The Regulation of MiTF/TFE Transcription Factors Across Model Organisms: from Brain Physiology to Implication for Neurodegeneration

Francesco Agostini¹ · Rossella Agostinis²,³ · Diego L. Medina²,⁴ · Marco Bisaglia¹ · Elisa Greggio¹ · Nicoletta Plotegher¹

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Abstract

The microphthalmia/transcription factor E (MiTF/TFE) transcription factors are responsible for the regulation of various key processes for the maintenance of brain function, including autophagy-lysosomal pathway, lipid catabolism, and mitochondrial homeostasis. Among them, autophagy is one of the most relevant pathways in this frame; it is evolutionary conserved and crucial for cellular homeostasis. The dysregulation of MiTF/TFE proteins was shown to be involved in the development and progression of neurodegenerative diseases. Thus, the characterization of their function is key in the understanding of the etiology of these diseases, with the potential to develop novel therapeutics targeted to MiTF/TFE proteins and to the autophagic process. The fact that these proteins are evolutionary conserved suggests that their function and dysfunction can be investigated in model organisms with a simpler nervous system than the mammalian one. Building not only on studies in mammalian models but also in complementary model organisms, in this review we discuss (1) the mechanistic regulation of MiTF/TFE transcription factors; (2) their roles in different regions of the central nervous system, in different cell types, and their involvement in the development of neurodegenerative diseases, including lysosomal storage disorders; (3) the overlap and the compensation that occur among the different members of the family; (4) the importance of the evolutionary conservation of these protein and the process they regulate, which allows their study in different model organisms; and (5) their possible role as therapeutic targets in neurodegeneration.

Keywords MiTF/TFE · TFEB · Autophagy · Neurodegeneration · Lysosomal storage disorders

Introduction

The transcription factors of the microphthalmia/transcription factor E (MiTF/TFE) family are crucial for the regulation of different cellular functions [1]. Among the four members of the mammalian MiTF/TFE family, the transcription factor EB (TFEB) is considered the master regulator of autophagy and lysosomal biogenesis because its nuclear translocation, which is controlled by different kinases and phosphatases, triggers the transcription of numerous genes involved in the regulation of this pathway. However, many aspects related not only to TFEB but also to the other MiTF/TFE transcription factors remain to be elucidated. For instance, the different functions of these proteins in different cellular types and tissues, such as the central nervous system (CNS), are still unclear. Indeed, how and to what extent defects in the regulation of the MiTF/TFE transcription factors contribute to the toxic events associated with neurodegenerative disorders are key questions in the understanding of the molecular mechanisms common to these pathologies [2–6].

Multiple other roles have been associated with the members of the MiTF/TFE family, including the regulation of mitophagy [7], lipid catabolism [8, 9], and mitochondrial
biogenesis [10]. Although some of their activities may overlap, each homolog of the MiTF/TFE family seems to have a specific pattern of expression and individual functions, which will be addressed in the following sections. Despite the different cellular roles proposed, the most characterized process regulated by MiTF/TFE transcription factors remains to be autophagy.

Autophagy is a crucial process in cellular physiology and is responsible for the degradation of unnecessary and defective cellular components [11]. The autophagic machinery is known to be highly conserved throughout evolution. In fact, the orthologues of many of the genes necessary for this cellular mechanism are ubiquitously expressed in all eukaryotic organisms. Moreover, genetic, morphological, and sequence-based evidence for autophagy confirms the presence of this mechanism in metazoans, in plants, and also in Protista and fungi [12, 13].

Autophagy is a multistep process that determines the engulfment of cytoplasmic components, such as protein aggregates, damaged organelles, and cell debris in double membrane vesicles called autophagosomes (Fig. 1). These vesicles fuse with the lysosomes, membrane bound organelles characterized by an acidic lumen, and lead to the formation of autolysosomes, where the autophagic cargo is degraded [11]. The acidic pH of the lysosomes represents the ideal environment for the hydrolytic enzymes to exert their activity [14]. The products of the autophagic catabolic activity are then recycled back to the cytoplasm to sustain cell homeostasis [11].

Autophagy is ubiquitously performed at the basal level; what differs among cells and tissues is the regulation of the process and the speed of the autophagic flux, which measures the rate of autophagic degradation activity [15].

Autophagic flux is finely regulated by multiple signaling pathways, which are activated by different stimuli, including nutrients, reactive oxygen species and calcium, and by energy imbalance [11, 16]. Autophagy is particularly relevant in the pathogenesis of neurodegenerative diseases, including Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), and in lysosomal storage disorders (LSDs) [17]. All these diseases share a common pathological hallmark, which is the accumulation of aggregated proteins or dysfunctional organelles, such as mitochondria, which are not properly cleared because of defective degradative pathways.

As the MiTF/TFE family is conserved in many different organisms, ranging from mice to fruit flies, and from zebrafish to worms, their study in these model organisms can provide a better perspective for the interpretation of different findings also in the field of neurodegeneration. The possibility of exploiting different model organisms to characterize the function of the MiTF/TFE family, the processes that they can regulate and their role in neurodegeneration, is also crucial for the identification of new targets for the development of novel therapeutic strategies against neurodegeneration. Finally, the activation of MiTF/TFE transcription factors, particularly of TFEB, can promote the clearance of intracellular waste in both LSDs and more common neurodegenerative diseases [18–20]. This may represent a novel therapeutic strategy to burst lysosomal and autophagic pathways in these disorders by targeting MiTF/TFE proteins.

The role of these transcription factors in autophagy and their link to neurodegeneration have been studied in different models. In this frame, the overexpression of the Caenorhabditis elegans orthologue of the MiTF/TFE proteins HLH-30 has been directly associated to autophagic induction and increased lifespan [21]. Coherently, a Drosophila melanogaster knockdown model for Mitf, the only fly orthologue of these
transcription factors, shows autophagic defects and accumulation of autphagic substrate [22]; the activity of Mitf has also been linked to the autophagosomal defects observed in a fly neurodegeneration model of amyotrophic lateral sclerosis (ALS) [23]. Moreover, overexpression of TFEB has been proved to be neuroprotective in a rat model of PD [24]. All these data, and others that will be discussed in detail in the following sections, clearly associate MiTF/TFE transcription factor activity with autophagy and suggest their important function in the field of neurodegeneration. Noteworthy, the knockout of Tfeb in mice leads to placental vascularization defects and embryonic death between 9.5 and 10.5 days [25], hampering the possibility to study the effects of TFEB knockout on the CNS in a mammalian model.

In this review, we will discuss the function and regulatory mechanisms of the MiTF/TFE family members by comparing their roles in different cell types and tissues, and in different model organisms. This will allow inferring their possible role in different brain cells and regions. We will also describe the role of MiTF/TFE family in neurodegenerative processes and the possibility of targeting these transcription factors to develop novel therapeutics.

By intersecting different aspects of this topic, ranging from function relevant to brain physiology to contribution to neurodegeneration, and by introducing an evolutionary perspective, we envision shedding light on different aspects of this scientific problem. This will also lead to discussing key issues and open questions with the aim of speculating on alternative research lines and on new experimental approaches within this research topic.

The MiTF/TFE Transcription Factor Family: an Overview

The microphthalmia/transcription factor E (MiTF/TFE) family is constituted in mammals by four members: (i) microphthalmia-associated transcription factor (MITF), (ii) transcription factor EB (TFEB), (iii) transcription factor E3 (TFE3), and (iv) transcription factor EC (TFEC) [4–6]. They share some common structural features: they all contain a basic domain, which is required for DNA binding, and a helix-loop-helix (HLH), and a leucine zipper (LZ) domain, which are critical for dimerization (Fig. 2). TFEB, TFE3, and MITF also contain a conserved transactivation domain, which is crucial for their transcriptional activation whereas TFEC, the most divergent member of the family, lacks this domain and appears to inhibit rather than activate transcription [5, 26, 27] (Fig. 2). The MiTF/TFE transcription factors bind the palindromic CACGTG E-box sequence, which conforms to the CANNTG motif that is recognized by other members of bHLH-zip family transcription factors. Flanking E-box sequences also influence the DNA binding specificity of the HLH/LZ family. The MiTF/TFE transcription factors have been described to prefer the GTCACGTGC consensus region, named Coordinated Lysosomal Expression and Regulation (CLEAR) motif. Unlike other bHLH-zip transcription factors, the MiTF/TFE family members are also able to bind the asymmetric TCACTGTG M-box sequence [28–30]. Sequencing of chromatin immunoprecipitate and mRNA analysis of HeLa cells overexpressing TFEB revealed that, through the binding with the CLEAR motif, TFEB enhances the expression of genes involved in lysosomal biogenesis, in lysosomal membrane formation, in acidification of lysosomes, in lysosomal hydrolases expression.

Fig. 2 Protein structure of MiT/TFE family members. MiT/TFE family members have high similarities in their sequences: they share basic-helix-loop-helix domain (bHLH) and a leucine zipper (LZ) domain. The activation domain is conserved in TFEB, MITF, and TFE3, but is missing in TFEC.
and in the autophagic process [29, 31]. Interestingly, TFEB transcriptional activity is not only limited to the modulation of genes involved in lysosomal homeostasis, but also in the Golgi vesicle transport, protein transport, and mitochondrial homeostasis [31]. These data confirm the close link between TFEB and the other MiTF/TFE proteins and autophagy and underline the crucial role of TFEB in the overall cellular homeostasis.

