-lowering effect, statins have immunomodulatory, anti-inflammatory, antioxidant and antiapoptotic functions. An increasing number of studies indicated NLRP3 inflammasome and their downstream mediators as important targets for statin drugs in inflammatory diseases. In this review, we discussed different aspect of the NLRP3 inflammasome signaling pathways and focused on the effect of statin drugs on NLRP3 inflammasomes in association to atherosclerosis in order to elucidate possible targets for future research and clinical settings.

1. Introduction

Vertebrates use two distinct mechanisms to recognize and eradicate pathogens: the innate and the acquired immune systems [1]. The innate immune system is the first line of response to microbial infections and tissue damage through molecular receptors known as pattern recognition receptors (PRRs). PRRs can sense specific microbial structures called pathogen associated molecular patterns (PAMPs) [2,3]. Tissue and cellular injury may influence PRRs by releasing damage associated molecular patterns (DAMPs) such as heat shock proteins (HSPs), uric acid crystals and high mobility group box protein1 (HMGB1) [4]. PRRs mainly consist of leucine-rich repeat (LRR)-containing protein (NLR), toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD) and AIM2-like receptor (ALR) [5].

NOD-like receptors (NLRs) contribute to crucial activity of cellular life including autophagy, apoptosis and development that are mostly expressed in the cytosol. The NLR family members organize nucleotide-binding domain (NBD) which play key roles in caspase activation and have multiple separate interaction sites for proteins [6]. Further, in some members such as apoptosis protease-activating factor 1 (Apaf-1), they has a variable N-terminal domain CARD and a C-terminal WD-40 repeat [7]. The *Apaf-1 complex* (known as the *apoptosome)* triggers *caspase-9* activation. *APAF-1* contains *WD/WD40* repeats region that are responsible for caspase-9 activation with *CARD* interactions. Apoptosome complex *brings multiple* procaspase-*9 into proximity and lead to* cross activation [8]. The NLR family is located in the second class of PRRs and has a core nucleotide binding domain (NBD). NLR can be divided into two categories based on the N-terminal domain including NLRP (Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing) and NLRC (CARD-

Abbreviations: NLRP3, pyrin domain containing 3; PAMPs, pathogen associated molecular patterns; Apaf-1, apoptosis protease-activating factor 1; P2X7, P2X purinergic receptor 7

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containing). Certain members of NLR family, NLRP1, NLRP3, and NLRC4, are defined as specified protein in NLRs capable of forming inflammasomes, although others consisting NLRP6 and NLRP12 are supposed as possible inflammasome sensors [9]. NLRP3 responds to a broad range of endogenous ligands in the pathogenesis of several inflammatory diseases [10].

While the exact mechanisms of NLRP3 inflammasomes in the atherosclerosis pathogenesis had been uncertain, emerging evidence demonstrated that NLRP3, which controls caspase-1 activity and following pro-IL-1*β*, leads to atherosclerosis development [11]. Several reports have demonstrated that atherosclerosis is a chronic disease that can lead to urgent or emergency disturbances following plaque rupture. However, the adapter apoptosis-associated speck-like (ASC) and caspase1 levels as key inflammasome agents were extremely increased in atherosclerotic progression [12]. This outcome is able to maintain the inflammasome hypothesis when lysosomal rupture occurred and induces components release from the mitochondria into the cytoplasm. The cholesterol accumulation in first phase of atherosclerotic is a symptom of coronary artery disease by triggering foam cell and cholesterol crystal formation [13]. Although several new classes of lipid-modifying agents have been introduced [128], statins still remain as the leading drug class. Besides their potent lipid-lowering effects, statins may control inflammation [14], and could be considered as a potential therapy upon the inflammatory cascade that involves atherosclerosis pathogenesis. In this review, we discuss the effects of statins on NLRP3 inflammasome in association with atherosclerosis.

1.1. NLRP family

The NLR family is comprised of 22 human and more likely mouse genes members that influence the majority of exogenous and endogenous molecules [15]. This family is divided into two NLRP or NLRC subgroups based on N terminal domain (Fig. 1). The NLRP contains pyrin (PYD) domains and NLRC which contain N-terminal caspase recruitment (CARD) [9]. Some NLRs have well-established signaling platforms, known as inflammasomes, which are organized in response to various pathogens or host-derived stimulator [16]. When disease-associated (DAMPs) or pathogen-associated molecular patterns (PAMPs) are identified by NLRPs, the PYD domain of NLRPs inflammasome binds to the ASC pyridine domain and subsequently links via procaspase-1 with CARD interaction. Later, caspase-1 is formed and IL- 1β and IL-18 are released and apoptosis is induced [17].

1.2. NLRP3 inflammasome

NLRP3 inflammasome was first identified to be linked by congenital auto-inflammatory disease, known cryopyrin-associated periodic syndromes, which is determined by fever episodes and rashes of skin [18]. Actually, about 100 diseases associated by nucleotide-binding domain (NBD) are detected which renders NLRP3 activation in human [19]. The NLRP3 is expressed in epithelial cells, and elevate immunity response through cleavage of inflammatory molecules such as IL-1β and IL-18, subsequently leading to pyroptotic cell death induction [20]. NLRP3 is a member of NLR family, which responds to a broad range of pathogens and endogenous stimuli, and is implicated in the molecular pathway of different autoinflammatory diseases [10].

1.3. Inflammasome complex assembly

Procaspase-9 activation occurs with three phases by the apoptosome: a) proximity; b) dimerization; and 3) conformational alternation. Until now, the exact mechanism of inflammasome assembly and activation is uncertain [21]. The recent evidence has been helpful to find the biochemical attributes and ASC function and can lead to novel potential impact for NLRP3 assembly. Most technical development such as electron and fluorescent microscopy has been elucidated in inflammasome organization.

