Chapter 13
Aging and the Inflammasomes

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Contents

Abstract The inflammasomes are innate immune system sensors that control the activation of caspase-1 and induce inflammation in response to infectious microbes and molecules originating from host proteins, leading to the release of

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pro-inflammatory cytokines, Il1b and IL18, and a particular inflammatory type of cell death termed pyroptosis. It is broadly considered that chronic inflammation may be a common link in age-related diseases, aging being the greatest risk factor for the development of chronic diseases. In this sense, we discuss the role of inflammasomes in non-infectious inflammation and their interest in aging and age-related diseases.

Keywords Inflammasomes · Aging · Age-related diseases · Chronic inflammatory diseases

Why does aging occur? Aging constitutes one of the biggest concerns for the human being and to ask why do we age is to enter the field of evolutionary biology, which is crucial to understand health and disease (Kirkwood 2005). Nowadays, the challenge for researchers lies in explaining the reasons for aging instead of the obvious drawbacks of the natural process. Aging is commonly characterized as a progressive and generalized impairment of function, resulting in an increased vulnerability to environmental and genetic factors (Ljubuncic and Reznick 2009; Jin 2010; Lipsky and King 2015). Getting older is in fact, a highly medically relevant and enigmatic biological process, because despite considering increased longevity a remarkable achievement for humankind, aging is the major risk factor for the development of chronic diseases and represents an extraordinary financial burden on the health care systems (Leon and Gustafsson 2016). It is estimated that in 15 years, a large percentage of the population will be aged 65 or older (North and Sinclair 2012). The aging process is linked to an accumulation of mutations and genomic instability resulting in a progressive functional and structural decline in multiple organs. Therefore, far from being considered an illness in itself, aging is the greatest risk factor for the onset of chronic age-related diseases such as cardiovascular disease, cancer, diabetes, Alzheimer's disease (AD), and a tendency to infection (Strowig et al. 2012).

However, and despite the current advances in medicine to date, some questions concerning the span of human life and health remain. Over the years, various principles to explain the reasons for aging have been proposed, but the mechanisms are still unclear, although many of the theories have arisen from the necessity of explaining how the aging process takes place (Kirkwood 2005).

13.1 The Science of Elderly

Biological aging is initiated from the time of the birth of organisms and refers to a progressive manifestation of accumulated cellular damage determined by both genetic and environmental factors. The process of aging is complicated and can be elucidated by many theories. One of the best-known and most conventional approaches to date is the mitochondrial free radical theory of aging, nowadays termed the "oxidative stress theory" (Chandrasekaran et al. 2017). The oxidative stress hypothesis interprets aging at a molecular level, explaining that aging occurs because of an imbalance between the production of reactive oxygen species (ROS) and the capacity of the biological system to repair the outcoming damage, resulting

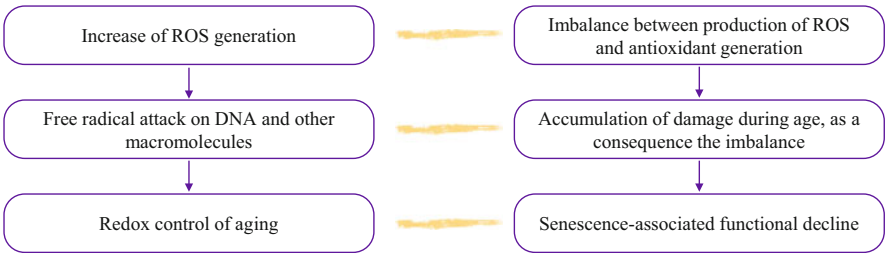

Fig. 13.1 Graphic image of the oxidative stress theory of aging. The primary element of this hypothesis is the increase in oxidant flux and the concomitant failure of antioxidant mechanisms, causing structural damage to macromolecules that accumulates with age, leading to the typical decline occurring in the elderly

in the failure to maintain the mitochondrial integrity and DNA repair (Fig. 13.1). ROS molecules include superoxide ($O_2^{\bullet -}$), hydroxyl radical ($OH^{\bullet}$), hydroperoxyl radical ($HO_2^{\bullet}$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), and peroxyl ($ROO^{\bullet}$), produced either as by-products during the mitochondrial electron transport of aerobic respiration or by oxidoreductase enzymes.

Nowadays, several aging mechanisms exist that are widely acknowledged. However, what is very restricting is that in practice, most research is focused on unique mechanisms of theories that indicate that molecular and cellular lesions hypothesized do occur as we age, but there are no data that demonstrate the theory itself to be sufficient to account for age-related disease. Therefore, recent initiatives state that there is a need to develop a net of aging theories considering the contribution of various mechanisms together, allowing the interaction of different processes (Kirkwood et al. 2003).

