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Mini-Review

The role of MiT/TFE family members in autophagy regulation

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ABSTRACT

The MiT/TFE family of proteins are important regulators of a number of metabolic processes. One of their most important roles is activating the autophagy pathway in the setting of nutrient deprivation or buildup of toxic metabolites. Their proper and improper functioning in this role has been linked to several types of disease, including cancer and multiple forms of neurodegeneration. In this review we will briefly outline what is known about individual family members' roles in regulating autophagy across a variety of contexts.

KEYWORDS: MITF, TFEB, TFE3, MiT/TFE, autophagy, Parkinson's, Alzheimer's, tanning, neurodegeneration, pigmentation.

INTRODUCTION

The MiT/TFE family of proteins is a closely-related group of transcription factors which share a basic helix-loop-helix leucine zipper (bHLHZip) structure and are highly conserved between higher vertebrate species [1]. Four family members have been previously described: *MITF*, *TFEB*, *TFEC*, and *TFE3* [2]. In lower invertebrates, such as *Drosophila melanogaster* and *Caenorhabditis elegans*, a single MITF/TFE orthologue exists, providing further support for a common evolutionary origin [1, 3]. The structure of each family member contains three important and highly conserved regions: a basic motif for DNA binding, and helix-loop-helix (HLH) and leucine zipper (Zip) regions necessary for dimerization, in addition to an activation domain, which is absent in family member *TFEC* in some species [4, 5].

Activation of MiT/TFE family members involves homo- or heterodimerization exclusively with other members of the MiT/TFE family, leading to changes in cellular localization and DNA binding activity [4]. Under normal conditions, with the exception of the "M-" isoform of MITF, MiT/TFE family members exist in monomeric form and predominantly localize to the cytoplasm. Upon activation and dimerization, active homo- or heterodimeric complexes traffic to the nucleus in order to bind DNA at known consensus sequences CA[C/T]GTG known as E-boxes usually in the promoter regions of target genes [6]. The one exception to this is the family member TFEC, which is comparatively poorly studied, and may play a role in inhibition of transcription rather than activation [5].

MiT/TFE family members control a broad range of cellular functions, with several hundred target genes having previously been identified. In particular, MiT/TFE proteins are known to help regulate metabolism, energy sensing, ER and oxidative stress responses, mitochondrial biogenesis, immunity, inflammation, and cellular differentiation, among others [7-9]. MITF plays a lineage specific role as master transcriptional regulator of the melanocyte lineage, which is manifest by its critical role in regulating expression of numerous components of the melanin biosynthetic, maturation, and transport pathway [10, 11].

A significant aspect of MiT/TFE family members' role in maintaining energy balance is through their regulation of lysosome formation and autophagy. The term "autophagy" describes a highly evolutionarily conserved process by which cells break down and recycle unneeded or toxic protein aggregates and organelles for use in new synthetic processes [12]. This is done through formation of membrane-bound organelles termed "autophagosomes", which develop from precursor omegasomes produced by the endoplasmic reticulum [13]. The formation of these organelles around target structures is coordinated by the ATG (AuTophaGy) family of proteins, which then facilitate fusion of autophagosomes with lysosomes. Lysosomes are a related class of membrane-bound organelles with an acidic lumen which contain over 60 different known enzymes responsible for the breakdown of proteins and other macromolecules for removal and later re-use [13]. The promoter regions of many lysosomal genes contain a 10 base pair (GTCACGTGAC) MiT/TFE consensus sequence known as a CLEAR (Coordinated Lysosomal Expression and Regulation) element. When activated, binding to CLEAR elements, as well as E-box sites, allows MiT/TFE family members to integrate autophagy with their many synthetic and other metabolic functions. Dysfunction of this MiT/TFE-autophagy axis has been suggested to play a role in a wide variety of disease processes, with different family members playing roles often in a tissue- and disease-specific fashion.

