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REVIEW

Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases

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Abstract Oxidative stress and low-grade inflammation are the hallmarks of the aging process and are even more enhanced in many age-related degenerative diseases. Mitochondrial dysfunction and oxidative stress can provoke and potentiate inflammatory responses, but the mechanism has remained elusive. Recent studies indicate that oxidative stress can induce the assembly of multiprotein inflammatory complexes called the inflammasomes. Nod-like receptor protein 3 (NLRP3) is the major immune sensor for cellular stress signals, e.g., reactive oxygen species, ceramides, and cathepsin B. NLRP3 activation triggers the caspase-1-mediated maturation of the precursors of IL-1β and IL-18 cytokines. During aging, the autophagic clearance of mitochondria declines and dysfunctional mitochondria provoke chronic oxidative stress, which disturbs the cellular redox balance. Moreover, increased NF-κB signaling observed during aging could potentiate the expression of NLRP3 and cytokine proforms enhancing the priming of NLRP3 inflammasomes. Recent studies have demonstrated that NLRP3 activation is associated with several age-related diseases, e.g., the metabolic syndrome. We will review here the emerging field of inflammasomes in the appearance of the proinflammatory phenotype during the aging process and in age-related diseases.

Keywords Ageing · Autophagy · Inflammasome · Inflammation · NF-κB · NLRP3

Abbreviations

AIM2	Absent in melanoma 2
ASC	Apoptosis-associated speck-like protein containing CARD domain
CARD	Caspase recruitment domain
CSF	Cerebrospinal fluid
DAMP	Damage-associated molecular pattern
dsDNA	Double-stranded DNA
ER	Endoplasmic reticulum
FPR	Formyl peptide receptor
HMGB1	High-mobility group protein B1
IAPP	Islet amyloid polypeptide
IFNβ	Interferon β
IKK	Inhibitory-κB kinase
IL	Interleukin
LPS	Lipopolysaccharide
LRR	Leucine-rich repeat
MAM	Mitochondria-associated ER membrane
MAVS	Mitochondrial antiviral signaling protein
MnSOD	Mitochondrial manganese superoxide dismutase
mtDNA	Mitochondrial DNA
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor-κB
NAIP5	NLR family, apoptosis inhibitory protein

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NLR	Nucleotide-binding domain leucine-rich repeat-containing receptor family
NLRC4	NLR family, CARD-containing 4
NLRP3	NLR family, pyrin domain-containing 3
NOD1	Nucleotide-binding oligomerization domain-containing protein 1
NOS	Nitric-oxide synthase
Nox1-4	NADPH oxidases 1–4
NRF2	Nuclear factor E2-related factor 2
P2X7	P2X purinoceptor 7
PMN	Polymorphonuclear neutrophil
PYD	Pyrin domain
RIG-1	Retinoic acid inducible gene-1
ROS	Reactive oxygen species
SAMP	Senescence-accelerated prone mouse
STAT1	Signal transducer and activator of transcription 1
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TRAF	TNF receptor-associated factor
TRIM30	Tripartite-motif protein 30
TRX	Thioredoxin
TXNIP	Thioredoxin-interacting protein
UCP	Uncoupling protein
UPR^{mt}	Mitochondrial unfolded protein response
UVB	Ultraviolet B

Introduction

For centuries, scientists have postulated a number of aging theories some of which have also received substantial support from modern molecular biology. One hypothesis is the rate-of-living theory, first proposed by Max Rubner in 1908 and recently reviewed by Hulbert et al. [1]. This theory emphasizes the role of metabolic rate in the aging process, suggesting that increased energy metabolism can enhance the aging process. The free radical theory of aging, presented by Denham Harman in 1956, maintains that oxygen-derived free radicals, byproducts of metabolic reactions, can attack cellular molecules and provoke oxidative damage [2]. This mechanism fits rather well with the rate-of-living theory since mitochondria are the major source of cellular ROS production. Oxidative respiration in the mitochondrial electron transport chain, particularly in dysfunctional mitochondria, can generate a considerable amount of ROS and in that way impair the housekeeping functions within the cell. There is an extensive literature supporting this concept [3, 4], although many critical studies have been published [5]. Recently, Jones [6] presented the thiol redox hypothesis speculating that the appearance of oxidative stress is dependent on disturbances in the cellular thiol redox status. Oxidative stress is associated with the pathogenesis of several age-related diseases, e.g., metabolic syndrome and age-related macular degeneration [7, 8].

Activation of the innate immune system and the presence of low-grade inflammation is a common hallmark of the aging process [9–12]. Franceschi et al. [9] termed this chronic pro-inflammatory state as inflammaging. Innate immunity is a crucial host defence system which can recognize both invading pathogens and endogenous, stress-related signals in order to prevent host injuries [13, 14]. TLR- and NLR-mediated pathways are the two major pattern recognition receptor systems. In particular, NLRs are danger-sensing receptors which, if they encounter an insult, they stimulate the assembly of inflammatory protein complexes, called the inflammasomes [13, 14]. Consequently, inflammasomes trigger the maturation and secretion of IL-1β and IL-18 cytokines. A variety of cellular stress-related danger signals activating inflammasomes has been identified [13–16]. Several studies have indicated that oxidative stress and disturbances in thiol redox balance may activate inflammasomes [17–19]. Moreover, release of cathepsin B from ruptured lysosomes can trigger inflammasomal activation [20, 21]. The mechanism of cathepsin B-provoked activation of NLRP3 still needs to be characterized. However, it is known that the viral-induced rupture of lysosomes triggers cathepsin B-dependent mitochondrial membrane destabilization and increased ROS production [22]. Recent studies have emphasized the role of mitochondria in the control of innate immunity and, in particular, the function of autophagy in the maintenance of mitochondrial integrity and thus prevention of ROS production and inflammasome activation [23, 24]. Since many inflammasome activators are common factors in the aging process itself, and even more frequent in many age-related diseases, we will review this emerging field of inflammasomes in the aging process and associated diseases.

