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Transcription factor EB controls both motogenic and mitogenic cell activities

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Transcription factor EB (TFEB) belongs to the microphthalmia family of bHLH-leucine zipper transcription factors and was first identified as an oncogene in a subset of renal cell carcinomas. In addition to exhibiting oncogenic activity, TFEB coordinates genetic programs connected with the cellular response to stress conditions, including roles in lysosome biogenesis, autophagy, and modulation of metabolism. As is the case for other transcription factors, the activities of TFEB are not limited to a specific cellular condition such as the response to stress, and recent findings indicate that TFEB has more widespread functions. Here, we review the emerging roles of TFEB in regulating cellular proliferation and motility. The well-established and emerging roles of TFEB suggest that this protein serves as a hub of signaling networks involved in many non-communicable diseases, such as cancer, ischaemic diseases and immune disorders, drug resistance mechanisms, and tissue generation.

Keywords: autophagy; cell motility; cell-cycle; TFEB

Transcription factor EB, which was cloned in 1990 as a transcription factor belonging to the microphthalmia (MiT) gene family of transcription factors, contains a bHLH and a leucine zipper motif and an acidic and proline-rich region [1,2]. It binds E-box (CAYGTG) sequences in gene promoter regions [1–4]. A new promoter motif (GTCACGTGAC overlapping the E-box sequence) has been identified, named the Coordinated Lysosomal Expression and Regulation Region, and characterized to be instrumental in regulating the transcription of genes involved in lysosome functions [4–6]. The TFEB–DNA interaction requires homodimerization or heterodimerization with TFE3 or MITF, each of which is also a member of the MiT family [2,7,8], but the biological meaning of this molecular feature is unknown.

In addition to being a key molecule orchestrating autophagy and a potential therapeutic target in lysosome storage diseases [9,10] and in pathological conditions dependent on autophagy dysfunction [11], recent data clearly indicate that TFEB has wider transcriptional competencies and activities, including roles in metabolism, immunity, angiogenesis, and inflammation [11–13]. Here, we briefly summarize the cellular mechanisms controlling TFEB activation and review emerging findings suggesting that TFEB might play crucial roles in cell motility and proliferation independent of its activities in the control of autophagic flux.

Cellular control of TFEB nuclear-cytosolic trafficking

The control of TFEB activity is mainly mediated by posttranslational modifications, which regulate its nuclear localization. Currently, the most important

Abbreviations
AMPK, AMP-activated kinase; CDK, cyclin-dependent kinase; EMT, epithelial-mesenchymal transition; ERK, extracellular-signal-regulated kinase; GSK, glycogen synthase kinase; HLH, helix–loop–helix; MAP3K3, mitogen-activated protein kinase 3; MiT, microphtalmia; PPA2, protein phosphatase 2A; TFEB, transcription factor EB.

regulatory mechanism relies on phosphorylation/phosphorylation events [6,14–22] (Fig. 1), but other mechanisms, such as acetylation/deacetylation [23–25], sumoylation [26], and interaction with other cytosolic proteins, such as the GTPase IRGM and the Atg8 protein [27], refine TFEB nuclear entry.

The general mechanism retaining TFEB in the cytosol and blocking its nuclear translocation is the phosphorylation of some specific serine residues (Table 1). Phosphorylated TFEB is sequestered in the cytosol through its binding to the 14-3-3 chaperone [6,14,15,17,28] and is involved in degradation mediated by the ubiquitin–proteasome pathway [29].

Transcription factor EB phosphorylation by the serine/threonine protein kinase mammalian target of rapamycin complex 1 (mTORC1) represents the most important mechanism occurring at the lysosomal surface, connecting TFEB activation to the nutritional condition of the cell [14,15,17,19]. When cells have sufficient amounts of amino acids, the Rag GTPase system mediates the localization of both mTORC1 and TFEB on the lysosomal cytosolic surface [15,30–33]. In the absence of amino acids, the Rag GTPase system is inactivated, and mTORC1 remains in the cytosol in an inactive state. mTORC1 phosphorylates TFEB at residues S122, S142, and S211. S211 phosphorylation is the key mechanism moving TFEB from the lysosome to the cytosol [6,14,15,17,28]. Phosphorylation of S142 and S211 is instrumental in TFEB proteolysis [29], while phosphorylated S122 enhances the effect of phosphorylated S211 [17].