Inflammasome sensor molecules include NLR scaffold, PYCARD

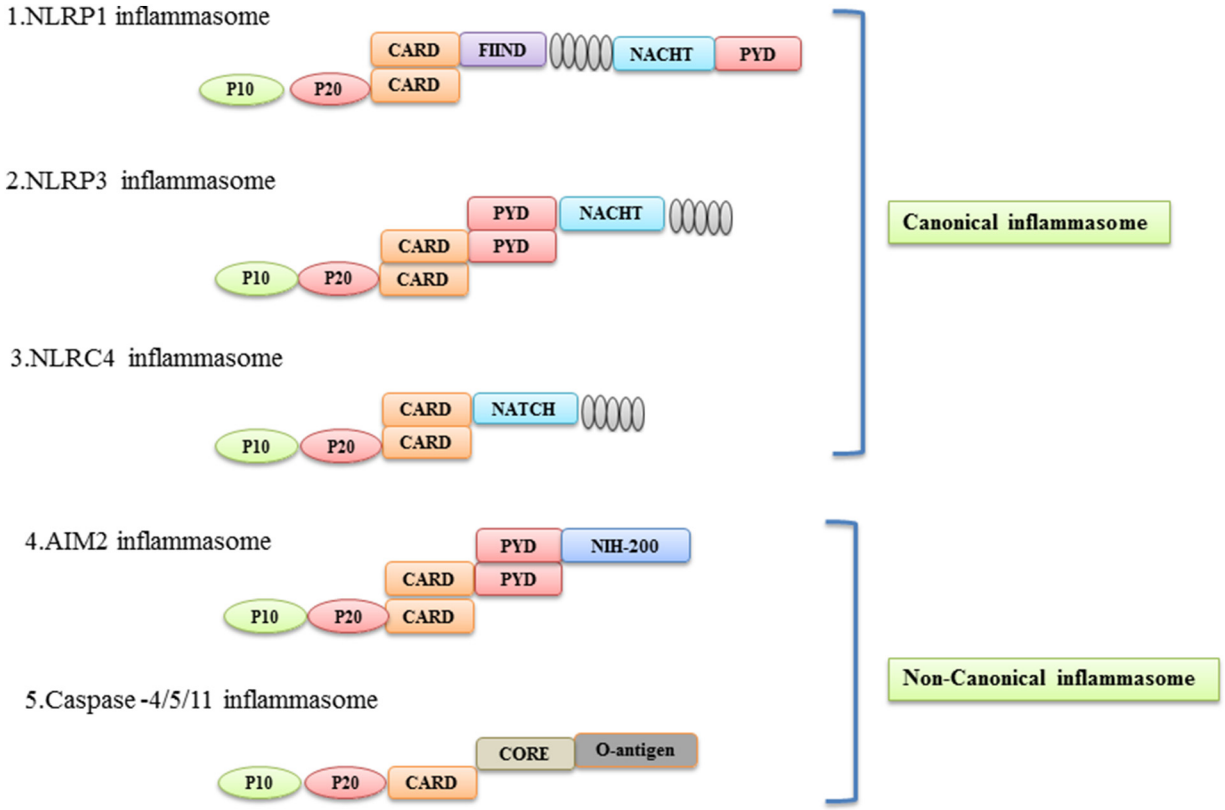

Fig. 1. Structure of inflammasome assembly. NLRP3: NOD-like receptor family and pyrin domain containing 3; PYD: pyrin.

(PYD and CARD domain) adaptor frequently referred to ASC that function as caspase1 activator. They are necessary for the recognition of some stimulators and lead to inflammasome assembly complex. It should be noted that, the majority of inflammasomes require the PYCARD adaptor protein to elevate caspase-1 activation [22,23].

The Pycard protein (also known as Apoptotic Speck protein containing a CARD [ASC]) is the ubiquitous molecule for inflammasomes activation that leads to prion-like oligomerization mechanism for the last inflammasome structural conformation. Pycard contains two terminal domains including an N-terminal PYD and a C-terminal CARD. PYD domain of NLRP3 plays a key role in ASC with PYD–PYD up-regulation and induces filamentous structures formation that is essential for assembling of protein aggregation [24].

1.4. NLRP3 activation

NLRP3 inflammasome activation requires two signals. The priming signal is initiated by NF-κB (nuclear factor kappa B) signaling pathway that detects several DAMPs or PAMPs by TLRs and triggers NF-κB activation which leads to proIL-1β, and proIL-18 regulation, while the second signal regards as the oligomerization of NLRP3 activation components such as ASC phosphorylation and caspase-1, which are involved in IL-1β and IL-18 secretion. Furthermore, different mechanisms have been identified for NLRP3 inflammasome activation. As for the first mechanism, potassium ion efflux is the main activator of NLRP3 that is induced by P2X purinergic receptor 7 (P2X7) and plays the role of NLRP3 agonist. Supporting this mechanism, spontaneous NLRP3 inflammasome assembly depends on maintenance of potassium level [25]. The K^+ efflux occurs through a P2X purinergic receptor 7 and adenosine triphosphate (ATP) related to hemi channel protein and pannexin-1. This event causes extracellular NLRP3 agonist to access the cytosolic space and directly engages the NLRP3 complex and releases IL-1β and IL-18 by the inflammasome multiprotein [26]. However, the precise link between NLRP3 activation and cytosolic potassium remains unclear. The second mechanism, PAMPs and DAMPs, as the activator, can induce reactive oxygen species (ROS) [27]. ROS conserved damaging signals, involved in NLRP3 assembling [28].

