Chapter 2
The Inflammasomes in Cardiovascular Disease

Gerardus P. J. van Hout and Lena Bosch

Contents

G. P. J. van Hout (✉)
Department of Cardiology, Utrecht University Medical Center, Utrecht, The Netherlands
e-mail: G.P.J.vanHout-2@umcutrecht.nl

L. Bosch
Department of Experimental Cardiology, Utrecht University Medical Center, Utrecht, The Netherlands
e-mail: L.bosch@umcutrecht.nl

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Abstract Cardiovascular disease (CVD) is the number one cause of death worldwide. The pathogenesis of various disease entities that comprise the area of CVD is complex and multifactorial. Inflammation serves a central role in these complex aetiologies. The inflammasomes are intracellular protein complexes activated by danger-associated molecular patterns (DAMPs) present in CVD such as atherosclerosis and myocardial infarction (MI). After a two-step process of priming and activation, inflammasomes are responsible for the formation of pro-inflammatory cytokines interleukin-1β and interleukin-18, inducing a signal transduction cascade resulting in a strong immune response that culminates in disease progression. In the past few years, increased interest has been raised regarding the inflammasomes in CVD. Inflammasome activation is thought to be involved in the pathogenesis of various disease entities such as atherosclerosis, MI and heart failure (HF). Interference with inflammasome-mediated signalling could reduce inflammation and attenuate the severity of disease. In this chapter we provide an overview of the current literature available on the role of inflammasome inhibition as a therapeutic intervention and the possible clinical implications for CVD.

Keywords Cardiovascular disease · Inflammasome · Atherosclerosis · Heart failure · Myocardial infarction · Inflammation

2.1 Cardiovascular Disease and the Inflammasome

Cardiovascular disease (CVD) comprises all disease entities of the heart and blood vessels. Together they are the primary cause of death worldwide, supporting the intensive investigation of the mechanisms that play a central role in CVD pathogenesis.[1] Identification of these mechanisms will enable the development of novel therapies that can hamper disease progression and decrease the burden on society.

The most abundant disease of the cardiovascular system is the formation of lipid-rich plaques in the arterial vessel wall, named atherosclerosis. Atherosclerosis can occur anywhere in the human body, yet it often develops at certain locations, such as the carotid and coronary arteries. It becomes clinically manifest when a stable plaque is significant enough to decrease blood flow or when a vulnerable plaque ruptures, thereby inducing thrombus formation leading to vessel occlusion. This results in ischemia of the tissue downstream of the occluded blood vessel. In the heart this leads to myocardial infarction (MI) and possibly heart failure (HF). Occlusion of vessels in the brain will lead to stroke. Apart from these organs, peripheral artery disease can result in ischemic damage to other parts of the body.

Inflammasomes are pattern recognition receptors (PRRs) that are formed in response to a multitude of stimuli. Inflammasome-based signalling seems to play a crucial role during the development of atherosclerosis and acute infarction of the heart. The most frequently studied inflammasome in CVD is the NLRP3

[1] http://www.who.int/mediacentre/factsheets/fs317/en

inflammasome, composed of NLRP3 (nod-like receptor protein 3) an adaptor protein ASC (Apoptosis-associated speck-like protein containing a CARD), and the protease caspase-1. The activation of this multimeric complex initiates downstream responses including the maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18) and inflammation-related cell death named pyroptosis (Tschopp et al. 2003; van Hout et al. 2016). Apart from atherosclerosis and acute MI, the role of the inflammasome in other inflammation-driven cardiovascular disease entities has been established. With regard to the heart, the most import diseases are affecting the heart muscle (cardiomyopathies) or involve inflammation of the myocardium (myocarditis) or pericardium (pericarditis). Concerning the blood vessels, the most important pathologies are dilation of the aorta (aortic aneurysm) and inflammation of the vessel wall (vasculitis).

In the current chapter, we will elaborate on the role of the inflammasome in CVD, especially focussing on atherosclerosis (leading to coronary artery disease), and its major consequence (MI). Additionally we will discuss the role of the inflammasome in HF and the less prevalent myocarditis and pericarditis, finishing with the evidence of inflammasome signalling in non-atherosclerotic vascular disease.

2.2 The Inflammasome in Atherosclerosis

2.2.1 Inflammation and Atherosclerosis

Atherosclerosis is the main cause of ischemic heart disease and stroke. It is characterized by the gradual development of lipid-rich plaques in the vessel wall. Lipoproteins, such as low-density lipoproteins (LDL), passively diffuse through the endothelial layer into the intima of the vessel wall (Lusis 2000). In the vessel wall, a complex set of biochemical reactions results in the oxidation of LDL. This so-called oxidized LDL, or oxLDL, serves as a pro-inflammatory mediator. OxLDL stimulates endothelial cells to produce pro-inflammatory molecules and increases the expression of adhesion factors on their cell surface (such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule 1 (VCAM-1)) to attract monocytes and lymphocytes to the vessel wall. Adhered monocytes transmigrate into the intima, differentiate into macrophages and phagocytose oxLDL, thereby forming foam cells. In contrast to LDL, high-density lipoprotein (HDL) is protective against atherosclerosis by removing cholesterol and inhibiting lipoprotein oxidation. The continuous accumulation of oxLDL particles and the phagocytosis of these particles by macrophages through scavenger receptors like CD36 lead to the formation of an early atherosclerotic plaque or fatty streak. From this stage onwards, the plaque progresses, as more immune cells infiltrate, smooth muscle cells (SMC) start to proliferate and calcium depositions take place (Lusis 2000).

Inflammation is the driving force behind the progression from a simple fatty streak to a complex, instable atherosclerotic plaque. The accumulated macrophages and lymphocytes produce inflammatory cytokines, such as TNFα, IL-1β, IL-6 and

IFNγ, inducing a positive feedback loop by attracting more circulating cells to the newly formed plaque. SMCs migrate from the media of the vessel wall to the surface of the plaque and start to form a fibrous cap. SMCs secrete fibrous extracellular matrix (ECM) further enhancing plaque growth, which eventually leads to expansion of the plaque into the vessel lumen (Libby and Hansson 2015). When the size of the plaque increases, blood vessels start to infiltrate the plaque to enable central oxygenation. However, this neovascularization leads to frequent intraplaque haemorrhage, thereby damaging and destabilizing the plaque. Moreover, since adequate blood supply fails, central necrosis of the plaque occurs. The local production of cytokines results in thinning of the fibrous cap, further destabilizing the plaque, making it prone to rupture. When the plaque ruptures, acute lumen occlusion due to thrombus formation occurs, leading to clinical complications such as MI. The pathogenesis of plaque formation is not only supported by experimental studies but also by observational data in which human vulnerable plaques generally have an increased number of inflammatory cells, a large necrotic core and a thin fibrous cap. Furthermore, plaque instability is associated with more intraplaque haemorrhage and more calcifications (Lusis 2000; Janoudi et al. 2016).

As outlined above, the key processes that drive the formation of atherosclerosis are inflammation on the one hand and lipid metabolism on the other (Gistera and Hansson 2017). Recently, many studies have shown that the inflammasome may serve as a central signalling structure in these processes and may be the link between cholesterol metabolism and immune activation (Janoudi et al. 2016). The expression, activation and role of the inflammasome in the pathogenesis of atherosclerosis are described below. In addition, inhibition of the inflammasome in preclinical and clinical studies is discussed.