Although many theories could explain the aging process (Chandrasekaran et al. 2017), recent studies have shown that immunological inflammation may be closely linked to aging. As we age, the adaptive immunity response significantly declines (Goldberg and Dixit 2015). This concept is known as immunosenescence, where the innate immunity response is markedly activated, leading to the senescent low-level, chronic inflammatory phenotype known as "inflammaging." The concept "inflammaging" describes the systemic low-grade inflammatory process that contributes to the development of chronic diseases and degenerative changes during the aging process. Franceschi et al. (2000) coined the word "inflammaging" in 2000, referring to a progressive increase in proinflammatory status, a significant characteristic of aging. This fact can be reflected in diseases where chronic and abnormal inflammation exists (Franceschi et al. 2000). Age-related inflammation in various organs may lead to a considerable decline, even in the absence of any disease. For example, chronic inflammation is simultaneously associated with aging and with age-related diseases, such as diabetes, atherosclerosis, cancer or neurodegenerative diseases.

It is believed that a systemic increase in inflammation contributes to incremented disease prevalence and severity during aging (Franceschi and Campisi 2014), because aging is associated with an increment in IL-18, IL-1b, and IL-6. Notably, Il-1b and IL-18 are produced after inflammasome-dependent caspase-1 activation, and interestingly, many of the endogenous signals that have been described as inflammasome activators are known to accumulate as we age.

13.2 Inflammasomes

13.2.1 Structure and Mechanisms of Activation

The "inflammasome," a term coined by Schroder and Tschopp in 2010, is a group of multimeric proteins that assemble in the cytosol when pathogenic microorganisms or sterile stressors are present, and is also involved in the onset and development of the inflammatory response. Stimuli related to infection are known as pathogen-associated molecular patterns (PAMPs); however, those referring to endogenous cellular stress derived from host proteins, are danger-associated molecular patterns (DAMPs) (Strowig et al. 2012). The inflammasome assembly culminates in the activation of caspase-1. Subsequently, active caspase-1 cleavage triggers a signaling cascade that leads to release of type I interferon (IFN alpha and beta) and pro-inflammatory cytokines (IL-1b and IL-18), finally inducing an inflammatory type of cell death termed pyroptosis (de Zoete et al. 2014; Guo et al. 2015). Dysregulation of inflammasomes has been linked with many autoinflammatory and autoimmune diseases, including metabolic disorders (type 2 diabetes [T2D] mellitus, obesity, atherosclerosis) and neurodegenerative diseases (multiple sclerosis, AD, Parkinson's disease). Therefore, the current understanding of inflammasome activation and its involvement in inflammatory pathological conditions have drawn scientific community attention to developing potential therapies targeting inflammasomes (Youm et al. 2013).

Structurally, inflammasomes consist of an intracellular sensor protein, which usually is a NOD-like receptor (NLR), the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the proinflammatory caspase-1 precursor (Schroder and Tschopp 2010). The first family of sensor proteins discovered to form inflammasomes was the nucleotide-binding domain and leucine-rich repeat-containing receptor, the NLR family consisting of 22 genes in humans and 33 in mice (Ting et al. 2008). NLRs are classified according to their domain structure. All NLRs, except NLRP10, contain a leucine-rich repeat (LRR) domain, which is thought to provide the critical structural framework for molecular interactions, and a signaling domain (Ting et al. 2008) that enables the recruitment of caspase-1, directly through caspase recruitment domain (CARD)–CARD interactions, such as NLRC4 inflammasome (Guo et al. 2015) or indirectly, through a PYRIN domain that is shown to bind to ASC. Apart from the NLR family, non-NLR proteins can also assemble to conform to inflammasomes and possess an HIN-200 DNA-binding domain instead of an LRR, such as the AIM2-like receptor (ALR) family. Then, as mentioned before, upon sensing certain stimuli, NLR or AIM2 can oligomerize to become a caspase-1-activated scaffold.

The most interesting and relevant question related to the inflammasome field is connected to the specific signals that lead to the assembly of the different NLRs or ALRs into active complexes, as the stimuli leading to activation of the different inflammasomes consist of a wide range of variable and selective activators.