There are *numerous* possible *sources* of *ROS such as NADPH-oxidases,* xanthine oxidase, cytochrome P450, *cyclooxygenases*, *lipoxygenases and* mitochondrial dysfunction [29]. The majority of ROS inducers mediate *IL-1β production* by regulating NLRP3 [30]. *Early atherosclerotic* lesions are caused by *vascular* endothelium impairment, in which nitric oxide (*NO·*) of the endothelium has essential role in vessel integrity. ROS can subsequently dissipate the anti-atherogenic and anti-inflammatory properties induced by NO [31]. Further, destruction of NADPH oxidase and molecular oxidative pathway leads to inflammasome activation [32]. Regarding the third mechanism, activation and assembly of NLRP3 is performed by large particulate environmental and biological irritants (i.e. alum, silica, asbestos and amyloid-β), which are engulfed by phagocytes [25]. The mentioned particles are fused into lysosome that give rise to lysosomal rupture and secretion of lysosomal contents such as cathepsin B [33]. This event can lead to destruction of recent phagolysosome. In return, crystals can act as the main mediator for IL-1β production [12]. The fourth mechanism, calcium-sensing receptor (CASR), cytoplasmic and endoplasmic reticulum play an effective role in the evaluation of intracellular Ca^{2+} by different activators i.e. ATP [34]. Also, one pharmacological study indicated that reduction of phospholipase C (PLC) and cyclic AMP (cAMP), which participates in inositol-1, 4, 5-trisphosphate signaling, leads to calcium flux reduction and eventually NLRP3 inflammasome activation [35]. Other factors involved in inflammasome activation include mitochondrial dysfunction, mitochondrial DNA(mtDNA) secretion or mitochondrial phospholipid cardiolipin, and epidermal fatty acid binding protein (*E*-FABP), which targets high level of fat diet and induces IL-1β and IL-18 secretion and NLRP3 activation [36,37].

2. NLRP3 in atherosclerosis

The NLRP3 inflammasome, a chief generator of cleaved IL-1 family cytokines, profoundly studied due to its necessary role in the pathogenesis of atherosclerosis. The NLRP3 inflammasome is regulated by preparing and several pathways controlling posttranscriptional modifications of NLRP3. Therefore, alterations in the local and or general microenvironment can impact the gene dose effect. One study showed that NLRP3 deficiency in mice model (Ldlr−/−) had merely small influences towards atherogenesis [38]. Nevertheless, regardless of the inconsistencies, numerous studies manifested the primarily significance of the NLRP3 inflammasome in atherosclerosis. In this line, separate studies verified double knockout mice (Apoe−/−/Caspase-1−/−) that display impaired progress of atherosclerotic plaque when being nourished an atherogenic regime with a minor cholesterol content along with a decreased impulsive expansion of atherosclerotic plaque after 26 weeks [39,40]. Additional proof for the involvement of NLRP3 inflammasome activation in diet-induced model of atherogenesis was delivered by lentiviral gene silencing of Nlrp3 in double Apoe knockout mice, which lessened atherosclerosis development [41]. Numerous epidemiological studies presented indirect proof for the prominence of the NLRP3 inflammasome in humans by associating aortic NLRP3 expression and CVD occurrence. It was shown that individuals with coronary atherosclerosis present great aortic expression of NLRP3, that is relating to disease severity and some medical risk factors for CVD [42]. Further studies have revealed meaningfully augmented expression of NLRP3 inflammasome elements in human carotid atherosclerotic lesion tissue [43]. Besides, protein levels of NLRP3 in peripheral blood monocytes were augmented in individuals with acute coronary syndrome and linked with disease severity [44]. Further study emphasized a potential therapeutic value of anti-inflammatories to develop the clinical consequences of CVDs, illustrated by IL-1β inhibition [45].

Atherosclerosis is a complex pathological process characterized by deposition and accumulation of atherosclerotic plaques in large arteries that leads to cardiovascular diseases (CVD) [46]. Atherosclerosis is a multifactorial disease and cause of high mortality and morbidity worldwide. In this chronic disease, arteries become stiffened through plaques formation and consist of two pathological mechanisms: atherosis (accumulation and oxidation of modified lipids by some macrophages) and sclerosis (inflamed fibrosis layer formed from smooth muscle cells [SMCs], foam cells and endothelial cells [EC]) [47]. The accumulating evidence indicated that atherosclerosis is inevitable degenerative that may alter to acute disease by thrombosis rupture. Through PAMPs or DAMPs recognition, the NLRP, as the first barrier, activates pro-caspase-1 to produce and activate cytokines and chemokines [48]. In this review we focus on NLRP3 inflammasome role in atherosclerosis progression.

