Inflammaging: disturbed interplay between autophagy and inflammasomes

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Abstract: Inflammaging refers to a low-grade pro-inflammatory phenotype which accompanies aging in mammals. The aging process is associated with a decline in autophagic capacity which impairs cellular housekeeping, leading to protein aggregation and accumulation of dysfunctional mitochondria which provoke reactive oxygen species (ROS) production and oxidative stress. Recent studies have clearly indicated that the ROS production induced by damaged mitochondria can stimulate intracellular danger-sensing multiprotein platforms called inflammasomes. Nod-like receptor 3 (NLRP3) can be activated by many danger signals, e.g., ROS, cathepsin B released from destabilized lysosomes and aggregated proteins, all of which evoke cellular stress and are involved in the aging process. NLRP3 activation is also enhanced in many age-related diseases, e.g., atherosclerosis, obesity and type 2 diabetes. NLRP3 activates inflammatory caspases, mostly caspase-1, which cleave the inactive precursors of IL-1β and IL-18 and stimulate their secretion. Consequently, these cytokines provoke inflammatory responses and accelerate the aging process by inhibiting autophagy. In conclusion, inhibition of autophagic capacity with aging generates the inflamming condition via the activation of inflammasomes, in particular NLRP3. We will provide here a perspective on the current research of the ROS-dependent activation of inflammasomes triggered by the decline in autophagic cleansing of dysfunctional mitochondria.

Inflammaging

In 2000, Franceschi et al. [1] coined the term "inflammaging" in order to refer to a low-grade pro-inflammatory status appearing during the aging process. They emphasized the role of macrophages as well as cellular stress and genetic factors in the generation of the inflamming condition. In addition, they hypothesized that this inflammatory environment could predispose the organism to the development of several age-related diseases. During recent years, this scenario has been confirmed by a plethora of experimental evidence. However, it seems that concurrently with the chronic, low-level inflammation one encounters several symptoms of immunosenescence, both in the innate and adaptive immune systems [2,3]. The presence of a pro-inflammatory phenotype in aged mammals is evident by (i) increased expression of genes linked to inflammation and immune responses in the tissues of old humans and rodents [4-6], (ii) higher level of cytokines in serum, e.g., IL-6 and TNF-α [7,8], (iii) activation of NF-κB signaling which is the master regulator of inflammatory responses [9-11]. There are tissue specific differences in the production of age-related inflammatory factors as well as in the onset and level of pathological changes [12].

It is known that systemic inflammation linked to inflamming aggravates e.g. the vascular pathology and provokes atherosclerosis [4]. Moreover, increased
systemic cytokine levels activate the hypothalamus-pituitary-adrenal (HPA) axis which augments the secretion of cortisol [13]. Cortisol is a potent anti-inflammatory agent although it not only induces protein catabolism, e.g. in muscle tissues, but it also promotes bone resorption. Chronic inflammation can also enhance the appearance of insulin resistance in muscles and adipose tissues as well as disturb the maintenance of energy homeostasis and subsequently cellular housekeeping functions. Interestingly, the aging process is simultaneously accompanied by both the features accelerating inflamming and the counteracting, so-called anti-inflamming characteristics [14]. It seems that the balance between these opposite forces controls the outcome of the aging process, either leading to frailty and degenerative diseases or a healthy old age and longevity.