The MiTF/TFE transcription factors have been shown to form, in vitro, both homodimers and heterodimers with any other family member, and the dimeric form is required for the binding to DNA and the transcriptional activation of target genes. However, they are unable to heterodimerize with other bHLH-zip transcription factors [4, 31]. The X-ray structure of MiTF was obtained using three fragments from the Mus musculus Mitf cDNA that were cloned in the pET-M11 vector and expressed in the Escherichia coli strain BL21 (DE3) RIL. This structural analysis revealed the presence of a three-residue shift within its ZIP domain, which generates an unusual leucine zipper kink, and is responsible for the specific dimerization of the MiTF/TFE members [31]. Multiple sequence alignment showed that this three-residue shift is conserved among all the MiTF/TFE members, while it is missing in the sequences of the canonical bHLH-zip transcription factors. However, the functional implication of the heterodimer formation has not been fully investigated, except for the MITF-TF3 heterodimer, which does not appear to be essential for proper functioning, as suggested by MITF and TFE3 redundant roles at least in the development of osteoclasts [32].

The Regulation of MiTF/TFE Transcription Factors

The regulation of MiTF/TFE transcription factors can occur at different levels. Even though the activity of these proteins is mainly modulated through post-transcriptional modifications and highly depends on their subcellular localization, their regulation can also be performed at the transcriptional level. In this regard, most of the literature available is about TFEB. However, the high degree of homology among the MiTF/TFE members suggests that they may share common regulatory mechanisms. Several transcription factors are known to modulate the expression of TFEB: among them, androgen receptors, peroxisome-proliferator activated receptors-α (PPARα) [33], cAMP response element-binding protein (CREB) [34], and Krüppel-like factor 2 (KLF2) [35], have been shown to enhance TFEB activity. Moreover, TFEB can also modulate its own regulation through a positive feedback loop [36]. The fact that TFEB is transcriptionally regulated by different transcription factors further suggests the importance of fine-tuning the expression of this protein and underlines that its level and activity are influenced by multiple stimuli. Another level of regulation is represented by alternative splicing. Tissue-specific expression of MITF, TFEB, and TFE3 seems to be mediated, at least in part, by alternative transcription start sites, that also allows modulating the activity of the three proteins in different cells. TFE3 is the only member of the MiTF/TFE family that does not present alternative first exons and is regulated by a single promoter [37].

At the post-transcriptional level, the necessary nuclear shuttling from the steady-state cytosolic localization, that activates TFEB-mediated transcriptional response, correlates with its phosphorylation status and it is positive regulated by de-phosphorylation in key serine residues [2]. The most known member of the family, TFEB, is characterized by several phosphorylation sites within its amino acid sequence. These sites are highly conserved throughout evolution and most of them are found in TFEB orthologues from invertebrates, as C. elegans, to humans. Moreover, the other mammalian MiTF/TFE transcription factors present the same phosphorylation sites: the most conserved are the residues crucial for the regulation, such as serine 141, serine 211, and serine 467 [38]. These data suggest that all the MiTF/TFE members may be regulated similarly to TFEB and that these mechanisms of modulation may be relevant for the activity of MiTF/TFE orthologues in different organisms. TFEB is the substrate of different kinase proteins, including extracellular-signal-regulated kinase (ERK)2, protein kinase C (PKC)β, and AKT, also known as protein kinase B (PKB). However, the most important protein involved in the regulation of TFEB is the mechanistic target of rapamycin (mTORC1), which phosphorylates the transcription factor at three serine residues, serine 122, serine 142, and serine 211 [39]. The mTORC1-mediated phosphorylation promotes the interaction between TFEB and 14–3–3 proteins, which sequester TFEB in an inactive state in the cytoplasm. It is important to note that through the binding to Rag (Ras-related GTP-binding) GTPases, both mTORC1 and TFEB are recruited at the lysosomal level, where the interaction occurs [40]. This mechanism is particularly important to respond to environmental cues and occurs in human, mouse, and Drosophila melanogaster-derived cells, providing evidence of a mechanism conserved both in mammals and in invertebrates [41, 42]. During normal nutrient conditions, a signaling pathway promoted by the availability of amino acids induces the binding between Rag GTPases and mTORC1 and its consequent activation at the lysosomal surface, where it phosphorylates TFEB [41]. In nutrient deprivation conditions, the calcium-sensitive phosphatase calcineurin dephosphorylates TFEB, thus promoting its nuclear translocation [2]. MITF and TFE3 have also been shown to be similarly regulated by...
mTORC1, while much less is known about TFEC. Given the high degree of homology with the other members of the family, it is likely that also TFEC is regulated similarly [1].

mTORC1 being the hub of several important cellular processes [43], it is crucial to intensively study its activity and all its regulatory mechanisms to thoroughly understand how TFEB and the other MiTF/TFE proteins are modulated. Nutrient conditions are not the only parameter that affects these mTORC1 and, consequently, MiTF/TFE transcription factor activity. In fact, mTORC1 function may also depend on the activity of AMP-activated protein kinase (AMPK). AMPK is considered the sensor of cellular energetic status and is regulated by different upstream stimuli, such as oscillations in the intracellular calcium levels, alterations in oxygen reactive species, and changes in AMP/ATP ratio. AMPK activation inhibits mTORC1 promoting MiTF/TFE nuclear translocation [44]. Moreover, it has been recently reported that AMPK can directly activate TFEB and TFE3 by phosphorylating a cluster of serine residues in the C-terminus of these proteins [45]. Interestingly, it has been also shown that in mice AMPK activation does not enhance autophagy in neurons, further suggesting that these pathways need to be characterized specifically in different cell types and tissues [46].

These data reinforce the concept of MiTF/TFE transcription factors as crucial players in the maintenance of cellular energy balance and strengthen the hypothesis that their activity is particularly essential in highly energy-demanding tissues, like the brain. Noteworthy, the AMPK phosphorylation sites in TFEB are also present in MITF and TFEC and at least one of these residues is found in the MiTF/TFE orthologues of several organisms, both vertebrates and invertebrates, suggesting that this regulation mechanism may be highly conserved throughout evolution [38]. This data may open the possibility to characterize AMPK-mediated regulation of MiTF/TFE proteins not only in cellular models but also in vivo in different model organisms.

The final regulation mechanism is achieved through the degradation of the proteins. The available data for TFEB show that the transcription factor is degraded through the ubiquitin–proteasome pathway and that the half-life of the protein is about 13.5 h in neuronal-like cells, such as SH-SY5Y [47]. The relevance of the degradation process in the modulation of TFEB activity is confirmed by the fact that proteasome inhibition not only causes the accumulation of the protein, but also promotes its nuclear translocation and, in turn, the increased expression of TFEB target genes [47]. Interestingly, it has been shown that mTORC1 activation enhances the rate of TFEB proteasomal degradation, providing feedback mechanisms through which the mTORC1-mediated phosphorylation of TFEB inhibits its nuclear translocation and promotes also its degradation [48, 49].

### Mammalian MiTF/TFE Transcription Factors

MiTF, TFEB, TFE3, and TFEC are the four members of the mammalian MiTF/TFE family. Human and mouse MiTF/TFE proteins share a very high sequence identity (Table 1) and the information currently available on these factors mainly derives from data obtained in mouse models. In the following paragraphs, we will detail the pattern of expression and the main functions of the MiTF/TFE transcription factors. Special care, when possible, will be used in comparing the functions, the localization, and the regulation of the different MiTF/TFE family members.

### MITF

In humans, the MITF locus is mapped in the short arm of chromosome 3 and spans 229 kbp, with the promoter region that is highly conserved with mice [26]. MITF transcription gives rise to several isoforms that are under the control of alternative promoters: MITF-A [50], MITF-B [51], MITF-C [52], MITF-D [53], MITF-E [54], MITF-H [55], MITF-J [56], MITF-Mc [57], and MITF-M [58] (Table 2). These isoforms share the same functional domains (transactivation domain, basic domain, bHLH domain, and LZ domain) but differ in the N-termini, as a result of alternative splicing of exon 1, and display a tissue-specific pattern of expression [37]. MITF is predominantly expressed in melanocytes, osteoclasts, mast cells, macrophages, NK cells, and B cells, and in the heart [59]. Moreover, it is expressed in the CNS. Immunohistochemical analysis of the mouse brain showed that MITF is especially expressed in the olfactory bulb (OB), and in tufted and mitral cells that receive signals from the olfactory neurons and transmit them to the olfactory cortex. MITF protein was not detected in other cell types of the OB, including granule cells or astrocytes [60], in contrast with a previous study based on an RT-PCR analysis showing the expression of MITF also in T98G and A-172 human glioblastoma cells [52]. One possible explanation for this discrepancy is that MITF expression is much higher in mitral and tufted cells of the OB, allowing the detection of the protein by immunohistochemical analysis only in these

| MiTF/TFE transcription factor | Identity (%) | Similarity (%) |
|--------------------------------|--------------|----------------|
| MITF                          | 93%          | 95%            |
| TFEB                          | 93%          | 95%            |
| TFE3                          | 96%          | 97%            |
| TFEC                          | 70%          | 76%            |

Table 1 Identity and similarity values obtained by PROTEIN BLAST search using the amino acid sequence of human and mouse MiTF/TFE family members
Little is known about the function of MITF in the olfactory bulb. A recent study reported that mitral and tufted neurons from mutant mouse knockout for Mitf are characterized by a reduced A-type potassium current (IA) likely because of the decreased expression of the potassium channel subunit KCND3, leading thus to hyperexcitability. Moreover, Mitf mutant mice exhibit increased olfactory dis-habituation, but reduced the ability to detect the odorant following long-term odor exposure. These findings suggest that MITF plays a key role in olfactory adaptation and intrinsic homeostatic plasticity through the regulation of Kcnd3 expression. Accordingly, MITF signaling has been demonstrated to upregulate Kcnd3 expression via an enhancer region located in an intron of Kcnd3 [6]. It remains to be elucidated the possible importance of MITF in the regulation of KCND3, and therefore of potassium currents in other neuronal types. Worth mentioning is the fact that Kcnbd3 mutations were associated with the neurodegenerative disorder spinocerebellar ataxia type 19 [61, 62], suggesting that MITF impact on Kcnbd3 may also regulate neuronal function in the central and peripheral nervous system.