TFEB

TFEB has been demonstrated to control a variety of genes involved in autophagosome initiation and elongation, substrate envelopment, autophagosome trafficking, and lysosome fusion [14]. Its precise role in connecting autophagy to other metabolic processes under normal physiologic conditions and in response to toxic insult is often tissue-dependent, but generally regulated by both mTORC1 and MAPK [15, 16] (Figure 1). In the liver, TFEB has been shown to drive autophagy, mitrochondrial turnover, energy balance, and lipid breakdown in the setting of fasting though the master mitochondrial transcription factor PGC1α [17]. In a liver-specific TFEB knockout mouse model, mice became highly sensitive to fatty liver disease when fed a high fat diet, while overexpression of TFEB was protective against liver disease relative to controls under identical conditions [17]. Similar results were seen with ethanol-induced steatohepatitis in the same mouse models [18]. Protective roles against various toxic insults have also been demonstrated in the heart [19], pancreas [20], placenta [21], cochlea [22], and retina [23], among other organs. TFEB has also been shown to participate in the physiologic adaptation of skeletal muscle to exercise by increasing mitochondrial biogenesis and fine-tuning the balance between aerobic and anaerobic metabolism in a PGC1α-independent manner [24]. TFEB activity in macrophages has been shown to play a role in preventing the buildup of atherosclerotic plaques in blood vessels [25], as well as in their ability to clear microbial pathogens in the setting of infection, particularly *M. tuberculosis* [26, 27]. Upregulation of autophagy by TFEB likely also plays a role in promoting the survival and structure of neurons in the setting of oxygen and glucose deprivation [28].

With regard to disease pathophysiology, one of the best-studied roles for TFEB in autophagy regulation is in the setting of neurodegeneration. Mice deficient in the key autophagy proteins ATG7 and ATG5 have been shown to develop progressive neuromotor deficits co-occurring with the appearance of aggregates of polyubiquitinated proteins in inclusion bodies in neurons, eventually leading to widespread neuronal death [29, 30]. Similar aggregate accumulation has been observed in the brains of patients with many neurodegenerative diseases, including Parkinson's Disease, Alzheimer's Disease, and Huntington's Disease [31], which are all histopathologically characterized by unique collections of different combinations of protein aggregates. The importance of lysosomal activity to prevention of these diseases is also corroborated by the known genetic linkage between neurodegeneration and rare genetic lysosomal storage disorders such as Gauchers Disease and Sanfilippo Syndrome [32]. Whether these aggregates are the root cause or a byproduct of neurologic disease is still poorly understood. Nevertheless, TFEB-mediated autophagocytic