**Inflammasomes: molecular platforms for danger signal recognition**

The aging process jeopardizes the maintenance of cellular homeostasis leading to the activation of a variety of host defence systems. Inflammasomes are intracellular multiprotein sensors which can recognize a large set of danger signals, induced either by pathogens or cellular stress, and once activated, they subsequently stimulate inflammatory responses [15-18]. There are several subfamilies of NOD-like receptors (NLR) but emerging data indicates that the NLRP subfamily, in particular the NLRP3 member, is the major sensor for "intracellular danger-associated molecular patterns" (DAMPs). Inflammasomes are signaling platforms which are assembled after the recognition of DAMP by the receptor protein. In the case of NLRP3, the activated receptor interacts with the adaptor protein ASC which recruits the inflammatory caspase-1 (CASP-1) to the complex which subsequently oligomerizes into pentamer or heptamer inflammasomes [16,19]. CASP-1 is the common effector molecule in inflammasomes which cleaves the inactive precursors of two proinflammatory cytokines, i.e. IL-1β and IL-18, into their mature forms which are then secreted from cells. In addition to CASP-1, some other inflammatory caspases, e.g. CASP-4, CASP-5 and CASP-12, can also process the proforms of these cytokine [16,20]. In general, the expression levels of NLRP3 receptor as well as the precursors of IL-1β and IL-18 remain low and activation of NLRP3 inflammasomes requires a priming phase while the expression of these proteins is clearly induced [17,21,22]. Interestingly, NF-κB signaling is a crucial inducer of NLRP3 expression [21]. It should be noted that different cellular stresses and the aging process can stimulate NF-κB signaling [11,23] and probably enhance the priming and potentiation of the inflammasome activation.

Infections and tissue injuries can trigger an inflammatory reaction as a physiological host defence mechanism but in addition, cellular stress can also alert the immune system and induce adaptive responses. This kind of inflammation was termed "para-inflammation" by Medzhitov [24]. Recent studies have revealed that NLRP3 is the major receptor for endogenous danger insults to facilitate inflammatory responses. Petrilli et al. [25] demonstrated that the efflux of potassium, an effect evoked by many noxious stimuli, could activate NLRP3 inflammasomes. After this initial observation, several different activation mechanisms have been identified but still there is an ongoing debate about whether they are physiological inducers and what kind of responses they stimulate. The increased level of reactive oxygen species (ROS) induced by oxidative stress was one of the first stimuli which was demonstrated to trigger NLRP3 activation and promote CASP-1-dependent IL-1β secretion [26,27]. Furthermore, several studies have indicated that the release of cathepsin B after lysosomal damage can activate NLRP3 [28,29]. Lysosomal destabilization is also associated with the NLRP3 activation induced by cholesterol crystals in macrophages [30], probably involved in the inflammation promoting atherosclerosis. There are some observations that amyloid fibrils, e.g. islet amyloid polypeptides (IAPP) and Alzheimer's amyloid-β, can trigger NLRP3 inflammasomes [28,31] and in that way stimulate inflammation and enhance pathogenesis in type 2 diabetes and Alzheimer's disease, respectively.

Recently, Wen et al. [32] demonstrated in macrophages that palmitate, a saturated fatty acid, could activate NLRP3 whereas the unsaturated oleate was not responsive. Interestingly, NLRP3 activation was ROS-dependent and secreted IL-1β impaired insulin signaling and promoted insulin resistance in mice. Vandannamgsar et al. [33] revealed that obesity was associated with the activation of NLRP3 in adipose tissue. These workers observed that the weight loss of obese humans, induced by caloric restriction and exercise, was associated with (i) a reduction of NLRP3 expression in adipose tissue, (ii) a decrease in the level of inflammation and (iii) an increase in insulin sensitivity. Supporting these results, Stienstra et al. [34] observed that transgenic mice which lack *Nlpr3*, *Asc* and *caspase-1* genes were resistant to the obesity induced by high-fat diet and protected from insulin resistance. It seems that NLRP3 could be a sensor for metabolic stress recognizing ROS production [35]. Tschopp and Schroder [36] speculated that
different danger signal pathways converge and activate NLRP3 inflammasomes via ROS production.

Recently, Zhou et al. [37] demonstrated that mitochondria were crucially involved in the activation of NLRP3. They observed that increased mitochondrial production of ROS stimulated NLRP3 whereas the inhibition of ROS production, either with an enhanced autophagic uptake of damaged mitochondria or by inhibiting the expression of voltage-dependent anion channels (VDAC2), significantly suppressed the stimulation of NLRP3. Their study emphasized the significant role of mitochondria and in particular, their proper clearance by autophagy in the regulation of NLRP3 activation. Autophagy was also shown to be a fundamental host defence mechanism against invading intracellular microbes [38]. Moreover, deficiency in autophagy, e.g. in Crohn's disease, triggers inflammatory responses and leads to tissue injuries [39]. It seems plausible that autophagy, a guardian of cellular sanctity, is a potent anti-inflammatory mechanism which controls the activation of danger sensors, i.e. NLRP3 inflammasomes (Figure 1).