The NLRs share a similar structure consisting of three domains:

1. A central nucleotide binding oligomerization domain NOD or NACHT.
2. A C-terminal domain LRR present in all members of the family (except for NLRP10) and believed to be used for PAMPs recognition.
3. An N-terminal domain of recruitment of effector molecules, which determines the classification of the different NLRs (Fig. 13.2).

a

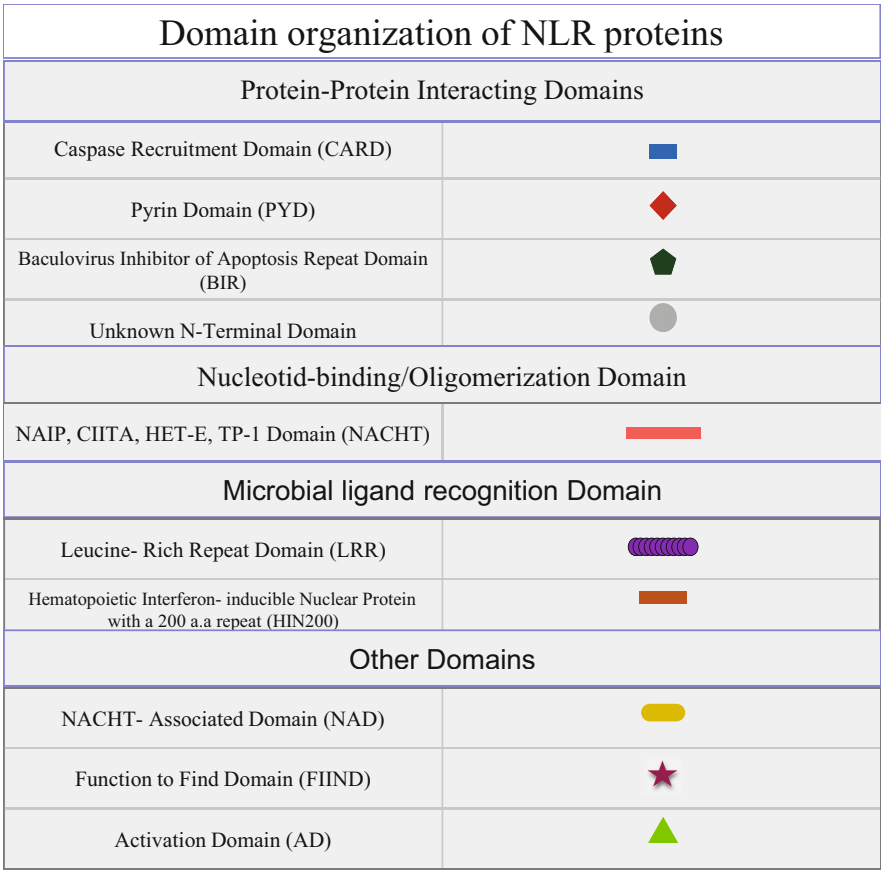

Fig. 13.2 (**a**) Domain key for inflammasome classification. Inflammasome names are based on the protein forming the scaffold. NLR proteins are categorized into four subfamilies, depending on the type of N-terminal domain; the NLRA subfamily refers to the acidic transactivating domain: CIITA. (**b**) Classification of different NLR proteins according to their domain structure. From the NLRB subfamily is for baculovirus inhibitor apoptosis repeats present in NLR family apoptosis-inhibiting proteins; NLRCs contain a CARD domain: NLRC1, NLRC2, NLRC3, NLRC5, and N-terminal domain in NLRP subfamily is PYD: NLRP1, NLRP2, NLRP3, NLRP4, NLRP5, NLRP6, NLRP7, NLRP8, NLRP9, NLRP10, NLRP11, NLRP12, NLRP13, and NLRP14. An additional subfamily has arisen, NLRX, but its N-terminal domain is still unknown

b

Domain organization of NLR proteins			
Human name	Mouse name	Family	CARD-containing NLRs
CIITA (NLRA)	Cllta (Nlra)	NLRA	
NOD1 (NLRC1)	Nod1 (Nlrc1)	NLRC	
NOD2 (NLRC2)	Nod2 (Nlrc2)	NLRC	
IPAF (NLRC4)	Ipaf (Nlrc4)	NLRC	
Human name	Mouse name	Family	BIR-containing NLRs
NAIP	Naip (1-7)	NLRB	
Human name	Mouse name	Family	PYD-containing NLRs
NLRP1 (NALP1)	Nlrp1a-c (Nalp1)	NLRP	
NLRP10 (NALP10)	Nlrp10 (Nalp10)	NLRP	
NLRP2-9 (NALP2-9), NLRP11-14 (NALP11-14)	Nlrp2, Nlrp3 (Nalp3), Nlrp4a-g (Nalp4a-g), Nlrp5, Nlrp6, Nlrp9a-c (Nalp9a-c), Nlrp12 (Nalp12), Nlrp14 (Nalp14)	NLRP	
Human name	Mouse name	Family	Unknown N-terminal domain
NLRC3 (NOD3), NLRC5 (NOD27)	Nlrc3, Nlrc5	NLRC	
NLRX1 (NOD9)	Nlrx1	NLRX	