As already reviewed by Haq and Fisher in 2011 [66], MITF is required for many other cellular processes. It mediates the survival of melanoblasts and regulates the expression of genes encoding proteins implicated in the cell cycle, cell invasion by affecting actin cytoskeleton and in DNA damage repair and cell metabolism. In this frame, MITF modulates not only catabolic pathways, like autophagy, but also mitochondrial biogenesis and oxidative phosphorylation [67, 68]. MITF regulation of intracellular metabolism and of actin cytoskeleton is likely crucial not only for neurons, but also for other types of brain cells. In fact, specific types of neurons are known to have increased metabolic demands that make them specifically susceptible to neurodegeneration, suggesting that the MITF role may be particularly relevant in those cases. Similarly, MITF actin cytoskeleton remodeling is critical for neuronal shape and for the regulation of dendritic spine morphology [69]. Defects in neuronal metabolism and in the structure of dendritic spines were associated to different neurodegenerative diseases [70].

Through the binding of the CLEAR motif, MITF is also able to promote the expression of lysosomal and autophagy-related genes. Interestingly, in metastatic melanoma tumors, the lysosomal and autophagy genes under the control of MITF are different compared to the ones regulated by TFEB and TFE3, suggesting a distinct role of MITF [71]. These data support the idea that each member of the MiTF/TFE family may regulate the expression of its target genes in a cell/tissue-specific manner, making it crucial to investigate each of them separately not only in different neuronal types, but also in astrocytes and microglia, when studying their role in neurodegeneration.

In light of the numerous functions attributed to MITF, it is not surprising that mutations in the gene encoding the protein are associated with several pathological conditions. For instance, in the mouse models, MITF mutations induce

| Protein name | Protein symbol | Transcripts | Expression | Referee |
|--------------|---------------|-------------|------------|---------|
| Microphthalmia-associated transcription factor | MITF | MITF-A | Ubiquitous | [50] |
| | | MITF-B | N/A | |
| | | MITF-C | Different cell types excluding melanocytes | [63] |
| | | MITF-D | Preferentially in RPE cells, macrophages, osteoclasts, and mast cells | [53] |
| | | MITF-E | Mast cells and osteoclasts | [54, 64] |
| | | MITF-H | Ubiquitous | [50] |
| | | MITF-J | Osteoclasts, RPE, and HeLa cells | [56] |
| | | MITF-Mc | Mast cells | [57] |
| | | MITF-M | Melanocytes, melanoma cells, and RPE cells | [65] |
| Transcription factor EB | TFEB | TFEB-A | Placenta, kidney, lung, and prostate | |
| | | | Different tissues | |
| | | TFEB-B | Different tissues excluding liver | |
| | | TFEB-C | N/A | [37] |
| | | TFEB-D TFEB-E | Brain | |
| | | TFEB-F | Brain | |
| | | TFEB-G | Spleen | |
| Transcription factor E3 | TFE3 | None | Ubiquitous with the highest expression levels in placenta, lung, and adrenal gland | [37] |
| Transcription factor EC | TFEC | TFEC-A | Testis, thymus, trachea, colon, and prostate | |
| | | TFEC-B | Different tissues excluding heart and liver | [37] |
| | | TFEC-C | Kidney and small intestine | |

Table 2 Pattern of expression of MiTF/TFE alternative transcripts
defects in neural crest-derived melanocyte and retinal pigment epithelium differentiation, osteoclastogenesis, mast cell differentiation, and notch signaling that manifest phenotypically as changes in coat color, small eyes, osteopetrosis, and a reduction in NK cell, B cell, and macrophage numbers [66]. In humans, different heterozygous and homozygous MITF mutations are associated with Waardenburg syndrome type 2A and type 4, respectively [72, 73]. Waardenburg syndrome is a neurogenic disorder characterized by the combinations of various degrees of sensorineural deafness and pigmentation abnormalities affecting the skin, hair, and eye [74]. Dominant-negative mutations in MITF are also associated with Tietz syndrome, which is characterized by profound deafness and generalized hypopigmentation [73]. Furthermore, biallelic MITF mutant alleles are associated with COMMAD syndrome characterized by coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness [75].

**TFEB**

Among all members of the MiTF/TFE family, TFEB is the most studied and best characterized since it plays a pivotal role in the regulation of autophagy and lysosomal biogenesis. In contrast with the MITF pattern of expression, TFEB is ubiquitously expressed. Seven alternative 5' exons of the TFEB gene have been identified that originate from seven different transcripts, which encode different TFEB isoforms: TFEB-A, TFEB-B, TFEB-C, TFEB-D, TFEB-E, TFEB-F, and TFEB-G. Each transcript displays a different tissue distribution pattern, even though the existence of TFEB-D transcript still needs to be confirmed since its expression has not been detected in any of the tissues analyzed by RT-PCR. This could be due to very low expression levels.

TFEB is considered the master regulator of lysosomal biogenesis and autophagy signaling pathways because it induces the transcription of both autophagic/lysosomal-related genes through the binding with the CLEAR motif. This binding determines increased expression levels of the entire network of genes that contain this specific motif (the CLEAR network) [28]. The fact that autophagy is an essential cellular process and that TFEB promotes the expression of the CLEAR network can explain the ubiquitous expression of the protein. Moreover, as autophagic activity can vary between different tissues or cell types, the existence of alternative TFEB transcripts with different expression patterns may account for a very specific regulation of this evolutionarily conserved process. As already mentioned, it is well known that the autophagy-lysosomal pathway (ALP) is key not only for neuronal cells but also for other cell types in the brain, as astrocytes and microglia. In this regard, the contribution of non-neuronal cells to the maintaining of brain homeostasis and their role in neurodegeneration is gaining increasing attention. For example, astrocytes, that are the most abundant glial cells, are involved in the clearance of aggregated proteins and cell debris through the endo-lysosomal pathway. Therefore, the characterization of TFEB activity in non-neuronal brain cells is also very relevant. Increasing the astrocytic or microglial clearance capacity through TFEB upregulation may represent a promising therapeutic strategy for neurodegenerative diseases.

It is already known that TFEB plays an essential role in the tuning of several other basic cellular processes through the regulation of autophagy or lysosomal function in different tissues and cell types. For instance, TFEB-mediated lysosomal biogenesis in differentiated osteoclasts plays a crucial role in bone matrix resorption. Accordingly, mouse osteoclasts lacking TFEB show decreased expression of lysosomal genes, reduced number of lysosomes, and enhanced bone mass [76].

TFEB is also involved in the regulation of lipid metabolism, via a starvation-induced transactivation of PPARα and PPARα co-activator 1α (PGC1α), which are two key regulators of lipid metabolism during TFEB-mediated starvation. This process has been deeply analyzed in a liver-specific Tfeb conditional knockout mouse that displays impaired lipid catabolism and a more severe metabolic imbalance in obese animals. Coherently, TFEB overexpression rescues obesity and associated metabolic syndrome in both diet- and genetically induced obese mice [77].

Through specific gain and loss-of-function approaches in mouse skeletal muscles, the role of TFEB in metabolic adaptation during physical activity has also been emphasized. As a result of exercise, TFEB is dephosphorylated via calcineurin and translocates into the nuclei of myofibers and directly controls glucose homeostasis by regulating the expression of glucose transporters and glycolytic enzymes. Moreover, TFEB modulates the expression of genes implicated in mitochondrial biogenesis, such as mitochondrial transcription factor A (TFAM) and nuclear respiratory factors 1 and 2 (NRF1 and NRF2). It is however unclear whether TFEB activation in response to the exercise depends or not on PGC1α [78, 79].

The overall metabolism of cells seems to be controlled by TFEB function. In neurons, glucose and lipid homeostasis, as well as mitochondrial ATP production, are key in the maintenance of neurons' capacity to meet the energy demands during neuronal activity. This suggests that if TFEB is defective, also these processes, together with the impairment of lysosomal function, may concur in damaging neuronal function.

