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REVIEW

Emerging roles for TFEB in the immune response and inflammation

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ABSTRACT

Inflammation is a central feature of an effective immune response, which functions to eliminate pathogens and other foreign material, and promote recovery; however, dysregulation of the inflammatory response is associated with a wide variety of disease states. The autophagy-lysosome pathway is one of 2 major degradative pathways used by the cell and serves to eliminate long-lived and dysfunctional proteins and organelles to maintain homeostasis. Mounting evidence implicates the autophagy-lysosome pathway as a key player in regulating the inflammatory response; hence many inflammatory diseases may fundamentally be diseases of autophagy-lysosome pathway dysfunction. The recent identification of TFEB and TFE3 as master regulators of macroautophagy/autophagy and lysosome function raises the possibility that these transcription factors may be of central importance in linking autophagy and lysosome dysfunction with inflammatory disorders. Here, we review the current state of knowledge linking TFEB and TFE3 to the processes of autophagy and inflammation and highlight several conditions, which are linked by these factors.

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The autophagy-lysosome pathway in immunity and inflammation

Autophagy describes the cellular recycling process by which intracellular waste, including aggregated cytosolic proteins and damaged organelles are turned over. Autophagic substrates are engulfed in a double-membrane phagophore that matures into an autophagosome and then fuses with the lysosome for degradation of the cargo into its component macromolecules for reuse. Autophagy is an essential process used by virtually all tissues and cell types to maintain homeostasis, and can be rapidly upregulated in response to various environmental stressors. In addition to its general homeostatic functions, the autophagy-lysosomal pathway has evolved numerous specialized functions in regulating different cellular processes.[1] One such area in which attention has been increasingly focused is autophagy's functions in regulating the inflammatory response, with unique roles in both the innate and adaptive immune system.

Inflammation is a critical component of the immune response, which aids in the elimination of pathogens, irritants, and dead cells as well as contributes to the subsequent process of tissue regeneration and repair.[2] Despite the essential roles of acute inflammation, uncontrolled chronic inflammation has been strongly associated with a growing number of pathological conditions including metabolic disorders, neurodegeneration, and cancer.[3] Perhaps the most thoroughly characterized roles of autophagy in regulating inflammation are its anti-inflammatory roles, which are mainly based on its ability to modulate the inflammasome response. The inflammasome is a key component of the innate immune system that includes a series of sensors and receptors capable of inducing the activation of CASP1/caspase-1 in response to pathogen associated molecular patterns (PAMPs) derived from invading pathogens as well as damage associate molecular patterns (DAMPs) released by stressed and damaged tissues. Active CASP1 cleaves the precursor cytokines pro-IL1B and pro-IL18, thus mediating their conversion into active secreted forms.[4] Active CASP1 can also induce pyroptosis, an inflammatory form of cell death.[5] Autophagy acts as a negative feedback regulator of the inflammasome by a 2-fold mechanism. First, PYCARD/ASC, a critical component of the inflammasome that regulates the recruitment of pro-CASP1, is ubiquitinated and targeted for degradation by the autophagy receptor protein SQSTM1/p62.[6] Second, autophagy targets SQSTM1-bound mitochondria that have been ubiquitinated by the E3 ligase PRKN/PARK2/parkin. Mitophagy results in the removal of damaged mitochondria, which are themselves a major source of upstream inflammatory signals due to their release of mitochondrial (mt)DNA and reactive oxygen species (mtROS), 2 potent activators of the inflammasome.[7]

The autophagy receptors, which include SQSTM1, NBR1, CALCOCO2/NDP52, and OPTN (optineurin), are also implicated in the direct removal of intracellular pathogens through the process of xenophagy.[2] The high concordance of components involved in mitophagy and xenophagy suggests an ancient evolutionarily conserved origin for both pathways. For example, both PRKN and SQSTM1 ubiquitinate and bind *Mycobacterium tuberculosis*, respectively, facilitating its removal by xenophagy.[8,9] OPTN, another autophagy receptor involved in eliminating damaged mitochondria, inhibits

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Salmonella enterica via xenophagy.[10] Much work remains to identify the full repertoire of xenophagy targets and their associated ubiquitin ligases and autophagy receptors; however, it is clear that autophagy plays an essential role in this aspect of innate immunity and indirectly serves to reduce inflammation through direct removal of the pathogenic source of such inflammation.