Concomitant risk elements including smoking, hypertension and high reception of saturated fatty acids and glucose may correlate with activated of NLRP3 protein in myeloid cells of atherosclerosis patients [49]. Meanwhile, some studies reported that NLRP3, caspase1 and ASC levels as the main inflammasome components were remarkably elevated in atherosclerotic lesions [50]. Duewell et al for the first time reported the effective function of NLRP3 inflammasome in atherosclerosis. They demonstrated that low-density lipoprotein receptor (LDLR) deficient mouse with deficiency in inflammasome components such as NLRP3, ASC, IL-1α and IL-1β in their transplanted bone marrow (BM) after receiving a high-cholesterol diet had significantly reduced primary atherosclerosis [13]. These results can support the inflammasome theory when lysosomal rupture happens and induces cathepsins releasing into the cytoplasm [13]. Cathepsin blockage restricts activity of the NLRP3. The mass of cholesterol in primary stage of atherosclerotic due to organized macrophage foam cells and cholesterol crystal clefts is a sign of severity of coronary artery disease. In other report with ApoE-null mice were atherosclerosis prone [13]. In parallel finding, IL-18 inhibitor has protective role against atherosclerosis on

ApoE null mice by reducing lymphocyte infiltration and attenuating plaque development [13]. However, the inflammasome function in atherosclerosis is resolute with recent results showing that genetic IL-1β or IL-1 receptor destruction may decrease atherosclerosis incidence; however, IL-1R antagonist cause elevation of coronary artery disease growth in another mice model with hyperlipidemia [51]. The discrepancy in these two studies was not clear and maybe it occurred due to differences of diet and mice model [52]. Some in vitro investigations showed that loss of lectin-like LDL receptor-1 (LOX-1) can decrease ROS activity, mtDNA damage and NLRP3 function in macrophages and also high fatty diet in null of LOX-1 in LDLR−/− mice can increase collagen deposition and aortic disease susceptibly [53,54]. It has been shown the positive correlation between NLRP3 level and severity of coronary atherosclerosis measured by GRACE and TIMI risk scores [44]. In addition, the expression of NLRP3 in subcutaneous adipose tissue, which is influenced by lifestyle-related diseases, is correlated with the intensity of coronary atherosclerosis [55]. Clinical confirmation of the NLRP3 role and its productions can lead to expansion of macrovascular complications that may be an efficient clinical marker for coronary artery events.

2.1. Anti-inflammatory treatments in atherosclerosis

The involvement of inflammatory mediators to expand atherosclerotic plaques is currently well-confirmed. In fact, anti-inflammatory therapies that are intended to decrease the hazard of a major adverse cardiac event are now in progress (Table 1). Previous clinical trial revealed that oral administration of pravastatin for 6 month considerably decreased serum CRP levels in individuals affected with or without CVD, exclusively of any alterations in LDL cholesterol [56]. This trial agreed the anti-inflammatory properties of pravastatin in the prevention setting. Further clinical studies have verified anti-inflammatory capacities of statins in reducing pro-inflammatory cytokines level and CRP in individuals with hypercholesterolemia [57]. In addition to statins, further hypolipidemic components hold lipid-lowering properties [58]. Documents on fibrates and niacin have delivered substantial results. The former showed valuable endothelial and vascular properties when used with statin [59]. The latter hinders pro-inflammatory genes upregulation in vascular wall and applies favorable properties on the function of adipose tissue [60]. Regardless of these anti-inflammatory effects of agents, statins as potent anti-inflammatory have been intensely linked with medical result. Through preventing the generation of intracellular isoprenoids, they overwhelm vascular and myocardial inflammation. Furthermore, clinical trials have revealed the favorable protective effects of statins on coronary heart disease. The recent milestone trial proposed that in cases without coronary heart disease, statins recovers clinical consequence [61].

2.2. Effects of statins therapy on atherosclerosis

The structural analogues of HMG-CoA reductase enzyme inhibitors known as statins presented in 1987 and regarded as the foundation stone of lipid-lowering drugs for management of cardiovascular risk lessening. Recent laboratory evidence indicates that statins, in addition to lipid reduction, have several pleiotropic effects like endothelial function improvement, immunomodulation and antioxidant activity (Fig. 2). In vitro and in vivo experiments demonstrated that long-term statin treatment inhibits cardiac hypertrophy and cardiomyocyte apoptosis, skin atrophy, osteoarthritis as well as improves age-associated endothelial dysfunction by suppression of the senescent phenotype through amelioration of inflammation and oxidative stress [62–64]. However, statins are also related with some established adverse events such as muscle complaints (i.e. myopathy and rhabdomyolysis), hepatic damage, and non-insulin dependent diabetes. However, the lipid-lowering mechanism of statins is known but the precise networks of these pleiotropic and side effects are not as understood. MicroRNAs as well as epigenetics, the group of reversible alterations to cellular DNA which influence gene transcription without affecting the DNA sequence may contribute in these effects [65,66].

Nevertheless, several published documents recommended that statins prevent CVD not only by lipid modifying and cholesterol lowering, but also through several pleiotropic actions including anti-inflammatory effect [67–75]. Multiple pleiotropic processes involve whole cells and mechanisms interfered in the atherosclerotic process. At present, direct anti-inflammatory treatments are expanded for management of atherosclerosis [67]. Their first commitment is blocking the synthesis of endogenous sterol. Statins target the LDL cholesterol along with hsCRP through reduction of cholesterol synthesis and an augmentation in the level of HDL cholesterol [76,77]. Statins exert their impacts via immune-modulatory functions as well. Like atorvastatin, a frequently administered statin impeded TLR4/MyD88/NF-kB pathway related to NLRP3 expression in the human monocytic cell line (THP-1) and induced IL-1β reduction [77]. More data indicated that NLRP3 is expressed in macrophages located in atherosclerotic plaque [78], suggesting that cholesterol has the capacity to activate the inflammatory characterized by local expression of IL-1β as well as invasion of leucocytes notably neutrophils into the plaque [79–81]. Another pleiotropic effects of statins happen with the inhibition of Rho-GTPase

Table 1
Effects of various anti-inflammatory drugs on the atherosclerosis.