The modulation of inflammatory and immune responses is another important function ascribed to TFEB. More specifically, depletion of Tfeb in murine macrophages results in a decreased expression and secretion of several pro-inflammatory cytokines, such as tumor necrosis factor (TNF),
interleukin-1β (IL-1β) and IL-6, and chemokines including (C–C motif)-ligand 2 (CCL2) and CCL5, after lipopolysaccharides (LPS) treatment [80]. Neuroinflammation is a well-established event that occurs in many neurodegenerative diseases, even if it is still unclear to which extent it contributes to the etiology of the disease and its progression. The findings on TFEB modulation of inflammation would suggest further investigating how TFEB impacts inflammatory mechanisms in brain-resident immune cells.

Overall, TFEB seems to transcriptionally regulate several pathways that are intertwined and that play a role in the maintenance of brain function, making it crucial not only to better understand each of them separately, but also to investigate how they cooperate.

**TFE3**

Like TFEB, TFE3 shows a ubiquitous pattern of expression with the highest levels observed in the placenta, lung, and adrenal gland. TFE3 seems to be regulated by a single promoter since only one transcript for the TFE3 gene has been identified [58]. Similar to TFEB, TFE3 binds CLEAR elements regulating the expression of genes related to lysosomal biogenesis and autophagy. However, the ability of TFE3 to control the transcription of lysosomal genes is TFEB-independent, suggesting that the relative abundance of TFEB or TFE3 and/or different regulatory mechanisms determine which of them prevails in activating the lysosomal response [81].

Coherently, many functions ascribed to TFE3 overlap with those associated with TFEB. For instance, like TFEB, also TFE3 is involved in the transcriptional regulation of the immune response. Both proteins orchestrate the cellular response to endoplasmic reticulum (ER) stress by upregulating the expression of the activating transcription factor 4 (ATF4) or other unfolded protein response (UPR) genes. While under prolonged ER-stress conditions, TFEB and TFE3 activation contributes to cell death by either a direct binding to pro-apoptotic factors promoters, such as C/EBP homologous protein (CHOP) and p53 upregulated modulator of apoptosis (PUMA), or, indirectly, through the regulation of ATF4, which is also involved in the control of CHOP and PUMA expression. These findings suggest that TFEB, TFE3, and ATF4 may play a dual role in cell fate depending on the severity of the stress [82]. Interestingly, TFE3 is also activated in response to Golgi stress and upregulates the transcription of Golgi-related genes [83].

Noteworthy, both ER and Golgi stress or dysfunction are frequently associated with neurodegeneration [84, 85]. Moreover, accumulating evidence links dyshomeostasis of these organelles with alterations in autophagy activity [86, 87], suggesting that it would be interesting to evaluate whether modulating TFE3 activity may affect the onset and progression of neurodegenerative disease, impacting not only ER and Golgi function but also autophagy.

**TFEC**

TFEC is the most divergent and least studied member of the MiTF/TFE family. Three alternative 5’ exons of the TFEC gene have been identified: TFEC-A, TFEC-B, and TFEC-C, with the latter encoding for a shorter protein lacking exons 2 and 3. Mouse and rat Tfec lacks exon 5 that is found only in the human homolog. Human TFEC transcripts have a restricted and distinct pattern of expression [37]. In mice, TFEC expression is restricted to macrophages [88, 89] and mice lacking Tfec develop normally. They are viable and fertile, and normally pigmented, have normal eyes and mast cells, and show no osteopetrosis, thus indicating a redundant role of TFEC in myeloid cell development. Tfec expression at both the mRNA and protein levels is specifically induced in mouse macrophages by the Th2 cytokine IL-4. In macrophages lacking TFEC treated with IL-4, only few genes are affected by TFEC deficiency including G-CSFR (Csf3r) gene, which is upregulated to a lesser extent compared to IL-4 treated wild-type macrophages [90]. TFEC remains functionally uncharacterized and no information are available on its role in the nervous systems; thus, further studies to unravel its role in different human tissues/cells are needed.

**TFEB and Autophagy in Neurodegeneration**

The demand for basal autophagy differs among cells, and it appears to be particularly crucial in post-mitotic cells, like neurons, whose survival depends upon a strict regulation of cell homeostasis [91, 92]. Moreover, the role of glial cells is also crucial in the removal of extracellular waste and damaged neurons, which makes ALP important also in these cell types in the frame of neurodegenerative processes [93]. This suggests that autophagy and in particular TFEB and the other members of the MiTF/TFE family of transcription factor may be key not only in the development but also in the treatment of neurodegeneration. Further pieces of evidence supporting this idea are discussed in the following sections.

**Autophagy and TFEB Impairment in Age-Related Neurodegenerative Diseases**

It is established that autophagy impairments often occur in age-related or inherited neurodegenerative disorders and accumulating evidence suggests a primary involvement of this process in the pathogenesis of many of them, including PD, HD, and AD [94–96]. Several aggregation-prone proteins, such as huntingtin (HTT), α-synuclein (α-syn), amyloid beta (Aβ), and hyperphosphorylated-tau, are
eliminated through autophagy [46, 97–99]. Importantly, these proteins can also negatively impact the autophagic pathway, further contributing to their toxicity [100–103].

The link between autophagy and neurodegeneration is further supported by the fact that several genes whose mutations are associated with the familial forms of different neurodegenerative diseases have a role in the autophagic pathway and removal of key autophagy genes in the mouse brain leading to neurodegeneration [104, 105]. Interestingly, the dysregulation of autophagy in neurodegenerative diseases may also present as an increase in autophagy or TFEB activation, as discussed in Section “TFEB and Autophagy in Neurodegeneration.” This suggests that special care must be taken when designing possible therapeutic approaches impacting these mechanisms, in order to preserve autophagy homeostasis, rather than pushing the autophagic machinery without considering possible undesired effects.

Overall, these pieces of evidence suggest that basal clearance of cytosolic waste through autophagy is crucial for preventing the accumulation of cytoplasmic inclusion in neurons, and in astrocytes and microglia, which are involved in the clearance of brain waste via phagocytosis [93]. Therefore, the upregulation of autophagy may have beneficial effects and many research efforts in the field are aimed at finding molecular modulators of this process, possibly in a cell-type specific manner [6, 7].

TFEB, which is by far the most investigated protein in the MiTF/TFE family, shows impaired activity and regulation in many age-related neurodegenerative diseases, further supporting the importance of its role in the maintenance of cellular homeostasis (Fig. 3) [106].

For instance, analysis of postmortem PD midbrains revealed a selective loss of nuclear TFEB. In this frame, TFEB colocalizes with α-syn in Lewy bodies contained in surviving nigral neurons in PD human brains [107]. α-Syn shares structural homology with several regions of 14–3–3 proteins, and 14–3–3 proteins are well-established binding partners of the phosphorylated form of TFEB and prevent its translocation to the nucleus. This homology could lead to the binding between α-syn and TFEB that, consequently, is maintained inactive in the cytoplasm. Indeed, impaired α-syn degradation due to defective autophagy could initiate a vicious cycle leading to non-physiological α-syn-TFEB interaction, which may further amplify ALP dysfunction [107, 108].

The expression of TFEB and its target genes was found to be reduced also in the striatum of a mouse model of HD [16]. A reduction of TFEB expression levels and its nuclear localization was also observed in postmortem AD brains as well as in monocytes and lymphocytes from patients with AD [16, 109]. Mouse embryonic fibroblasts from double KO of the AD-associated proteins presenilin 1 and 2 and human AD neurons display higher levels of TFEB phosphorylation compared to the controls, which correlates with TFEB cytoplasmic retention and a decreased CLEAR gene network activity [110].

TFEB nuclear translocation appeared to be negatively affected in a dose-dependent manner in primary microglial cells treated with different concentrations of Aβ [111]. All

![Fig. 3](image-url)
these data support the presence of an inverse correlation between TFEB nuclear levels and the pathological state, but the picture is more complex and presents also some contrasting results. For example, increased TFEB expression levels were detected in patient-derived fibroblasts carrying the AD-associated presenilin 1 A246E mutation [112]. Another study reported an upregulation of genes within the CLEAR network in brains of presenilin 1, 2 double knockout mice with no changes in TFEB expression level [113]. Analysis of hippocampal CA1 neurons of AD patients microaspirated by laser capture microdissection revealed increased expression levels and nuclear translocation of TFE3, together with an elevated expression of its target genes, while no changes in TFEB levels were detected in the same neurons. Increased TFEB expression levels and nuclear translocation were observed in glia from AD hippocampal tissues, suggesting that TFEB, in this cellular type, may play a crucial role in scavenging aggregated proteins and neuronal debris [114]. Furthermore, these data suggest that TFEB could be upregulated as a compensatory mechanism in certain conditions: if this has a positive effect on the degradation of intracellular waste or contributes to further clump the system is still controversial.

A decline in TFEB levels with age in human immune cells has been recently reported [115], suggesting that it could negatively affect the ALP. This mechanism could contribute to the accumulation of toxic aggregation prone proteins at the early stages of the development of neurodegenerative diseases.

