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Cellular and molecular mechanisms involved in the resolution of innate leukocyte inflammation

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Abstract

Inflammation is a host response to infection or damage and is vital for clearing pathogens and host debris. When this resolution fails to occur, chronic inflammation ensues. Chronic inflammation is typically characterized as a low-grade, persistent inflammatory process that can last for months or even years. This differs from acute inflammation, which is typically a fast, robust response to a stimulus followed by resolution with return to homeostasis. Inflammation resolution occurs through a variety of cellular processes and signaling components that act as “brakes” to keep inflammation in check. In cases of chronic inflammation, these “brakes” are often dysfunctional. Due to its prevalent association with chronic diseases, there is growing interest in characterizing these negative regulators and their cellular effects in innate leukocytes. In this review, we aim to describe key cellular and molecular homeostatic regulators of innate leukocytes, with particular attention to the emerging regulatory processes of autophagy and lysosomal fusion during inflammation resolution.

Keywords

cellular and molecular mechanisms; dynamic modulation; leukocyte homeostasis; negative regulators; lysosome fusion

1 INTRODUCTION

The processes of inflammation, generally defined as host responses to challenges, are instrumental to maintain host defense and homeostasis.¹ Decades of studies reveal closely intertwined signaling circuits composed of molecular and cellular components that finely modulate the initiation, maintenance, and resolution phases of inflammation. Innate leukocytes, such as monocytes and neutrophils, are critical first responders to challenges during inflammation. Extensive studies have revealed complex signaling networks involved in the activation of innate monocytes/neutrophils during the initiation phase of inflammatory responses.^{2,3} Recent advances suggest equally complex molecular and cellular mechanisms responsible for the resolution phase of leukocyte activation.⁴ Furthermore, molecular and

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DISCLOSURE

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cellular circuitries that control the activation and resolution phases of monocyte inflammatory responses are closely integrated.^{5,6} The dysfunction of cellular and molecular “brakes” may underlie the pathogenesis of chronic nonresolving inflammatory diseases in humans and experimental animals.⁷ This review will focus on the intracellular homeostatic circuitries responsible for inflammation resolution and pathological implications of disrupted homeostatic signaling networks.

1.1 Cellular processes mediating homeostasis and attenuating inflammation

In order to ensure proper inflammation resolution, activated leukocytes undergo critical cellular alterations including programmed cell death, efferocytosis of neighboring inflamed and/or damaged cells, as well as autophagic clearance of intracellular inflammatory signals. Although apoptosis and efferocytosis have been reviewed extensively elsewhere,^{8–10} the role of autophagy during inflammation resolution and its relationship to chronic inflammatory diseases is still being explored. Thus, we will focus specifically on the role and regulation of autophagy during the process of inflammation resolution.

1.1.1 A brief overview of autophagy—Within the last decade, the cellular process of autophagy has surfaced as a prominent negative regulator of inflammation. Autophagy is a process where cytoplasmic materials and/or organelles are enclosed by a double-membrane vesicle called the autophagosome, which then fuses with the lysosome where its contents are degraded. This process itself has been studied and reviewed extensively elsewhere,¹¹ but, in brief, it consists of three main stages: initiation (induction), maturation, and lysosomal fusion (completion). A conserved family of autophagy-related genes (ATGs) has been identified as the key machinery for autophagosome formation and maturation.¹² In mammalian cells, Unc-51 like autophagy activating kinase (ULK1) is critical for the initiation of autophagosome where it forms a complex with the proteins ATG13, ATG17, and ATG101.¹³ This activated ULK1 complex then recruits the transmembrane protein ATG9 followed by the UV radiation resistance-associated gene protein (UVRAG) containing a phosphatidylinositol 3-kinase (PIK3) complex. Subsequently generated phosphatidylinositol-3-phosphate recruits the ATG2/WD-repeat protein interacting with phosphoinositides (WIPI) 2 complex for vesicle nucleation.^{14,15} The most downstream ATG12/ATG5/ATG16L complex is conjugated with microtubule-associated proteins 1A/1B light chain 3B/LC3 (MAP1LC3B (LC3)), mediating the maturation of autophagosome. During autophagy, ubiquitinated autophagic cargos can be recognized by sequestosome 1 (SQSTM1, also known as p62), which binds with LC3 and functions as a cargo adaptor to facilitate the delivery of components to the autophagosome.^{13,16,17} Upon completion, the mature autophagosome fuses with the lysosome, which contains acid hydrolases and other enzymes in order to degrade the autophagic contents including the cargo-receptor p62. Despite these exciting advances, however, the molecular and cellular details regarding the fusion process of lysosome with autophagosome are not clearly understood.¹⁸ At the translational level, the process of autophagy has been widely associated with diverse pathophysiological consequences including the dynamic balance of resolving versus nonresolving inflammation, which we will discuss in the next section of this review.