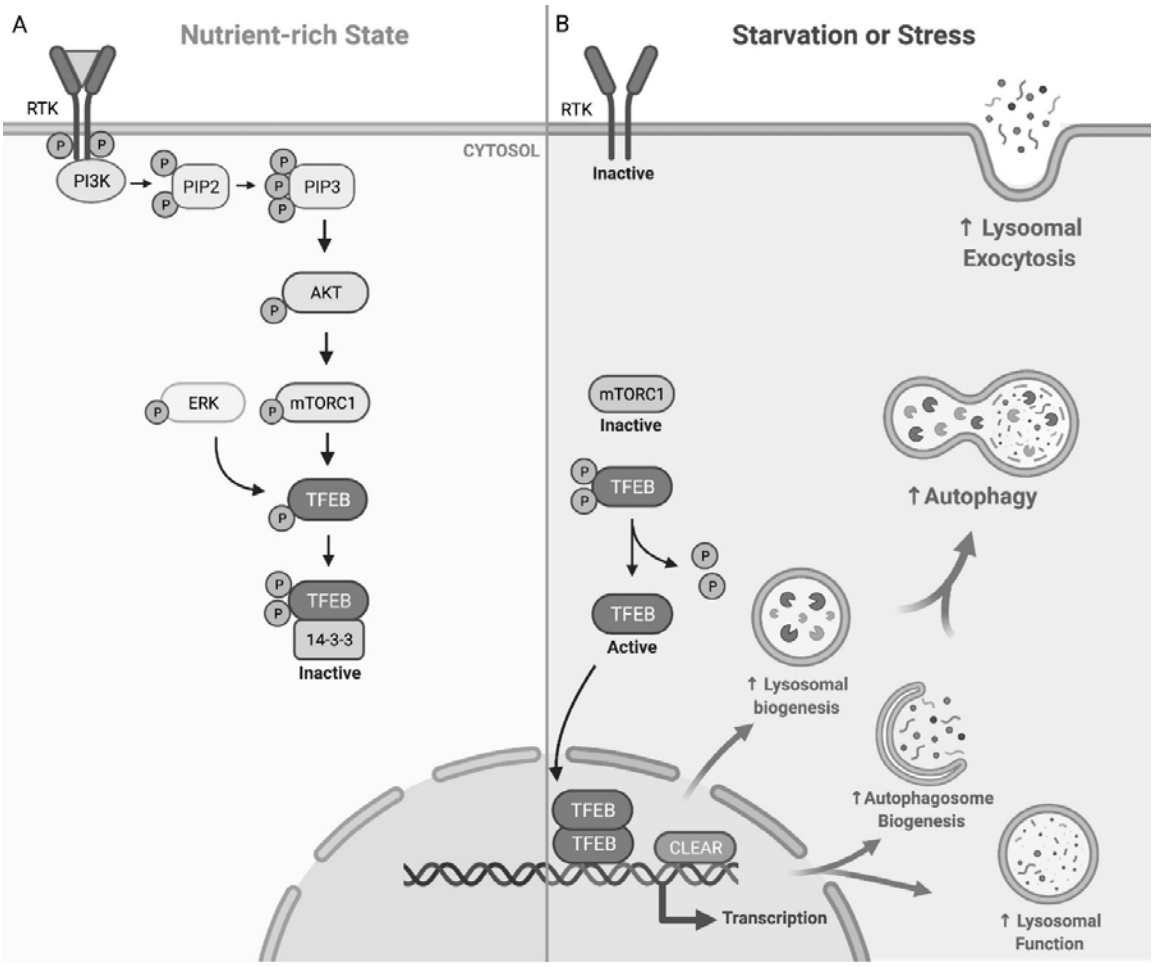

Figure 1. TFEB activity is regulated by nutrient availability. TFEB is phosphorylated by mTORC1 and remains bound to 14-3-3 and inactive in nutrient rich conditions (A). Under starvation or stress conditions, mTORC1 activity decreases, increasing the fraction of TFEB available for homodimerization and translocation to the nucleus (B).

activity has been broadly shown to play a protective role, with overexpression models showing slowing or amelioration of disease onset in animal models of all three of the above [32-34]. Upregulation of TFEB-mediated autophagy seems to provide protection not only through clearing of aggregates, but also by reducing oxidative stress and normalizing mitochondrial activity [33]. The inciting cause of dysfunction in this pathway is not well established, and may vary between diseases. Studies done in the context of Parkinson's Disease suggest that alpha-synuclein, one of the key components of the Lewy Body protein aggregates that characterize PD, may itself bind to and interfere with cytoplasmic TFEB, preventing induction of the autophagy response [32]. Huntingtin, the major protein component of aggregates in Huntington's Disease, has been shown to have significant sequence homology with ATG11, and may serve as a scaffold for autophagosome formation; a function which is lost in the mutated form [35]. Interestingly, a mouse model of Alzheimer's Disease containing five separate familial AD mutations shows significant upregulation of TFEB targets and autophagocytic flux but appears insufficient to deal with a progressive amyloid aggregate load [36]. The authors of this study hypothesize that a similar process may go on in human AD, in which over time seeding and formation of new aggregates may gradually exceed the TFEB-mediated catabolic capacity of neural tissue and

local microglia. An interesting corollary to this model appears in the literature on prion diseases, which occur when misfolded proteins trigger misfolding of nearby normal proteins in a spreading, infection-like fashion. In studies on prions, it has been noted that partial lysosome digestion may paradoxically lead to worsening of disease through generation of prion fragments which themselves have a higher capacity to seed formation of new aggregates: an observation also noted in models of PD and AD [31, 37-39] (Figure 2). This may explain why autophagy inhibitors such as quinacrine have shown benefit in models of prion disease: by inhibiting deleteriously ineffective autophagocytic activity [31].

TFEB control of autophagy has also been demonstrated to play a major role in cancer progression. Autophagocytic dysfunction is broadly observed across cancer types, and is generally thought to be important both in obtaining sufficient energy and macromolecules to fuel rapid growth, and also as a way to safely remove toxic byproducts of this elevated metabolic flux [40]. Indeed, increased TFEB expression has been noted in a variety of cancer types, including pancreatic, oral squamous cell, renal, and lung, though one series found TFEB levels to be lower relative to adjacent normal tissue in colorectal cancer [41], with TFEB-mediated autophagocytic activity observed to be decoupled from nutrient sensing [41, 42]. Notably, some renal cell carcinomas are known to be driven by gene translocations or fusions involving MiT/TFE family members, including TFEB [43]. In keeping with these observations, several clinical trials combining traditional chemotherapy and radiotherapy with chloroquine (CQ) and hydroxychloroquine (HCQ) for glioblastoma have shown marginal benefit in increasing overall survival [44, 45]. Other studies of CQ and HCQ in a number of cancers, such as pancreatic, lung, multiple myeloma, NHL, have shown inconsistent benefit, though degree of actual *in vivo* autophagy suppression is difficult to measure, and patients receiving antimalarial therapy are often frequently affected by dose-limiting toxicities, such as myelosuppression [40].