Inflammasomes: danger sensing inflammatory platforms

Inflammasomes are intracellular multiprotein complexes which can be activated by a large set of danger signals evoked by the presence of pathogens and cellular stress, e.g., oxidative stress, potassium efflux, and lipid accumulation [13, 14, 25]. The inflammasomal platform was discovered in the laboratory of Jürg Tschopp in 2002 [26], and, currently, inflammasomes are being intensively investigated for their role in inflammatory and metabolic diseases [15, 16, 27, 28]. The recognition component of the inflammasome is the receptor protein which subsequently recruits an inflammatory caspase, i.e., human caspase-1, -4, -5, and -12 to the

complex via the CARD or PYD domains. There exist 22 human NLR proteins which can bind inflammatory caspases, normally caspase-1, either directly or via the ASC adaptor, an apoptosis-associated speck-like protein containing CARD and PYD domains. The NLR type of inflammasomes can be subdivided based on their structures and assembly model into the NLRA, NLRB, NLRC (containing, e.g., NOD1, NLRC4, NLRC5, and NLRX), and NLRP (e.g., NLRP1 and NLRP3) subfamilies [16]. The stimulation of NLRP triggers the assembly of NLRP, ASC, and caspase-1 components which subsequently oligomerize into penta- or heptameric structures. This active inflammasome cleaves the precursor forms of IL-1β and IL-18 into mature cytokines [16, 26, 28]. The secretion of these cytokines can subsequently expand the inflammatory response since these molecules signal through their specific cellular receptors [29]. Moreover, caspase-1 can also stimulate the secretion of a set of intracellular molecules, called the caspase-1 secretome, many of which are associated with inflammatory responses [30]. Lamkanfi et al. [31] demonstrated that the secretion of HMGB1, a pro-inflammatory protein, was a caspase-1-dependent process which required the assembly of NLRP3 inflammasome. In addition, cytosolic flagellin stimulated the expression of inducible NOS, which was a caspase-1-dependent response, but involved NLRC4 and NAIP5 inflammasomes in macrophages [32]. Both of these processes were caspase-1-dependent, but independent of IL-1β and IL-18 secretion. These studies indicate that inflammasomes can promote inflammation via different effector mechanisms.

A plethora of bacterial peptides and viral RNA and DNA can activate cellular inflammasomes. AIM2- and RIG-1-types of receptors recognize cytosolic RNA and DNA and trigger inflammasomes [25, 33]. Pathogenic ligands have been reviewed in detail elsewhere [33, 34]. The inflammatory responses induced by infections and tissue injury have been understood for years, but endogenous, stress-related inflammation mechanisms have remained elusive. Medzhitov [35] termed this inflammatory mode "para-inflammation". Para-inflammation can induce adaptation to noxious stimuli, but if the stress is overwhelming or sustained, it can recruit macrophages and initiate a low-grade chronic inflammation [35]. Stress-induced, chronic inflammation aggravates the condition, and this can provoke the pathology of age-related diseases. Currently, it is known that both the TLRs and NLRs can be activated by cellular stress and damage-associated stimuli [24, 28, 36]. The stress-related activation of inflammasomes is mostly characterized by NLRP3 inflammasomes (also known as NALP3 and cryopyrin), but NLRP1 can also be activated by DAMPs.

Petrilli et al. [37] were the first investigators who observed that NLRP3 inflammasomes could be activated by the efflux of potassium in human monocytes. For instance, extracellular ATP, released from damaged cells, can induce potassium efflux by activating the ATP-gated P2X7 receptors. Potassium efflux can also activate the NLRP1 but not NLRC4 inflammasomes [37]. Later studies have indicated that many other activators of NLRP3 can also reduce the intracellular potassium concentration and thus activate inflammasomes [38, 39]. However, potassium efflux is linked to increased intracellular calcium concentration. It is well known that excessive cytosolic calcium level can be balanced by its intake to mitochondria which stimulates mitochondrial ROS production [4, 40]. The exact mechanism of inflammasome activation induced by potassium efflux is not known, but it seems that it is associated with a ROS-dependent activation mechanism (see below). Uptake of certain crystal particles such as asbestos, silica, monosodium urate, and calcium phosphate crystals can also induce changes in ionic concentrations [16, 25, 28]. During aging, lipofuscin accumulates in lysosomes of post-mitotic cells. These insoluble aggregates may physically cause lysosomal damage. Lysosomes are iron-rich organelles and thus sensitive to ROS-mediated oxidation of proteins and lipids [41], which can also induce lysosomal membrane rupture. The membrane damage can lead to the release of cathepsin B, which is known to stimulate inflammasomes. For instance, cholesterol crystals activate NLRP3 inflammasomes via cathepsin B release in human macrophages [21] (Fig. 1).

Tattoli et al. [42] observed that NLRX1 was localized in mitochondria where it was involved in ROS generation. Moreover, NLRX1 enhanced ROS production, NF-κB signaling, and inflammatory response after TNFα exposure. However, recent studies have indicated that NLRX1 can interact with MAVS and interfere with the signaling of the RIG-1/MAVS and TRAF6/NF-κB pathways [43]. The RIG-1 pathway has a major role in the cellular viral defence system. Xia et al. [44] observed that NLRX1 negatively regulated TLR-mediated NF-κB signaling and the inflammatory response. They also revealed the mechanism upon LPS stimulation, i.e., NLRX1 was ubiquitinated and subsequently interacted with the IKKα/β complex inhibiting its activity. Knocking down of NLRX1 clearly increased NF-κB signaling and sensitized mice to LPS-induced septic shock [44]. Recently, Cui et al. [45] revealed that NLRC5 receptors inhibited the activation of IKKα and IKKβ and thus NF-κB signaling. It seems that NLRX1 and NLRC5 have an important role in the homeostatic regulation of innate immunity.