Anti-inflammatory drug	Mechanism	Dosage and treatment time	Effects on inflammatory responses	Ref
Statins	-Prevented HMG-CoA reductase enzyme -Reduce LDL cholesterol	-40 mg/day dose of pravastatin -6 months	-Decreased CRP in CVD patient	[120,121]
Succinobucol (AGI 1067)	-Decrease lipoproteins oxidation and avoid their localization into blood vessel wall	-300 mg -14 days	-Elevated LDL cholesterol and systolic blood pressure -Reduce glycated haemoglobin and HDL cholesterol	[122,123]
Varespladib (PLA2 inhibitors	-Alter LDL turnover	-15 mg/kg (low dose A-002) or 150 mg/kg (high dose A-002) -12 weeks	-Decrease atherosclerosis in dose-dependent manner -Synergistic effect by pravastatin	[124]
Veliflapon (DG-031)	-Lipooxygenase(5-LO)-activating protein inhibitor	-250, 500,750 mg/d (3 tablets per day) -4 weeks	Suppression of biomarkers-associated with increased risk of MI events	[125]
Atreleuton (VIA-2291)	-Significantly reduce the leukotriene metabolites production	-25, 50, or 100 mg -12 weeks	-Decrease leukotriene production	[126]
Plozalizumab (VI-MLN1202)	-Blocking CCR2 chemokine receptors on the surface of innate immune cells (macrophages and monocytes)	-10 mg/kg IV infusion(30 min to an hour) -1 day to113 days of the trial	-Increase the effect of CCR2 blockade in decrement of CRP level	[127]

Aberrations: CCR2: C−C Chemokine Receptor-, 2 CRP: C-reactive protein, CVD: cardiovascular disease, HDL: high-density lipoproteins, HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, LDL: low-density lipoproteins, MI: Myocardial infarction, PLA2: phospholipids'A2.

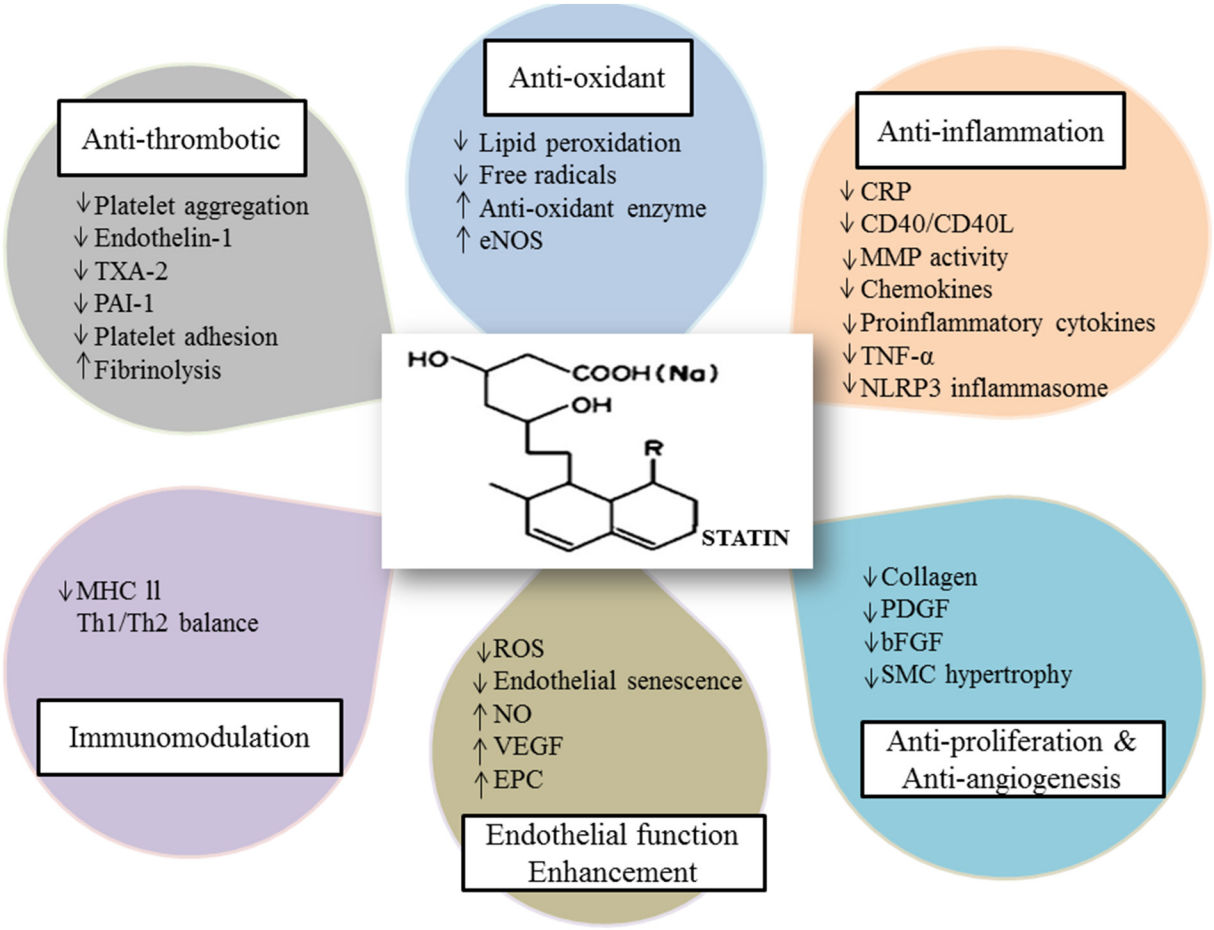

Fig. 2. Pleotropic effect of statin. bFGF: basic fibroblast growth factor; CRP: C-reactive protein; EPC: Endothelial progenitor cells; PDGF:platelet derived growth factor; eNOS: endothelial nitric oxide synthases; MHC: major histocompatibility complex; MMP: matrix metalloproteinase; NLRP3:NOD-like receptor family and pyrin domain containing 3; NO: nitric oxide; ROS: reactive oxygen species; PAI-1:plasminogen activator inhibitor-1; SMC: smooth muscle cell; TNF: tumor necrosis factor; TXA-1: thromboxane A2; VEGF: vascular endothelial growth factor.