Fig. 13.2 (continued)

13.2.1.1 NLRP1

Martinon et al. discovered the NLRP1 inflammasome in 2002, this inflammasome being the first to be revealed. Some studies report (Boyden and Dietrich 2006; Faustin et al. 2007) that there are two natural ligands for its activation: muramyl dipeptide (MDP), a peptidoglycan fragment from both Gram-positive and -negative bacteria, and the *Bacillus anthracis* lethal toxin (Fig. 13.3). Moreover, these activators are selective, as MDP can activate human NLRP1 inflammasome whereas the lethal toxin stimulates mouse NLRP1. Genetically, there are some differences between human and murine NLRP1. Humans have a single NLRP1 gene, whereas mice have a group of three homologous genes, Nlrp1a, Nlrp1b, Nlrp1c (Fig. 13.2). The activation of the Nlrp1 inflammasome is not directly through its LRR motif. Lethal toxin consists of a zinc metalloprotease lethal factor, which is responsible for Nlrp1b cleavage, and subsequently, this cleavage of Nlrp1 itself will make macrophages susceptible to pyroptosis (Levinsohn et al. 2012). However, human NLRP1 binds directly to MDP, inducing a conformational change that allows the binding of ATP as well. When ATP hydrolysis occurs, NLRP1 oligomerizes, promoting caspase-1 recruitment and activation (Faustin et al. 2007). It has been reported that in addition to caspase-1, caspase-5 is also involved in the assembly of the NLRP1 inflammasome complex (Martinon et al. 2002).

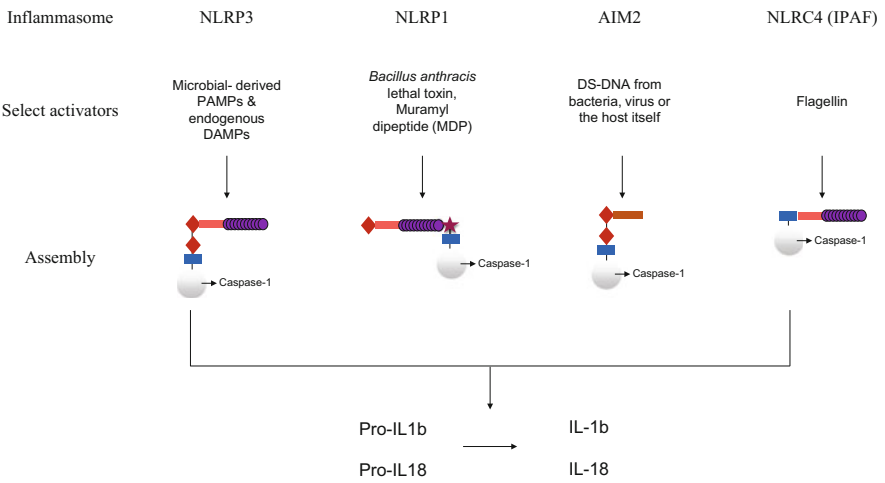

Fig. 13.3 Examples of oligomerized inflammasome complexes. Models for inflammasome-selective activation and assembly. NLRs are characterized by a NACHT domain with or without an N-terminal PYD domain and a variable number of LRRs. AIM2 contains a N-terminal PYD domain followed by a DNA-binding HIN-200 domain. The PYD domain of NLRP3 and AIM2 recruit the adaptor protein ASC via homotypic binding to its PYD domain, allowing indirect recruitment of caspase-1 through interaction with the CARD domain. NLRP1 and NLRC4 directly recruit caspase-1 through a CARD domain. Activation of the inflammasome leads to maturation and secretion of IL-1β and IL-18 and inflammatory cell death by pyroptosis. *AIM2* absent in melanoma 2, *ASC* adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain *CARD* caspase recruitment domain, *DAMP* danger-associated molecular pattern, *FIND* domain with function to find, *LRR* leucine-rich repeat, *NACHT* nucleotide-binding and oligomerization domain, *NLR* NOD-like receptor, *PAMP* pathogen-associated molecular pattern, *PYD* pyrin domain