1.1.2 Role of Autophagy in inflammation resolution—While autophagy has traditionally been viewed as a survival mechanism under cell stress conditions such as nutrient deprivation, it also serves as a key homeostatic process contributing to inflammation resolution.¹¹ For instance, its role in regulating TLR signaling and inflammasome signaling has been well documented. Saitoh et al. demonstrated that Atg16L1^{-/-} macrophages exhibited higher levels of the proinflammatory cytokines IL-1 β and IL-18 upon LPS stimulation, an indication of increased inflammasome activity.¹⁹ Further, Shi et al. found that autophagy was initiated downstream of NLR family pyrin domain containing 3 (NLRP3) and absent in melanoma 2 gene (AIM2) inflammasome activation and could negatively feedback to degrade ubiquitinated inflammasome components.²⁰ In addition, IL-1 β itself was found to be colocalized with autophagosomes following LPS treatment, suggesting that autophagy can regulate inflammation at the cytokine level as well.²¹ Autophagy can also reduce protein levels of the TLR4 scaffolding protein Pellino-3, which interacts with IL-1 receptor-associated kinase (IRAK-1) to enhance NF- κ B signaling and IL-1 β expression. Pellino-3 levels, and consequently IL-1 β levels, were shown to accumulate when autophagy was blocked in RAW 264.7 cells as well as in murine bone-marrow-derived macrophages.²²

Given the key role of autophagy during inflammation resolution, it is not surprising that defects in autophagy have been associated with chronic inflammatory diseases, such as irritable bowel disease, neurodegenerative disease, and metabolic diseases including obesity and diabetes. The initial link between autophagy and chronic inflammatory diseases came from genome-wide association studies in the setting of Crohn's disease, where SNPs in the gene encoding for the autophagy protein ATG16L were found to be correlated with Crohn's disease.²³ In addition, Atg16L1^{-/-} mice showed a higher sensitivity to dextran sulfate sodium (DSS) induced colitis.¹⁹ Defects in autophagy have also been associated with insulin resistance in both genetic and diet-induced mouse obesity models where loss of the protein ATG7 resulted in increased hepatic endoplasmic reticulum stress, insulin resistance, and decreased glucose intolerance.²⁴ Recently, autophagy has been shown to play a key role in neurodegenerative diseases as well. For instance, a lack of the initiation protein ATG5 in mouse neurons leads to a loss of basal autophagy resulting in a buildup of cytoplasmic inclusion bodies and neuronal loss.²⁵ Defects in the autophagy protein beclin1 have been implicated in the pathogenesis of Alzheimer's disease,²⁶ Parkinson's disease,²⁷ and Huntingtin's disease.²⁸ Further studies that thoroughly explore the regulation of autophagy and its involvement with inflammation resolution may hold promise for developing effective therapies to treat diverse inflammatory diseases.²⁹

1.1.3 Autolysosome fusion during inflammation resolution—As mentioned previously, autophagy completion is dependent upon fusion of the autophagosome with the lysosome where the contents are degraded. Failure of autophagosome-lysosome fusion results in an accumulation of autophagosomes and hinders the homeostatic/anti-inflammatory ability of autophagy.³⁰ As we discuss later in this review, lysosome biogenesis and autophagy are closely intertwined. Lysosomal fusion is also required for termination of endosomal pathways, such as those involved in the degradation of cell-surface receptors, which may also act as a means to modulate inflammatory signaling. For example, Wang et