**Autophagy: master of housekeeping prevents inflammasome activation**

Autophagy is an ancient housekeeping mechanism which controls the cellular homeostasis by facilitating the removal of misfolded proteins and dysfunctional organelles, e.g. mitochondria and endoplasmic reticulum, for degradation in lysosomal system [39,40]. There are three pathways which can deliver cytoplasmic material for autophagic degradation, i.e. macro- and microautophagy as well as chaperone-mediated autophagy. Macroautophagy, segregating organelles like mitochondria, is the major type of autophagy associated with innate immunity [41,42] and it is hereafter shortly called "autophagy". In addition to the cleansing function, autophagy can regulate cellular energy balance, e.g. during starvation it can trigger energy production from its own components [43]. Autophagy may also be involved in lipid metabolism by sequestering lipid droplets [44]. In conjunction with this increased knowledge on inflammasomes, the role of autophagy in the regulation of inflammatory responses has started to emerge.

![Figure 1. The interplay between autophagy and inflammasomes in the generation of inflamming](image)

**Figure 1. The interplay between autophagy and inflammasomes in the generation of inflamming.** Normally, the autophagic uptake of dysfunctional mitochondria prevents the excessive ROS production and in that way the activation of inflammasomes. However, during aging, the autophagic capacity declines and increased ROS production and aggregated proteins activate inflammasomes which provoke a low-grade inflammation in several tissues and in that way inhibit autophagy and accelerate the aging process. There are several activators of autophagy which can delay the aging process. It is known that mTOR inhibitors and AMPK activators can extend lifespan in certain conditions.
Several studies have clearly indicated that autophagy can suppress inflammatory reactions [42,45-47]. For instance, loss of autophagy proteins, e.g. Atg16L1, potentiates endotoxin-induced IL-1β production [48]. Moreover, genetic studies have revealed that two autophagy genes, Atg16L1 and IRGM are associated with the pathogenesis of Crohn's disease, an inflammatory bowel disease [39]. It is known that autophagy regulates the inflammatory reaction, e.g. in adipocytes [49] and keratinocytes [50]. Meng and Cai [51] demonstrated that defective autophagy in hypothalamus induced inflammation and subsequently led to obesity and insulin resistance when mice were fed a high-fat diet. Interestingly, these workers observed that the effects of reduced autophagy were reversed by the inhibition of inhibitory-κB kinase β (IKKβ)) indicating that inflammation was induced by NF-κB signaling. On the other hand, potentiation of autophagy, e.g. by inhibitors of mammalian target of rapamycin (mTOR) and activators of AMP-activated protein kinase (AMPK), can reduce inflammation and tissue pathology in several diseases [39,45,52] (see also below). Shi et al. [53] demonstrated in human macrophages that increasing the autophagy by starvation and rapamycin treatment reduced CASP-1 activity and secretion of IL-1β whereas blocking the autophagy clearly enhanced inflammasome activity. They also observed that autophagic adaptors protein, p62/sequestosome-1, delivered ubiquitinated inflammasomes to degradation in autophagosomes.