The opposite findings of TFEB being up- or downregulated during neurodegeneration suggest that the extent and length of the neurodegenerative process may impact differently TFEB expression, with an increase in the early phases and a reduction in the late stages of the disease. The same could be hypothesized for TFEB nuclear or cytoplasmic localization. A further degree of complexity is represented by cell type and tissue specificity, which are still understudied, and by the role of the different MiTF/TFE family members in neurodegeneration. The investigation of these aspects in both familial and sporadic forms of these diseases in suitable models may provide interesting clues about the role of these transcription factors in their etiology and further help in the identification of novel therapeutic targets for these disorders.

**Autophagy and TFEB Impairment in Lysosomal Storage Disorders**

Another group of diseases in which TFEB and the other transcription factors of the MiTF/TFE family seem to play an important role are lysosomal storage disorders (LSDs). They comprise more than sixty diseases caused by mutations in genes involved in lysosomal function, such as lysosomal hydrolases or lysosomal membrane proteins. About two-thirds of LSDs determine neurological symptoms and are counted among the neurodegenerative disorders [116, 117].

Although these pathologies are characterized by lysosomal defects, in the majority of the cases, they can affect various stages of the autophagic process causing impairments in autophagosome maturation and in autophagosome-lysosome fusion and, eventually, accumulation of undigested material in cells [117]. Because of its role in the regulation of ALP, TFEB has been extensively investigated in the context of LSDs, as a factor that can contribute to the progression of the pathology and as a possible therapeutic target.

As expected, both the activity of TFEB and its nuclear localization together with the autophagic process are affected in several lysosomal disorders (Fig. 3).

Gaucher disease (GD) is the most common LSD and in the most severe cases it determines neurological defects. The pathology is caused by mutation in the GBA1 gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), and is characterized by a decrease in the degradation of autophagosome content after its fusion with lysosomes [118]. Lysosomal GCase is responsible for the hydrolysis of the lipid glucosylceramide into glucose and ceramide. When GCase is mutated, accumulation of the substrate and ALP impairment occur in many cell types [118].

Decreased levels of TFEB have been observed in induced pluripotent stem cell (iPSC)-derived neurons from GD patients, probably due to an increased proteasomal degradation of the transcription factor. In the same iPSC-derived model, the instability of TFEB was linked to the hyperactivation of mTORC1 [119]. mTORC1-mediated phosphorylation of TFEB has been shown not only to inhibit its nuclear translocation, but also to promote the targeting of the protein to the proteasomal degradation machinery [48]. Surprisingly, even though mTORC1 activity is increased in GD-derived cells, TFEB was shown to be predominantly localized in the nuclei compared to control cells [118, 119]. These data suggest that another mechanism of TFEB regulation, besides the mTORC1-mediated one, may act in GD cells to stimulate the nuclear translocation and, in turn, the activity of the transcription factor to compensate for the lysosomal defects.

Another study, Sardiello and colleagues investigated the subcellular localization of TFEB in embryonic fibroblast from mouse models of three LSDs: mucopolysaccharidoses types II and III (MPSII, MPSIII) and multiple sulfatase deficiency (MSD). The first two diseases belong to a group of metabolic disorders caused by impairment of lysosomal enzymes required for the degradation of glycosaminoglycans, while the latter is caused by the deficiency in the formylglycine-generating enzyme [120]. As in the case of GD, TFEB was predominantly observed in the nuclei, further supporting the idea that the activation of TFEB is
promoted in this type of diseases as a cellular response to enhance lysosomal activity [28].

Despite the nuclear translocation of TFEB observed in several LSDs, this compensatory mechanism does not seem to be enough to counteract the progression of the disease and TFEB activity is not sufficient to properly remove the intracellularly accumulated debris. As observed in GD, it is possible that the stability and accumulation of TFEB are affected by increased proteasomal degradation, resulting in a decreased total amount of the protein. This hypothesis is supported by an experiment performed on myotubes in a mouse model of Pompe disease, another LSD caused by mutation in the GAA gene. This disease is characterized by deficiency of the lysosomal enzyme acid α-glucosidase and leads to the accumulation of lysosomal glycogen [121, 122]. While cells treated with the mTOR inhibitor Torin1, which induces a downstream activation of TFEB, failed to rescue the lysosomal phenotype in this model, the overexpression of TFEB in the same model was able to induce cellular clearance, suggesting that in these pathological conditions the amount of endogenous TFEB is not enough to support lysosomal function [121]. Similarly, the overexpression of TFEB in both cellular and mouse models of MSD and MPSIII-A diseases promotes clearance and ameliorates phenotypic hallmarks of these diseases [18].

As previously discussed, also the other members of the MiTF/TFE family are involved in the regulation of the autophagy and lysosomal activity. However, as in the case of the neurodegenerative disorders previously discussed, little is known about the involvement of TFEC and MITF in the onset and progression of LSDs. Recently, it has been demonstrated that the overexpression of TFEB can induce lysosomal exocytosis and cellular clearance in a model of Pompe disease, suggesting that also this homologue of TFEB can play an important function in the regulation of cell fate in these disorders [123].

**TFEB as a Possible Therapeutic Target in Neurodegeneration**

Although the contribution of TFEB to the pathogenesis of neurodegenerative disorders is still under debate, several studies have evaluated the effects induced by the exogenous TFEB overexpression (Fig. 3). In a mouse model of tauopathy, the adenovirus-mediated overexpression of TFEB drastically reduces the levels of the disease marker phospho-Tau 16 weeks post-injection. In this model, TFEB has been shown to participate in the selective elimination of misfolded and hyperphosphorylated tau by promoting the expression of the phosphatase and tensin homolog (PTEN) protein, attenuating neurofibrillary tangles pathology. Moreover, injected mice displayed increased neuronal survival and brain weight, associated with a rescue of behavioral and synaptic deficits [19].

Another study reported decreased levels of tau aggregates in the hippocampus and cortex upon neuron-targeted TFEB overexpression [124], together with attenuated learning and memory skill deficits, in a different mouse model of tauopathy [124].

Extracellular tau is considered to be responsible for the spreading of tau pathology and represents the primary target for tau immunotherapy [125]. Interestingly, TFEB loss of function in PS19 mice, a transgenic mouse line expressing P301S mutant tau, causes a reduction of intestinal fluid tau. The authors proposed a model in which TFEB plays an active role in the secretion of mutant tau via lysosomal exocytosis mediated by TFEB and Transient Receptor Potential Mucolipin 1 (TRPML1) signaling [125]. Accordingly, astrocyte-specific TFEB overexpression in the hippocampus of PS19 mice was able to reduce tau spreading from the ipsilateral to the contralateral hippocampus [126]. A recent study reported that TFEB overexpression in another AD mouse model is responsible for a reduction of the levels of the β-secretase-derived β-amyloid precursor protein fragment C99, which is a precursor of the toxic Aβ peptide. Consequently, the overexpression of TFEB in hippocampal astrocytes contributed to the reduction of Aβ levels in the brain interstitial fluid and of the hippocampal amyloid plaque load [127, 128]. A recent study reported that intracerebral injection of TFEB in the substantia nigra pars compacta of a PD rat model overexpressing the human disease-associated A53T α-syn mutant reduced the accumulation and the aggregation of α-syn as well as astrogliosis and prevented the behavioral deficits typical of this PD model [24]. Furthermore, TFEB injection in the striatum of HDQ175/Q7 mice reduced the levels of mutant HTT (mHTT) while preserving the levels of wildtype HTT. However, in this model, TFEB overexpression was also accompanied by ER stress and reactive gliosis [129].

In contrast with the later work, another study reported that the co-injection of human TFEB and mHTT in the mouse striatum has no impact on the level of mHTT aggregates even though autophagy appears to be activated. In this case, the accumulation of late autophagic structures seems to impair the global process [130].

Overall, these results seem to indicate that TFEB might represent a promising therapeutic target for the treatment of neurodegenerative disorders. However, it is important to notice that autophagy must be strictly regulated to guarantee the correct homeostasis in each type of cell. Therefore, while a regulated induction of autophagic flux may have positive effects in neurons, the overactivation of this process may be deleterious in other cells. Thus, deciphering the physiological and pathological role of TFEB in the different cell types that constitute the central nervous system will be necessary.
to develop efficient and safe therapeutic strategies for neurodegenerative disorders.

The possibility of modulating the activity of the MiTF/TFE factors, and in particular of TFEB, has also generated a great interest as a possible therapeutic strategy for LSDs. The role of TFEB as a potential target for the treatment of several LSDs has been largely investigated, and the overexpression of TFEB or its activation through the inhibition of mTORC1 has been reported to be beneficial in the rescue of the lysosome-associated pathological phenotype.

Despite the promising observations in cellular models of LSDs and the first proof of concept in vivo, additional data on the effects of chronic activation of TFEB in animal models is required. Thus, the uncontrolled expression of MiTF/TFE factors is linked to various human rare genetic cancers [131]. In this regard, the most logical approach to promote clearance is the pharmacological activation of TFEB. Using small molecules could allow the modulation of the amplitude and duration of TFEB activity in vivo. Also, this approach could be combined to other therapeutic approaches such as enzyme replacement therapy (ERT) or gene therapy.