isoprenylation through decreasing the production of geranyl-geranylpyrophosphate (GGPP) in the process of cholesterol synthesis [82]. This issue results in augmentation of endothelial nitric oxide synthase (eNOS), as well as nitric oxide production [83]. The next pathway which is influenced by statins is PI3K-Akt pathway by Akt phosphorylation that is led to a raise in NO production [84]. Additionally, statins are capable of repressing the function of NADPH oxidase in the endothelium cells [85]. Besides, statins change the white blood cells trafficking at the region of inflammation. Statins drug family including simvastatin, cerivastatin and atorvastatin, lead to a low expression of intercellular adhesion molecule-1(known as ICAM-1) as well as lymphocyte function-associated antigen-1 regarded as (LFA-1) on ECs and PBMCs [86]. Other studies have been revealed that statins can decrease the production of the C—C chemokine ligand-2 and matrix metalloproteinase-9 in cell lines [87]. Therefore, various clinical trial data support the advantage of statins usage in the primary and the recurrent CVDs [88,89].

2.3. Statins target NLRP3 pathway in cardiovascular disease

The broad participation of the NLRP3 inflammasome complex in extensive variety of illnesses makes it extremely a favorable drug target [90]. Luckily, frequent reliable inhibitors of NLRP3 complex activation have been emerged. Augmented production of pro-inflammatory cytokines (IL-1β andIL-18) through NLRP3 inflammasome activation paves the way for atherosclerotic plaque development and formation [91–93]. As mentioned earlier, cholesterol crystals proceed as the main activator of atherogenic inflammation by stimulation of IL-1β secretion by NLRP3 complex [78]. IL-1β is a key proinflammatory cytokine for several stages in maintaining atherogenic inflammation, including amplifying the secretion of alternative cytokines and chemokines, leading to the up-regulation of adhesion molecules and stimulating nitric oxide (NO) synthase enzyme in endothelial cells [78]. Rosuvastatin is a potent HMG-CoA reductase inhibitor with documented safety and efficacy [94]. Zaca et al., highlighted the role of rosuvastatin, as a quite novel drug that is not only efficient for reducing LDL and elevating HDL levels in individuals, but also has a safety profile comparable to or better than the generally applied doses of other statins [94]. They declared that early and longstanding monotherapy with high-dose rosuvastatin (HD RSV) stops the progressive dysfunction as well as remodeling of LV in dogs with moderate heart failure. Additionally, the benefits obtained with HD RSV on LV function and remodeling were associated with a reduced volume fraction of interstitial fibrosis, augmented capillary density, enhanced oxygen diffusion distance, and decreased cardiomyocyte enlargement. Furthermore, HD RSV regulated the expression of tumor necrosis factor (TNF-α) and matrix metalloproteinase-2 in the LV tissue expression. These results support the concept that rosuvastatin inhibits heart failure exacerbation.

The key mechanisms by which statins drug family influence atherosclerotic development are not evidently detected. A number of studies have recommended its efficacy in the hindrance of CV events happen through anti-inflammatory influences. Fig. 3 showed schematic representation of the NLRP3 inflammasome activation pathway and statins' effects. The majority of surveys on NLRP3 are performed on animal