2.2.2 Inflammasome Expression in Atherosclerosis

Many studies have shown that NLRP3 inflammasome activity is increased in atherosclerosis and that the level of activation correlates with the severity of disease. The inflammasome components (NLRP3, ASC, caspase-1) and its downstream effector molecules (IL-1β and IL-18) are present in human atherosclerotic lesions, with increased expression levels compared to healthy arteries (Paramel Varghese et al. 2016; Mallat et al. 2001). Vulnerable plaques (characterized by erosions, bleeding or ulcers) also show increased expression of the inflammasome (on histology and mRNA level) compared to morphologically stable plaques (Shi et al. 2015). The same is seen in symptomatic plaques, expressing higher IL-18 mRNA levels compared to asymptomatic plaques (Mallat et al. 2001). The inflammasome is localized in different areas of the human atherosclerotic plaque. IL-1β, IL-18 and the IL-18 receptors are mainly localized in macrophage-rich regions (Folco et al. 2014), and the IL-18 receptor is also expressed in endothelial

cells (Mallat et al. 2001). In circulating human peripheral blood mononuclear cells (PBMCs), NLRP3 protein levels correlate with the severity of coronary artery disease (on coronary angiography assessed by SYNTAX scores) and with clinical risk scores (GRACE score) (Afrasyab et al. 2016). Apart from local expression in the vessel wall and in circulating mononuclear cells, the levels of NLRP3, IL-1β and IL-18 (mRNA) in subcutaneous adipose tissue also correlate with and are independent predictors of the severity of coronary atherosclerosis (GEMINI and SYNTAX scores) (Bando et al. 2015).

2.2.3 Inflammasome Activators in Atherosclerosis

As mentioned, the inflammasome is considered an important link between lipid metabolism and inflammation (Janoudi et al. 2016). In the setting of atherosclerosis, multiple players in lipid metabolism are able to induce inflammasome activation. Cholesterol crystals, oxLDL and oxHDL can all activate the inflammasome and induce the secretion of IL-1β and IL-18 in human monocytes and macrophages in vitro (L'Homme et al. 2013; Thacker et al. 2016; Bleda et al. 2016; Xiao et al. 2013). OxLDL is recognized by CD36 receptors on recruited monocytes, leading through lysosomal pathways to NLRP3 inflammasome activation (Chen et al. 2014). In LPS-primed human monocytes, saturated fatty acids can also induce the release of IL-1β, whereas unsaturated fatty acids cannot (L'Homme et al. 2013). In contrast, HDL is able to suppress inflammasome activity in response to cholesterol crystals in human monocyte-derived macrophages (Thacker et al. 2016). Like monocytes, endothelial cells in vitro also show NLRP1 inflammasome activation after stimulation with plasma from patients with high triglyceride and cholesterol levels (Bleda et al. 2016).

Apart from lipid metabolism, other mechanisms are thought to be involved in inflammasome activation in atherosclerosis. Hypoxia, generally present in atherosclerotic plaques, is able to increase NLRP3 expression in human macrophages and limit degradation of pro-IL-1β, thereby prolonging its half-life (Folco et al. 2014). Atheroprone oscillatory shear blood flow is also able to induce NLRP3 inflammasome activation in endothelial cells. This is thought to happen via sterol regulatory element-binding protein 2 (SREBP2) (Xiao et al. 2013; Chen et al. 2014). The process of autophagy (controlled intracellular degradation of cell content) is often dysfunctional in atherosclerotic plaques. Mice lacking ATG5 (a protein important for autophagy) in macrophages showed decreased autophagy, resulting in an increased inflammasome activation and plaque size. Caspase-1 inhibition in these autophagy-deficient ATG5−/− macrophages reduced the IL-1β response. These results indicate that just like lipid products, hypoxia and oscillatory flow, dysfunctional autophagy can lead to inflammasome activation in atherosclerotic plaques (Razani et al. 2012).

2.2.4 *The Inflammasome in the Pathogenesis of Atherosclerosis*

Apart from associative evidence in human atherosclerotic plaques, most research on the role of the inflammasome in atherosclerosis is performed in knock-out mouse models to establish a causative role for the inflammasome. Widely used mouse models include LDLr−/− and ApoE−/− mice. Both mice develop atherosclerosis in a matter of weeks on a high-fat diet. The advantage of the ApoE−/− model is that complex vascular lesions also develop on a normal diet, but a high-fat diet results in more rapid lesion development with more foam cells present in the plaque. A downside of the ApoE−/− mice model is that ApoE has pleiotropic effects apart from plasma lipid levels. For instance, ApoE is described to have a function in macrophages and adrenal cells. The advantage of the LDLr−/− mice is that the LDL receptor does not have multiple functions as described for ApoE. However, on a normal diet, limited lesion development occurs in the LDLr−/− mice (Getz and Reardon 2015).

In LDLr−/− mice on a high-cholesterol diet, haematopoietic deletion of NLRP3, ASC or IL-1a/IL-β resulted in markedly decreased atherosclerosis and a reduction of inflammasome-dependent IL-18 levels (Duewell et al. 2010). Haematopoietic deletion of caspase-1/11 in LDLr−/− mice also resulted in a strong reduction in atherosclerotic plaque size with a reduced necrotic core (Hendrikx et al. 2015). Earlier studies in ApoE−/− mice indicated that IL-1 plays a role in fatty streak formation (Elhage et al. 1998; Kirii et al. 2003). In addition, the role of IL-18 was established in atherosclerosis development in ApoE−/− mice. ApoE−/− IL-18−/− double knock-out mice showed reduced IFN-γ responses and increased α-smooth muscle actin^{+} (αSMA) SMCs, indicating a more stable plaque phenotype. Surprisingly, the serum cholesterol and triglyceride levels were higher in the IL-18-deficient mice (Elhage et al. 2003; Whitman et al. 2002). ApoE−/− caspase-1−/− mice or ApoE−/− mice in which the NLRP3 gene was silenced also showed smaller atherosclerotic plaque areas compared to ApoE−/− alone, with less pro-inflammatory cytokine production (such as IL-1β) and reduced macrophage numbers in the plaque. Silencing of NLRP3 increased SMCs and collagen, leading to a more stabilized plaque phenotype (Zheng et al. 2014). In contrast, Usui et al. showed that in ApoE−/− caspase-1−/− mice, the amount of vascular SMCs in the plaques was reduced (Usui et al. 2012). Surprisingly, a study by Menu et al. was unable to show a difference in plaque progression, stability or infiltration of macrophages in ApoE−/− NLRP3−/− and ApoE−/− ASC−/− and ApoE−/− caspase-1−/− double-deficient mice compared to ApoE−/− (Menu et al. 2011). The reason for this discrepancy is unclear; the only difference with the study by Usui et al. (2012) is the amount of cholesterol (0.15% or 1.25%) the food pellets contained. Mice deficient in the $P2X_7$ receptor (ApoE−/− $P2X_7$r−/− mice), a receptor involved in activation of the NLRP3 inflammasome, showed less aortic atherosclerosis compared to ApoE−/− mice (Peng et al. 2015; Hansson and Klareskog 2011; Stachon et al. 2017). Apart from LDLr−/− and ApoE−/− models of atherosclerosis, the role of the inflammasome was also studied in a model of vascular injury and

neointima formation. This study showed that bone marrow-derived ASC is critical for neointima formation after vascular injury (Yajima et al. 2008).