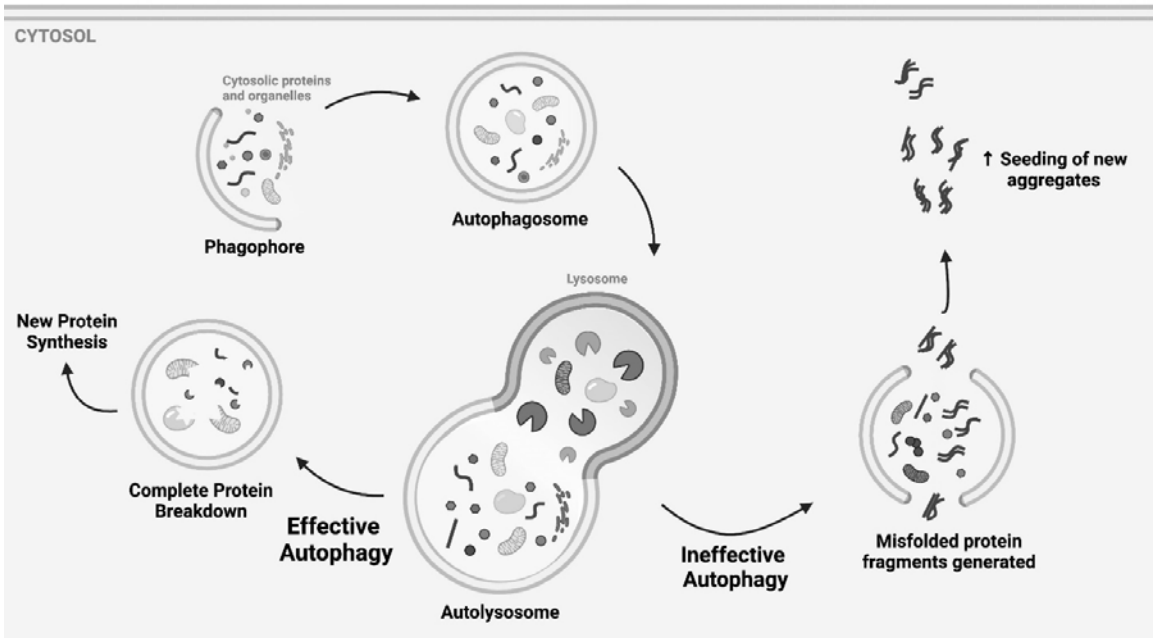

Figure 2. Ineffective autophagy may drive propagation of protein misfolding. Under normal conditions, autophagy is responsible for clearing damaged or unneeded proteins and organelles from the cell. It has been theorized that when autophagy is incomplete, it may generate misfolded protein fragments that go onto seed misfolding of other proteins and pathologic protein aggregation.

In recent years, a number of direct and indirect small molecule TFEB agonists have been identified, with many now undergoing preclinical evaluation [46]. There are also arguments against therapeutic autophagy inhibition, however, due to its suppressive effects on the immune system, particularly as immunotherapy continues to play an increasingly large role in standard of care for many cancer types. Autophagy is known to be important in immunogenic tumor death, which is important for tumor antigen recognition by the immune system, and is also important for tumor antigen cross-presentation [47, 48]. It is unclear to what degree inhibition of this activity may or may not adversely impact outcomes in patients treated with these classes of therapeutics.

MITF

MITF is well known as an oncogene independent of its role in regulating autophagy. It has been found to be amplified in 10-20% of melanomas, particularly advanced and metastatic tumors, with amplification being shown in one series to be associated with a five-year decrease in overall survival [49]. The same study also showed that MITF expression conferred immortalized primarily melanocytes with growth ability in soft agar, providing experimental evidence for MITF's importance in melanoma spread.