Despite the abundance of evidence linking the autophagy-lysosome pathway with anti-inflammatory roles, several instances of its involvement in pro-inflammatory processes have also been identified. Unconventional secretion of IL1B has long been known to involve components of the autophagy machinery, and a recent study showed that IL1B is transferred to the intermembrane space of autophagosomes before secretion.[11] In addition, specialized secretory lysosomes can mediate the release of both pro- and anti-inflammatory cytokines from macrophages and other immune cells depending on the phase of the inflammatory response.[12]

Finally, regulated degradation of anti-inflammatory signaling components such as NR3C1/glucocorticoid receptor by lysosomes can tip the balance toward an inflammatory milieu.[13] These seemingly paradoxical actions of the autophagy-lysosome pathway suggest multiple intricate and finely tuned mechanisms by which it regulates inflammatory processes and highlight the importance of a properly controlled inflammatory response in pathogen defense and tissue repair.

TFEB and TFE3 as master regulators of the autophagy-lysosomal pathway

Lysosome biogenesis and function have long been regarded as housekeeping processes involved in terminal processing of cellular material destined for degradation. However, recent work has challenged this original paradigm by describing a finely orchestrated transcriptional regulation of the lysosomal and autophagic pathways. Accordingly, bioinformatics and functional genomic analysis found that the promoter regions of numerous lysosomal genes contain one or more repetitions of a palindromic 10-base pair motif (GTCACGTGAC) named the coordinated lysosomal expression and regulation (CLEAR) element.[14] This CLEAR consensus sequence, commonly found within 200 base pairs from the transcription start site in lysosomal gene promoters, is a type of E-box (CANNTG) sequence described as a recognition site for the binding of members of the basic helix-loop-helix leucine zipper (bHLH-LZ) MiT/TFE family of transcription factors. MITF (melanogenesis associated transcription factor), TFEB, TFE3 and TFEC, which constitute the MiT/TFE subfamily of transcription factors, are of particular interest because they have been implicated in many cellular and developmental processes by promoting the expression of several lysosomal and lysosome-related organelle genes.[15-17]

TFEB was the first described member of the MiT/TFE family to directly bind to CLEAR elements. TFEB overexpression induces the upregulation of genes involved in lysosomal function and increases the number of lysosomes, thus suggesting that TFEB functions as a master regulator of lysosomal biogenesis.[14] A subsequent and more detailed genomic analysis showed that TFEB not only controls the expression of lysosomal genes but also binds the promoters and regulates the expression of a large number of genes involved in lysosomal-related processes including lysosomal exocytosis, phagocytosis, endocytosis, and autophagy.[18] Interestingly, TFEB overexpression results in the activation of the autophagy pathway in vitro and in vivo,[19] the modulation of specialized types of autophagic processes such as mitophagy,[20] and lipophagy,[21] and enhancement of lysosomal fusion with the plasma membrane promoting cellular clearance.[22] It is important to mention that recent studies have shown that several transcription factors and various histone modifications are part of a network responsible for the transcriptional and epigenetic modulation of autophagy.[23] Moreover, a mechanism of long-term autophagy regulation mediated by the direct interplay between TFEB and the activation of a specific epigenetic program driven by the histone arginine methyltransferase CARM1 has been recently proposed.[24]

Work from different laboratories have shown that the overexpression of either TFEB or TFE3 enhances the expression of metabolic genes involved in lipid metabolism and insulin signaling, and alleviates obesity in vivo,[21,25] suggesting that these transcription factors may share regulatory characteristics. Accordingly, new evidence revealed that TFE3 also binds CLEAR elements and induces upregulation of multiple genes involved in lysosomal biogenesis and autophagy, and enhances lysosomal exocytosis and cellular clearance when overexpressed in a Pompe disease model of lysosomal storage disorder.[26] Several studies also suggest that TFEB and TFE3 may have critical specialized functions depending on the type of stress, cell and tissue where they are expressed[27] (Fig. 1).

Overall, the simultaneous regulation of lysosomal biogenesis and autophagy induction indicates that TFEB and TFE3 are central players in coordinating the transcriptional control of 2 major cellular degradative pathways in the cell and as such are considered bona fide master regulators of these processes.