There are both structural and functional differences between NLRP1 and NLRP3 inflammasomes [16, 25, 46]. For instance, NLRP1 protein but not NLRP3 contains a CARD domain and it does not need ASC for the activation of caspase-1 [46]. These receptors also exhibit dissimilar

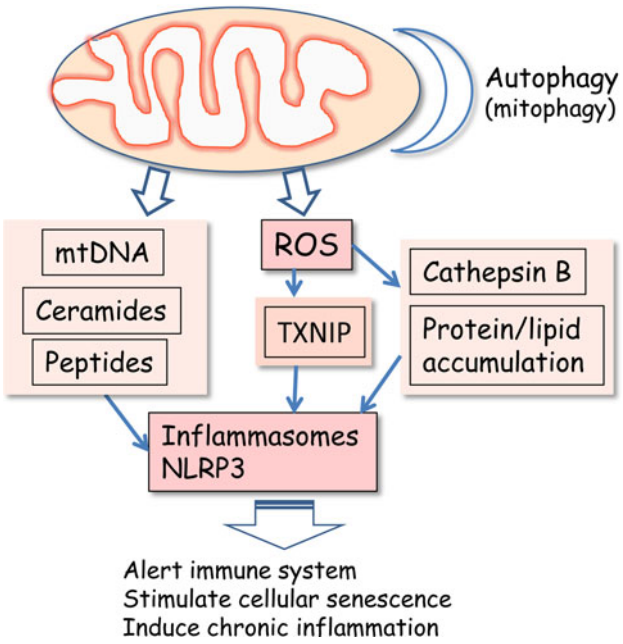

Fig. 1 Mitochondrial dysfunction activates ROS production and secretion of mitochondrial DAMPs which activate NLRP3 inflammasomes and subsequently enhance the appearance of the proinflammatory phenotype during the aging process and in age-related diseases. Loss of mitochondrial integrity triggers the release of mtDNA and synthesis of ceramides and formyl peptides. Autophagic clearance of damaged mitochondria maintains mitochondrial integrity and prevents the activation of NLRP3 inflammasomes

expression profiles, e.g., NLRP1 is highly expressed in T and B lymphocytes and neurons [47, 48]. Moreover, anti-apoptotic proteins Bcl-2 and Bcl-xL can interact with NLRP1 and in that way inhibit NLRP1 activation and inflammatory responses [49]. On the other hand, the overexpression of NLRP1 can induce apoptosis, e.g., in cerebellar granule neurons [50]. Genetic variants of NLRP1 are associated with Alzheimer's disease [51] and vitiligo-associated autoimmune diseases [52]. NLRP1 also has a crucial role in the inflammatory response initiated by spinal cord injury [53]. Potassium efflux activates both these inflammasomes [37], but it seems that ROS can activate only NLRP3 receptors. The current understanding on inflammasomes including receptor types and their activation mechanisms has been recently reviewed in detail elsewhere [15, 16, 25, 28].

Mitochondrial dysfunction stimulates inflammatory responses

Mitochondrial dysfunction is associated with the aging process as well as with the pathogenesis of several diseases, e.g., metabolic and neurodegenerative diseases [54–57]. These effects are commonly attributed to disturbances in energy metabolism and increased ROS production and to the important role of mitochondria in apoptotic cell death. Moreover, recent studies have revealed that mitochondria have a crucial role in the regulation of inflammatory responses via their ROS production [24, 57, 58]. It is well known that UCP2 and UCP3 can control immune responses and the appearance of metabolic diseases [59–61]. UCP2 proteins are expressed in most tissues whereas the presence of UCP3 is restricted to skeletal muscles and adipose tissue [62]. UCP proteins are located in the inner mitochondrial membrane where they dissipate the mitochondrial proton gradient and in that way can reduce ROS production and subsequently prevent inflammatory reactions. In ischemic brain damage, UCP2 deletion enhances cytokine production and increases neuronal damage [63]. Bai et al. [64] revealed that deletion of UCP2 stimulated NF-κB signaling under basal conditions and, in particular, after inflammatory insults. Antioxidants seem to be able to inhibit this inflammatory response which indicates that ROS production was involved. Horvath et al. [61] observed that the overexpression of UCP2 and UCP3 prevented inflammatory changes and obesity in transgenic mouse models.

Recent studies have demonstrated that a sterile cellular injury can trigger the release of DAMPs from mitochondria which can induce local and systemic inflammatory responses [65, 66]. Zhang et al. [67] demonstrated that, in tissue injury, mtDNA and formyl peptides were released from mitochondria, and, subsequently, they activated human PMNs through TLR9 and FPRL1 receptors and promoted their migration and tissue penetration. Through the same membrane receptors, mtDNA and formyl peptides stimulated inflammatory responses in local microenvironments. Moreover, at the cellular level, mitochondrial DAMPs were reported to activate inflammasomes and thus induce an inflammatory reaction [65, 66]. Interestingly, mitochondria can trigger both the assembly of apoptosomal and inflammasomal protein complexes, and thus alert the immune system about expected apoptotic cell death.