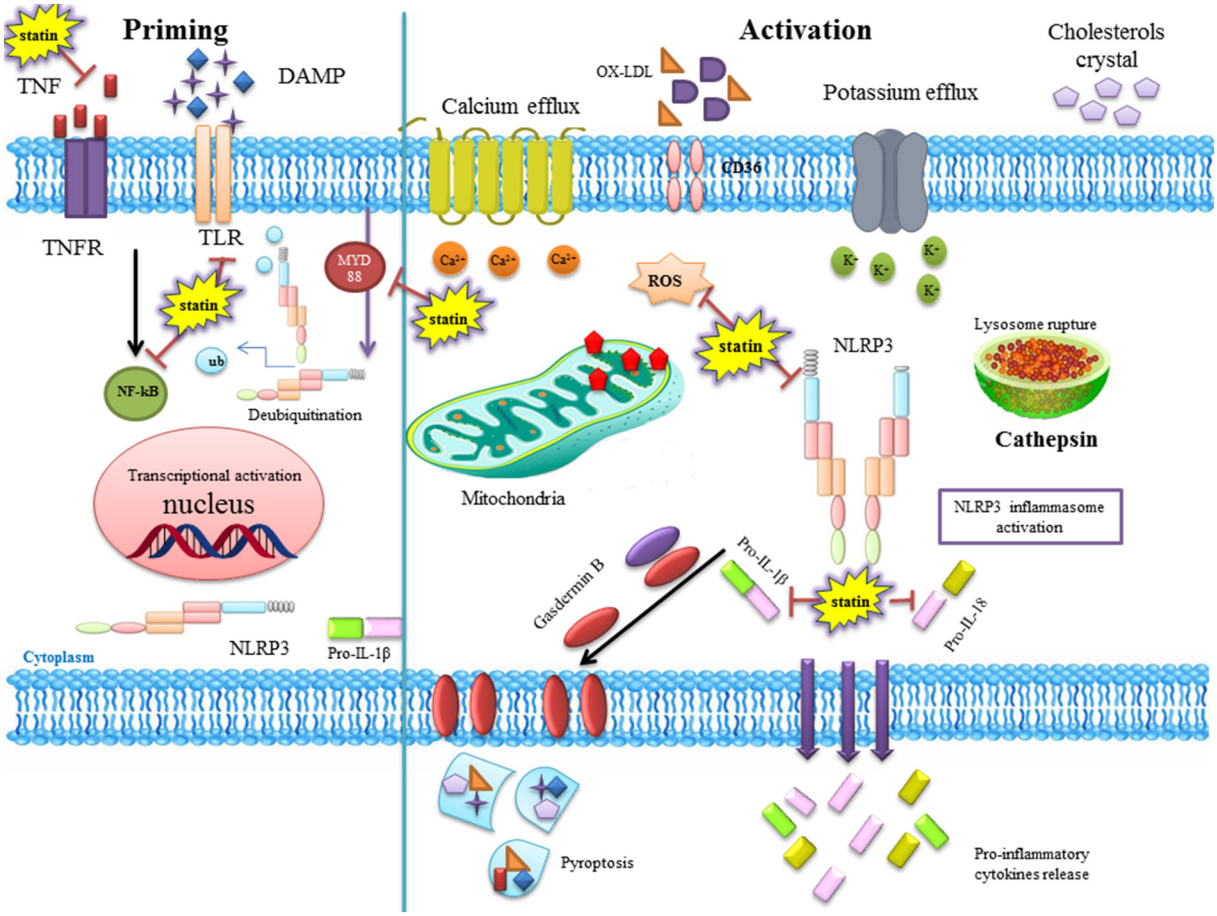

Fig. 3. The NLRP3 inflammasome activation pathway and statins effects. DAMP: damage associated molecular patterns; interleukin; NF-κB: nuclear factor; NLRP3: NOD-like receptor family and pyrin domain containing 3; ox-LDL: oxidized LDL; ROS: reactive oxygen species; TLR: toll-like receptors; TNF: tumor necrosis factor.

models and cell cultures, with restricted the transferring data on its function in humans [95]. Furthermore, regardless of the enormous anti-inflammatory influences of statins drug family, it is uncertain whether they can uncover any function on NLRP3 and downstream cathepsin-B. Therefore, Altaf et al aimed to assess the levels of NLRP3 and cathepsin-B in their study populations, as well as the effect of rosuvastatin dose on NLRP3 up-regulation and expression, and the last but not least potential relationship of NLRP3 with cathepsin-B along with alternative inflammatory elements. They manifested that high-dose of rosuvastatin has a further pleasing results on the alterations in mentioned elements. These findings insert different insight into the immune-pathogenesis and supervision of acute coronary syndrome, with NLRP3 as the new emerging target [91].

Since nuclear factor kappa-light-chain-enhancer of activated B cells plays an essential regulatory function in transcription of the NLRP3 and pregnane X receptor (PXR) inhibited activation of NF-kB [96], Wang and colleagues evaluated the influences of statin-activated PXR on NF-kB binding activity to the human NLRP3 promoter. They revealed that statins can block oxLDL or TNF-α-induced NLRP3 complex activation in vascular endothelial cells and this feature is mediated as a result of PXR activation and expression [97]. In addition, they declared that oxLDL and TNF-α prompted NLRP3 complex activation in vascular endothelial cells and, notably, that statins neutralized oxLDL or TNF-functions on NLRP3 activation [97]. Furthermore, it was shown that cholesterol crystals and oxLDL can trigger NLRP3 activation in macrophages and exert pathological functions in atherosclerosis [13,98]. Several clinical trials have shown that statins have anti-inflammatory properties. Nevertheless, the principal molecular pathway still remains vague. After synthesis of interleukin-1β, it is transformed into its active form by the caspase-1 component of inflammasomes. Recent report has suggested a novel signaling pathway in which an intermediate 28 KD form of IL-1β can hinder the activation of IL-1 receptor-1. As an alternative, it impedes mature IL-1β signaling and may consequently diminish initiated inflammatory responses [99]. Actually, blockage of IL-1 β is the only existing approach for analysis the inflammatory hypothesis of cardiovascular disease risk that was resulting from statins. On the contrary, it is reasonable that anti-inflammatory drugs could trigger the activation of NLRP3 inflammasome. Recent report showed that statins could also promote insulin resistance via stimulating the activation of NLRP3 inflammasome [100]. Moreover, Turner and colleagues showed that statins increase IL-1 β secretion in bone marrow-derived macrophages that was dependent on NLRP3 and reversed with the inflammasome inhibitor, glyburide [101]. Next, Henriksbo and co-workers provided new evidence presenting the significance of statin-NLRP3 impact in metabolic tissues that regulate blood glucose. Administration of a statin to overweight mice for numerous weeks decreased insulin-induced glucose uptake in the adipose tissue. Statin caused amplification of caspase-1 activity in adipose tissue that was dependent on NLRP3 and also was lessened with glyburide. Predominantly, statin therapy damaged insulin signaling in adipose tissue; however, it was regular in adipose tissue from mice with null NLRP3 or those cured with glyburide [100].