These in vivo mice data support a role for the inflammasome and its downstream molecules IL-1β and IL-18 in the development of atherosclerosis. Different cell types, such as macrophages, SMCs and endothelial cells are proposed to be involved in this proatherogenic role of the inflammasome. Macrophages show reduced migratory capacity and increased susceptibility to lipid deposition after NLRP3 inflammasome activation in vitro; this can facilitate retention in the arterial wall and foam cell formation (Li et al. 2014). In vitro stimulation of SMCs with IL-1β induces VCAM-1 and monocyte chemoattractant protein-1 (MCP-1) expression and can in this way facilitate the recruitment of inflammatory cells to the atherosclerotic lesions (Wang et al. 1995). Inflammasome activation in SMCs can also lead to calcifications, a process involved in plaque progression (Wen et al. 2013). As mentioned before, endothelial cells can activate the inflammasome upon atheroprone oscillatory shear flow. This activation of the innate immune response can result in endothelial dysfunction, an important first step of atherogenesis (Xiao et al. 2013). Figure 2.1 summarizes the role of the inflammasome in atherosclerosis development.

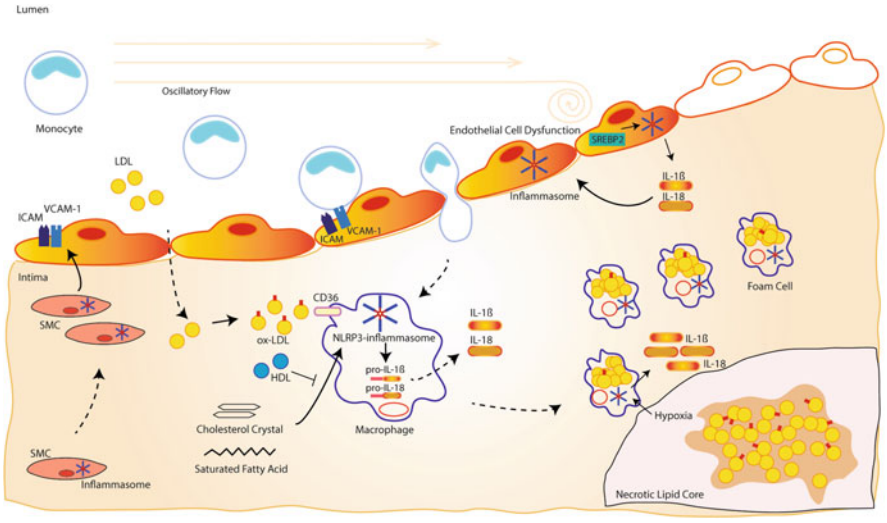

Fig. 2.1 Inflammasome activation in the pathogenesis of atherosclerotic plaque development. Low-density lipoprotein (LDL) migrates through the endothelial layer into the intima of the vessel wall, where it is oxidized, forming oxLDL. OxLDL and oscillatory blood flow activate the NLRP3 inflammasome in endothelial cells (the latter through sterol regulatory element-binding protein (SREBP2)), stimulating the expression of the adhesion molecules ICAM and VCAM-1. This facilitates monocyte adherence and migration to the intima of the vessel. OxLDL, cholesterol crystals and saturated fatty acids again induce NLRP3 inflammasome activation in macrophages present in the vessel wall. This results in the formation of foam cells and the production of IL-1β and IL-18. This results in local inflammation, inducing SMC migration and the formation of a fibrous cap. Activation of the inflammasome in SMCs, macrophages and endothelial cells initiates a vicious circle of endothelial dysfunction, monocyte recruitment and more foam cell formation, leading to the formation of a hypoxic, necrotic lipid core, intraplaque haemorrhage and eventual thinning of the fibrous cap, making the plaque prone to rupture

2.2.5 *Inflammasome Inhibition in Atherosclerosis*

Since genetic mouse models suggest a role for the inflammasome in the development of atherosclerosis, various inflammasome inhibitors for the prevention and treatment of atherosclerosis have been proposed. Injection of an anti-IL-1β monoclonal antibody in ApoE−/− mice inhibited the formation of atherosclerotic lesions and is associated with lower plasma non-HDL/HDL cholesterol ratios (Bhaskar et al. 2011). The most specific NLRP3 inflammasome inhibitor described today, MCC950 (Coll et al. 2015), has been tested in an ageing mouse model of atherosclerosis. Mice with TET2−/− bone marrow (causing somatic mutations in haematopoietic cells representing ageing) on an LDLr−/− background showed increased levels of inflammasome activity compared to LDLr−/− on a high-fat diet alone. The NLRP3 inflammasome inhibitor MCC950 significantly reduced atherosclerotic plaque size by 50% in the TET2−/− LDLr−/− mice compared to saline. In the LDLr−/− mice alone, a nonstatistically significant 20% reduction of plaque size by MCC950 was witnessed (Fuster et al. 2017). DPP-4 inhibitors, widely used in the treatment of patients with type-2 diabetes, can suppress NLRP3 activation and IL-1β release in a human monocyte cell line. LDLr−/− mice treated for 12 weeks with a DPP-4 inhibitor showed markedly decreased aortic plaque size with a reduced plaque macrophage content. Furthermore, DPP-4 inhibition in atherosclerosis led to reduced proliferation of vascular smooth muscle cells, inflammatory reaction, improved endothelial function and reduced thrombogenesis (Dai et al. 2014; Shah et al. 2011). Another compound that influences inflammasome activity is the plant-derived compound arglabation. Arglabation is able to attenuate atherosclerosis in ApoE−/− mice compared to untreated animals. Apart from NLRP3 inflammasome inhibition, a possible mechanism of action of arglabation is reducing plasma cholesterol and triglyceride levels (Abderrazak et al. 2015).

2.2.6 *Clinical Trials*

No clinical trials have been performed that specifically inhibit the inflammasome in human atherosclerosis. However, a major clinical trial on inhibition of IL-1β, one of the downstream effector molecules of the inflammasome, has recently produced very interesting results. The CANTOS (The Canakinumab Antiinflammatory Thrombosis Outcome Study) trial showed that the IL-1β antibody canakinumab in patients with stable coronary artery disease led to a significant lower rate of recurrent cardiovascular events than placebo. This double-blinded randomized trial enrolled 10,061 patients with coronary artery disease. Patients with elevated high-sensitive C-reactive protein (CRP) (>2 mg/L), despite contemporary secondary prevention, were included. CANTOS proves the hypothesis that after sufficient lipid lowering, there remains a ‘residual inflammatory risk’ and shows for the first time that targeting inflammatory processes in patients with cardiovascular disease significantly improves outcome

(Ridker et al. 2017). Blocking IL-1β is not the same as inflammasome inhibition. Direct inflammasome inhibition can theoretically prevent a broader range of potentially pathologic processes such as IL-18 signalling and pyropotosis. Moreover, IL-1beta signalling is not completely abolished by inflammasome inhibition, thereby presumably reducing severe infections, which were major adverse events in CANTOS.

Colchicine was also tested for its effects on recurrence rates in MI patients. Colchicine is a drug long known for its effectiveness in gout. Apart from other mechanisms, colchicine has shown to exert its effects through upstream inhibition of the NLRP3 inflammasome, thereby reducing the secretion of IL-1β and IL-18 (Martinon et al. 2006). In this trial, low-dose colchicine (LoDoCo) was tested in patients with stable coronary artery disease. The LoDoCo trial showed a strong effect of colchicine on the primary composite endpoint of acute coronary syndrome, out-of-hospital cardiac arrest or ischemic stroke (Nidorf et al. 2013). These promising effects of colchicine will be validated in a large, multicentre, double-blind LoDoCo2 trial which is currently being conducted.