Mitochondrial origin of inflammasome activation

Recent studies have revealed that mitochondria are crucial regulators of innate immunity [24, 66, 68]. Even though these organelles have an endosymbiotic origin, mitochondria can trigger sterile inflammation by activating inflammasomes, in particular NLRP3, in cellular stress. Some inflammasomes are specialized to recognize different microbe products, i.e., flagellin activates NLRC4, bacterial muramyl peptides and lethal toxins stimulate NLRP1, and cytoplasmic DNA induces AIM2 activation [69]. For comparison, ROS is the key product of mitochondria which

induces the stimulation of NLRP3 [25, 28, 57]. Recently, Bauernfeind et al. [70] demonstrated that the ROS-induced activation of NLRP3 was clearly attributable to the priming process, since ROS inhibitors blocked the priming step in NLRP3 activation. Under normal conditions, the expression levels of NLRP3 protein and pro-IL1β and pro-IL18 cytokines are low, and a clear increase in their expression level has been required prior to the efficient activation of NLRP3. Bauernfeind et al. [71] revealed that NF-κB-dependent signaling was clearly able to upregulate the expression of NLRP3 and thus permitted the activation of NLRP3 inflammasome. They also demonstrated that the priming process was only involved in the activation of NLRP3, but not in that of AIM2 or NLRC4 [71]. These studies emphasize the crucial role of NF-κB signaling in the ROS-dependent activation of NLRP3 inflammasomes.

Mitochondrial production of ROS activates inflammasomes

The mitochondrial respiratory chain, NADPH oxidases, and 5-lipoxygenase are the major cellular sources of ROS production. It is important to be aware of the origin of ROS production evoking the activation of inflammasomes if one wishes to target them through therapeutic interventions. There are many earlier observations indicating that increased ROS production could induce the expression and secretion of interleukin-1β, e.g., in PC12 cells [72] and alveolar type II epithelial cells [73]. Cruz et al. [17] revealed that ATP activated ROS production and induced IL-1β secretion via caspase-1 activation in macrophages. Anna Rubartelli [74–76] and her group have demonstrated in several experiments that the cellular redox status regulates the processing and secretion of IL-1β. Blocking of ROS production and increased expression of antioxidants can reduce IL-1β secretion. Hu et al. [77] observed that the expression of TRIM30 protein decreased NLRP3 activation by attenuating ROS production. Moreover, Tsai et al. [78] demonstrated that epigallocatechin-3-gallate, a major polyphenol in green tea, inhibited NLRP3 activation by stimulating NRF2-mediated antioxidant response and thus prevented lupus nephritis development in mice.

Several experimental approaches have demonstrated that autophagic uptake capacity can regulate mitochondrial integrity, ROS production, and subsequent NLRP3 activation [79, 80]. Recently, Zhou et al. [80] demonstrated that the inhibition of autophagy triggered the accumulation of damaged, ROS-generating mitochondria which augmented the activation of NLRP3 inflammasomes in human macrophages (Fig. 1). Earlier studies had indicated that inhibition of autophagic uptake increased the ROS production [81] and that changes in autophagy could regulate the inflammatory responses [82]. Zhou et al. [80] observed that the NLRP3 protein co-localized with ER marker in non-stimulated macrophages. After danger-signal stimulation, NLRP3 protein relocalized into the perinuclear space, and several cytochemical markers indicated that the structure was the MAM, which is the physical site of the interaction between ER and mitochondria. The MAM is known to regulate many processes, e.g., calcium homeostasis and the release of apoptogenic proteins which can subsequently assemble apoptosomes [83]. Interestingly, NLRP3 co-localized with ASC and TXNIP, which implies that the NLRP3 inflammasomes located in the MAM were active, probably being triggered by TXNIP [80]. These observations revealed an important mechanistic role for mitochondria as inducers of inflammasomes and apoptosomes, two multiprotein complexes with very different functions. Moreover, it is known that the overwhelming stimulation of macrophages with proinflammatory insults can induce the assembly of the pyroptosome complex in which ASC itself can activate caspase-1 and apoptotic cell death, a process called pyroptosis [84].

The exact mechanism involved in ROS-induced NLRP3 activation is still unclear. Zhou et al. [18] demonstrated that oxidative stress could activate NLRP3 inflammasomes via the redox regulation of TRX/TXNIP balance (Fig. 1). They used a two-hybrid screening system to demonstrate that TXNIP could bind to the LRR domain of NLRP3 protein. The binding of TXNIP activated the NLRP3 inflammasome and increased IL-1β secretion in human macrophages. Several inflammasome inducers, such as ATP, silica, and uric acid crystals, triggered the dissociation of TXNIP from THR in a ROS-dependent manner and allowed its binding to NLRP3, and subsequently stimulated NLRP3 activation. Their experiments also revealed that the glucose-induced stimulation of IL-1β secretion was triggered by the TXNIP/NLRP3 activation in mouse beta cells. On the other hand, Masters et al. [85] could not repeat these results concerning the role of TXNIP in NLRP3 activation in bone marrow-derived macrophages. They did not perform direct binding assays between TXNIP and NLRP3. However, there are two other recent studies which have confirmed the role of TXNIP in the activation of NLRP3. Xiang et al. [19] demonstrated that ROS produced by NADPH oxidase induced the binding of TXNIP to the NLRP3, which caused inflammasome activation and IL-1β secretion from lung endothelial cells. Interestingly, they observed that HMGB1, a well-known DAMP [86], could stimulate NLRP3 via ROS production triggered by NADPH oxidase. Recently, Lunov et al. [87] demonstrated that a specific type of nanoparticles accumulated in lysosomes and induced the release of cathepsin B which stimulated ROS production from mitochondria. Subsequently, ROS triggered the dissociation of TXNIP from TRX and its binding to NLRP3 which induced caspase-1-

dependent IL-1β production. They also revealed in silico that the binding of TXNIP to the NLRP3 evoked the exposure of the pyrin domain of NLRP3 to ASC which triggered inflammasomal activation. Currently, three studies have confirmed the role of TXNIP in the ROS-dependent activation of NLRP3 inflammasome.

