

Review Article

Mechanism underlying effect of autophagy on interleukin-1 β

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Introduction

Autophagy is a highly conserved, bulk degradation system in which portions of cytoplasm, damaged organelles or long-lived proteins are sequestered into double-membraned structures, called autophagosomes, which eventually deliver their contents for degradation in the lysosomal compartment. Autophagy is deeply implicated in the regulation of numerous physiologic functions including cell development and differentiation, survival and senescence, and it also affects fundamentally the inflammatory process, and the innate and adaptive arms of immune responses [1]. Autophagy can also regulate a number of important immune response, including clearance of intracellular bacteria, antigen presentation, and the regulation of cytokines production and secretion. In particular, Autophagy regulates endogenous inflammasome activators, as well as inflammasome components and Interleukin 1 (IL-1) family cytokines, especially for IL-1 β . The production and secretion of IL-1 β from inflammatory cells is a tightly regulated process that has been extensively described and studied. However, our review provides more comprehensive regulation of IL-1 β by autophagy [2].

IL-1 β and innate immunity

IL-1 β is not present in health or at levels not detected by standard assays. IL-1 β is a product of blood monocytes, tissue macrophage, and dendritic cells and so on. The rate-limiting step in the production of IL-1 β is transcription, but IL-1 β mRNA requires an additional signal for synthesis. The stimulus can be a microbial product but cytokines, such as TNF α , IL-18, IL-1 α or IL-1 β itself induce IL-1 β [3]. Typically, the release of IL-1 β is a two stage process. First, transcription of pro-IL-1 β is induced by inflammatory stimuli (such as lipopolysaccharide (LPS)). This is followed by activation of inflammasome assembly by a second stimulus, such

Abstract

Autophagy has been linked to myriad biological processes as a response to nutritional deprivation, hypoxia and stress conditions in general. Moreover, autophagy has a potentially pivotal role to play in the regulation of inflammatory responses. In particular, autophagy regulates all kinds of cytokines, especially IL-1 β . This review focus specifically on the role of autophagy in regulation the transcription, secretion, signaling of IL-1 β . and the consequences of these important functions.

Keywords: Autophagy; ATG16L1; IL-1 β ; Immune response; ROS

as reactive oxygen species (ROS), ATP, particulates (e.g., silica, alum), protein aggregates, or lysosomal disruption[4].

IL-1 β is a proinflammatory cytokine, which is responsible for the recruitment of myeloid cells, including neutrophils, to sites of inflammation. IL-1 β markedly increases in the expansion of naïve and memory CD4+ T cells. Blocking IL-1 β reduces IL-17 production. Recently, studies have suggested that IL-1 β can drive the release of both IL-1 α and IL-23 further highlighting the importance of this cytokine in regulating inflammatory responses. Also, IL-1 β induction of itself is part of the mechanism of autoinflammation [4]. A growing number of chronic inflammatory disorders without a known genetic basis respond to reducing IL-1 β activity. Therefore, the implications for decreased IL-1 β may have clinical importance for diseases.

Autophagy and innate immunity

Autophagy is an evolutionarily conserved catabolic process that, by facilitating the breakdown and recycling of damaged organelles and long-lived proteins, is essential to maintaining cellular homeostasis [5]. The autophagy pathway is highly regulated during development and also by environmental factors such as nutrient availability/starvation, hypoxia, and ROS. The process is controlled by a number of autophagy-related genes (Atg) and starts with the formation of a double-membrane vesicle (the autophagosome) engulfing the cytoplasmic components to be delivered to the lysosome for degradation. Formation of the autophagosome requires the concerted action of two ubiquitin-like conjugation systems in which Atg12 is covalently linked to Atg5 and microtubule-associated protein 1A/1B-light chain 3 (LC3) is conjugated to phosphatidylethanolamine [6]. During the process, Atg16L1 is essential for the localized conversion of LC3 to a phosphatidyl-ethanolamine-conjugated form, LC3-II, and thus drives autophagosome formation [7].