2.2.7 Conclusion

Numerous animal and human studies show associative evidence for the inflammasome and the formation and severity of atherosclerosis. Mechanistic experiments have identified, e.g. oxidized lipid products and cholesterol crystals as the inducers of inflammasome activation in macrophages, leading to foam cell formation and IL-1β and IL-18 production. This results in a pro-inflammatory milieu that induces a vicious circle of endothelial dysfunction, recruitment of more inflammatory cells and additional foam cell formation.

Mouse models of atherosclerosis have established a key role for inflammasome activation in plaque development. These findings have led to clinical testing with the anti-IL-1β antibody canakinumab in patients with stable coronary artery disease in the CANTOS trial. This large phase III clinical trial showed for the first time that targeting inflammatory processes in patients with atherosclerosis significantly improves outcome and sets the stage for future trials specifically targeting the inflammasome in the setting of cardiovascular disease.

2.3 The Inflammasome in Myocardial Infarction and Heart Failure

2.3.1 From Myocardial Infarction to Heart Failure

Myocardial infarction (MI) is a major consequence of progressive atherosclerosis. MI occurs when an instable atherosclerotic plaque ruptures. This enables clot

formation, leading to sudden coronary artery occlusion, thereby hampering nutrients and oxygen delivery to the myocardium. In turn, this results in irreversible ischemic cell death and life-threatening deterioration of cardiac function. The primary treatment for MI should be immediate to confine as much damage as possible. Therapies have evolved rapidly in the past few decades from conservative approaches to minimally invasive low-risk percutaneous coronary interventions.

The ultimate treatment goal is to salvage viable myocardium from ischemic damage by re-establishing coronary perfusion (reperfusion) as soon as possible, thereby limiting infarct size and preserving cardiac function. It has been unequivocally proven that this rapid reperfusion is very beneficial to patients and reduces mortality (Steg et al. 2012). Paradoxically, a large body of evidence suggest that reperfusion itself can also damage viable myocardium (Vander Heide and Steenbergen 2013). Among other mechanisms, the damage induced by ischemia and reperfusion (ischemia-reperfusion injury or IRI) in the heart is due to activation of an exaggerated inflammatory reaction.

This acute phase of reperfusion injury (minutes to hours) is followed by a more chronic phase (days to weeks), in which the heart adapts to the loss of contractile function. A collagen-based scar is formed, and alteration of regional contractility, pressure and volume leads to geometric adaptations of the left ventricle. This process is termed adverse cardiac remodelling and is a major risk factor for the development of HF.

The syndrome of HF results from various structural and functional impairments of the cardiac muscle. Not only MI but also different aetiologies like hypertension, infections and genetic causes can lead to persistent cardiac damage and subsequent HF. The disease remains a major cause of morbidity and mortality, and despite improvements in therapy, overall prognosis continues to be poor (mortality rates approaching 50% in 5 years) (Braunwald 2015).

2.3.2 Inflammation as a Key Process

The post-MI inflammatory response is to some extent essential since the irreversibly damaged myocardium should be replaced by a strong collagen-based scar to prevent cardiac muscle rupture. However, inflammation after MI also results in additional cardiomyocyte death and further deterioration of cardiac function in the acute (minutes to hours), subacute (days to weeks) and chronic (weeks to months or years) phase after MI (van der Laan et al. 2012a, b; Maekawa et al. 2002; Takahashi et al. 2008).

Following cardiac ischemia, intracellular molecules such as ATP, mitochondrial DNA and high levels of potassium are released from the damaged cardiomyocytes. Reperfusion amplifies this effect, and as a result, these molecules are swiftly released into the systemic circulation. These so-called danger molecules or danger-associated molecular patterns (DAMPs) can be recognized by certain PRRs. These PRRs then

induce a pro-inflammatory state by activation of intranuclear transcription factors leading to activation of cytokines.

The activation of PRRs results in the induction of a pro-inflammatory state and the subsequent influx of circulating leucocytes. These circulating cells, of which neutrophils and monocytes are the first responders, cause injury to endothelial cells due to the excretion of reactive oxygen species (ROS), cytokines and proteases (Vinten-Johansen 2004). This will lead to the expression of cell adhesion molecules by endothelial cells, enabling the transmigration of circulating leucocytes, into the damaged myocardium. Here these inflammatory cells generate more ROS and proteases resulting into tissue breakdown and cellular clearance, thereby directly contributing to myocardial IRI (Arslan et al. 2011). Additionally, neutrophils produce matrix metalloproteinases (MMPs) that degrade the intermyocyte collagen struts thereby destabilizing the ventricular wall. This leads to infarct expansion, a process that is known to occur within hours from initial myocyte injury (Fig. 2.2) (Sutton and Sharpe 2000).

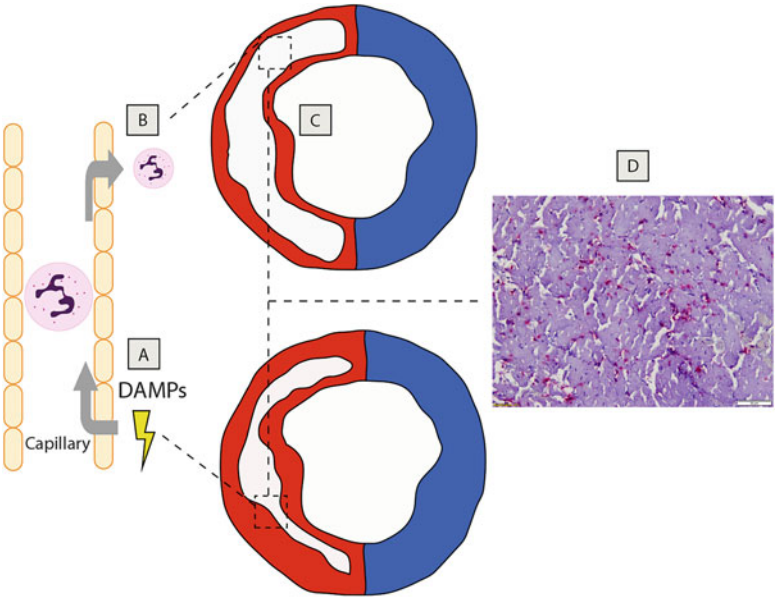

Fig. 2.2 Schematic overview of the occurrence of infarct extension after MI. Due to ischaemia-reperfusion injury, the infarct becomes larger according to a wave-front principle, with early subendocardial involvement and progression towards a transmural infarction. Due to ischaemia-reperfusion, DAMPs are released from the damaged myocardium and enter the systemic circulation (**a**). Here they activate circulating leucocytes, which subsequently transmigrate out of the circulation into the damaged tissue (**b**). Once resided, these inflammatory cells cause damage, thereby inducing infarct enlargement (**c**). (**d**) Histological sample of infarct tissue containing neutrophils in porcine myocardium 72 h after ischaemia-reperfusion injury (van Hout et al. 2016)

Depending on the size and location of the infarct, the loss of contractile myocardium leads to an alteration of ventricular pressure and increased wall stress. The increased wall stress again results in DAMP release and chronic low-grade inflammation. This gradually induces cardiomyocyte slippage in the left ventricle. Together with infarct expansion, this leads to further left ventricular wall thinning and progressive dilatation within the first days to weeks after MI. This process, referred to as adverse cardiac remodelling, initiates systemic neurohormonal adaptations and eventually culminates in HF (Sutton and Sharpe 2000; Heusch et al. 2014).

As in cardiac IRI and adverse cardiac remodelling, different chronic HF animal models indicate a role for the innate immune system in the pathophysiology of HF. In this phase of cardiac disease, DAMPs also play a central role and modulate interstitial cardiac fibrosis, cardiomyocyte apoptosis and hypertrophy. Low-grade chronic inflammation is present in HF, and pro-inflammatory cytokines (such as TNFα, IL-6, IL-1β, CRP) are increased in patients, and their levels relate to HF severity and prognosis (Hofmann and Frantz 2013; Butts et al. 2015).