al. found that the lysosomal-associated protein, Rab protein 7b/Ras-related protein in brain 7b (Rab7b) promoted the degradation of TLR4 by lysosomes in macrophages stimulated with LPS.³¹ In a separate report, Tanaka et al. suggested a role for the lysosome in the regulation of IL-6 signaling through the lysosomal degradation of the gp130 receptor subunit.³² Similarly, in the case of efferocytosis, lysosomal fusion is key to degrading ingested apoptotic cells and preventing inflammation.³³ If this process is blocked, an accumulation of harmful and potentially inflammatory apoptotic bodies may accumulate. At the translational level, our group has demonstrated that the lysosome fusion process within low-grade inflammatory monocyte is disrupted both in vitro and in vivo and is closely related to the pathogenesis of chronic diseases such as atherosclerosis and impaired wound healing.^{34–36} Together, these studies suggest a key role for lysosomal fusion during inflammation resolution. Further studies regarding this process and its relationship with disease pathogenesis are necessary and may provide novel insights for the treatment of chronic inflammatory diseases.

1.2 Key signaling molecules involved in cellular homeostasis and attenuation of inflammation

With increasing interests in the dynamic involvement of subcellular homeostasis during inflammation modulation, several key signaling molecules that bridge these 2 processes have drawn significant attention. For example, key molecular switches, such as Toll-receptor interacting protein (Tollip), sirtuin1 (SIRT1), and IRAK-M, are not only involved in sending suppressive signals to inhibit NF- κ B-mediated inflammatory responses, but also involved in facilitating subcellular homeostasis such as autophagy and lysosome fusion.^{37–42} These homeostatic molecules may enhance subcellular homeostasis not only through facilitating autophagy and lysosome fusion but also through inducing autophagy components by activating homeostatic transcription factors such as the CREB and transcription factor EB (TFEB). Together, these molecular processes contribute to the resolution of inflammation and cellular homeostasis.

1.2.1 Key signaling molecules facilitating autophagy/lysosomal fusion and suppressing inflammation

Tollip: Tollip is an adaptor protein that was first identified in 2000 in association with IRAK-1 downstream of IL-1 receptor (IL-1R).⁴³ Upon stimulation with IL-1 β , Tollip releases IRAK-1, allowing it to transmit IL-1 β signaling. Tollip has also been shown to be a negative regulator of TLR2 and TLR4 signaling in a similar fashion (inhibiting IRAK-1)⁴⁴ and has been found to contribute to IL-1R degradation via the endolysosomal pathway. In addition to its direct role as a negative regulator of inflammation through its effects on TLR and IL-1R signaling, Tollip may contribute to cellular homeostasis by facilitating endosomal trafficking and lysosomal fusion.^{29,45,46} Tollip was found to be associated with endosomes and recruits target of Myb protein 1 and ubiquitinated proteins.⁴⁵ Tollip-deficient macrophages exhibit an accumulation of p62 as well as a decrease in endosomal acidity compared to wild-type cells.²⁹ The expression of key lysosomal fusion molecules was also compromised in Tollip-deficient cells and tissues.⁴⁶ At the pathological level, ApoE^{-/-} Tollip^{-/-} mice had an increase in atherosclerosis with atherosclerotic plaques containing increased amounts of p62, suggesting a defect in lipophagy (a specialized form of autophagy

involved in lipid degradation) in vivo.⁴⁶ Due to compromised autophagy, Tollip-deficient mice also exhibit an elevated accumulation of protein aggregates in other tissues such as the brain and have increased risks for neurological diseases.^{47,48} Our lab reported that Tollip deficiency in ApoE^{-/-} mice led to an accumulation of autophagosomes and the protein p62, correlated with decreased lysosomal fusion. This was coupled with neurodegeneration and increased levels of α -synuclein in hippocampal neurons as compared to ApoE single knockout mice.⁴⁷ Similarly, in a separate study, Lu et al. found that Tollip deficiency led to an accumulation of Huntington's disease-associated polyQ proteins in Hela cells, while overexpression was found to enhance autophagic clearance of the highly aggregate-prone polyQ proteins.⁴⁸ In addition to its role in neurodegenerative disease, Tollip-deficient neutrophils demonstrated an inflamed but incompetent phenotype with compromised bacterial killing capacity, which was coupled to an increased sensitivity to DSS-induced colitis in Tollip-deficient mice.⁴⁹ Tollip may also play a role in promoting tolerance as indicated by studies with regulatory dendritic cells (DCregs).⁵⁰ CD11c⁺/CD40^{low}/IL-10⁺ DCregs have been identified as a DC subset that primes naïve T cells into regulatory T cells (Tregs) and ameliorates autoimmune ovarian diseases. Silencing Tollip inhibited the function of DCregs to prime Tregs in vitro and Tollip-deficient DCregs failed to promote tolerance in vivo.⁵⁰ Taken together, these studies suggest Tollip serves as a critical homeo-static molecule to suppress inflammation through facilitating lysosome fusion and maintaining cellular homeostasis.