Mitochondrial DAMPs: mtDNA, ceramides, and formyl peptides

Nakahira et al. [79] demonstrated that the block of autophagy clearly activated caspase-1 and increased the secretion of IL-1β and IL-18 in human macrophages. The inhibition of autophagic degradation impaired mitochondrial homeostasis and stimulated the generation of ROS. Subsequently, increased ROS production enhanced mitochondrial permeability and triggered the leakage of mtDNA into cytosol (Fig. 1). They observed that the release was dependent on the presence of both ROS and NLRP3. In cytoplasm, mtDNA potentiated the activation of caspase-1 in conjunction with LPS and ATP treatments. However, this response was independent of AIM2, a typical inflammasomal receptor activated as a result of viral DNA exposure. Choumar et al. [88] revealed that LPS treatment induced mtDNA depletion and mild inflammation in liver of wild-type mice whereas mitochondrial MnSOD overexpressing mice were protected. The exact mechanism how cytosolic mtDNA induces inflammasome activation is still unknown, but it seems that mtDNA and viral RNA/DNA use separate pathways. In several pathological conditions, mtDNA is known to be a potent mitochondrial DAMP and it can trigger systemic and local inflammation via TLR9 [65, 66].

Ceramides, which are composed of sphingosine and fatty acid, may be involved in the ROS-dependent regulation of TXNIP/NLRP3 balance. Vandanmagsar et al. [89] observed that the lipotoxicity-associated increase in the intracellular level of ceramides activated NLRP3 inflammasomes in macrophages and adipose tissue (Fig. 1). Ceramides and oxidative stress have been linked to each other in several pathological conditions, e.g., in aging and inflammation [90]. Yu et al. [91] demonstrated that, in stroke, mitochondrial ceramide synthase was activated and ceramides were abundantly accumulated in mitochondria where they induced mitochondrial respiratory dysfunction. Ceramides can also form channels in mitochondrial membranes [92] and thus trigger the release of mitochondrial DAMPs. Ceramides can also induce the expression of TXNIP [93, 94] and in that way activate NLRP3 inflammasomes.

N-formyl peptides are mitochondrial DAMPs which can provoke systemic inflammatory responses via formyl peptide receptors [24]. Mitochondrial N-formylated peptides activate monocytes and trigger neutrophil chemotaxis in response to tissue injuries [95]. It seems that mitochondria can also have other cell non-autonomous effects such as those involved in immune defence. Recently, Andrew Dillin and his team [96] identified so-called mitokines which could induce systemic effects on the mitochondrial pool in *C. elegans*. They observed that tissue-specifically induced mitochondrial unfolded protein response (UPR^{mt}) could be translocated from the nervous system and muscle tissue into the intestine. The molecular mechanisms of this type of mitochondrial DAMP still need to be clarified. In general, UPR^{mt} has many beneficial effects in mitochondria, e.g., it can enhance respiration and increase organismal longevity.

Potential significance of inflammasomes in the aging process and age-related diseases

Inflammasomes are sensors of intracellular sanctity when this is challenged by oxidative stress and lysosomal destabilization. The aging process involves a progressive accumulation of waste products, mostly oxidized proteins and lipids. Lipofuscin is a characteristic hallmark of the aging process in non-mitotic cells, e.g., in cardiac muscle cells [97]. There is also abundant evidence indicating that the deposition of harmful intra- and extracellular material occurs in several age-related diseases. These aggregates jeopardize cellular homeostasis and can provoke the activation of NLRP3 inflammasomes. The aging process involves a plethora of changes indicating that the pro-inflammatory phenotype could be initiated by danger-sensitive NLRP3 activation. However, direct evidence is still lacking.

Inflammasomes in age-related diseases

Recent studies indicate that inflammasomes have a crucial role in the pathogenesis of several age-related diseases, e.g., metabolic syndrome [27, 98]. Vandanmagsar et al. [89] demonstrated that, in obesity, the increased secretion of IL-1β and IL-18 cytokines was induced by NLRP3 activation in adipose tissues. The intense expression of NLRP3 protein was localized to macrophages in adipose tissues. They observed that chronic caloric restriction and physical exercise reduced the weight of animals and simultaneously clearly decreased the expression of *Nlrp3*, *Asc*, and *IL-1β* mRNA in both visceral and subcutaneous adipose tissues. They extended their study to type II diabetic humans who undertook a 1-year weight loss intervention. They observed that the expression levels of the same inflammasomal markers as observed in mice were also reduced in human subcutaneous adipose tissue. The decreased expression levels were coupled with lower

glycemia and improved insulin resistance. Moreover, Stienstra et al. [98] observed that caspase-1 and IL-1β activities were increased in both diet-induced and genetically obese mice, and that the NLRP3-mediated caspase-1 activation directed adipocyte differentiation toward a more insulin-resistant phenotype whereas caspase-1 knockout mice were more insulin sensitive. These studies indicate that metabolic stress can trigger NLRP3 inflammasomes in adipose tissues and lead to metabolic syndrome [27].