The exaggerated inflammatory response after MI thus enhances acute IRI and is associated with an increased risk of adverse remodelling, HF and a worse prognosis. As outlined above, the activation of PRRs by DAMPs plays a central role in both these processes. Among these PRRs, the inflammasomes, of which the NLRP3 inflammasome has been studied in most detail, are thought to play a crucial role in MI. Inflammasome-based signalling involves a two-step process by which it is first primed (e.g. through Toll-like receptor (TLR) activation). This leads to the formation of inactive NLRP3 and IL-1β. The second activation step results in the formation of the inflammasome by adherence of the NLRP3 protein to ASC and caspase-1. Cleavage of caspase-1 then results in the formation of active IL-1β and IL-18. Importantly, triggering of the inflammasome alone in the heart is insufficient to induce cardiac dysfunction in mice in the absence of priming. Inflammasome formation in the heart is thus dependent on this priming signal and a subsequent separate triggering signal to activate the inflammasome (Toldo et al. 2015).

The evidence that the (NLRP3) inflammasome plays such a central role in the inflammatory reaction in MI, adverse remodelling and HF is generally derived from the observation that (1) different inflammasome components are upregulated, (2) the absence or inhibition of the inflammasome leads to damage reduction or (3) the effector molecules (IL-1β and IL-18) play a role in the pathogenesis of MI and HF. These three observations will be discussed here in more detail.

2.3.3 Inflammasome Upregulation in Myocardial Infarction and Heart Failure

The first direct evidence implicating the NLRP3 inflammasome as a key component in post-MI inflammation was provided by Kawaguchi et al. (2011). The investigators observed an upregulation of the inflammasome component ASC in human cardiac

tissue after MI. This was confirmed in a murine model of IRI. Importantly, both ASC−/− and caspase-1−/− mice subjected to 30 min of IR of the left coronary artery had smaller infarcts as a percentage of the area at risk at 48 h of reperfusion compared to wild-type mice. These hearts also showed less neutrophil and macrophage infiltration. Chimer experiments pointed to an upregulation of the inflammasome in both cardiac resident cells (fibroblast) and circulating cells, equally contributing to myocardial IRI.

In the same year, Mezzaroma et al. also provided strong evidence on the role of the NLRP3 inflammasome in MI (Mezzaroma et al. 2011). This study revealed increased inflammasome activation in isolated mouse cardiomyocytes when exposed to either ischemic conditions or a combination of the TLR primer LPS and ATP, a $P2X_7$ receptor activator. The investigators also observed a significantly increased expression of ASC in mice subjected to permanent coronary artery ligation. ASC activation was upregulated in cardiomyocytes, as well as cardiac fibroblast and infiltrated leucocytes, both after 3 and 7 days following MI.

It was revealed that, although cardiomyocytes do not secrete IL-1β or IL-18, the NLRP3 inflammasome is most certainly activated in this cell type. Instead of cytokine secretion, in cardiomyocytes, the activation of the NLRP3 inflammasome directly leads to pyroptosis (Mezzaroma et al. 2011). These experiments showed that the key role of the inflammasome in MI is not only due to an indirect effect, which is the secretion of the pro-inflammatory cytokines IL-1β or IL-18, but also directly on the viable myocardium by inducing cell death (Fig. 2.3).

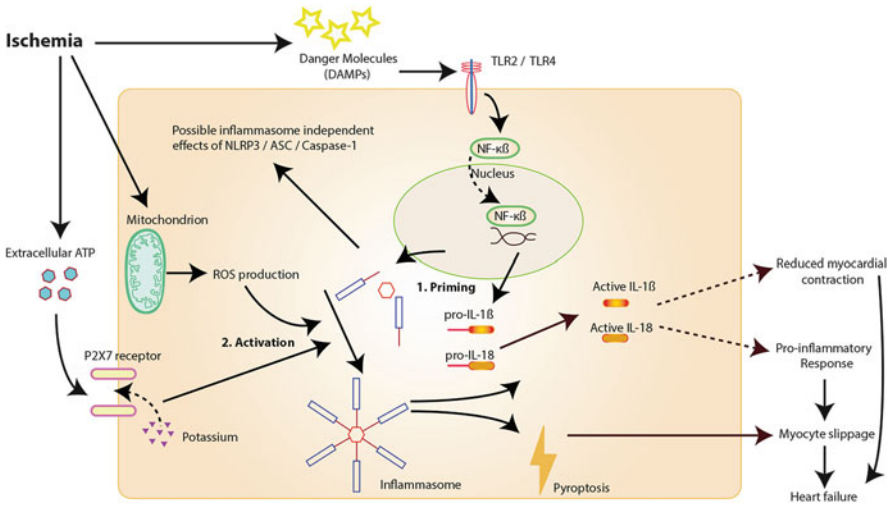

Fig. 2.3 Simplified schematic overview of inflammasome activation after myocardial infarction. Ischaemia results in the release of DAMPs that activate PRRs (e.g. Toll-like receptors (TLRs)) and induce nuclear migration of NF-κβ, resulting in priming of the inflammasome and production of pro-IL-1β. The inflammasome is then activated, for example, by activation of the $P2X_7$ receptor or reactive oxygen species (ROS) production after mitochondrial damage. This leads to the release of active forms of IL-1β and IL-18 and pyroptosis. Figure is adapted from (van Hout et al. 2016)

In addition to these data, clinical evidence indicates that certain polymorphisms in the NLRP3 gene protect against the development of MI, especially in women (Varghese et al. 2013). Another murine study showed that NLRP3−/− hearts were not susceptible to ischemic preconditioning, while wild-type and interestingly also ASC−/− hearts did show an infarct size reduction tested ex vivo in murine hearts (Zuurbier et al. 2012), indicating that the NLRP3 protein may be essential in cardioprotection. Moreover, when subjected to ex vivo global IR, NLRP3−/− hearts also show a preservation of cardiac function compared to ASC−/− hearts subjected to the same conditions (Sandanger et al. 2013). Interestingly, these data are contradictory with studies that showed that a lack of ASC was protective in mice subjected to MI.

Importantly, also negative results on the role of the NLRP3 inflammasome have been reported. In a closed-chest murine model of IR, NLRP3−/− mice did not show a reduction in infarct size compared to wild-type mice, possibly indicating that the NLRP3 inflammasome fulfils a role in the subacute and not acute time frame after MI (Jong et al. 2014). In extension to these findings, one study also reported larger infarcts as percentage of the area at risk in NLRP3−/− mice subjected to MI compared to wild-type or ASC−/− mice after both 3 and 24 h (Sandanger et al. 2016). These observations suggest a complex role for the inflammasome and its different components (NLRP3, ASC, caspase-1). It has been postulated that especially NLRP3 may have inflammasome-dependent and inflammasome-independent effects (Mezzaroma et al. 2014). These results also imply that the role of the inflammasome in MI is greatly dependent on the animal model and experimental conditions.

The NLRP3 inflammasome also plays a role in adverse remodelling and HF. The NLRP3 inflammasome enhanced fibrosis through increased expression in infiltrated M1 macrophages, a subset of macrophages that is believed to be the driving force behind the development of fibrosis (Liu et al. 2015). Increased methylation of the intron region of the ASC gene in PBMCs from HF patients was negatively associated with IL-1β levels and with an increased peak VO_2 during exercise testing, a surrogate marker for cardiac performance (Butts et al. 2017).