IRAK-M: IRAK-M is another negative regulatory molecule involved in the modulation of TLR4 signaling and is found mostly in monocytes/macrophages in humans, whereas in mice the expression is broader, including neutrophils and B cells as well as a variety of other cell/tissue types.⁴² IRAK-M has been shown to interact with the myeloid differentiation primary response 88 (MYD88) TLR adaptor protein as well as IRAK-1 and IRAK-4 and reduce inflammatory signaling as evidenced by increased production of IL-12p40, IL-6, and TNF- α and a failure to induce tolerance after repeat stimulation with LPS in murine macrophages lacking IRAK-M.⁵¹ Further evidence of the anti-inflammatory role of IRAK-M comes from a recent study by Wu et al., where overexpression of IRAK-M enhanced autophagy in human lung epithelial cells treated with human rhinovirus 16 (HRV16). This was accompanied by increased viral replication and decreased expression of the inflammatory cytokines IFN- β and IFN- λ 1.⁵² Thus, IRAK-M may be able to attenuate inflammation through enhancing autophagy in addition to its role in suppressing TLR4 signaling. IRAK-M has also been associated with chronic inflammatory disease pathogenesis. For instance, IRAK-M deficiency was associated with increased proinflammatory cytokine expression in colitis and mouse models of colitis-associated cancer.^{53,54} IRAK-M deficiency was also shown to exacerbate the autoimmune disease systemic lupus erythematosus resulting in the induction of interferon-related genes and inflammatory cytokines, as well as the expansion of autoreactive T cells.⁵⁵ In addition, IRAK-M-deficient nonobese diabetic mice showed more severe type 1 diabetes mellitus with enhanced T cell activation and elevated production of proinflammatory cytokines.⁵⁶ Thus, IRAK-M plays a key role during inflammation resolution in a variety of settings and the underlying mechanisms in autophagy regulation requires further clarification.

SIRT1: SIRT1 is an NAD-dependent deacetylase involved in the regulation of a wide variety of cellular processes from metabolic pathways to inflammation to aging and senescence.^{57–59} Loss of SIRT1 in myeloid cells leads to increased acetylation of NF- κ B RelA/p65 and increased proinflammatory gene induction.⁶⁰ In vivo studies confirmed that experimental diabetes and insulin resistance due to high-glucose diet may reduce SIRT1 protein levels, leading to an increase in IL-1 β and TNF- α .^{61,62} On the contrary, overexpression of SIRT1 protected mice from the development of nonalcoholic fatty liver disease (NAFLD) in response to high-fat diet and reduced LPS-induced inflammatory cytokine signaling when compared to wild-type control mice.⁶³ SIRT1 has also been found to be decreased in patients with chronic obstructive pulmonary disorder, which was correlated with hyperacetylated RelA/p65 in innate immune cells collected from these patients.⁶⁴ In addition to a direct inhibitory effect of SIRT1 on NF- κ B, SIRT1 has been shown to activate basal autophagy and was shown to deacetylate Atg5, Atg7, and Atg8 gene products.⁶⁵ In neurons, SIRT1 was shown to inhibit mammalian target of rapamycin, a protein known to prevent autophagy induction, thereby contributing to cellular homeostasis and leading to their survival.⁶⁶ Further, a recent study by Sathyanarayan et al. showed that SIRT1 was able to induce autophagy and reduce lipid droplet accumulation in mouse hepatocytes.⁶⁷ Thus, the induction of autophagy through SIRT1 may provide a viable approach to treat metabolic defects. For example, berberine, a compound from rhizome coptidis, which can stimulate SIRT1 deacetylation activity and induce autophagy, has been shown to attenuate hepatic steatosis in high-fat, high-sucrose diet fed obese mice in a SIRT1-dependent manner.⁶⁸ Likewise, low molecular weight fucoidan (a product from brown seaweeds) was shown to have protective effects against liver injury in a mouse model of NAFLD via activating the SIRT1/AMPK/peroxisome proliferator-activated receptor coactivator 1- α (PGC1 α) signaling pathway.⁶⁹