Atherosclerosis is an inflammatory disease of the arterial vessel wall and a well-established age-related disorder [99]. Oxidative stress is a crucial factor in the pathogenesis of vascular aging and atherosclerosis [100]. Two recent studies have demonstrated that cholesterol crystals can activate NLRP3 inflammasomes in human macrophages by causing lysosomal damage and cathepsin B release [21, 101]. Duewell et al. [101] observed that microscopic cholesterol crystals were present during the very early stages of the appearance of diet-induced atherosclerotic lesions and that this coincided with the signs of inflammatory changes. After intraperitoneal injection, cholesterol crystals could induce peritonitis which did not occur in mice deficient in NLRP3, cathepsin B and L, or IL-1β [101]. Rajamäki et al. [21] demonstrated that cholesterol crystals induced leakage of lysosomal cathepsin B into the cytoplasm which subsequently triggered IL-1β secretion in human macrophages. It seems that cholesterol crystals as well as monosodium urate crystals can induce inflammation via their phagocytosis and the release of lysosomal cathepsin B, mostly in macrophages but probably also in other endocytotic cells, e.g., endothelial cells.

Halle et al. [20] revealed that fibrillary amyloid-β peptides, key players in Alzheimer's disease, could also activate NLRP3-mediated IL-1β production in brain microglial cells. The NLRP3 activation was also dependent on the phagocytosis of aggregates and the release of cathepsin B which took place via the destabilization of lysosomes. We have recently observed that the expression of IL-18 was increased in the brains of Alzheimer's disease patients, in particular in the frontal lobe [102]. The expression was localized in microglia, astrocytes, and also, surprisingly, in neurons. The level of IL-18 cytokine was also increased in the CSF of men with Alzheimer's disease. These observations imply that amyloid-β oligomers or aggregates can trigger neuroinflammation via the inflammasomal activation. We have recently reviewed this topic in Alzheimer's disease [103]. Moreover, Jha et al. [104] demonstrated that the expression of NLRP3 was greatly increased in the cuprizone-induced, mouse demyelination and neuroinflammation model. The lack of the *Nlrp3* gene clearly attenuated the neuroinflammation and the amount of demyelination. A similar outcome was observed in *Casp*$^{-/-}$ and *IL-18*$^{-/-}$ mice, but not in *IL-1*$\beta^{-/-}$ mice, indicating that NLRP3 inflammasomes were associated with caspase-1 activation and IL-18 secretion in mouse brain.

Necrotic cell death is involved in the aging process, although necrotic lesions are particularly present in the age-related diseases. Several studies have demonstrated that cells dying through necrosis associated with autophagic process but not via apoptosis can trigger inflammasome activation in host tissue phagocytes [82, 105–107]. In necrosis, the leakage of intracellular ATP can stimulate NLRP3 via P2X7 receptors. In addition, necrotic lesions trigger the release of DAMPs from extracellular matrix, e.g., biglycan and hyaluronan oligosaccharides, which stimulate inflammasome priming via TLRs [108]. Subsequently, the secretion of cytokines and chemokines recruit neutrophils to the sites of sterile inflammation [109].

IL-1β and IL-18 secretion as marker of inflammasome activation

The activation of caspase-1 cleaves the pro-IL-1β and pro-IL-18 into mature forms, and thus the secretion levels of IL-1β and IL-18 represent the degree of inflammasomal activation. This is a widely used parameter in both cellular and in vivo experiments. However, caspase-1 is not the only IL-1β-converting enzyme which can cleave and induce the secretion of IL-1β. For instance, pro-IL-1β can be processed by the chymase enzyme in mast cells and proteinase-3 and elastase in neutrophils [110–112]. These studies indicate that there may be a cell-type-specific processing of pro-IL-1β, and that caspase-1 and inflammasomes are active mainly in monocytes and macrophages. Moreover, Harris et al. [113] demonstrated that increased autophagy reduced the secretion of IL-1β in response to inflammatory insults by sequestering the cytokine into the lysosomal degradation, whereas the inhibition of autophagy increased IL-1β secretion via the NLRP3 activation in macrophages. The inflammasome-independent IL-1β secretion has also been observed in human peripheral blood mononuclear cells [114]. The inflammasomal origin of IL-1β and IL-18 processing in non-myeloid cells needs to be clarified, although inflammasome receptors are widely expressed in different tissues [47, 48].

Bearing in mind the above limitation, several studies have been conducted using transgenic mice lacking *Nlrp3*, *Txnip*, *Asc*, *Casp1*, *IL-1*β, and *IL-18* genes, which have verified that caspase-1-dependent inflammasome activation has a key role in IL-1β and IL-18 production and induction of inflammatory reactions, e.g., in oxidative [18, 80] and metabolic [27, 89] stresses. There is abundant evidence that increased systemic inflammation is associated with the aging process and age-related diseases and that it correlates with the mortality risk. The serum levels of TNF-α and

IL-6 are clearly upregulated in elderly individuals [115, 116], although the observations on the serum levels of IL-1β and IL-18 have been conflicting. Instead, the expression levels of IL-1β and IL-18 seem to be increased with aging, e.g., in the brain tissue and vascular system [117, 118]. Recently, Niemi et al. [119] demonstrated that serum amyloid A, an acute phase protein, activated NLRP3 via the P2X7 receptors in human and mouse macrophages. They observed that NLRP3 activation was dependent on cathepsin B activity, but, interestingly, not on lysosomal destabilization. It is known that the increase in serum amyloid A level correlates with the risk for several age-related diseases.

Vascular aging evokes a clear proinflammatory shift in cytokine expression which has been linked in several studies to conditions of increased oxidative stress, in particular to mitochondrial ROS production [100, 120]. Csiszar et al. [117] demonstrated that the expressions of IL-1β, TNF-α, and IL-6 were significantly increased in the coronary arteries of the aged rat. They observed that the expression of IL-1β and IL-6 was localized in endothelium whereas TNF-α was present in smooth muscle. These age-related changes in the vascular wall can enhance the atherosclerotic process. Atherosclerosis induced by gout and hyperuricemia seems to be mediated via NLRP3 activation [121]. Yajima et al. [122] demonstrated that the expression of ASC as well as IL-1β and IL-18 were markedly increased in the lesions of wire-mediated vascular injury. The expression level of cytokines and neointimal formation were significantly lower in $Asc^{-/-}$ mice compared to their wild-type counterparts.