To evaluate the effect of TFEB modulation in vivo, it would be very useful to take advantage of the different transgenic animal models already used to study LSDs, which are quite reliable compared to the transgenic mouse models for some age-related neurodegenerative diseases. Animal models can provide the opportunity to assess the effects of the constitutive long-term activation of TFEB, for example by evaluating in which way TFEB activation affects the lifespan, the homeostasis, and the function of neurons and of other CNS cell types. They could also help to understand to what extent the modulation of TFEB may be beneficial in the context of LSDs, and how to prevent possible negative effects.

### MiTF/TFE Family Transcription Factors: Putative Therapeutic Targets in Neurodegenerative Diseases and Lysosomal Storage Disorders?

In recent years, several compounds able to modulate TFEB activity have been found to enhance autophagy and lysosomal biogenesis and might have therapeutic potential for the treatment of neurodegenerative diseases and LSD (Table 3). Very recently, a repurposing approach to identify drugs able to ameliorate two subtypes of Batten disease, the most frequent of rare neurodegenerative disorders in children, resulted in the identification of tamoxifen [20]. Tamoxifen ameliorates the phenotype of disease relevant cellular models of CLN3 and CLN7 disease, including neuronal progenitor cells (NPCs) from CLN7 patient-derived induced pluripotent stem cells (iPSC). Also, the treatment with tamoxifen was able to ameliorate the phenotype of a mouse model of CLN7 disease. Interestingly, tamoxifen exerts its action through a mechanism that involves activation of the transcription factor EB (TFEB) [20].

The idea of enhancing autophagy to counteract neurodegeneration has been explored by many [152] and in most cases the preferred molecular target for the proposed therapeutic strategies is mTOR, particularly using specific mTOR inhibitors. Despite their efficacy in certain models, they have also proved to have limited capacity of impacting neurodegenerative diseases in certain clinical trials. We suggest that this may be associated to the fact that mTOR regulates not only TFEB and its downstream pathways but also many other targets, and this could be an issue when proposing a therapeutic approach for a chronic progressive disease. Nevertheless, TFEB is a non-canonical substrate of mTOR and can be activated by inhibitors that impact Rags pathways but not on canonical mTOR substrate, such as the ribosomal protein S6 kinase (S6K). For example, in a recently published paper, the mTOR inhibitor fluoxetine was identified as a possible corrector of neurodegeneration in MPS-IIIA via TFEB activation in a Rag-dependent manner [153]. This suggests that careful evaluation of mTOR inhibitors should be performed before moving them towards tests in pre-clinical models for neurodegenerative diseases or to clinical trials. Or, even better, specific therapeutic strategies targeting TFEB should be identified and tested.

Another interesting aspect to evaluate is the fact that research is mainly focused on TFEB among all MiTF/TFE family members, but even though MiTF/TFE transcription factors display some functional overlap, it remains to be established to which extent they have common functions, whether they are complementary or differ, and which factors orchestrate their interplay. Therefore, despite the promising perspective to fight neurodegenerative diseases and LSDs by enhancing autophagy/lysosomal biogenesis via TFEB modulation, a better understanding of the factors that regulate TFEB activity as well as the interplay between TFEB and the MiTF/TFE transcription factors is strongly required. This would ensure a safe development of targeted therapies for the treatment of these diseases. In fact, enhancing autophagy and lysosomal activity may be beneficial for the treatment of neurodegenerative diseases and LSD but could have adverse effects. For example, it is quite well established that altered regulation of MiTF/TFE proteins can be linked to cancer development. MITF gene amplification was found in 20% of melanomas. Translocations and rearrangements of TFE3 and TFEB are associated with a rare subtype of kidney cancer termed translocation-renal cell carcinoma (tRCC) and alveolar soft part sarcomas (ASPS), a rare lung cancer variant [154]. A recent study reports that TFEC is expressed at higher levels in ovarian cancer tissues, compared to normal tissues, and correlates with malignant progression and
| Name compound | Mechanism of action | Effect | Reference |
|---------------|---------------------|--------|-----------|
| 2-Hydroxypropyl-β-cyclodextrin (2-HPβCD) | Nuclear translocation and consequent activation of TFEB upon treatment | Increased clearance of ceroid lipopigment in late infantile neuronal ceroid lipofuscinosis (LINCL) fibroblasts | [132] |
| | | Increased autophagic clearance of aggregated α-syn in H4 cells stably transfected for the expression of α-syn-EmGFP | [133] |
| Aspirin (acetylsalicylic acid) | Upregulation of TFEB and increased lysosomal biogenesis via PPARα | Enhanced uptake and degradation of Aβ in primary astrocytes. Reduced intraneuronal Aβ accumulation. Decreased amyloid plaque pathology in 5XFAD mice | [134] |
| | | Promoted clearance of ceroid lipopigment in fibroblasts derived from a patient with late infantile neuronal ceroid lipofuscinosis (LINCL) | [135] |
| Cerium oxide nanoparticles (nanoceria) coated with N-acetylglucosamine, polyethylene glycol, and polyvinylpyrrolidone | Nuclear translocation and consequent activation of TFEB upon treatment | Promoted lysosomal activity in APP/PS1 mice and Aβ25-35-exposed SHSY5Y cells. Improved spatial memory and attenuated neuron damage in APP/PS1 mice | [136] |
| Chlorogenic acid (CGA) | Upregulation of cathepsin D, protein expression induced by the mTOR/TFEB signaling pathway | Promoted lysosomal activity in APP/PS1 mice and Aβ25-35-exposed SHSY5Y cells. Improved spatial memory and attenuated neuron damage in APP/PS1 mice | [137] |
| Cinnamic acid | Upregulation of TFEB via PPARα | Enhanced lysosomal biogenesis in mouse primary brain cells. Decreased amyloid plaque pathology and improved memory in 5XFAD mice | [138] |
| Curcumin analog C1 | Activation of TFEB and promotion of autophagy and lysosome biogenesis in a mTOR-independent manner | Reduced APP, CTF-β/α, β-amyloid peptides, and Tau aggregates accompanied by improved synaptic and cognitive function in mouse models of beta-amyloidosis, tauopathy, and combined amyloidosis-tauopathy | [139] |
| Curcumin derivative (E4) | Activation of TFEB by AKT-MTORC1 inhibition and promotion of autophagy and lysosome biogenesis | Decreased level of overexpressed α-syn in In Neuro2a (N2a) cells transfected with A53T α-syn and reduced cell death in PC12 cells treated with MPP⁺ | [140] |
| Dynasore | Blocking of mTORC1 activity by repressing the lysosomal localization of mTOR, which induces nuclear translocation of TFE3 and TFE6 | Enhanced autophagy promotes the clearance of protein aggregates formed by mutant huntingtin | [141] |
| Fisetin (3,7,3′,4′-tetrahydroxyflavone) | Activation of TFEB via mTORC1 inhibition | Decreased level of phosphorylated tau in cortical cells or primary neurons | [142] |
| Flubendazole | Induced TFEB nuclear translocation via mTOR deactivation caused by disruption of dynamic microtubules | Reduction of p-tau in N2a cells | [143] |
| Genistein (5,7-dihydroxy-3 (4-hydroxyphenyl)-4H-1 benzopyran-4-one) | Impairment of glycosaminoglycans (GAGs) synthesis and enhancement of their degradation. It also alters the expression of genes involved in lysosomal metabolism via TFEB nuclear translocation | Genistein might have beneficial effects for the treatment of lysosomal storage disorders such as mucopolysaccharidoses caused by mutations leading to impaired degradation of GAGs | [144] |
| GSK3 inhibitor VIII | Activation of TFEB by GSK3 inhibition | Lysosomal clearance of APP in N2a cells stably transfected with the APP-695 Swedish mutation and of its CTF in CHO cells inducibly expressing the APP-CTF | [145] |
| Name compound                  | Mechanism of action                                                                 | Effect                                                                                                                                                                                                 | Reference |
|-------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Gypenoside XVII (GP-17)       | TFEB activation by releasing TFEB from TFEB/14–3-3 complexes                         | Elimination of AβPP, Aβ40, and Aβ42 in APP695swe cells. Formation of Aβ plaques in the hippocampus and cortex of APP/PS1 mice is prevented and spatial learning and memory are restored | [146]     |
| Ibudilast                     | Enhanced TFEB nuclear translocation by inhibiting mTORC1 activity                   | Increased clearance of disease-linked TAR DNA binding protein (TDP-43) and superoxide dismutase 1 (SOD1) protein aggregates in cells transfected with corresponding mutated forms. Protective effect of TDP-43-induced cytotoxicity in motor neuron-like NSC-34 cells | [147]     |
| Ouabain                       | Activation of TFEB via inhibition of the mTOR pathway                              | Reduced accumulation of p-tau in GFP-TauP301S-overexpressing SH-SY5Y, in primary cortical neurons, in a Drosophila melanogaster tau model and in TauP301L mice. Ameliorated memory defects in in TauP301L mice       | [148]     |
| Pseudoginsenoside-F11 (PF11)  | Induced TFEB nuclear translocation by suppressing mTORC1 activity                   | Increased degradation of oligomeric Aβ in cultured microglia                                                                                                                                              | [149]     |
| Threalose                     | Inhibition of Akt which in turn activates TFEB independently of mTORC1             | Enhanced clearance of lipopigments and reduced neuropathology in a mouse model of Batten disease. Promoted cellular clearance in fibroblast derived from patient with Batten disease                                           | [150]     |
|                              | Rapid enlargement and transient permeabilization of lysosomes leading to calcineurin activation and subsequent TFEB dephosphorylation and nuclear translocation | Promoted clearance in mouse motoneuron-like hybrid cell line (NSC34) of polyQ-containing androgen receptor, TDP-43, and SOD1 mutated forms                                                                 | [151]     |
poor survival for ovarian cancer patients [155]. Moreover, increased TFEB expression is found in glioblastoma patients and contributes to the glioblastoma resistance to chemotherapy. In fact, drug-mediated inhibition of TFEB expression and oligomerization can enhance glioblastoma cell sensitivity to conventional chemotherapeutic agents [156]. All these observations deserve attention, and therefore a comprehensive characterization of the potential deleterious effects of uncontrolled expression of MiTF/TFE3 factors in vivo. We must consider that alterations to the regulation of MiTF/TFE transcription factors are accompanied by the hyperactivation of other key pathways involved in tumorigenesis and cell proliferation [131, 157]. Therefore, we can expect that controlled pharmacological activation of MiTF/TFE proteins will recapitulate the pathological features of MiTF/TFE-driven cancer.