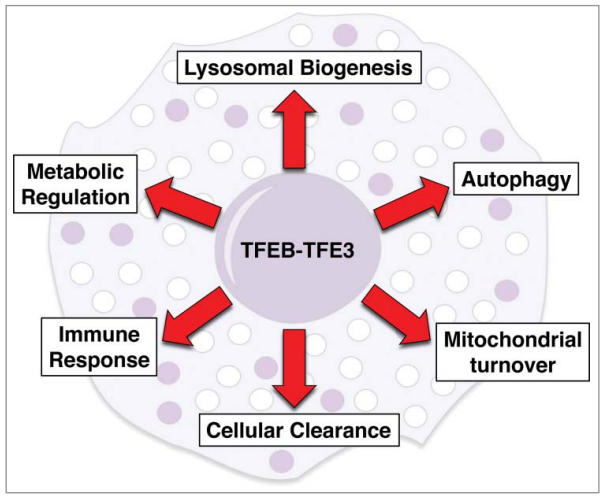

Figure 1. TFEB and TFE3 regulate multiple cellular processes. TFEB and TFE3 participate in the regulation of many different cellular processes, including lysosomal biogenesis, autophagy induction, mitochondrial turnover, and clearance of undigested and aberrant cellular components through lysosomal exocytosis. In addition, TFEB and TFE3 play important roles in many metabolic processes as well as in the innate immune response.

TFEB and TFE3 in innate and adaptive immunity

TFEB and TFE3 have recently been identified as serving many critical and diverse roles in both the innate and adaptive immune systems (Fig. 2). In the innate immune response, TFEB and TFE3 are activated in macrophages exposed to bacteria and various toll like receptor (TLR) ligands, where they mediate the transcription of cytokines and chemokines involved in antimicrobial host defense along with their already established transcriptional targets involved in lysosome biogenesis and autophagy.[28,29] This pathway represents an evolutionarily ancient adaptation in metazoans, as the *Caenorhabditis elegans* homolog of both TFEB and TFE3, HLH-30, functions in a similar capacity.[29] This functional conservation was further demonstrated in a recent study showing that HLH-30 is activated by bacterial pore forming toxins in *C. elegans* intestinal cells leading to xenophagy and membrane repair transcriptional programs.[30]

As the metazoan lineage diversified, TFEB and TFE3, which exhibit partially redundant functions in terms of autophagy-lysosome pathway regulation, likely gained new functions in the innate immune response. In macrophages and in a *Tfe3* and *Tfeb* knockout mouse model, these transcription factors were shown to promote lysosome biogenesis and the induction of autophagy in response to innate immune activation largely independently of each other, although a maximal response requires the presence of both factors.[28] As discussed previously, expansion of the autophagosome and lysosome compartments are essential for xenophagy and subsequent destruction of intracellular pathogens. A simultaneously released study by Gray et al. supports a direct role for a TFEB-mediated increase in lysosome activity, leading to enhanced bactericidal properties in macrophages undergoing phagocytosis.[31] These studies suggest that TFEB (and TFE3) activation in macrophages occurs during both FCγ-dependent and independent phagocytosis as well as by stimulation with TLR4 and TLR7 ligands, suggesting multiple converging modes of activation exist.[28,31]