Already a decade ago, the role of caspase-1 was described in HF. Caspase-1 mRNA is upregulated in left ventricular myocardium of murine and human failing hearts. Transgenic mice that overexpress cardiac caspase-1 result in cardiomyocyte hypertrophy and fibrosis. With increasing age, these mice show cardiac dilatation and develop HF. Caspase-1-deficient mice displayed improved survival, less hypertrophy and cell death compared to wild-type mice after permanent ligation of the left anterior descending coronary artery (LAD) but show a similar infarct size (Merkle et al. 2007).

2.3.4 Inhibition of the Inflammasome

Apart from observational data, mechanistic experiments and studies with knock-out mice, important evidence for the role of the NLRP3 inflammasome in MI, also come

from the pharmacological inhibition of inflammasome formation in preclinical MI models. Mice subjected to permanent coronary artery ligation showed a marked infarct size reduction when pretreated with silencing RNA for either NLRP3 or the $P2X_7$ receptor that, after activation by ATP, opens a cation channel allowing for potassium efflux that can lead to NLRP3 inflammasome activation in MI (Mezzaroma et al. 2011). Similar results were obtained when a pharmacological inhibitor of $P2X_7$ was administered.

A newly developed small-molecule inhibitor named 16,673-34-0 has also shown to decrease infarct size in a pretreatment mouse model of permanent coronary artery ligation (Marchetti et al. 2014). These findings were later confirmed in both a permanent ligation and IR model of MI (Marchetti et al. 2015). Importantly a recent study revealed that when administering this compound up to 1 h after reperfusion, it could still effectively decrease the infarct size in a murine model of 30-min transient coronary artery occlusion. This effect could be detected no sooner than 24 h, suggesting that NLRP3 inflammasome inhibition in the first hours is not sufficient to render a clinically significant effect (Toldo et al. 2016).

Recent evidence has also revealed that reperfusion therapy with recombinant human relaxin-2 (serelaxin) reduces infarct size in a murine model of IRI through inhibition of the NLRP3 inflammasome (Valle Raleigh et al. 2017). Interestingly, also L5-LDL, an electronegative LDL particle that is increased in patients suffering from MI, is able to activate the NLRP3 inflammasome and could therefore be a clinically relevant DAMP of the inflammasome in acute MI (Yang et al. 2017). Moreover colchicine administered to mice undergoing permanent coronary artery ligation leads to a reduction in inflammasome expression as well as infarct size compared to these parameters in control animals (Fujisue et al. 2017). In addition, in patients with an acute coronary syndrome, colchicine is able to inhibit the production of IL-1β and IL-18 (Martinez et al. 2015).

Calcineurin-transgenic (CNTg) mice develop progressive cardiac dysfunction. NLRP3−/− CNTg double-deficient mice show improved cardiac function assessed by fractional shortening compared to CNTg mice, indicating a role for the inflammasome in this HF model. IL-1 receptor antagonism for 2 weeks in CNTg mice resulted in significantly reduced left ventricular dilatation and an improved FS compared to saline. Mononuclear cell infiltrate was reduced in the treated mice, but no changes were observed at the level of hypertrophy (Bracey et al. 2013).

To translate these findings to a clinical application, a study with a highly translational pig model of MI with a clinically feasible treatment protocol has recently been performed. In this study pigs were subjected to a 75-min transient coronary artery occlusion. The selective NLRP3 inflammasome inhibitor MCC950 showed a dose-dependent effect on both infarct size and cardiac function. Moreover, this resulted in decreased inflammasome expression and a reduction of cardiac inflammation (van Hout et al. 2017).

2.3.5 Targeting the Downstream Cytokines IL-1β and IL-18

Activation of the NLRP3 inflammasome leads to the formation and subsequent release of active IL-1β and IL-18. The role of het NLRP3 inflammasome in cardiac IRI and adverse remodelling could therefore not only be determined by direct inhibition of the inflammasome but also through interference with signalling of both these cytokines.

2.3.5.1 Interleukin-1β

IL-1β is thought to play a central role in post-MI inflammation (Frangogiannis 2015). Interference with IL-1β signalling by genetic deletion of the IL-1 receptor (IL-1R1) protected against both cardiac IR and permanent ligation in mice (Bujak et al. 2008; Abbate et al. 2011). Overexpression of the naturally occurring IL-1R antagonist also resulted in a preservation of cardiac function, and deletion of this antagonist culminates in deterioration of cardiac function in mice (Abbate et al. 2011; Suzuki et al. 2001). Moreover, administration of the IL-1 receptor blocker anakinra resulted in enhanced cardiac performance and reduced cardiomyocyte apoptosis, presumably independent of infarct size (Abbate et al. 2008; Salloum et al. 2009). Additionally, pretreatment with anakinra also led to infarct size reduction in a mouse model of MI (Feng et al. 2010).

After the development of anakinra, another IL-1 inhibitor was developed, consisting of the IL-1 receptor, the IL-1 receptor-associated protein and the Fc fragment of an immunoglobulin (Van Tassell et al. 2010). This recombinant protein, named the 'IL-1 trap' (rilonacept), showed to have beneficial effects on remodelling in a mouse model of MI. These data suggest that the role of IL-1β is pivotal, since it not only deteriorates cardiac function through directly decreasing cardiac contractility but also through the enhancement of myocardial infarct size.

Importantly, by blocking the IL-receptor, IL-1α signalling is also hampered, so part of the effect that was seen in these studies could be due to interference with signalling of this IL-1 isoform (Van Tassell et al. 2013a, 2015). To further investigate this, several IL-1β antibodies have been developed, enabling identification of the specific role of IL-1β in cardiac remodelling. The first study on an antibody directed at IL-1β reported impaired healing of the heart and favoured cardiac rupture in a permanent MI model (Hwang et al. 2001). Since studies that investigated inference with combined IL-1β and IL-1α signalling showed opposite results, it was suggested that selective IL-1β blockade would induce adverse effects. Recently, more thoroughly characterized antibodies, specially developed for in vivo use, were tested. In both of these studies, beneficial effects were seen in mice subjected to MI and treated with these compounds (Toldo et al. 2013; Abbate et al. 2010a). The adverse effects seen in the first study were therefore believed to be caused by pleiotropic effects of the antibody.

Since anakinra has been registered for clinical usage in rheumatoid arthritis, off-target testing of these compounds was feasible, and clinical evidence on the role of IL-1β in the healing process of MI is also available. Two pilot studies (VCU-ART and VCU-ART2) have been performed (Abbate et al. 2010b, 2013). Both of these studies included ST-segment elevation MI patients that were clinically stable and had undergone percutaneous coronary intervention with successful reperfusion. Patients were treated with anakinra and were followed up for 3 months. Although no significant results were seen regarding major adverse cardiac events, the anakinra-treated patients did show lower levels of CRP at 72 h and were less likely to develop new-onset HF. Although not significant when corrected for baseline differences, a trend towards improved left ventricular geometry was also seen in these patients. Future phase III trials should further investigate if anakinra is effective in MI patients.