MITF control of autophagy has also more recently been appreciated as playing a role in the growth and progression of cancer, though the exact nature of its contribution remains unclear. In a model of pancreatic ductal adenocarcinoma, together with TFEB and TFE3, MITF-dependent expression of CLEAR element genes was shown to be required to maintain amino acid pools [42]. For example, in primary melanocytes and melanoma lines, MITF homodimer binding to CLEAR elements has been shown to promote expression of a distinct set of genes from TFEB and TFE3, suggesting complementarity in function between family members in other tissue types [50]. While multiple studies have demonstrated targeting of MITF to CLEAR elements, several have called into question the degree to which MITF actually induces autophagocytic flux [50, 51], particularly given that many key autophagy genes (ATG7, ATG12, ATG5) have been found to be highly negatively correlated with MITF expression [52]. Indeed, a separate GSEA study showed that while MITF significantly induced CLEAR element genes related to lysosomes, it failed to significantly increase expression of autophagy-specific genes [51], though there is some evidence that this may be tissue- or isoform-specific [53]. Other experiments have suggested that induction of multvesicular bodies by MITF activation of CLEAR element genes may drive melanoma progression through sequestration of GSK3 and stabilization of beta catenin, further complicating the relationship between MITF and autophagy in cancer [51]. MITF control over autophagy in melanocytic cells has also been suggested to exist in a balance with TFEB, with overexpression of MITF leading to increased TFEB levels and overexpression of TFEB leading to decreased MITF levels in melanoma cell lines [6]. This same study also showed evidence of direct regulation of TFEB levels by MITF through binding of MITF to a regulatory element in intron 1 of *TFEB*. The exact nature of this relationship between MITF and TFEB in melanocytic cells has not been fully elucidated, but could be hypothesized to be related to the unique synthetic activity of MITF in pigmented cells, and the need to simultaneously activate catabolic pathways for removal of byproducts of melanin synthesis.

Outside of cancer biology, the importance of MITF regulation of autophagy to other disease states or to normal physiologic processes has not been fully explored. Multiple studies have identified defects in autophagy as contributing to disorders or pigmentation [54-57], though a direct link between MITF, autophagocytic flux, and pigmentation status under physiologic conditions has not been clearly drawn. Autophagy has been implicated as both a cause of and a protective factor against the autoimmune depigmenting disorder vitiligo, though the exact role of MITF in these processes is similarly poorly understood [58-60]. Knockout of MITF in the retinal pigment epithelium of C57BL/6J mice yielded progressive lipofuscin accumulation in the form of yellow spots not seen in WT mice, suggesting that MITF, like TFEB, may play a role in general lipid and protein aggregate clearance in pigmented cells, much like TFEB in other tissue types [61, 62].

Given MITF's established role in transcription of CLEAR element genes, the functional importance of this relationship in different contexts remains a prime area for further study.

TFE3

While TFE3 has been identified as being able to bind to CLEAR elements and drive transcription of lysosome and autophagy-related genes in the setting of starvation in an mTORC1-dependent manner [53, 63], its functional importance is much more poorly understood compared to TFEB and MITF. There is thought to be significant overlap between autophagy genes regulated by TFEB and TFE3, suggesting some level of redundancy between the two family members [15, 53]. Additionally, studies have implicated TFE3 as being important in the immune response against microbial pathogens, similar to TFEB [64]. A few investigations have suggested a general role for TFE3 in regulating autophagocytic flux in response to nutrient deprivation and oxidative stress in multiple cancer types, including breast cancer [65], melanoma [66], and papillary thyroid carcinoma [67], though to date TFE3 has not been widely explored as a potential therapeutic target. Interestingly, TFE3 has also been suggested to play a role in clearing toxic ROS buildup generated by wound healing in the CNS, with promising preliminary results in explorations of its potential as a therapeutic target in improving post-surgical outcomes [68].

TFEC

TFEC expression is believed to be restricted to cells of the monocyte lineage [69]. It may act as a transcriptional repressor when heterodimerized with other MiT/TFE family members [5, 69]. Relatively little else is known about the function of TFEC currently, but hopefully awaits future analysis.

CONCLUSION

Autophagy plays a critical role in a number of physiologic and pathophysiologic processes. Its regulation by MiT/TFE family members represents an important control node integrating a number of environmental factors to finely tune autophagocytic flux to meet the metabolic needs of the cell while simultaneously preventing the buildup of toxic or degraded proteins, which can lead to death or dysfunction. Given their importance to cellular health, MiT/TFE family members may offer a promising target for therapeutic development in a number of diseases, most prominently cancer, neurodegeneration, and lysosomal storage disorders.

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CONFLICT OF INTEREST STATEMENT

D. E. F. has a financial interest in Soltego, a company developing salt inducible kinase inhibitors for topical skin-darkening treatments that might be used for a broad set of human applications. The interests of D. E. F. were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. N. T. and A. P have no interests to report.

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