Mitochondria have a crucial role in the regulation of innate immunity responses [54,55]. In addition to the ROS-dependent activation of NLRP3 inflammasomes, mitochondria (i) are involved in the control of antiviral RIG-1-like receptor (RLR) signaling pathways, (ii) contain NLRX1 receptors which monitor e.g. ROS production, and (iii) secrete several DAMPs, such as ROS, mitochondrial DNA (mtDNA) and formyl peptides [54,56]. The studies by Zhou et al. [37] and Nakahira et al. [57] clearly demonstrated that secretion of ROS and mtDNA from mitochondria activated inflammasomes, i.e. mitochondria with disrupted integrity and impaired autophagic clearance are the crucial regulators of inflammasomal activation and subsequently inflammatory responses. Nakahira et al. [57] revealed that depletion of autophagic proteins impaired mitochondrial integrity and increased their ROS production. They also demonstrated that ROS were required for caspase-1 activation, a prerequisite for the maturation of IL-1β and IL-18. They also observed that NLRP3 mediates the release of mtDNA which seems to function as a co-activator of caspase-1. In contrast, Zhou et al. [27] reported that ROS could dissociate the complex between thioredoxin (TRX) and thioredoxin-interacting protein (TXNIP), and consequently TXNIP activated NLRP3. Xiang et al. [58] demonstrated in endothelial cells that ROS produced by NADPH oxidase stimulated the release of TXNIP and its binding to NLRP3 and subsequently induced IL-1β secretion. There is also the possibility that ROS could directly oxidize thiol groups in leucine-rich repeat (LRR) domain of NLRP3 and in that way activate the inflammasomal pathway [17]. Interestingly, there are several studies which demonstrate that ROS can activate autophagy and thus enhance the autophagic cleansing of dysfunctional mitochondria or misfolded proteins [59] and in that way reduce the activation of inflammasomes and the risk for tissue injuries.

In conclusion, all these observations emphasize that a deficiency in the cellular housekeeping can trigger the inflammatory danger sensor NLRP3, and also NLRP1 in some tissues like brain [60], and by this means stimulate inflammatory reactions in sensitive tissues. In this respect, the effective function of autophagic uptake and lysosomal degradation of dysfunctional mitochondria and aggregated proteins is a crucial element in maintaining tissue homeostasis. There are indications that autophagic capacity is compromised in certain diseases [61,62], e.g. in Alzheimer's disease [63]. On the other hand, there is growing evidence implying that inflammasomes are activated in many pathological conditions [64,65] and thus a deficiency in autophagic housekeeping could trigger an inflammatory component and aggravate their pathogenesis.

**Autophagy declines with aging enhancing the inflamaging process**

The aging process involves a progressive decline in cellular and organismal function. The major hallmark of aging is the deficient maintenance of proteostasis which permits the accumulation of damaged and defective cellular components, e.g. lipofuscin, within cells. Brunk and Terman [66] called this cellular status as "garbage can" hypothesis of aging. They proposed that lipofuscin accumulation would disturb lysosomal degradation thus inhibiting the cleansing of dysfunctional mitochondria. After ten years of experimental work, this hypothesis still seems to be valid since different research approaches have demonstrated that autophagy clearly declines with aging and the number of dysfunctional mitochondria augments. In particular, defects in mitochondrial uptake and degradation could increase ROS production and stimulate inflammasomes. Recently, this research topic has been extensively reviewed in detail elsewhere [67-72].

Many studies have indicated that the inhibition of autophagy by genetic manipulation provokes age-
related pathological changes and reduces the lifespan of many organisms, e.g. *C. elegans*, *Drosophila* and mice [71,73,74]. Wu et al. [75] demonstrated that the deletion of the *Atg7* gene induced mitochondrial disturbances, e.g. increased production of ROS and alterations in the metabolic profile, in mouse skeletal muscle. Cuervo and Dice [76] observed that also chaperone-mediated autophagy (CMA), not only macroautophagy, was impaired in rat liver during aging. They revealed that the decline was caused by an age-related decrease in the expression of LAMP-2A, the receptor protein of CMA. Interestingly, in subsequent studies [77], they demonstrated that the prevention of the age-related loss of LAMP-2A protein in transgenic mice could maintain efficient CMA and that this was associated with a reduction in the level of damaged proteins and improved liver function during aging. Many studies have also demonstrated that increasing the autophagic capacity by pharmacological or genetical manipulations can prevent the pathology linked to the aging process and even extend lifespan [78-80]. For instance, pharmacological induction of autophagy, e.g. by inhibiting mTOR by rapamycin can increase the lifespan of mice [79] (see below).