The autophagic response provides cytoprotective and homeostatic functions and intersects with a variety of general stress-response pathways, and recent studies have revealed an intimate linkage between the autophagic pathway and various innate immune responses [8]. Innate cytokine production is guided by three main transcription and processing systems. Toll-Like Receptor (TLR) signaling for example leads to NF- κ B activation, which allows the transcription of pro-inflammatory cytokines like TNF- α . In addition, pro-IL-1 β and pro-IL-18 are transcribed, which, however, requires processing by caspase-1 to be converted into the mature cytokines. Caspase-1 activation is under the control

of inflammasomes. And finally, interferon regulating factors (IRFs) guide the transcription of type I interferons after for example double-stranded RNA recognition in the cytosol via retinoic acid-inducible gene 1 (RIG-I) [9]. Those regulations have been most extensively studied for IL-1 β . This occurs through at least two distinct mechanisms [4]. Firstly, in macrophages and dendritic cells, inhibition of autophagy, either pharmacologically with 3-methyladenine (3-MA) or through siRNA deletion of autophagy genes, leads to increased release of IL-1 β , in response to TLR3 or TLR4 agonists. The second mechanism is more direct; autophagosomes can sequester and degrade inflammasome components, including the adaptor molecule apoptosis-associated speck-like protein containing a CARD (ASC), NOD-like receptor family, pyrin domain containing 3 (NALP3) [10]. Given such a substantial contribution to innate immunological processes by autophagy, it has been described as an emerging immunological paradigm.

Autophagy suppresses the secretion of IL-1 β

It was observed that IL-1 β production is enhanced upon autophagy deficiency, leading to gut inflammation in mice with reduced autophagy levels (Atg16L1 hypomorphic mice) [11]. Saitoh et al. [12] demonstrated that LPS induced IL-1 β secretion in embryonic liver macrophages from Atg16L1 $^{-/-}$ mice in a TIR-domain-containing adapter-inducing interferon- β (TRIF) - dependent manner, suggesting the role of autophagy in the secretion of IL-1 β . Inhibition of autophagy stimulated the production of IL-1 β by bone marrow-derived macrophages in an NLRP3-dependent manner [13]. In crystal-related inflammation, loss of functional Atg16L1 and Atg5 genes impairs autophagosome formation and significantly enhances monosodium urate monohydrate (MSU) crystal-induced IL-1 β production [14]. However, the mechanisms behind this observation have not been fully determined.

The machinery of autophagy for modulatory effect of IL-1 β

Autophagy controls IL-1 β secretion by targeting pro- IL-1 β for degradation

Many reports have indicated that IL-1 β production is enhanced at the post-transcriptional level by autophagy. Saitoh showed that immature IL-1 β synthesis following LPS was not increased in Atg16L1-deficient macrophages [12]. It is also reported that transcription of IL-1 β was comparable between WT and T316A macrophage following by heat-killed *Y. enterocolitica* or TLR and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) ligands stimulation [7]. Recently, however, important progresses have been made in understanding how autophagy controls IL-1 β secretion by targeting pro-IL-1 β . After treatment with rapamycin, a reduction in pro-IL-1 β was observed in BMM stimulated with either LPS or TLR agonists. There is not any processed IL-1 β in the supernatants from these cells, suggesting that induction of autophagy is inducing degradation of pro-IL-1 β , rather than processing and secretion of the mature form [13]. Coupled with the observation, in macrophage treated with TLR agonists, pro-IL-1 β could be seen in autophagosome; these data suggest that autophagy specifically targets pro-IL-1 β for lysosome degradation, thus acting as an internal regulatory mechanism controlling the availability of pro-IL-1 β for subsequent processing [14]. Therefore, it is suggested that inhibition of autophagy prevents degradation of pro-IL-1 β , leaving more of the cytokine available in the cytosol for processing and secretion.

And also in the human peripheral blood mononuclear cells (PBMCs), IL-1 β mRNA levels were increased in the presence of 3MA. On the other hand, caspase-1 activation was not changed after inhibition of autophagy, which is suggested that autophagy did not inhibit inflammasome activation in human PBMCs, and its effects were the consequence of the modulatory effect on transcription of cytokine genes [15].