Overall, given that (1) autophagy and TFEB translocation may already be overactivated in certain neurodegenerative diseases or LSDs to compensate for the defective mechanisms already in place and to remove undigested cellular waste, (2) uncontrolled boosting of autophagy may impact the overall cellular homeostasis, and (3) overactivation of TFEB may trigger downstream pathways other than ALP, the final goal of novel therapeutic strategies would be to restore the homeostatic regulation of these processes and the homeostasis of the MiTF/TFE transcription factors, rather than promoting their uncontrolled activation.

What Can We Learn from the Study of MiTF/TFE Family in Non-mammalian Organisms?

Non-mammalian model organisms can have a role in the implementation of our current knowledge on MiTF/TFE transcription factors. All MiTF/TFE family members are conserved in vertebrates, while invertebrates have only a single MiTF orthologue (Fig. 4). Considering the high degree of conservation of the entire autophagic machinery, also organisms that are phylogenetically distant from humans can be exploited for the in vivo characterization of these proteins and these pathways (Fig. 5). These animal models can give information on unclear or uncharacterized aspects that would otherwise be difficult to study in humans or mice. Every animal model is characterized by specific features that provide unique advantageous tools to understand in detail the activity and the complex mechanisms of regulation of MiTF/TFE transcription factors. For example, the transparent body of worms and zebrafish larvae allows exploiting these organisms for the in vivo visualization of these proteins to study their intracellular localization and movements across the cell compartments. The complex behavioral features of fruit flies may be of great interest for the evaluation of phenotypes associated to the modulation of MiTF/TFE transcription factors activity to study short/long-term collateral effects (if any) and to perform rescue experiments. In addition, exploiting invertebrate models may allow the analysis of a high number of individuals that could be highly valuable for the screening of drugs or compounds that modulate MiTF/TFE protein activity. These simpler organisms are usually easier to be genetically manipulated; they allow the possibility to generate animals carrying specific mutations or useful constructs for imaging that help the understanding of the role of these transcription factors. These are only few of the reasons why the use of non-mammal animal models in the research may be worthwhile. The choice for the proper organism should be based on the questions the researchers want to assess. Moreover, the exploitation of different models to answer the same biological question may be crucial to get more informative results, and to increase the soundness of the data and the value of the research.

The following paragraphs will describe the current knowledge about MiTF/TFE transcription factor in model organisms other than rodents, by focusing, when possible, on phylogenetic and mechanistic aspects.

Caenorhabditis elegans

The nematode Caenorhabditis elegans is one of the most used model organisms in biology [158]. Several features of
C. elegans make this animal an advantageous model for biology research. First, it is relatively easy to produce transgenic worm lines that overexpress or lack a gene of interest; it is possible to limit the expression of genes to specific cell types and to study protein activity by tagging them with fluorescent probes. Several studies characterized TFEB activity in worm lines lacking the C. elegans TFEB orthologue gene or studied its subcellular localization by expressing the protein tagged with a GFP [159–161]. It is also possible to assess autophagic activity in worms through the expression of specific construct for the analysis of autophagic flux [162].

Second, the small size of this organism and the possibility of analyzing many individuals allow performing large-scale screens. While its nervous system is relatively simple compared to that of other model organisms, several cellular and molecular pathways are well conserved. Moreover, about 70% of genes linked to human diseases have orthologues in worm genome. For these reasons, this animal is considered a good model for the neurodegeneration research [163].

A functional orthologue gene of human TFEB has been found in C. elegans, called hlh-30, which shares high homology to the human protein in both the DNA-binding and activation domain. The protein HLH-30 is the only member of the MiTF/TFE family, which is present in C. elegans and, like the human orthologue, it modulates autophagy and lysosomal function [164].

Interestingly, also the regulation of HLH-30 protein seems to be conserved, with the worm transcription factor that is modulated via post-transcriptional modifications, in a similar manner to its mammalian orthologues. In fact, the silencing of mTOR has been demonstrated to enhance the HLH-30 nuclear localization and to increase the expression of several genes that are the Nematoda orthologues of the human TFEB targets, including autophagy-related genes [159].

Moreover, the C. elegans HLH-30 downstream genes are characterized by the presence in their promoter region of an E-box sequence that overlaps with that of the CLEAR motif, further confirming the conservation between the HLH-30 and its mammalian orthologues. This region in C. elegans is crucial for the specificity of HLH-30 binding to DNA [159, 164].

**Drosophila melanogaster**

*Drosophila melanogaster*, commonly known as fruit fly, is one of the most used model organism in biology and in biomedical research [165]. In particular, it is a powerful organism to model the physiology and pathology of the brain, mainly because it can be genetically manipulated and because many genes and molecular pathways are conserved between humans and flies [166]. Synapse formation, membrane trafficking, and neuronal communication are a few examples of processes that are similar in flies and in more complex organisms [167]. In addition, D. melanogaster brain is developed enough to promote elaborated behavioral features, but it is still small enough and relatively simple, thus allowing the detailed analysis of its structure and functions.

The genome of *Drosophila melanogaster* contains a single Mitf, which shares several features and functions with its mammalian orthologues, providing evidence of high
conservation of this gene throughout the evolution. Interestingly, Mitf is not phylogenetically closer to the mammalian MITF than to TFEB, suggesting that the ancestral gene underwent multiple duplication events after the separation of the invertebrate to the vertebrate lineages [22]. The presence of only one gene in flies and the high degree of conservation with the four mammalian MITF/TFE family members make the fruit fly an advantageous organism to study its physiological role in a simplified model.

Like the mammalian transcription factors of the MiTF/TFE family, Drosophila melanogaster Mitf can regulate gene expression through the binding to the DNA. The conservation of the DNA binding region in the protein suggests that the fly transcription factor recognizes the same target domain of its mammalian orthologues. This DNA region is represented by the already described CLEAR motif, which is crucial for the binding specificity to the DNA. The conservation of the CLEAR motif in Drosophila has been confirmed in the promoter region of genes whose expression resulted significantly upregulated by overexpression of Mitf protein [22, 23, 168].

In fruit flies, Mitf has been shown to play a role in the transcriptional regulation of lysosomal biogenesis, in autophagy, and in the catabolism of lipids, further supporting a functional similarity with its mammalian orthologues TFE and TFE3 [22]. Moreover, a reduction in Mitf activity leads to an impairment of autophagic flux with accumulation of autophagy substrates, such as polyubiquitinated proteins and dysfunctional mitochondria. Mitf determines the cellular response to starvation, which is well known to activate autophagy. Upon starvation, Mitf upregulates lysosomal biogenesis and several autophagy-related genes, especially those involved in the formation and maturation of autophagosomes [22, 168]. In this frame, mTOR has been shown to negatively modulate Mitf activity, and also in flies the treatment with Torin1, a specific inhibitor of mTOR, is able to induce the activation and the nuclear translocation of Mitf [22]. Interestingly, the similarity goes further at the structural level. It is well established that Ser142 and Ser211 are the residues of human TFE that are phosphorylated by mTORC1, inhibiting TFEB activity. Corresponding serine residues, Ser240 and Ser346, respectively, are also present in the fly orthologue.

Besides its role in autophagy, D. melanogaster Mitf is involved in eye development, a function that is performed by MITF in mammals. More specifically, Mitf is expressed in the eye-antennal imaginal disc during the second and third larval stages of the fruit fly and the expression of a dominant negative Mitf mutant impairs the correct development of the eye [168].

Overall, the data concerning D. melanogaster Mitf suggest that the protein function is highly conserved and that the distinct roles described for the mammalian proteins might coexist in the unique fly orthologue. This makes D. melanogaster a perfect asset to test drugs able to modulate Mitf activity in a cost-effective but valuable model organism, and before moving towards more complex organisms.