Caloric restriction (CR) is the most common anti-aging intervention which can extend lifespan in organisms ranging from yeast to humans [81]. CR is a potent physiological activator of autophagy [82,83]. Several studies have demonstrated that autophagy is required for the CR-mediated lifespan extension [71,83]. Colman et al. [84] revealed that CR delayed the onset of many age-related pathologies, e.g. incidence of diabetes, cancer, cardiovascular disease and brain atrophy, as well as reducing the mortality of rhesus monkeys. Moreover, it is known that CR effectively protects against inflammatory responses and can combat age-related pro-inflammatory phenotype [85,86]. CR has also several beneficial effects on mitochondrial quality control, e.g. ROS production [87,88], which can improve cellular housekeeping and prevent inflammasomal activation. Many studies have indicated that mitochondrial quality control has a key role in the regulation of the aging process [89,90]. For instance, Trifunovic et al. [91] demonstrated that triggering of point mutations and deletions into mtDNA induced a premature aging phenotype in mice.

There are several regulatory mechanisms which could augment the appearance of inflammasomal phenotype during the age-related deficiency of autophagy. It is well-known that increased levels of ROS can activate NF-κB signaling via multiple mechanisms [92-94]. For instance, several redox-sensitive protein kinases and phosphatases can stimulate IKK-NF-κB signaling and thus induce and maintain an elevated priming state of inflammasomal system. Moreover, a decline in autophagy can stimulate the activating kinases of the NF-κB complex, i.e. IκB kinase α and β (IKKα/β) and NF-κB-inducing kinase (NIK), which are degraded via selective autophagy [95-97]. Sequestosome-1/p62 is a cargo receptor for selective autophagy [98] and changes in autophagy regulate the p62 level which controls the formation of protein aggregates as well as activation of NF-κB signaling [99,100]. Both of these responses are typical hallmarks of inflamming and inducers of inflammasomes.

In conclusion, the decline in autophagy during aging creates problems in cellular housekeeping functions which stimulate NF-κB signaling in order to directly or via inflammasomes trigger an age-related pro-inflammatory phenotype. Moreover, there are indications that inflammatory signaling can repress autophagy and thus induce this destructive interplay between autophagy and inflammasomes. For instance, tumor necrosis factor-α (TNF-α), an inflammatory cytokine, can induce or repress autophagy in an NF-κB-dependent manner [101]. In the presence of NF-κB signaling, TNF-α activates mTOR, a major autophagy inhibitor, whereas in cells lacking NF-κB activation, TNF-α treatment stimulates the expression of Beclin 1, an enhancer of autophagy. Both of these responses are dependent on the TNF-α-induced ROS production. Moreover, inflammasomes can also enhance inflammasome activation without autophagy since e.g. glucocorticoids, known as anti-inflammatory compounds secreted with aging (see above), can strongly induce the expression of NLRP3 in macrophages [102]. Thus, it seems that the elevated cortisol level as an anti-inflammaging response could increase the priming state of inflammasomes and thus potentiate their response sensitivity during aging.