In the brain, the expression of IL-1β, IL-18, and several other cytokines are increased during aging along with the appearance of neurodegenerative changes. Gemma and Bickford [123] observed that caspase-1 activity and IL-1β expression were increased in the aged rat hippocampus. Intracerebroventricular infusion of a specific caspase-1 inhibitor decreased the caspase-1 activity and IL-1β expression and, interestingly, improved the memory functions. Gemma et al. [124] also demonstrated that the blockade of caspase-1 could increase neurogenesis in the hippocampus of aged rat. Alboni et al. [125] have recently reviewed in detail the role of IL-18 in neuroinflammation and degeneration in the central nervous system.

Several studies indicate that aging alters the function of microglial cells, e.g., they constitutively secrete TNF-α and IL-6, and their cytokine responses to insults are strikingly increased [126]. Microglial cells from old rats contain clearly reduced glutathione levels which could provoke oxidative stress and activate NLRP3. A similar shift in microglial responses has been observed in aged, transgenic Alzheimer's mice [127]. Thiamine deficiency has been shown to trigger oxidative stress and inflammation in specific areas of brain, e.g., in thalamus [128]. The deficiency induced neuronal loss and a 43-fold increase in IL-1β expression in affected regions. In conclusion, the aging process is linked to increased inflammatory profiles in many tissues which can be triggered by inflammasomal activation.

Mitochondrial integrity, autophagy and redox balance in aging and age-related diseases

During the past decades, a strong link between mitochondrial ROS production and the aging process has been revealed [2–4]. It seems that the mitochondrial dysfunction occurring during aging is caused by impaired turnover of mitochondria via the autophagy, a process called mitophagy. Brunk and Terman [129] presented the garbage-can hypothesis of impaired autophagocytosis of damaged mitochondria during aging. Subsequently, an abundant literature has appeared demonstrating that the efficiency of autophagic uptake declines and waste material accumulates with aging [130–132]. Moreover, it has been observed that increased autophagy can extend the lifespan, and, conversely, the repression of autophagy reduces both healthspan and lifespan. Wu et al. [81] demonstrated that the inhibition of autophagy by the deletion of the *Atg7* gene induced a defect in mitochondrial respiration which led to increased production of mitochondrial ROS and provoked oxidative stress. A decline in autophagic capacity has been observed in several age-related diseases, e.g., in Alzheimer's disease [133] and type II diabetes [134]. Dysfunction of mitochondria increases the production of ROS which activates NF-κB system [135]. NF-κB signaling induces the expression of pro-IL-1β and pro-IL-18 which are required for the priming of NLRP3 inflammasomes. Under chronic conditions, NF-κB signaling can also inhibit IL-1β secretion by inducing the expression of caspase-1 inhibitors and thus form a negative feedback loop which supports the resolution of inflammation [136].

Oxidative stress regulates the TRX/TXNIP balance via different pathways, e.g., excessive ROS can oxidize TRX that induce the dissociation of TXNIP from the complex and in that way stimulate NLRP3 activation [18]. TXNIP expression can be induced by ceramides, hyperglycemia, oxidative stress, and heat shock [93, 137], all of which trigger NLRP3 activation. On the other hand, treatments that increase TRX expression can prevent oxidative stress and increase the lifespan in transgenic mice [138]. It is known that the increased expression of TRX represses inflammation whereas TXNIP is an enhancer of inflammatory diseases [137]. These studies indicate that the TRX/TXNIP balance is a crucial regulator in the aging process as well as in many age-related diseases, e.g., in Alzheimer's disease [139] and metabolic syndrome [140].

Recently, Shi et al. [141] demonstrated that autophagocytosis regulates the clearance of NLRP3 inflammasomes and thus controls IL-1β secretion and inflammatory potential of human macrophages. The ASC component of NLRP3 inflammasomes undergoes Lys63-linked polyubiquitination and is subsequently bound by p62 adaptor protein which targets the NLRP3 complex to autophagic degradation. It seems that a decline in autophagic efficiency with aging could increase the presence of NLRP3 inflammasomes during aging.

Immunosenescence and photoaging

The age-related, progressive decline in the function of the immune system is a major hallmark of aging. This process, called immunosenescence, has recently been reviewed extensively elsewhere [10, 142–144]. Major deficiencies occur in the adaptive immunity system including thymic involution and a decline in naive CD4+ T cells concomitant with clonal expansion of CD4+ memory T cells. Interestingly, Guarda et al. [145] demonstrated that the co-culture of mouse memory CD4+ T cells with macrophages blocked the LPS-primed, ATP-dependent activation capacity of macrophage NLRP3 inflammasomes whereas other T cell subsets only slightly affected the inflammasomal activation. Memory CD4+ T cells inhibited both the NLRP1 and NLRP3 activation but they did not affect NLRC4 inflammasomes. Moreover, caspase-1 activity and secretion of IL-1β were suppressed whereas the release of other inflammatory mediators, e.g., IL-6 and TNF-α, remained intact [145]. Guarda et al. [146] also revealed that IFNβ suppressed the activation of NLRP1 and NLRP3 in mouse bone marrow-derived macrophages as well as in human primary monocytes. IFNβ inhibited NLRP3 activation in a STAT1-dependent manner. They also observed that type I IFNs increased vulnerability to *C. albicans* infection in mouse, probably as a result of NLRP3 inhibition. Recently, Youm et al. [147] demonstrated that the aging-associated accumulation of free cholesterol and ceramides into mouse thymus activated NLRP3 inflammasomes and clearly promoted the age-related thymic involution and decreased the number of T cell progenitors. The deletion of NLRP3 reduced thymic atrophy and improved the maintenance of different T cell subsets. This study clearly demonstrated that NLRP3 is a crucial player in age-related Immunosenescence.