The presence of a unique Mitf orthologue both in C. elegans and D. melanogaster points at them as good organisms to study this protein in a simple model in which the presence of only one protein of the MiTF/TFE family removes the potential uncertainty derived from the redundancy. On the other side, this hinders the possibility of studying the interplay among the different MiTF/TFE family members, which may be crucial for the understanding of the molecular mechanisms that regulate the downstream pathways of these transcription factors. Under these circumstances, it may be worthwhile to exploit more complex model organisms.

**Danio rerio**

Among the vertebrates, Danio rerio, commonly known as zebrafish, is one of the most studied model organisms [169]. As a vertebrate, it is evolutionary closer to humans than invertebrate models and present several advantages over other vertebrate organisms, such as the high rate of fecundity, the external fertilization, and the fact that in the first developmental stages the organism is transparent and allows to visualize internal structures and tissues by in vivo imaging [169]. Furthermore, in the neurodegenerative field, zebrafish is largely used because its brain organization shows high similarities with human brain, with specific brain regions of zebrafish that are highly conserved and can be related to mammal brain [169]. Genomic analyses have demonstrated that zebrafish and other teleost species underwent an event of gene duplication that may have occurred at least 100 million years ago and determined the presence of approximately 20–30% of an extra complement of genes in their genome. This is probably the reason for the presence in zebrafish of six genes belonging to the MiTF/TFE family. Besides tfeb and tfec, it also presents two orthologues of the mammalian MITF (Mitfa and Mitfb) and two orthologues of the mammalian TFE3 (Tfe3a and Tfe3b). Since often-duplicated genes are characterized by tissue-specific expression or by the activation in precise developmental stages, the research may take advantage of the duplication of the genome to study in detail the role of the protein of interest in different cell types or at different times. This feature seems to apply to the proteins Mitfa and Mitfb that share high homology in their sequence, with the differences mostly located in their amino and carboxy termini. Interestingly, Mitfa seems to correspond to the mammal melanocytic “M” isoform, whereas Mitfb shares the highest homology with the mammalian “A” isoform. Moreover, the zebrafish Mitf genes have restricted expression profiles that approximate the localized expression of their mammalian orthologue [170].
Regarding the role of tfeb, the major functions of this transcription factor are conserved. In zebrafish, as in mammals, it controls the network of genes involved in lysosomal biogenesis and autophagy. Moreover, similarly to its mammalian orthologue, tfeb activation is regulated by mTORC1 and Rag-GTPases. Like in mouse, tfeb can repress in zebrafish the process of myelination during the development of the CNS. More specifically, tfeb has been shown to upregulate several of its target genes in the oligodentrocytes, leading the authors to speculate that the activity of tfeb may impair the trafficking of endo-lysosomal organelles to the membrane and the synthesis of lipids, two crucial processes for the membranous myelin sheath. As the activity of tfeb might disrupt the process of myelination, it appears to be specifically repressed by mTORC1 and other inhibitory kinases during myelination [171]. This function of tfeb, although poorly investigated, may be crucial for neuronal physiology and could be very relevant in the context of neurodegeneration. Thus, it would be very worthwhile to investigate whether this activity of tfeb is conserved in other models and in mammal and understand how it impacts brain homeostasis.

In comparison to Mitf and Tfeb, which are the most studied and characterized genes among the members of the MiTF/TFE family in zebrafish, much less is known about the two tfe3 genes. Tfe3a has been described to encode a protein of 539 amino acids that shares about 50% of homology with the human TFE3. As observed for the other members of the family, the most conserved region of Tfe3a is the helix-loop-helix/leucine zipper region. Like the human orthologue that has been shown to regulate immunoglobulin expression, tfe3a in zebrafish is present in the ventral mesoderm, which gives origin to blood cells, suggesting a possible functional conservation of this gene between different organisms [170].

Tfe3 genes seem to be co-expressed with mitf genes in several tissues. In fibroblast cell cultures, the two genes share comparable activities, suggesting a possible redundant role. Nevertheless, in mitf knockout zebrafish models, Tfe3 has been demonstrated to support very inefficiently the role of Mitf [170], indicating that, in vivo, the different members of the MiTF/TFE family exert different roles being only partially redundant at the functional level [170].

In zebrafish, Tfec is the less characterized member of the Mitf family. The protein has been proposed to be a key regulator of zebrafish embryonic hematopoiesis, the process responsible for the formation of all types of blood cells from hematopoietic stem cells (HSCs) [172]. How and if this has a role in the nervous system, at least in this model, remain to be elucidated.

Other Organisms

Besides the most common and studied animal models, orthologues of the MiTF/TFE family of transcription factors have been found in other organisms. Even though these organisms are considered irrelevant in biomedical research, they may inspire the study of alternative pathways or regulatory mechanisms in more conventional models.

Among the organisms in which an orthologue of Mitf has been described, *Paracentrotus lividus* is a sea urchin that has an important phylogenetic position because it belongs to the phylum of Deuterostome, like vertebrates. Given the conservation of many important molecular pathways, the study of Mitf in *Paracentrotus lividus* may provide interesting information about the role and the signalling pathways of this transcription factor.

PL-Mitf protein is characterized by all the functional domains of the MiTF/TFE protein family, including the DNA binding domain and the bHLHzip domain. However, in this domain, only four out of five canonical leucine residues are observed and two of them are conservative substitutions. This imperfect leucine zipper has also been found in *D. melanogaster*. Among the phosphorylation sites of PL-Mitf, some of them are conserved, further providing evidence of a possible common pattern of regulation of this protein. Mitf has been found in the pigment cells of the sea urchin, coherently to the role of the mammalian orthologue in melanocyte. Moreover, while MITF in mammals is an important transcription factor in osteoclasts, PL-Mitf is expressed in the presumptive mesenchymal cells (PMC) that are progenitor cells of the sea urchin larval skeleton. Some studies have highlighted similar features between PMC and osteoclasts: both cell types are involved in the skeleton development, have migratory capability, and can form multinucleated syncytia. These data may suggest an unknown role of Pl-Mitf in the skeletogenesis of sea urchin [173].

Given the well-established role of MITF in the pigment cells, another group of organisms may be interesting to study the function of this gene. In fact, molluscs are characterized by a vast pattern of colors, mainly in shells. The yesso scallop, *Patinopecten yessoensis*, is a large group of molluscs that live in the bottom of the northwestern Pacific Ocean. The genome and the transcriptome of Yesso scallop have been widely studied and a unique orthologue of MITF (Py-Mitf) has been found in this organism. It shares less homology with vertebrate organisms, highlighting the fact that the evolution of this gene is consistent with the species taxonomy. This gene is formed by eight exons, in contrast with the mammalian MITF that is organized into nine exons. As observed in other organisms, the most conserved region of the Py-Mitf gene is the bHLH-LZ motif [174]. Shell color is determined in these organisms by the presence of biological pigments, like melanin, carotenoids, and tetrapyrrroles.
but the mechanisms that underline these features are poorly understood. Melanin biosynthesis is initiated with tyrosine oxidation and tyrosine in mammals is known to be positively regulated by MITF, which has been reported to be a master regulator of melanogenesis. Interestingly, in yesso scallop, the expression of Py-Mitf has been shown to correlate with the shell color, further confirming the high degree of conservation of these genes among different organisms. Moreover, the higher level of Py-Mitf mRNA was detected in the mantel, the organ involved in shell color formation. Notably, even though the two valves of the same organism usually are characterized by different colors, no difference in the level of Py-Mitf expression was detected between the right and the left mantels. This result may indicate that Py-Mitf is strictly regulated, and a different regulation process may modulate the shell color in the same animal. Reports about Mitf involvement in autophagic regulation in these organisms are lacking; however, given the high conservation of autophagy throughout evolution and the similarities between mammalian MITF and the invertebrate orthologue, it is highly probable that this transcription factor may control ALP also in these invertebrates.

The high degree of conservation of the MiTF/TFE transcription factors across evolution should be exploited for the research of modulators of these proteins. The possibility of being inspired not only of many classical model organisms but also of several non-canonical animal models may be very relevant to implement the in vivo characterization of these factors and represent very good tools to analyze in detail different aspects of the MiTF/TFE transcription factors that are still unclear.

Conclusions and Future Directions

Autophagy dysfunction has been described in different neurodegenerative disorders. All the members of the MiTF/TFE family have been shown to participate in the regulation of autophagy, and in other processes that are relevant for brain physiology. However, many aspects related to the basic biology of these transcription factors remain unknown. For instance, MiTF/TFE transcription factors can form both homodimers and heterodimers with any other family member, but little is known about the functional difference between homodimers and heterodimers. Furthermore, with the exception of TFE3, all family members have alternative transcripts which display different tissue distribution patterns, and it remains to be determined the functional importance of these transcripts and whether this may result in cell-type-specific regulatory networks. As MiTF/TFE transcription factors are conserved across species, comparing MiTF/TFE protein function and regulation in different and appropriate animal models may provide a better understanding of their physiological function in the CNS. Moreover, the use of different model organisms may provide a valuable tool for understanding the roles of these transcription factors common to all forms of eukaryotic life and how their impairment may be implicated in neurodegeneration. Thus, it appears fundamental to decipher the factors that are responsible for MiTF/TFE transcription factor regulation and their interplay. This would allow modulating autophagy and other relevant pathways for brain cells via MiTF/TFE family members in a tissue/cell-specific manner thus avoiding negative side effects.

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