13.2.1.2 NLRP3

The most in depth studied inflammasome complex is the NLRP3, in part because of its gamut of well-known activators. The NLRP3 inflammasome requires two signals for activation (Fig. 13.3). The first signal depends on NF-κB activation of NLRP3 (Bauernfeind et al. 2009) and IL-1B (Barker et al. 2011). The second signal consists of sensing a broad range of PAMPs and stress-associated signals or host-derived DAMPs to trigger complex assembly. Most of the DAMPs that activate the inflammasome include ROS (Dostert et al. 2008), ATP (Mariathasan et al. 2006), uric acid crystals (Martinon et al. 2006), and endogenous host metabolic products that stimulate caspase-1 cleavage in an NLRP3-dependent mechanism, and, importantly, are shown to increase during aging (Goldberg and Dixit 2015). NLRP3 is expressed in myeloid cells (Guarda et al. 2011), including macrophages, which use PRRs to recognize PAMPs and initiate the inflammatory signal pathway, this process being crucial to controlling pathogenic propagation.

Several studies have focused on age-related changes in myeloid cells concerning infection. In general, lipopolysaccharide (LPS) stimulation from an aged host results in lower tumor necrosis factor (TNF)-alpha and IL-6 secretion compared with adult macrophages. Although this helps to explain why old hosts exhibit poor control of bacterial spread and increased susceptibility to bacterial infections, the production of these cytokines is independent of NLRP3 activation. Nowadays, it is becoming progressively evident that sterile inflammation, which is inflammation in the absence of overt infection, is a more consistent contributor to age-related inflammation and disease. A wide spectrum of sterile particles can stimulate inflammation; some examples of these particles include silica dioxide, asbestos, cholesterol crystals, or amyloid-β fibrils (Rock et al. 2010). Moreover, as we age, it has been reported that the basal elevation of the NLRP3 inflammasome interferes with the specific up-regulation of caspase-1 that is required for a successful immune response against infections in mice (Knrone et al. 2013). This fact emphasizes the importance of maintaining an adequate balance between tissue homeostasis and host defense during infection.

Although the Nlrp3 inflammasome is the most thoroughly studied NLR, its complex activation has been shown to be even more complicated with the discovery of noncanonical inflammasome activation (Kayagaki et al. 2011). Here, the authors show that caspase-11 (also known as caspase-4) is critical for caspase-1 activation and IL-1β production in C57BL/6 Casp11 gene-targeted mice macrophages infected with *Escherichia coli*, *Citrobacter rodentium* or *Vibrio cholerae*, and they also realized that the published Casp1(−/−) mice lacked both caspase-11 and caspase-1. Thus, they concluded that Casp11(−/−) macrophages secreted IL-1β, usually in response to ATP and monosodium urate, indicating that caspase-11 is engaged by a noncanonical inflammasome.

13.2.1.3 NLRP6 and NLRP12

NLRP6 inflammasome and NLRP12 present several characteristics in common. NLRP6 is mainly expressed in nonhematopoietic cells. Specifically, NLRP6 is highly expressed in intestinal epithelial and goblet cells (Wlodarska et al. 2014) where it is involved in the vital role of maintaining intestinal homeostasis (Hu et al. 2013). Recent studies suggest that NLRP6 might form inflammasome complexes, as its combined expression with ASC results in caspase-1 activation (Grenier et al. 2002). Both inflammasomes, NLRP6 and NLRP12, seem to maintain intestinal homeostasis through negative MAPK and NF-κB inflammatory pathway regulation (Anand and Kanneganti 2013). Moreover, the NLRP12 inflammasome has recently played a protective role in colitis and colon cancer induced with dextran sulfate sodium (DSS) and azoxymethane/dextran sulfate sodium (AOM/DSS) respectively (Zaki et al. 2011). However, the specific and selective activators for these inflammasomes remain unclear.

13.2.1.4 NLRC4

The NLRC4 inflammasome is also known as ICE protease activating factor, when N-terminal domain is a CARD. NLRC4 responds to a more defined range of stimuli than the NLRP3 inflammasome. *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Shigella flexneri* are responsible for NLRC4 inflammasome activation (Mariathasan et al. 2004; Amer et al. 2006; Miao et al. 2006, 2008; Lamkanfi et al. 2007; Sutterwala et al. 2007; Suzuki et al. 2007). NLRC4 senses bacterial flagellin and Gram-negative bacterial type III secretory system (T3SS) that are leaked into the host cell (Miao et al. 2010). These bacterial components are directly bound by NLR family apoptosis-inhibiting proteins (NAIPs), forming complexes in the cytosol. In mice, there several subtypes of NAIP proteins, whereas in humans only one NAIP protein has been characterized (Fig. 13.2), and it was discovered to bind T3SS needle protein. Murine NAIP1 binds T3SS needle protein. However, NAIP2 tends to bind T3SS rod protein, whereas NAIP5 and NAIP6 bind bacterial flagellin (Kofoed and Vance 2011). NAIPs then interact with NLRC4, triggering the complex conformation, activating caspase-1 and leading to the release of pro-inflammatory cytokines and finally, to pyroptosis.