1.2.2 Transcription factors regulating lysosomal biogenesis/fusion and inflammation—Tollip, IRAK-M, and SIRT1 are not only directly involved in facilitating autophagy and lysosome fusion processes, these signaling molecules also indirectly contribute to cellular homeostasis by inducing the expression of key autophagic and lysosomal molecules.⁷⁰ Although the precise mechanisms for the induction of autophagic molecules through Tollip, IRAK-M, and SIRT1 are not yet well understood, some of the key transcription factors such as TFEB and CREB have been implicated as discussed below.

TFEB: Recently, a transcription factor of the microphthalmia family of transcription factors named TFEB has emerged as a master regulator of genes involved in lysosomal biogenesis and autophagy.^{71–73} The Sardiello group found that TFEB can bind to a coordinated lysosomal expression and regulation (CLEAR) element and results in the up-regulation of key genes associated with lysosomal biogenesis and function. Overexpression of TFEB is associated with an increased number of lysosomes while TFEB silencing can lead to an opposite effect.⁷³ They also observed that overexpression of TFEB in a rat model of Huntington's disease resulted in a decrease in the polyQ-Huntington proteins characteristic of the disease.⁷⁴ In addition to modulating the expression of lysosomal genes, TFEB is also required for the up-regulation of autophagy-related genes such as UVRAG, MAP1LC3B, SQSTM1, and ATG9B. TFEB overexpression resulted in an increase in autophagosomes (as

well as lysosomes and autolysosomes) in Hela cells.⁷² These studies indicate that TFEB plays a critical role in the regulation of both autophagy and lysosomal-related genes, earning it a role as a “master” transcriptional regulator of these processes. Given the important roles of autophagy and lysosome fusion during cellular homeostasis, it is not surprising that TFEB overexpression was shown to alleviate the development of proinflammatory macrophage foam cells in a model of atherosclerosis through the rescue of the autophagosome-lysosomal pathway.⁷⁵ Overexpression of TFEB is also correlated with decreased inflammation, decreased leukocyte recruitment, and decreased atherosclerotic plaque formation in mice fed with high-fat diet in a recent report by Lu et al.⁷⁶ This anti-inflammatory effect of TFEB may be due to a reduction of cellular oxidative stress in addition to its role in autophagy/lysosomal fusion.⁷⁶ Accumulating studies also unveiled the protective role of TFEB-mediated autophagy in the pathogenesis of neurodegenerative diseases. Decressac et al. reported that Parkinson’s disease progression is accompanied with dysfunctional TFEB and impaired autophagy, leading to the aggregation of α -synuclein, and TFEB overexpression or pharmacological stimulation of TFEB function exerts significant protection of dopamine neurons from α -synuclein toxicity.⁷⁷ Also, Xiao et al. have demonstrated that neuron-specific TFEB expression expedites the degradation of amyloid precursor protein and attenuates amyloid plaque deposition in Alzheimer’s disease.⁷⁸ Moreover, Polito et al. have found that delivery of TFEB into cortex and hippocampus promotes the clearance of hyperphosphorylated and misfolded Tau species and alleviates neurodegeneration in rTg4510 mice, a model of Alzheimer’s disease.⁷⁹

The activation of TFEB can be induced by upstream molecules as described previously in this review. For example, SIRT1 was shown to induce deacetylation of TFEB, which can lead to the nuclear translocation and activation of TFEB.⁸⁰ In this study, Bao et al. identified the acetylation site of TFEB affected by SIRT1 through mass spectrometry and observed a direct interaction of TFEB with SIRT1. Furthermore, they reported that the overexpression of a deacetylated TFEB mutant can stimulate lysosomal biogenesis.⁸⁰ In a separate study, Sakamaki et al. showed that SIRT1 may also indirectly contribute to TFEB-mediated lysosomal biogenesis gene expression by displacing the transcriptional suppressor G9a.⁷⁰