In HF patients, IL-1β also seems to play an important role. In patients with idiopathic dilated cardiomyopathy, plasma Il-1β levels correlate with left ventricular mass and severity of mitral valve regurgitation. In these patients, IL-1β is also a predictor of outcome (death or cardiac transplantation) (Aleksova et al. 2017). From mice models we know that IL-1β negatively influences myocardial contractility. Injection of IL-1β (3 μg/kg) in healthy mice reduces cardiac function measured by left ventricular fractional shortening (LVFS) already at 4 h after injection. Stressing these mice with β-receptor stimulation (using isoproterenol), an impaired contractile reserve with a right shift of the dose-response curve was revealed. After stopping IL-1β injections, LVFS returned to baseline levels. This indicates that IL-1β is able to induce a reversible contractile dysfunction (Van Tassell et al. 2013b). Two pilot studies investigated the effect of anakinra on cardiopulmonary exercise testing performance in patients with HF with a reduced ejection fraction (HFrEF) (Van Tassell et al. 2012) and in patients with HF with a preserved ejection fraction (HFpEF) (Van Tassell et al. 2014). In both HF groups, anakinra led to an improvement of peak oxygen consumption (VO_2) and resulted in a reduction of CRP. The improved aerobic exercise capacity in these patients by anakinra could be predicted by baseline exercise capacity and not by baseline CRP or BNP (Canada et al. 2014).

2.3.5.2 Interleukin-18

Similar to IL-1β, IL-18 is also secreted after activation of the (NLRP3) inflammasome as a result of caspase-1 cleavage. Unlike IL-1β, however, the inactive precursor of IL-18 is not formed through cellular priming (e.g. by TLR activation) but is abundantly present in inactivated cells of almost every cell type. Also similar to IL-1β, the activity of IL-18 is balanced by its counterpart, the IL-18-binding protein (Dinarello et al. 2013). Inflammation caused by the downstream effects of both IL-1β and IL-18 therefore not only depends on inflammasome activation but also on the balance between these cytokines and their naturally occurring antagonists (Dinarello and van der Meer 2013).

Several experimental studies have been performed, showing that blocking IL-18 signalling is protective in cardiac injury. Administration of IL-18 in mice results in left ventricular hypertrophy and increased collagen formation, both predictors of long-term cardiac failure (Platis et al. 2008; Woldbaek et al. 2005). In another study, mice infused with the well-characterized danger molecule lipopolysaccharide showed a depressed cardiac function. When IL-18 signalling was neutralized in this study, animals showed a preserved cardiac function, presumably through decreased release and expression of TNFα and adhesion molecules (Raeburn et al. 2002).

Interestingly, IL-18 and IL-1β not only enhance myocardial damage and suppress cardiac function separately but also work in a synergistic way (Toldo et al. 2014a). In these experiments, mice lacking IL-18 did not show decreased cardiac contractility when treated with recombinant IL-1β, whereas the control group did. Importantly, downstream IL-6-mediated signalling was not affected in this study. This suggests that IL-18 is essential for IL-1β-mediated reduced contractility, but not for IL-1-β-mediated inflammation, the two processes by which these cytokines directly and indirectly induce cardiac dysfunction. Inflammasome inhibition could therefore be more effective than blocking either one of these cytokines by both directly preserving cardiac contractility as well as attenuation of the inflammatory response.

Human studies also show evidence for an important role of IL-18 in relationship to cardiac damage and contractility. HF patients have elevated levels of IL-18, and a correlation between these levels and mortality exists (Mallat et al. 2004). Experiments with ex vivo human atrial muscle strips revealed increased contractility and increased intracellular tissue creatine kinase when IL-18-binding protein was added to the perfusate after inducing cardiac ischaemia (Pomerantz et al. 2001). In a large cohort of 1229 patients with a median follow-up of almost 4 years, levels of plasma IL-18 correlated with future cardiac events and mortality (Blankenberg et al. 2002).

2.4 Inflammasome in Myocarditis

Myocarditis is characterized by an acute or chronic inflammatory response of the heart to environmental (such as viruses) or endogenous triggers (such as autoimmune myocarditis). The pathogenesis of myocarditis varies per trigger. In virus-mediated myocarditis, within hours after viral entry in the cardiomyocyte, type 1 interferon is produced leading to myocyte cell death. The second phase evolves after hours to days, involving activation of innate immune responses, including the inflammasome. The inflammatory response in myocarditis can rapidly escalate into an auto-inflammatory cycle, leading to chronic autoantigen-driven inflammation. This can progress in dilated cardiomyopathy and HF (Heymans et al. 2016).

2.4.1 Inflammasome Activation in Myocarditis

Endomyocardial biopsies from patients with acute lymphocytic myocarditis or myocarditis diagnosed in post-mortem samples showed signs of inflammasome

activation by ASC aggregation in leucocytes, cardiomyocytes, fibroblasts and endothelial cells, whereas in control samples, these aggregates were absent. The number of inflammasome-activated cells was higher in patients presenting with severe HF (NYHA III–IV compared to I–II) and in patients with no recovery of LVEF after 6 months (Toldo et al. 2014b). In vitro experiments with cardiomyocytes exposed to Coxsackie B (CVB3) virus (a well-known trigger for myocarditis) reveal an upregulation of inflammasome activity. In a mouse model of CVB3-induced viral myocarditis, levels of ASC, caspase-1 and IL-1β were upregulated in cardiac tissue. Importantly, IL-1β production correlated positively with myocarditis severity (Wang et al. 2014).

2.4.2 Inflammasome Inhibition in Myocarditis

CVB3-induced viral myocarditis mice treated with a caspase-1 inhibitor (Ac-YVAD-CHO) or an IL-1β blocking antibody showed less severe myocarditis expressed by creatine kinase levels and increased cardiac LVEF compared to placebo (Wang et al. 2014). In humans only case reports of inflammasome pathway inhibition by IL-1β blockade using anakinra have been described in fulminant, viral myocarditis. Standard clinical management for these patients includes mechanical support, but no specific treatments are available. A patient with fulminant myocarditis that developed severe biventricular dysfunction with systemic inflammation leading to cardiogenic shock received anakinra. Already 24 h after initiation of anakinra (100 mg/day), clinical improvement was witnessed with fever reduction, lowering of infection parameters and improvement of LVEF (Cavalli et al. 2017; Noji 2016). Another report describes a similar case with fulminant myocarditis treated with anakinra; within 4 days of treatment, clinical improvement and weaning from mechanical support were achieved (Cavalli et al. 2016). These case reports might indicate that IL-1 blockade is effective for the treatment of fulminant myocarditis, although further confirmation in the setting of clinical trials is needed. No reports on the role of the inflammasome in autoimmune myocarditis are available.

2.5 Inflammasome in Pericarditis

Pericarditis is inflammation of the pericardium. Most cases (80–90%) are thought to be idiopathic, although unidentified viral infection may to some extent be responsible. Among severe complications is recurrent pericarditis. Recurrent pericarditis affects up to 30% of patients after a first episode of acute pericarditis and is a difficult clinical problem. The cause of recurrent pericarditis is unknown but appears to be autoimmune mediated. The primary treatment for pericarditis is colchicine as an adjunctive therapy to NSAIDs. One of the working mechanisms of colchicine is through upstream inhibition of the NLRP3 inflammasome (Stack et al. 2015).

Colchicine effectively reduces recurrence rates in patients with recurrent pericarditis or acute pericarditis (Alabed et al. 2014). However, there are patients with recurrent pericarditis with colchicine resistance and corticosteroid dependence. In these patients, the effect of anakinra was studied in two small clinical trials. These preliminary reports appear promising. However, further larger randomized controlled trials are required (Baskar et al. 2016; Brucato et al. 2016).