13.2.1.5 NLRC3

The NLRs are cytoplasmic immune sensors that are involved in intestinal homeostasis (Zaki et al. 2010; Allen et al. 2012). NLRC3 (also known as NOD3) is still insufficiently characterized. Some authors classify NLRC3 as NLRs non-inflammasome-forming (Sharma and Jha 2016). However, they contribute considerably to inflammatory regulation by regulating inflammation pathways (Ting et al. 2010). Non-inflammasome-forming NLRs modulate NF-κB and other significant inflammation regulatory pathways, which are crucial in chronic inflammation and inflammation-induced tumorigenesis (Allen 2014). In fact, some studies have reported that NLRC3 expression is remarkably reduced in tumors from patients with colorectal cancer in comparison with healthy tissues (Liu et al. 2015; Karki et al. 2016). In this study, they investigate the role of NLRC3 in colorectal cancer using a mouse model of AOM/DSS colitis-induced and colorectal tumorigenesis. The conclusion is that mice lacking in Nlrc3 are significantly more susceptible to colitis and colorectal tumorigenesis. NLRC3 is presumably a protector against colorectal tumors through the inhibition of the mTOR pathway.

13.2.1.6 NLRCX

Another non-inflammasome-forming NLR is NLRCX. Unlike the other NLR proteins mentioned above, it constitutes the first noncytoplasmic NLR protein, and is localized in the mitochondria (Moore et al. 2008; Xiao and Ting 2012). The Nlrx1

expression is highest in mitochondria-rich tissues such as muscle and heart. The main functions of Nlrx1 include negative regulation of anti-viral inflammatory response via the MAVS-RIG1 signaling pathway or TLR-induced NF-κB signaling by targeting the TRAF6 and IKK signaling pathway. These data indicate that NLRX1 attenuates tumorigenesis through the negative regulation of AKT and NF-κB signaling, although it is a potential target for managing immune response in inflammation-associated diseases and cancer pathology (Allen et al. 2011). These results show specific knockdown of Nlrx1, resulting in increased gene expression of the cytokines TNF-α and IL-6 in response to LPS treatment (Xia et al. 2011). NLRX1 also plays an important role in regulating the balance between intrinsic and extrinsic apoptosis in cancer cells. NLRX1 positively regulates apoptosis in response to intrinsic apoptosis signals, and this may be why the Nlrx1 expression is down-regulated in cancer cells. Nlrx1−/− mice develop fewer tumors than wild-type mice in the AOM-induced colorectal cancer murine model (Soares et al. 2014).

13.2.2 AIM2-Like Receptors and RIG-1-Like Receptors

The non-NLR AIM2 has an HIN-200 domain consisting of proteins that contain a PYRIN domain and the conserved DNA-binding domain hematopoietic IFN-inducible nuclear protein with 200-amino acids (HIN-200) domain (Schattgen and Fitzgerald 2011) that can directly bind its cytosolic dsDNA (Fig. 13.3). Besides, it is also able to form a caspase-1-containing inflammasome. Therefore, these proteins can theoretically bind nucleic acids and recruit ASC to trigger the conformation of an inflammasome. Indeed, AIM2 can form an inflammasome whose assembly is stimulated by recognition of cytosolic DNA of bacterial or viral origin (Fernandes-Alnemri et al. 2010; Jones et al. 2010; Rathinam et al. 2010), or self-DNA from apoptotic cells (Choubey 2012; Zhang et al. 2013). Recent studies about crystal structures of AIM2 complexes with DNA have provided an insight into the mechanism of AIM2 inflammasome activation (Jin et al. 2012). Binding of DNA to the HIN-200 domain of AIM2 results in a conformational change and AIM2 oligomerization around the DNA molecule, which then allows the recruitment of ASC and caspase-1 and inflammasome assembly (Jin et al. 2013).