The senescence of innate immunity cells, monocytes/macrophages, neutrophils, and dendritic cells, exhibits specific changes, i.e., the TLR system is repressed with aging whereas a low-grade innate immunity upregulation occurs in old tissues [10, 142–144]. There have been several observations that the functional properties of tissue macrophages change with aging. This has been mainly studied with the cells of brain, lung, and vascular wall [126, 148, 149]. Microglial cells represent the resident macrophage population within the brain. In brief, the microglial cells in old brain are converted into a "primed state" where they exhibit markers of activated microglia without secreting any inflammatory factors. After the insult, the inflammatory response of those primed microglia is more rapid and exaggerated in comparison to the microglia from young animals. Currently, there is no direct evidence whether or not inflammasomes are involved in this priming process. Nakanishi and Wu [148] have reviewed several observations indicating that autophagic dysfunction and oxidative stress induce the age-related phenotype of microglia.

Skin is an active immune organ housing an array of innate and adaptive immunity cells and it can respond to a variety of insults, as reviewed by Nestle et al. [150]. Keratinocytes are the immune sentinels which regulate skin pathology in conjunction with dendritic cells, macrophages, and T cells. Photoaging is a well-known pathological state of the accelerated aging process of skin induced by ultraviolet light [151]. Photoaging involves mitochondrial damage, oxidative stress, activation of NF-κB signaling, and histological characteristics of chronic skin inflammation [151, 152]. Feldmeyer et al. [153] were the first workers to demonstrate that UVB irradiation triggered the caspase-1-dependent secretion of IL-1β in human keratinocytes. The inflammatory response was mediated by NLRP3 inflammasomes. Watanabe et al. [154] revealed that isolated human keratinocytes expressed several NLRP mRNAs and, moreover, NLRP3 inflammasomes were involved in the appearance of contact hypersensitivity and eczema in skin. Cho et al. [155] observed that IL-17 and IL-22 secreted by Th17 cells can activate NLRP3 inflammasomes and stimulate IL-1β secretion in human keratinocytes. They also revealed that the IL-17- and IL-22-induced NLRP3 activation was ROS-dependent. It is observed that inflammasomal activation occurs in several skin diseases, e.g., psoriasis [156] and atopic dermatitis [157]. For instance, Dombrowski et al. [158] demonstrated that, in psoriasis, the expression of AIM2 and IL-1β were clearly increased in keratinocytes. In psoriatic lesions, increased cytoplasmic DNA activated AIM2 inflammasomes, and secretion of IL-1β was enhanced, aggravating this chronic skin disease. These observations indicate that skin will be an important tissue in the studies of inflammasomes in the aging process.

Inflammasomal concept in age-related pathology

During aging, the adaptive immunity deteriorates whereas the innate immunity is clearly activated and is more responsive to insults. The appearance of a low-grade

pro-inflammatory phenotype involves, (1) serum levels of many cytokines are increased with aging [115, 116, 159], (2) the expression level of inflammatory and immune response genes is upregulated in the tissues of old rodents and humans [12, 117, 160] as well as in peripheral and intestinal leukocytes [161], and (3) NF-κB signaling is activated in several tissues [11, 162]. The NF-κB system is involved in TLR signaling but it also has a crucial role in the priming process preceding the NLRP3 activation. NF-κB signaling controls the expression of NLRP3 and in that way NF-kB signaling is required; however, it is not sufficient to trigger NLRP3 activation [71]. Currently, the molecular mechanisms of NLRP3 activation in cellular stress have not been conclusively resolved. Several studies indicate that NLRP3 activation is dependent on the increased generation of ROS, in many cases produced by mitochondria [57, 163]. Moreover, van Bruggen et al. [164] demonstrated that blocking the ROS production by Nox1-4 enzymes, another rich source of ROS generation in many cell types, did not affect NLRP3 activation. These observations imply that mitochondria may be involved but ROS do not directly activate NLRP3. The activation could be mediated indirectly by disturbances in (1) the thiol redox balance between TRX/TXNIP, (2) ceramide synthesis, (3) mitochondrial integrity leading to the leakage of mtDNA, and (4) lysosomal stability triggering release of cathepsin B (Fig. 1).

Many observations link inflammasome activation to metabolic disturbances. For instance, the promoter of TXNIP contains the transactivation site for the MondoA:Mlx complex which is a key sensor for the cellular glucose concentration [165]. Hyperglycemia is a potent activator of TXNIP-mediated caspase-1 activation and IL-1β secretion in human adipose tissue [166]. Hyperglycemia is also a potent activator of NF-κB signaling [167], and thus it can stimulate the priming process of inflammasomes and trigger the inflammatory phenotype observed in hyperglycemia. Recently, Wen et al. [168] demonstrated that saturated fatty acid palmitate, but not unsaturated oleate, activated the NLRP3 inflammasome in macrophages. They also revealed that palmitate inhibited AMP-activated kinase which is a well-known inducer of autophagy and inhibitor of inflammation [169]. Inhibition of autophagy impaired the autophagic clearance of mitochondria and in that way increased ROS production and NLRP3 activation [168]. In conclusion, there is growing evidence linking energy metabolism, autophagy, and inflammation to the regulation of healthspan and even lifespan, as proposed in the rate-of-living theory (see "Introduction").

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