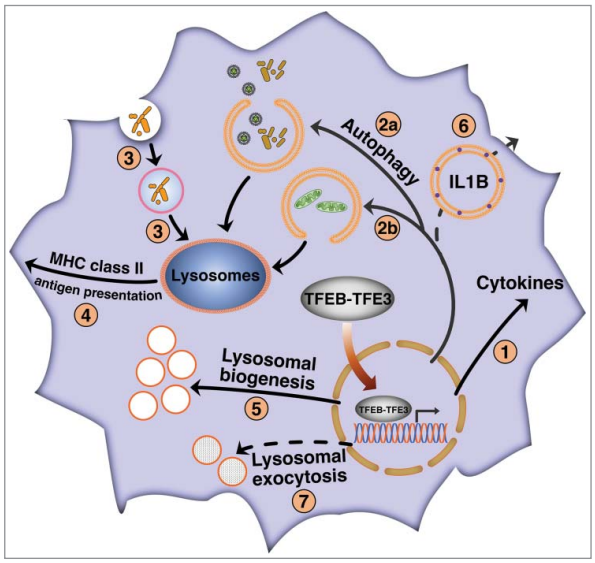

Figure 2. Immune-specific functions of TFEB and TFE3. TFEB and TFE3 control a multitude of cellular processes involved in inflammation and the immune response, including cytokine and chemokine production (1), induction of autophagy with immune specific implications such as xenophagy (2a) and mitophagy (2b), phagosome and lysosome acidification and bactericidal activity (3), enhancement of MHC class II antigen presentation and inhibition of cross-presentation (4), and induction of lysosomal biogenesis, further driving degradation of cargoes captured by autophagy and phagocytosis (5). Despite the lack of direct evidence, it is also likely that TFEB and TFE3 play a role in unconventional secretion of the pro-inflammatory cytokines (6) and in the secretion of immune-specific molecules through the exocytosis of secretory lysosomes or lysosome-related organelles (LRO; 7).

In contrast to the partially redundant roles of TFEB and TFE3 in enhancing autophagy and lysosome activity in activated macrophages, the transcription of pro-inflammatory cytokines such as TNF/TNF-α and IL1B, required the presence of both TFEB and TFE3, which are expressed in a more temporally restricted fashion. Following sustained exposure to lipopolysaccharide (LPS), the levels of TFE3 in macrophages remains constant, whereas dramatic fluctuations in *Tfeb* mRNA and protein levels were observed.[28] It is therefore tempting to speculate that TFE3 and TFEB might define unique transcriptional modules governing cytokines/chemokines versus autophagic/lysosomal genes depending on their respective activity together, which would allow fine tuning of the innate immune response to prevent runaway inflammation.

TFEB also regulates the activity of other pathways in the innate immune system through its control of lysosome biogenesis. The interferon-independent activation of a subset of interferon-stimulated genes (ISGs) is thought to provide an early response to viral infection before a more robust interferon response can be stimulated by dedicated interferon-producing cells. Aberrant activation of this pathway caused by mutations in the resident endoplasmic reticulum exonuclease TREX1 are associated with the autoimmune diseases Aicardi-Goutières syndrome and systemic lupus erythematosus. Work by Hasan and colleagues demonstrated that TFEB plays a key role in activating the ISG pathway downstream of TREX1 and this effect is dependent on the expansion of the lysosomal compartment and not by direct transcriptional control of ISG expression.[32] The precise mechanism of this TFEB-dependent enhancement of ISG expression is unclear, but a requirement for increased lysosome activity appears relevant. Given the lysosome's roles in degrading peptides and nucleic acids, it is conceivable that dysregulation of this activity may disrupt the normal antigen presenting roles of lysosomes, leading to a breakdown of immunotolerance. Collectively, these studies highlight the diverse roles of TFEB and TFE3 in innate immunity and suggest heretofore unappreciated degrees of redundancy and cross-talk between seemingly disparate pathways controlling both host-pathogen response and autoimmunity.

The autophagy-lysosome system plays a key role in the adaptive immune system by regulating various aspects of antigen presentation. Presentation of intracellular antigens such as viral antigens is generally achieved by degradation of cytosolic proteins by the proteasome followed by transport into the endoplasmic reticulum where the processed antigen is loaded onto the major histocompatibility complex (MHC) class I. Presentation of exogenous antigens is limited to professional antigen-presenting cells such as dendritic cells (DCs), macrophages, and B-cells and involves partial lysosomal degradation of the internalized antigen before loading onto MHC class II.[33] In addition to these canonical pathways, exogenous antigens can be presented by MHC class I through the process of cross-presentation. Recently, TFEB was demonstrated to

play a key role in regulating the balance between these different pathways through its enhancement of lysosomal activity. In DCs, TFEB activity is induced by phagosome maturation and results in increased MHC class II antigen presentation while inhibiting cross-presentation of exogenous antigens by MHC class I.[34] Thus, control of TFEB activity by different immunological stimuli may allow DCs and other antigen-presenting cells to adapt their antigen presenting strategy to fit the unique challenges faced by the immune system at any given time.