Additionally, although mice have a wide range of ALRs that includes 13 members, humans have three more: IFI16, IFIX, and MNDA, but most of these ALRs remain insufficiently characterized. However, some murine ALRs were found to trigger IL-1β production, suggesting that they might form inflammasomes (Brunette et al. 2012). Activation of IFI16 in CD4 T cells during HIV infection was found to trigger pyroptosis of T cells (Monroe et al. 2014). Finally, the RIG-I-like receptor family member, which is best known as an inducer of type I IFN production in response to recognition of viral RNA, was also shown to form an inflammasome (Poeck et al. 2010). However, it remains unclear what determines when RIG-I forms an inflammasome versus when it merely triggers type I IFN production.

13.3 Inflammasomes in Age-Related Diseases

The role of inflammasomes becomes even more significant in the elderly, as they are more susceptible to infections owing to the drastic decrease in the immune system. However, a highly important event takes place during aging, starting with DAMPs accumulation (Goldberg and Dixit 2015) and the subsequent activation of the NLRP3 inflammasome due to the stimuli induced by endogenous by-products. Then, endogenous by-products are recognized by PRRs in macrophages (Schroder and Tschopp 2010; Medzhitov 2008) to trigger the singular chronic, low-grade inflammation that occurs during aging (Spadaro et al. 2016). Numerous studies have reported (Goldberg and Dixit 2015; Ferrucci et al. 2005) that systemic low-grade inflammation contributes to the onset of chronic diseases and degenerative changes as we age. Chronic inflammation also plays an essential role in the initiation and progression of metabolic disorders, such as T2D, obesity, gouty arthritis, and atherosclerosis.

Heart disease, including atherosclerosis, is the leading cause of death in the elderly (Leon and Gustafsson 2016; North and Sinclair 2012). Cholesterol crystals (Grebe and Latz 2013) and white blood cells accumulate on the arterial wall, limiting the flow of oxygen-rich blood to the organs, which can lead to life-threatening complications such as heart attack and stroke. It has long been suggested, based on evidence from mouse models (Duewell et al. 2010; Elhage et al. 2003; Mallat et al. 2001), that IL-18, a product of inflammasome activation, may play a crucial role in the initiation and progression of atherosclerosis. Furthermore, human atherosclerotic plaques have elevated concentrations of IL-18 and IL-18 receptors compared with disease-free arterial tissues. Apolipoprotein E (ApoE) is necessary for a proper cholesterol metabolism. In ApoE-deficient mice, which spontaneously develop atherosclerotic lesions, elevated IL-18 levels have been shown to cause vascular inflammation and enhance the instability of atherosclerotic plaques, whereas IL-18-deficiency resulted in reduced atherosclerotic lesion size (Tan et al. 2010; De Nooijer et al. 2004). Elevation of low-density lipoprotein and free fatty acids (FFAs) in human blood due to imbalanced lipid metabolism can induce pro-IL-1β production through TLRs, providing the first signal for inflammasome activation (Masters et al. 2011).

Another major global age-related health threat is T2D, resulting in insulin resistance and a chronic inflammatory disease characterized by elevated circulating levels of TNF, interleukins, and cytokine-like proteins known as adipokines released from adipose tissue (Donath and Shoelson 2011). IL-1β, in particular, has been strongly linked to the pathogenesis of T2D by promoting insulin resistance and causing β-cell functional impairment and apoptosis. In cell culture, IL-1β depresses insulin sensitivity by inducing JNK-dependent serine phosphorylation of insulin receptor substrate-1, resulting in the disruption of insulin-induced PI3K-Akt signaling in insulin-targeted cells. At the same time, IL-1β induces the expression of TNF-α (Wen et al. 2011), which could independently impair insulin signaling (Hotamisligil et al. 1993). Together with elevated FFAs in circulation because of imbalanced lipid

metabolism, IL-1β induces metabolic stressors, such as endoplasmic reticulum stress and oxidative stress, both of which are involved in the induction of inflammation and β-cell loss, thereby leading to the pathogenesis of T2D (Robbins et al. 2014; Legrand-Poels et al. 2014). Furthermore, clinical trials in humans reported that either IL-1 receptor antagonist (IL-1RA) or anti-IL-1β-neutralizing antibody improved control of glucose levels and β-cell function. Larger-scale clinical trials have been undertaken to definitively determine the potential of this treatment strategy (Larsen et al. 2007; Böni-Schnetzler and Donath 2013). Furthermore, neuromodulatory lipids known as endocannabinoids are lipids that have recently been found to induce NLRP3 inflammasome-dependent IL-1β production by pancreatic-infiltrating macrophages through the peripheral cannabinoid receptor type 1 (CB1R), resulting in pancreatic β-cell death in a paracrine manner (Jourdan et al. 2013). Moreover, blockade of CB1R by an inhibitor delayed the progress of T2D in the Zucker diabetic fatty rat, which carries a spontaneous mutation of the leptin receptor gene and develops hyperglycemia progressively with aging accompanied by reduced β-cell apoptosis and hyperglycemia. This finding implicates CB1R as being a potential therapeutic target in T2D (Böni-Schnetzler and Donath 2013).