Another randomized clinical survey has demonstrated that mRNA and protein levels of NLRP3 in PBMCs have elevated in the coronary artery individuals and are affirmatively associated with the plasma levels of downstream inflammatory cytokines (IL-1β and IL-18) of NLRP3. Notably, atorvastatin leads to a dramatic reduction in NLRP3 and the levels of IL-1β/IL-18 after 8 months of therapy [102]. Since

NLRP3 elements are routinely expressed in innate immune cells such as macrophages, monocytes and dendritic cells as well as adaptive immune cells such as T cells [93,103]. The majority of the studies on atherosclerosis has conducted on the alteration of inflammasome activation and expression level in these cells. In a variety of animal models of atherosclerosis, an increase in NLRP3 expression levels was detected in innate immune cells [104]. Existing treatments with possible effect on the activation of NLRP3 in atherogenesis process are statins and colchicine. Other emerging drugs try to focus on regulating NLRP3 expression and inhibit the formation of cholesterol crystal. Nevertheless, the majority of these remedies stay at the preliminary phases of in vitro and or in vivo trials. Hence, more investigation is needed to validate the impact of these treatments on the progression of atherosclerosis [105].

A contrary study is reported by Liao YH and colleagues, whom investigated whether an increase in IL-1 cytokine through statin can be observed in human monocytic cell line. They found that, in Lipopolysaccharide-induced monocytes from Peripheral Blood Mononuclear Cells, fluvastatin has the capacity to amplify mature IL-1. Furthermore, the viability and cytotoxicity assay and uptake of Propidium iodide did not show any toxicity in fluvastatin-treated human monocytic cell lines. However, fluvastatin–induced IL-1 production did not influence by NLRP3 ligands [106]. Other investigations also present evidences that showed statins could impact the NLRP3 upregulation in a dose dependent manner [107]. However, studies declared that statins can hinder the aggregation of cholesterol crystals in foamy macrophages and led to inflammation reduction in human atherosclerotic plaque [108]. Interestingly, a randomized clinical trial manifested that atorvastatin in CAD individuals stimulates a noticeable reduction not only in NLRP3 expression level, but also in plasma levels of proinflammatory downstream cytokines, while rosuvastatin had no effect on neither the mRNA level of NLRP3 nor the downstream cytokines [102].

Rosuvastatin may have also a significant therapeutic potential in the treatment of diabetic cardiomyopathy by suppression of NLRP3 inflammasome, and is linked with inhibiting the MAPK pathways [109]. Recently, effect of simvastatin on hyperglycemia-induced endothelial dysfunction of cardiovascular complications was investigated. Simvastatin treatment remarkably inhibited vascular endothelial hyper-permeability and elevated the expression of tight and adherence junction proteins through abolishing the HMGB1 release via NLRP3inflammasome-dependent in aortic endothelial cells [110]. Abderrazak et al demonstrated that arglabin, a natural inflammasome NLRP3 inhibitor, potentially has anti-atherogenic effects in ApoE2.Ki mice receiving a high fat diet. Their results indicated that targeting NLRP3 inflammasome is an promising approach for atherosclerosis treatment [111].

2.4. Clinical trials targeting NLRP3 pathway in atherosclerotic patients

Up to the present time, no country has reported to target the inflammasome in diminishing cardiovascular disease. However, United States of America and Canada have conducted two clinical trials assessing the effects of anti-inflammatory agents in CVD. HsCRP has been displayed to have a convincing association with recurrence of cardiac disease in numerous randomized clinical trials [112]. HsCRP is upregulated in the liver followed by activation and expression of IL-1β, IL-6 and TNF-α. According to the fundamental animal model surveys, hindering the function of these proinflammatory cytokines and chemokines could dramatically lessen CVD. Anti-inflammatory Thrombosis Outcomes Study “CANTOS” is the primary great randomized controlled clinical trial investigating the use of canakinumab (a human monoclonal antibody that blocks up IL-1β selectively) on prevention of secondary cardiovascular events in individuals with steady CAD [113–115]. Initial records confirmed that using canakinumab as a possible curative method considerably decreases inflammation [116], even though it did not appear to influence vascular function in the related individuals [117]. Recently, the results of CANTOS have been released, revealing a significant reduction in major adverse cardiovascular events, particularly in those achieving greater CRP reductions [115]. There was a significantly reduced incidence of arthritis, osteoarthritis, gout and cancer mortality in the canakinumab group. However, safety evaluations revealed a higher incidence of neutropenia, thrombocytopenia and death due to infection or sepsis in those receiving canakinumab.

3. Conclusions

Latest studies on atherosclerosis have highlighted new documents and pathways implicated in its pathogenesis. An important inflammatory pathway is NLRP3-dependent, which has frequently been investigated in animal models and cell culture surveys. NLRP3 complex activation in atherosclerosis is triggered through identification of modified LDL particles [118] by TLRs and scavenger receptors on macrophages. Afterwards, ProIL-1β and caspase-1 are activated and upregulated. The modified LDL particles stimulate cholesterol crystal formation in macrophages and lysosomal rupture occurs followed by the release of cathepsins release [91]. In general, to develop new anti-inflammatory therapy, a comprehensive knowledge of the immune-pathogenesis of atherosclerosis is crucial. Since the immune system represents a new and hopeful target for prevention or cure of atherosclerosis [119], it will be significant not to underestimate the troubles that will be hidden in transferring the outcomes from experimental animals to humans. Moreover, detailed evaluation of the safety of inhibiting NLRP3 inflammasome for the treatment of atherosclerosis and other inflammatory diseases is necessary.

A growing body of evidences supported the significant role of NLRP3 in the development of atherosclerosis and other CAD. It has been suggested that inhibiting NLRP3 can potentially be considered as a novel approach in prevention and treatment of cardiovascular complications. At present, the common promising targets for inhibiting NLRP3 inflammasome include anti-IL-1, P2X7 receptors antagonist and blockade of caspase-1. Future investigation on the NLRP3 activation mechanism and molecular targeted drugs on NLRP3 are required.

Conflict of interest

The authors declare no conflict of interests.

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