In addition to the aforementioned antigen-presentation pathways, a growing number of intracellular antigens have been identified that are loaded onto MHC class II in an autophagy-dependent manner.[35] Further cell biological characterization of this pathway demonstrated that autophagosomes directly fuse with lysosomal MHC class II loading compartments in antigen-presenting cells, leading to enhanced CD4+ T-cell activation.[36] Conversely, exogenous tumor-derived autophagosomes have been shown to stimulate cross-presentation in DCs,[37] suggesting a considerable degree of crosstalk between autophagy and the different antigen-presenting pathways under differing cellular contexts. Given TFEB's (and potentially TFE3's) role in increasing lysosomal activity and its resultant effect on the balance between canonical MHC class II presentation and cross-presentation, it will be critical to assess if its role in regulating autophagy has similar regulatory effects on these related antigen-presentation pathways.

TFEB and TFE3 play essential roles in humoral immunity by promoting B-cell dependent immunoglobulin G (IgG) and IgA production in response to $CD4^+$ T-cell activation.[38] Much like some of TFEB's and TFE3's activities on the autophagy-lysosome system in activated macrophages, these transcription factors have redundant roles in $CD4^+$ T-cells by promoting CD40LG (CD40 ligand) expression through direct binding of its promoter. This TFEB- and TFE3-dependent CD40LG expression by T-cells is critical for B-cell-mediated isotype switching. It is possible that TFEB and TFE3 activate other T-cell specific genes that have yet to be identified. Moreover, TFEB levels are increased post-transcriptionally in response to T-cell activation, whereas TFE3 levels remain constant suggesting the possibility of additional modes of gene regulation echoing observations in activated macrophages in the innate immune system.

A role for TFEB and TFE3 in activating lysosome exocytosis has been established in cell models. This role is at least partially attributable to their ability to induce transcription of the lysosomal Ca^{2+} channel, MCOLN1, which promotes fusion of lysosomes with the plasma membrane.[22,26] It has been long recognized that the lytic granules released by cytotoxic T-lymphocytes and natural killer cells represent a specialized type of lysosome-related organelle, highlighting the importance of lysosome exocytosis in cell-mediated immunity.[39,40] More recently, it has become apparent that lysosome exocytosis acts as a critical mechanism behind a wide variety of immune-related functions. During macrophage internalization of a single large particle ($> 5\ \mu m$) or multiple smaller particles, MCOLN1-mediated lysosomal exocytosis serves to provide membrane for the expansion of phagocytic cups, whereas lysosome fusion with internalized phagosomes occurs at a later stage to acidify and deliver hydrolases to degrade internalized material.[41] In B cells, polarized lysosome secretion into the immunological synapse containing the B cell receptor-antigen complex leads to localized acidification and release of lysosomal proteases, which promotes MHC class II antigen loading, a critical event for mounting a humoral immune response.[42] Finally, lysosome exocytosis is involved in chemokine-induced chemotaxis in a variety of immune cell types.[43,44] In microglia, lysosome exocytosis triggered by chemokine signaling results in secretion of ATP, providing a chemotactic signal that promotes distal microglia migration to the site of injury.[44] In DCs, lysosomal Ca^{2+} release also contributes to cellular maturation and chemotaxis, although it is unclear if lysosome exocytosis per se is involved in this process.[45] Given the well-established link between TFEB, TFE3 and lysosome exocytosis, it is possible to conceive a model in which TFEB and TFE3 play an important role coordinating chemokine production, lysosome exocytosis, and chemotaxis.

Mechanism of TFEB and TFE3 activation

Under unfavorable nutrient conditions cells must adapt and restore homeostasis to survive. It is well established that autophagy and lysosomal function are inextricably linked to the survival process. While autophagy recycles dysfunctional cellular components to provide energy and nutrients, lysosomes provide the degradative capacity and nutrient signaling platform to reestablish homeostasis. A key player in this process is the evolutionarily conserved multiprotein complex MTORC1, which is activated at the lysosomal surface and conveys cellular growth and proliferation signals in response to nutrient availability, energy levels, and growth factors. Under nutrient-poor conditions, MTORC1 dissociates from lysosomes and its inactivation promotes protein synthesis inhibition and autophagy induction.[46,47] Nutrient-dependent MTORC1 association to lysosomes is mediated by the coordinated action of the vacuolar-type H^+-translocating ATPase and LAMTOR/Ragulator complexes, which modulate the nucleotide status of the heterodimeric RRAG GTPase complex.[47-49] In nutrient-rich conditions, active RRAGs at the cytoplasmic side of the lysosomal surface recruit MTORC1[49], leading to its activation by the small GTPase RHEB, which is itself activated by growth factor signals.[50,51] Conversely, starvation conditions result in an inactive conformation of RRAGs promoting lysosomal dissociation and subsequent inactivation of MTORC1.[49] Evidence from different laboratories has demonstrated that the cellular localization of TFEB and TFE3 is also dependent on the nutrient availability within the cell.[26,52] In nutrient-rich conditions, TFEB and TFE3 show a mainly cytoplasmic localization, whereas both transcription factors rapidly activate and translocate to the nucleus under nutrient-deprivation conditions, leading to the upregulation of many genes involved in lysosomal biogenesis and autophagy.[26,52]