Apart from metabolic alterations, aging also constitutes a primary risk factor for many neurodegenerative diseases. Recent studies have suggested that misfolded protein aggregates lead to activation of the NLRP3 inflammasome in two neurodegenerative diseases: AD and amyotrophic lateral sclerosis (Masters and O'Neill 2011; Walsh et al. 2014). AD is a chronic neurodegenerative disease that mainly affects cognitive functioning and is the most common cause of dementia. Amyloid-β peptide is regularly formed in brain tissue by cleavage of the amyloid precursor protein, but it can form prion-like misfolded oligomers in the case of AD (Heneka et al. 2015). Amyloid-β was the first molecule associated with neurodegenerative disease models that was found to activate the murine NLRP3 inflammasome, resulting in IL-1β production (Halle et al. 2008). Fibrillar amyloid-β induces NLRP3-inflammasome-dependent caspase-1 activation through a mechanism dependent on endosomal rupture and cathepsin B release in LPS-primed murine macrophages (Halle et al. 2008). Interestingly, administration of cathepsin B inhibitors significantly improved memory deficit and reduced amyloid plaque load in the brain in the AD mouse model, suggesting a potential therapeutic approach for Alzheimer's treatment in which the inflammasome is targeted (Hook et al. 2008).

Parkinson's disease results in the death of dopamine-generating neurons in the substantia nigra and the presence of aggregated inclusions mainly composed of α-synuclein (αSyn) in neurons (Shulman et al. 2011). αSyn can form fibrils with a cross β-sheet structure, morphologically similar to the amyloid fibrils from AD (Chiti and Dobson 2006). Recent research has shown that in a Parkinson's disease mouse model in which Parkinson's disease is induced by the loss of nigral dopaminergic neurons caused by treatment with neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, mice lacking Nlrp3 are resistant to developing PD. This provides in vivo evidence for a visible link between the NLRP3 inflammasome and Parkinson's disease (Yan et al. 2015).

13.4 Conclusions and Future Prospects

It is sufficiently clear that one of the major beneficial roles of the inflammasome is to sense microbial infection and mediate a rapid plan to host defense through the immediate secretion of cytokines. These responses are highly effective against infectious agents. However, inflammasomes can also function as sensors of nonmicrobial signals (e.g., sterile mediators of membrane damage or cellular stress). Most of these nonmicrobial triggers of the inflammasome have been studied, mainly because of their pathological roles in disease, whereas there are few examples of beneficial effects of inflammasome activation by nonmicrobial triggers. Inflammasome activation cannot all be considered harmful, and the therapeutic inhibition of this pathway has to be balanced against its beneficial contribution. As the mechanistic insight of the inflammasomes increases, opportunities for creating new therapies for patients with inflammatory diseases are expected to be enhanced proportionately. It is however possible that the beneficial effects of inflammasome activation by nonmicrobial triggers have been ignored. It is also notable that almost all known non-infectious triggers of the inflammasome mediate activation through NLRP3, which seems to be uniquely able to respond to a wide range of stimuli. So far it remains unclear whether other NLRs can also sense nonmicrobial signals of physiological stress, although there remain many NLRs whose respective roles in host defense are beginning to be understood and described, such as NLRP10 (Eisenbarth et al. 2012), NLRC5 (Cui et al. 2010; Meissner et al. 2010), and NLRC3 (Schneider et al. 2012; Zhang et al. 2014). With these NLRs, one of the major obstacles to overcome seems to be identifying the activating signals. For example, inflammasome activation by pore-forming toxins triggers caspase-1-dependent activation of membrane repair (Gurcel et al. 2006), and NLRC4 activation induced by cytosolic delivery of flagellin has been shown to trigger rapid production of inflammatory lipid mediators in a caspase-1-dependent manner (von Moltke et al. 2012). Furthermore, it is clear that inflammasomes exist in multiple cell types, including both hematopoietic and nonhematopoietic cells, and play a determinant role in the onset and development of age-related and chronic inflammatory diseases.

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