2.6 The Inflammasome in Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAA) are permanent and localized aortic dilations that mainly develop below the renal arteries. Often the aneurysms remain asymptomatic and undiagnosed, but with increasing size, the risk of rupture dramatically increases. Histological features include chronic medial and adventitial inflammatory cell infiltration (neutrophils, T- and B-cells, macrophages, mast cells, NK cells) and elastin degeneration. Chronic inflammation is a driving force in the pathogenesis of AAA, resulting in progressive remodelling and deterioration of the aortic wall (Libby and Hansson 2015; Shimizu et al. 2006). The inflammasome is thought to play a role in these inflammatory pathways. This is suggested by increased plasma IL-1β levels in AAA patients compared to controls (Wu et al. 2016). Immunohistochemistry also revealed higher expression of NLRP3, ASC, caspase-1 and caspase-5 and AIM2 in AAA compared to control aortas (Dihlmann et al. 2014; Wu et al. 2017). In PBMCs isolated from AAA patients, caspase-1 and IL-1β mRNA levels were also increased compared to controls. These differences were especially pronounced in males with AAA and not present in females. In contrast, PBMC AIM2, NLRP3 and ASC mRNA levels did not differ between AAA patients and controls (Wu et al. 2016).

The structural integrity of the aortic wall depends on vascular smooth muscle cells (SMCs) and the extracellular matrix. SMC contractile dysfunction is thought to play a role in aortic aneurysm and dissection development. Stressing SMCs leads to tropomyosin and myosin heavy chain degradation. Caspase-1 is able to cleave these contractile proteins. Reduction of inflammasome activity (by siRNA or pharmacological inhibition) prevents the degradation of tropomyosin and myosin heavy chain in SMCs in vitro. These findings indicate that the inflammasome might be involved in SMC dysfunction.

In vivo mice models are available to study the role of the inflammasome in AAA. Mice on a high-fat diet receiving angiotensin II (AngII) infusion develop aortic aneurysms and dissections. In these aortic lesions, inflammasome activity is increased compared to healthy arteries. AngII infusion in NLRP3−/− and caspase-1−/− mice resulted in a preserved aortic structure and reduced aortic enlargement and dissection development compared to the WT phenotype (Wu et al. 2017). The same reduction was seen in AngII-infused double knock-out Apoe−/−NLRP3−/−, Apoe−/− ASC−/− and Apoe−/−casp-1−/− mice, compared to Apoe−/− alone. One of the possible mechanisms may be inhibition of

mitochondria-derived ROS that is stimulated by AngII infusion in the inflammasome-deficient animals (Usui et al. 2015). In aortic rings from these aneurysm-developing mice, the contractile response to phenylephrine is reduced. NLRP3−/− and caspase-1−/− aortic rings showed preserved contractile response to phenylephrine (Wu et al. 2017). In another mice model of AAA development (by perivascular calcium phosphate treatment), lentiviral silencing of NLRP3 resulted in a smaller diameter of the aorta compared to empty virus (Sun et al. 2015).

2.7 The Inflammasome in Vasculitis

Vasculitides are heterogeneous clinical entities all characterized by inflammation of the vessel wall. In most cases, the cause of vasculitis is unknown, but often autoimmune processes are thought to play a role. Therapy depends on the specific type of vasculitis but most of the time includes immune suppression. The different types of vasculitis are grouped by size of the affected blood vessels: large, medium or small. The role of the inflammasome is described in a subset of vasculitides and will be summarized below (Ramirez et al. 2014).

2.7.1 Giant-Cell Arteritis

Giant-cell arteritis (GCA) is a chronic systemic vasculitis affecting large- and medium-sized arteries. It is the most predominant vasculitis in Western countries mainly affecting females. Pro-inflammatory cytokines play a major role in the pathogenesis of GCA, and the inflammasome may be involved in this complex polygenic disease. IL-1β and IL-18 are expressed in temporal arteries from patients with GCA (Hernandez-Rodriguez et al. 2004; Blain et al. 2002), but IL-18 expression does not correlate with clinical manifestations or haematological parameters (Shahriar Nabili et al. 2008). IL-18 gene polymorphisms (rs1946518) have been described to be associated with GCA susceptibility, but again not with clinical manifestations (Palomino-Morales et al. 2010). Also NLRP1 gene polymorphisms (rs8182352) are associated with biopsy-proven GCA (Serrano et al. 2013).

2.7.2 Kawasaki Disease

Kawasaki disease (KD), a medium-sized vessel vasculitis, is the most common cause of acute vasculitis in children. It is the main cause of acquired heart disease affecting mainly children below the age of 5. The disease characterizes itself by coronary arteritis with inflammatory cell infiltration and extracellular matrix distraction. Consequences of KD are coronary artery aneurysms, MI and sudden cardiac

death. Standard therapy includes intravenous immunoglobulins, but up to a third of patients fail to respond to therapy. These children are at increased risk for development of coronary abnormalities. The cause of KD is unknown, but abnormal immune responses to infectious agents could be involved in the pathophysiology. Many cytokines and chemokines are elevated during the acute phase of the disease, including IL-1β (Takahashi et al. 2014). Peripheral blood mononuclear cells (PBMCs) from KD patients spontaneously release IL-1β in greater levels compared to healthy controls (Suzuki et al. 1996). Higher IL-1β release is seen in patients that failed to respond to standard therapy with intravenous immunoglobulins and in patients that develop coronary artery abnormalities (Leung et al. 1989).

Genetic data show that polymorphisms in the IL-1β gene that are related to increased IL-1β production are associated with intravenous immunoglobulin resistance (Weng et al. 2010). In patients unresponsive to immunoglobulins, transcript abundance for IL-1 pathway genes is found to be higher compared to responsive KD patients (Fury et al. 2010). To study the causative role of the inflammasome in KD, mice models are used. A frequently used model is the lactobacillus casei cell wall extract (LCWE)-induced model of coronary arteritis. A single injection of LCWE reproducibly induces proximal coronary arteritis with histopathologic characteristics very similar to the coronary arteritis observed in human KD (Lehman et al. 1985). In this model, IL-1β increased in an inflammasome-dependent manner. NLRP3−/−, caspase-1−/−, IL-1β−/− and IL-1R−/− mice were all protected from LCWE-induced vasculitis and coronary arthritis and showed less vascular inflammation (Lee et al. 2012, 2015). LCWE injection induced NLRP3 activity in endothelial cells and in $CD11^+$ macrophages in the vascular lesions, resulting in increased caspase-1 activity and IL-1β production (Chen et al. 2015). Experiments with chimeric mice showed that stromal IL-1β signalling is required for LCWE-induced vasculitis and coronary arteritis and that IL-1 signalling is not required in haematopoietic cells (Lee et al. 2015). In LCWE-induced vasculitis, anakinra (IL-1R antagonist) was able to block development of coronary lesions and myocarditis (Lee et al. 2012). Quercetin, an antioxidant (found in fruits, vegetables and nuts), was able to inhibit both the NLRP3 and AIM2 inflammasome by preventing ASC oligomerization. Intraperitoneal injection with quercetin for 7 days following LCWE injection reduced coronary arteritis and aneurysm formation. Quercetin inhibited local caspase-1 activity in vascular lesions resulting in less intimal and myofibroblast proliferation (Domiciano et al. 2017).

2.7.3 Inflammasome in Behçet

Behçet's syndrome is a systemic inflammatory disorder with multiple disease manifestations including vasculitis, affecting both small and large vessels. In Behçet patients with vascular involvement, IL-1β production after whole blood LPS stimulation was significantly increased compared to healthy controls and to patients without vascular involvement (Yuksel et al. 2014). For the treatment of Behçet's,

anakinra and canakinumab have proven to be safe and efficacious in refractory Behçet's disease, strengthening the hypothesis that Behçet's may be considered an IL-1-mediated disease (Emmi et al. 2016).

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