Interestingly, the nutrient-dependent mechanism of regulation of TFEB and TFE3 is mediated by RRAGs and MTORC1 activity. In amino acid-rich medium active RRAGs recruit TFEB and TFE3 to the lysosomal surface where active MTORC1 directly phosphorylates TFEB and TFE3 at several serine/threonine residues including serine 211 (S211) and S321, respectively, creating a binding site for the cytosolic chaperone-

like protein YWHA/14–3–3.[26,53-55] Interaction of the phosphorylated transcription factors with YWHA results in the cytosolic sequestration of TFEB and TFE3. Conversely, starvation conditions induce RRAGs and MTORC1 inactivation, preventing TFEB and TFE3 phosphorylation at the lysosome surface, thus promoting their dissociation from YWHA and resulting in their nuclear accumulation.[26,53-55] Importantly, the nutrient-dependent mechanism of TFEB and TFE3 regulation seems to be evolutionarily conserved across species, suggesting the existence of a regulatory process involved in the control of the cellular response to nutrient deprivation.[56,57]

A multistep process that regulates the subcellular distribution of TFEB mediated by MTORC1 has been recently described. Work by Vega-Rubin-de-Celis and colleagues identified a novel MTORC1-dependent TFEB phosphorylation site at S122, and dephosphorylaiton of both, S211 and S122 must occur to achieve efficient TFEB nuclear translocation.[58]

As mentioned earlier, recent observations have suggested an important role of TFEB and TFE3 in the transcriptional regulation of the innate immune response to pathogens.[28,29] Interestingly, TFEB and TFE3 nuclear translocation in activated macrophages does not require MTORC1 inactivation.[28] In contrast, it was found that PLC-1 and DKF-1, the *C. elegans* orthologs of mammalian PLC and PRKD1/PKD, respectively, are required for HLH-30 activation during infection of nematodes with *Staphylococcus aureus*.[59] Whether the *C. elegans* ortholog of MTORC1 is required in this process needs to be further investigated. A similar mechanism of TFEB activation was observed in mouse macrophages infected with pathogenic bacteria, although in this case PRKCA/PKCα activity seems to be also required,[59] thus suggesting that the mechanism of TFEB activation in response to pathogen infection is conserved throughout evolution.

Interestingly, active PRKCA promotes TFEB-mediated regulation of lysosomal biogenesis and cellular clearance in HeLa cells and an animal model of Alzheimer disease through an MTORC1-independent mechanism.[60] PRKCA activation leads to inactivation of GSK3B/GSK3β, resulting in reduced TFEB phosphorylation and subsequent nuclear activation of this transcription factor. Notably, this mechanism seems to be coupled to the inactivation of ZKSCAN3, a known transcriptional repressor of autophagy, through activation of MAPK8/JNK and MAPK14/p38 MAPK pathways.[60]

An additional calcium-mediated mechanism to regulate TFEB activation has been recently described. The release of local lysosomal Ca^{2+} through MCOLN1 activates the protein phosphatase PPP3/calcineurin, which dephosphorylates TFEB leading to its nuclear translocation and promoting the CLEAR network response.[61] Interestingly, PPP3 is also responsible for the activation, initiated by dephosphorylation, of members of the transcription factor family collectively known as nuclear factors of activated T-cells /NFAT, which are key players in the transcriptional regulation of several immune specific genes.[62] This finding highlights the intriguing possibility of the existence of cross-talk between TFEB- and NFAT in the regulation of the immune system.