**Activators of autophagy: promising drugs for inflamming and related diseases**

As Cuervo [67] outlined, the role of autophagy is to "keep that old broom working" with aging. As discussed above, there is much evidence that caloric restriction can activate autophagy and also extend lifespan, probably via its beneficial health effects. Currently, there are a number of drug discovery programs aimed at finding safe chemicals which would be able to activate autophagy. There are two potential groups of compounds acting in this way; mTOR inhibitors [103,104] and AMPK activators [105,106] (Figure 1). mTOR is the major inhibitor of autophagy and is involved in aging [107,108]. Rapamycin and other mTOR inhibitors are either used or under investigation
for therapy of cancer and many age-related diseases [107-110]. mTOR is a key protein kinase which couples nutritional and growth factor signaling to protein synthesis, transcription and critical responses in cellular growth, proliferation and survival. Moreover, many studies have reported that lifespan extension induced by CR is associated with the down-regulation of mTOR activity [108,111]. Harrison et al. [79] observed that rapamycin, a recognized inhibitor of mTOR, could extend lifespan in mice if fed late in their life. Recently, Anisimov et al. [112] demonstrated that the lifelong administration of rapamycin extended lifespan in inbred female mice. Moreover, rapamycin could also increase maximal lifespan in cancer-prone mice [113]. Cao et al. [114] observed that rapamycin treatment reversed the senescent phenotype of Hutchinson-Gilford progeria cells in culture by stimulating autophagy. Rapamycin treatment has also been reported to be able to reduce age-related cognitive defects. Majumder et al. [115] demonstrated that life-long administration of rapamycin improved the spatial learning and memory performance in aging mice. Interestingly, this was associated with a decrease in the brain level of IL-1β but not that of TNF-α which could be interpreted to imply that the inflammasomal activity had been reduced by rapamycin therapy. This suggestion is in agreement with the results of Mawhinney et al. [116] which indicated that increased inflammasome activation was linked to age-related cognitive impairment in rats. Rapamycin, also called sirolimus in clinical use, has been intensively studied as an anti-cancer agent [109]. Rapamycin is a macrolide antibiotic and powerful immunosuppressant which causes some serious complications, e.g. lung toxicity. Currently, there are intensive drug discovery programs planned at developing rapalogues, i.e. rapamycin analogues, such as everolimus and temsirolimus [104].

The utilization of AMPK activators is another strategy with which to stimulate autophagy for therapeutic purposes. AMPK is an evolutionary conserved sensor for disturbances in cellular energy balance and a major inducer of autophagy [117,118]. We have recently reviewed the integrated signaling network through which AMPK regulates the aging process [119]. For instance, AMPK can activate autophagy by directly targeting ULK1 which triggers mitophagy [120]. Moreover, AMPK can inhibit the activity of the mTOR complex 1 (mTORC1), either phosphorylating the regulatory Raptor component or activating TSC2 which subsequently inhibit mTOR activity [118]. Interestingly, several studies have indicated that the responsiveness of AMPK signaling declines with aging [118] which could impair autophagic responses during aging. For instance, Reznick et al. [121] observed that physical exercise and AICAR, a chemical activator of AMPK, induced a robust increase in AMPKα2 activity in the skeletal muscles of young mice whereas in old rats no stimulation was apparent. In addition, Liu et al. [122] demonstrated in a mouse model that stroke induced a major activation of AMPK in young animals but no response occurred in their older counterparts. These studies and many other observations indicate that the aging process impairs the activation capacity of AMPK signaling and in that way, disturbs autophagic activity, evokes oxidative stress and triggers the activation of inflammasomes. Moreover, AMPK activity represses NF-κB signaling [123] which could suppress the priming of inflammasomes in young animals but this effect may be lost during aging. There are several pharmacological activators of AMPK, e.g. AICAR (5-aminoimidazole-4-carboxamide ribonucleoside) and the clinically-used antidiabetic drug metformin [105]. Both of these compounds also have AMPK-independent effects. AICAR stimulates AMPK-dependent autophagy via ULK1 and FoxO3a [124,125]. Several natural products, e.g. berberine, curcumin and quercetin, have been reported to activate AMPK signaling [105].

In conclusion, there is substantial evidence indicating that autophagy is a significant regulator of innate immunity responses in host defence. The decline in autophagy with aging impairs cellular housekeeping and exposes cells to the risk of inflammasome activation. There is now convincing experimental data demonstrating that efficient autophagic activity can prevent the activation of inflammasomes and induction of inflammatory responses. AMPK activators and mTOR inhibitors are promising pharmacological agents which can effectively stimulate autophagic degradation. However, many of the present agents have toxic side effects and they can trigger apoptotic cell death. Moreover, it is still a matter of debate whether excessive autophagy can lead to autophagic cell death or not [126]. It seems that generally autophagy is a cell survival mechanism but it can be used for cell death e.g. during development [127] and in some contexts such as in tumor cell death after chemotherapeutic drug treatment [128].

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CONFLICT OF INTERESTS STATEMENT

The authors of this manuscript have no conflict of interest to declare.
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