Thus, the role of autophagy in regulating IL-1 β secretion may depend on timing and context; in the absence of an inflammasome-activating signal, autophagy may act to remove pro-IL-1 β and inflammasome components from the cells, while in the presence of such a signal, autophagy may act as a secretory pathway for IL-1 β release.

Autophagy controls IL-1 β secretion by targeting ROS production

TLR ligands, particularly LPS, are the first signal to induce pro-IL-1 β formation, but in many cases, this is not enough to stimulate inflammasome activation and secretion of the mature cytokine. Instead, a second signal is commonly required, and this can come from a number of endogenous and exogenous sources, including ATP and particulates, including uric acid crystals, asbestos, synthetic microparticles, and alum. Alternatively, others have proposed that NLRP3 agonists induce inflammasome assembly by stimulating the production of ROS. Numerous studies have demonstrated a role for ROS, particularly peroxynitrite, in the processing and secretion of IL-1 β , although other studies have suggested that ROS are not involved in IL-1 β processing or may in fact dampen IL-1 β -induced inflammation [16, 17]. Saitoh et al. [12] found that Atg16L1-deficient macrophages generated higher levels of ROS in response to LPS compared with WT or Atg16L1/TRIF double-deficient cells, suggesting that autophagy is an important regulator of intracellular ROS. Also James et al. showed that ROS scavenger inhibited IL-1 β secretion in response to LPS in combination with either wortmannin or 3-MA. But the source of ROS was not from NADPH oxidase, one possible alternative source of ROS is from altered or damaged mitochondria and peroxisomes [12]. However, in a recent study, it is also reported that NADPH-dependent ROS deficiency results in autophagic dysfunction that subsequently contributes to increased interleukin 1 β production [18]. However, the higher ROS source for this regulation need to further studied.

Autophagy controls IL-1 β secretion by targeting sequestosome1 (SQSTM1, p62) production

P62/SQSTM1 is a multifunctional adaptor molecule in autophagosome formation, promoting degradation of poly-ubiquitinated proteins through a proteasome pathway [19, 20]. In recent research, ATG16L1 suppresses IL-1 β signaling by down-regulating p62 levels via both autolysosomal and proteasomal pathways. In the absence of ATG16L1, p62 levels are increased. This increase in p62 levels promotes oligomerization and activation of TNF receptor associated factor (TRAF) [21,22], resulting in over activation of NF- β b and Mitogen-activated protein kinases (MAPK) upon IL-1 β stimulation that leads to a hyper-inflammatory response.

P62 is involved in the activation of caspase-1 as an important component within the inflammasome complex. Impaired autophagosome formation by Atg16L1 siRNA significantly amplified p62 levels, thereby leading to caspase-1 activation and over-expression of IL-1 β under stimulation of MSU crystals [14]. However, the function of p62 in activating caspase-1 should be further investigated.

IL-1 β induces autophagy

Numerous cytokines are known to regulate autophagy in macrophages. IFN- γ and TNF- α can induce autophagy, while IL-4, IL-13 and IL-10 inhibit it [23, 25]. Amongst those that have been shown to activate autophagosome formation are IL-1 α and IL- β [26]. Moreover, other cytokines associated with inflammatory responses, including IL-23, have been shown to drive autophagy [27]. Thus autophagy may represent an important mechanism in a negative feedback loop to control the secretion of inflammatory cytokines.

Conclusion and future directions

The initial sporadic observations that autophagy can play a role in cell-autonomous defense against intracellular bacteria such as *Mycobacterium tuberculosis* and streptococci have been extended in the past several years to various facets of immunity. The connections of autophagy with the normal function of innate immunity, especially specialized mechanisms of autophagy as regulator of IL- β processes presented in this review. In particular, autophagy modulates the transcription, processing, and secretion of IL-1 β , acting as an important negative feedback mechanism for the control of inflammatory responses, both in vitro and in vivo. As such, autophagy may represent a potent target for novel anti-inflammatory therapeutics.

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