Overall, these studies indicate that different coexisting mechanisms of TFEB and TFE3 activation may operate to modulate the transcriptional regulation of the cellular adaptation to stress depending on the cell type and/or the nature of the stimulus.

Modulation of TFEB activation during pathogen infection

The important contribution of TFEB and TFE3 to the immune response is further evidenced by the fact that many pathogens have developed mechanisms to modulate TFEB and TFE3 activation for their own benefit. This is the case with HIV, which inhibits autophagy by promoting TFEB sequestration. Shortly after macrophage exposure to HIV, TFEB is activated through a mechanism that requires TLR8.[63] This activation leads to a transient increase in autophagy that is critical for HIV replication.[64] However, sustained autophagy may increase HIV degradation; therefore, the virus has developed ways to downregulate autophagy in chronic infection conditions. Campbell et al. recently showed that the HIV protein Nef directly binds BECN1/Beclin, resulting in MTOR activation, TFEB phosphorylation and cytosolic retention, and thus leading to autophagy inhibition.[63] Conversely, APOL1 (apolipoprotein L1), a major component of the innate immune response, contributes to HIV suppression not only by increasing degradation of the viral proteins Vif and Gag and but also by inducing TFEB-dependent lysosomal biogenesis and autophagy.[65] Furthermore, flubendazole-mediated TFEB nuclear translocation and subsequent autophagy induction is sufficient to prevent transmission of HIV from dendritic to $CD4^+$ T cells.[66] Therefore, regulation of TFEB activation during HIV infection is critical for virus survival.

Another example of TFEB modulation by bacteria is seen with *Mycobacterium tuberculosis* (Mtb). Mtb can survive inside macrophages by preventing its delivery to lysosomes and by promoting formation of lipid droplets, which are used as a source of energy by the bacteria. Recent evidence suggests that the production of specific microRNAs (*Mir33* and *Mir33**) induced by Mtb is essential for bacterial survival.[67] While *Mir33* and *Mir33** directly target and repress multiple genes implicated in autophagosome formation, autophagy regulation, and lysosomal function, they also reduce *Tfeb* mRNA levels through a process that is dependent on AMPK (PRKA). Given the many important roles played by TFEB in macrophages, it is likely that TFEB repression severely impairs not only delivery and degradation of Mtb in lysosomes but also lipid droplet catabolism,[21] host-defense, and inflammatory response.[28]

Finally, TFEB may increase susceptibility to invasion by *Trypanosoma cruzi*, a protozoan parasite that causes Chagas disease. It was recently reported that gp82, a glycoprotein present on the surface of metacyclic trypomastigotes that is essential for invasion, is sufficient to induce MTOR inactivation, TFEB nuclear translocation and lysosomal biogenesis.[68] The newly synthesized lysosomes distribute in close proximity to the cell edges and fuse with the plasma membrane. Although the mechanism has not yet been elucidated, it has been proposed that the presence of peripheral lysosomes facilitates parasite entry into the cell.[69]

It is important to note that in many cases an initially protective immune response against pathogens may lead to serious pathologies such as sepsis. Sepsis occurs when the massive production of immune regulators triggers a systemic inflammatory

response that results in tissue damage, organ failure and death. Recent evidence suggests that lysosomes may play a protective role against sepsis. Microarray analysis of blood samples from patients with sepsis showed aberrant mRNA expression of multiple genes implicated in the lysosomal pathway,[70] whereas lysosomal dysfunction decreases survival of septic mice.[71] Sepsis-induced mitochondrial damage is especially harmful for cardiomyocytes and the elimination of impaired mitochondria through the autophagy-lysosome system is crucial to prevent cardiac injury. Consistently, cobalt protoporphyrin IX ameliorates septic liver injuries in rats by inducing TFEB-dependent autophagy and lysosomal reformation.[72] Autophagy and lysosomal activities decline with age, which may explain the increased susceptibility of elderly patients to sepsis. Accordingly, TFEB nuclear translocation is decreased in LPS-treated aged mice when compared with young ones.[73] It is important to note that TFEB may not always have a protective role in sepsis. Current evidence suggests that in hepatocytes and mouse embryonic fibroblasts, LPS treatment not only induces lysosomal-mediated degradation of damaged mitochondria but also mitochondrial secretion into the medium. Released mitochondria may induce activation of monocyte-derived macrophages, further contributing to systemic inflammation. Importantly, TFEB is involved in mitochondrial exocytosis in LPS-stimulated cells,[74] indicating that TFEB activation may exacerbate inflammation. In summary, TFEB and TFE3 likely play a pivotal role in the pathobiology of sepsis.