CREB: The involvement of CREB in the modulation of inflammation in immune cells, such as macrophages and monocytes, has also been well documented. In 1996, Ollevier et al. found that elevated levels of cAMP inhibited NF- κ B activity in monocytes,⁸¹ and in 1997 members from the same group confirmed that this was due to phosphorylation of CREB which competed for access to the cofactor CREB-binding protein with the p65 (RelA) subunit of NF- κ B, thereby inhibiting p65’s activity.⁸² More recently, phosphorylated CREB has been implicated in the induction of the anti-inflammatory cytokine IL-10 in monocytes and macrophages.⁸³ Further, CREB has been linked to promoting the anti-inflammatory M2-like polarization of macrophages derived from mouse bone marrow and in a mouse model of obesity.⁸⁴ Among its many gene targets, CREB can induce the up-regulation of various genes involved in autophagy and was shown to enhance lipophagy.⁸⁵ Interestingly, among the genes up-regulated by p-CREB was TFEB, one of the master regulators of autophagy described in the previous section.⁸⁵ In return, SIRT1 can lead to deacetylation of CREB-associated transcription factor complexes and activate CREB-mediated gene expression.⁸⁶

Together, these studies reveal a homeo-static positive-feedback loop contributing to autophagy and lysosomal biogenesis (Fig. 1).

In addition to SIRT1-mediated CREB activation, IRAK-M is also implicated in the induction of CREB and the expression of anti-inflammatory mediators such as IL-10.⁸⁷ Future systems studies are needed to better define the molecular and cellular networks involving these important molecules that are involved in restoring cellular homeostasis.

2 CONCLUSION

Inflammation resolution has been increasingly recognized as a key step for restoring homeostasis and resolving inflammatory diseases. Studies briefly reviewed herein provide some promising molecular targets that are critical for initiating proper inflammation resolution, through facilitating autophagy and lysosome function, which have emerged as key cellular processes in restoring homeostasis. These molecular players are closely intertwined and can establish either competitive or synergistic circuitries to enable complex dynamics of cellular inflammation and homeostasis. In order to better harness their homeostatic potential, future studies are needed to clarify their context-dependent effects at various stages of inflammatory activation and resolution both in vitro and in vivo. Translational studies regarding these molecules using samples from patients with inflammatory diseases at various remitting and relapsing phases should be implemented to explore their potential clinical relevance. Undoubtedly, future studies will reveal additional molecules and subcellular processes critical for the coordinated modulation of inflammation resolution. The key would be, in our perspective, future systems studies that combine experimental and computational approaches to assemble complex information into a cohesive network informative for predicting as well as intervening cellular and tissue behaviors conducive for inflammation resolution and treatment of chronic diseases.

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Abbreviations:

ATG	autophagy-related gene
CD	cluster of differentiation
DCreg	regulatory dendritic cell
DSS	dextran sulfate sodium
IL-1R	interleukin-1 receptor
IRAK-1	interleukin-1 receptor associated kinase 1
MAP1LC3B	microtubule-associated proteins 1A/1B light chain 3B/LC3
NAFLD	nonalcoholic fatty liver disease

SIRT1	sirtuin 1
SQSTM1	sequestosome 1/p62
TFEB	transcription factor EB
Tollip	Toll-receptor interacting protein
Treg	regulatory T cell
ULK1	Unc-51 like autophagy activating kinase
UVRAG	UV radiation resistance-associated gene protein

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FIGURE 1. Emerging competitive dynamics involving autophagy and lysosome fusion that control the resolution of inflammation within innate leukocytes.

Innate leukocytes such as monocytes, macrophages, and neutrophils mediate host responses to infectious or inflammatory signals through innate receptors such as TLRs. Responses of innate leukocytes are finely tuned by homeostatic signaling molecules, such as IRAK-M, Tollip, and SIRT1, potentially through modulating the fusion of lysosomes with phagosomes or autophagosomes