Future perspectives

The importance of the autophagy-lysosome system in promoting an efficient and well-regulated inflammatory response has been firmly established and additional discoveries in this growing field continue to refine our understanding of the complex interplay between these phenomena. The recent discoveries relating the activation of TFEB and TFE3 to autophagy induction and increased lysosome biogenesis and activity present a new link to a variety of pro- and anti- inflammatory functions in a wide variety of immune cells under different physiological conditions. In brief, TFEB and TFE3 have been implicated in the activation of macrophages in the innate immune system, including promotion of their bactericidal functions, and the production of various cytokines and chemokines (Fig. 2). In the adaptive immune system, TFEB plays a role in regulating different antigen-presentation pathways in DCs, and TFEB and TFE3 are involved in T-cell mediated isotype switching in B cells. More broadly, TFEB and TFE3 likely play more generalized roles in inflammatory signaling pathways through their modulation of lysosomes and autophagy, including roles in interferon-stimulated gene expression in DCs, phagocytosis, chemotaxis, and other autophagic-inflammatory functions such as inflammasome signaling and xenophagy.

Autoimmune disorders and other pathological conditions linked with excessive inflammation, such as neurodegenerative diseases, obesity and cancer, have long been linked with dysregulation of lysosomal and autophagic pathways. Not surprisingly, TFEB and TFE3 have also been associated with an increasing number of such diseases and conjecturally linked to many other disease processes based on common pathways they regulate. In many cases TFEB and TFE3 localization, levels, and activity are affected in disease states, and modulation of these parameters represents a promising therapeutic goal for a wide variety of inflammatory diseases.

Abbreviations

AMPK	5′ AMP-activated protein kinase
APOL1	apolipoprotein L1
BECN1	Beclin 1
CALCOCO2/ NDP52	calcium binding and coiled-coil domain 2
CARM1	coactivator associated arginine methyltransferase 1
CASP1	caspase 1
CD40LG	CD40 ligand
CLEAR	coordinated lysosomal expression and regulation
DAMP	damage associated molecular pattern
DC	dendritic cell
DKF-1	*C. elegans* protein kinase D ortholog
GSK3B	glycogen synthase kinase 3 β
HIV	human immunodeficiency virus
HLH-30	*C. elegans* TFEB/TFE3 ortholog
IL18	interleukin 18
IL1B	interleukin 1 β
ISGs	interferon-stimulated genes
LAMTOR	late endosomal/lysosomal adaptor-MAPK and MTOR activator
LPS	lipopolysaccharide
MAPK8/JNK1	mitogen-activated protein kinase 8
MAPK14/P38	mitogen-activated protein kinase 14
MCOLN1	mucolipin 1
MHC	major histocompatibility complex
MiT/TFE	microphthalmia transcription factor family
MTORC1	mechanistic target of rapamycin complex 1
NBR1NBR1	NBR1autophagy cargo receptor
NFAT	nuclear factors of activated T-cells
NR3C1	nuclear receptor subfamily 3 group C member 1
OPTN	optineurin
PAMP	pathogen associated molecular pattern
PRKN	parkin RBR E3 ubiquitin protein ligase
PLC-1	phospholipase C1
PRKCA	protein kinase C α
PRKD1/PKD	protein kinase D1
PYCARD/ASC	PYD and CARD domain containing
RHEB	Ras homolog enriched in brain
ROS	reactive oxygen species
RRAG	Ras related GTP binding
SQSTM1	sequestosome 1
TFE3	transcription factor binding to IGHM enhancer 3
TFEB	transcription factor EB
TLR	toll like receptor
TNF	tumor necrosis factor
TREX1	3 prime repair exonuclease 1

YWHA	14–3–3 phospho-serine/phospho-threonine binding protein
ZKSCAN3	zinc finger with KRAB and SCAN domains 3

Disclosure of potential conflicts of interest

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