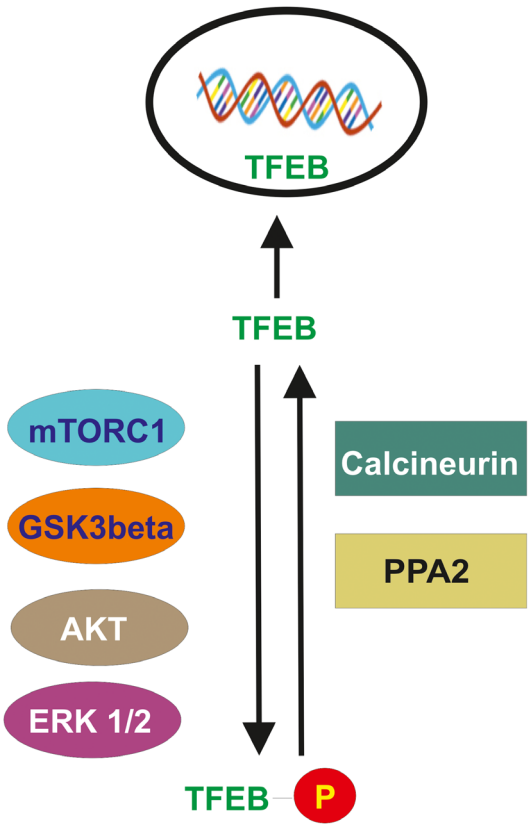

Fig. 1. Schematic representation of the phosphorylation- and dephosphorylation-based mechanism on regulating TFEB translocation into nucleus. Phosphorylated TFEB is sequestered in the cytosol. Upon dephosphorylation, it can translocate into the nucleus, where it fulfills transcriptional activity (see text and Table 1 for further details).

The opposite effect on TFEB activity is exerted by 5′ AMP-activated protein kinase (AMPK), the sensor of low-energy status. Phosphorylation of S466, S467, and S469 by AMPK is essential for the transcriptional activity of TFEB [34]. Furthermore, AMPK might indirectly activate TFEB by inhibiting mTORC1 [35].

Transcription factor EB is also recognized and phosphorylated by other serine/threonine kinases, which fine-tune the mechanisms supporting TFEB degradation, nuclear translocation in stressed conditions, or TFEB export from the nucleus when transcriptional activity needs to be blocked (Table 1) [6,14–19,21,36–38].

The behavior of phosphorylated TFEB is clearly controlled by dephosphorylation mechanisms. When activated lysosomes release Ca^{++} through the calcium channel mucolipin 1, the calcium- and calmodulin-dependent serine/threonine protein phosphatase calcineurin binds TFEB and dephosphorylates residues S211 and S142, thus promoting its nuclear translocation [20]. This activity is also promoted by the protein phosphatase 2A (PPA2) [22,39], which dephosphorylates TFEB at residues S109, S114, S122, and S211.

Mitogenic and motogenic functions of TFEB

Proliferating or moving cells have to integrate many subcellular processes (e.g., cell growth, cell division, cytoskeleton, and microtubule dynamics) with metabolic pathways fuelling either biomass or ATP generation. Lysosomes are not just lytic organelles; they also organize the connection between nutrient availability and cellular metabolic needs to support biological processes, including proliferation and migration [40,41]. Transcription factor EB regulates lysosome-mediated autophagic flux and lysosome biogenesis, which are known to be involved in cell growth and motility [42]. Therefore, TFEB may indirectly regulate these cellular functions by controlling autophagy, but there is accumulating evidence indicating that TFEB regulates

Table 1. Effects of serine/threonine protein kinases on TFEB localization [6,14–19,21,36–38]. Abbreviations not present in the text: CytR, cytosolic retention; ERK, extracellular-signal-regulated kinase; GSK, glycogen synthase kinase; MAPK3, mitogen-activated protein kinase 3; NucE, nuclear export; NucT, nuclear translocation; PKC, protein kinase C; TFEB stabilization, PKCβ-dependent phosphorylation protects TFEB from degradation; X, No effect.

	Serine residue													
Kinase	3	122	134	138	142	211	461	462	463	466	467	468	469
mTORC1	X	Increasing S211 phosphorylation effect	X	X	CytR NucE	CytR	X	NucT	NucT	NucT	NucT	X	NucT
GSK3β	X	X	CytR	CytR	X	X	X	X	X	X	X	X	X
ERK1/2	X	X	X	X	CytR NucE	X	X	X	X	X	X	X	XX
PKCβ	X	X	X	X	X	X	TFEB stabilization	TFEB stabilization	X	TFEB stabilization	X	TFEB stabilization	X
Akt3	X	X	X	X	X		X	X	X	X	CytR	X	X
CDK4	X	X	X	X	NucE	X	X	X	X	X	X	X	X
AMPK	X	X	X	X	X	X	X	X	X	X	NucT	NucT	NucT
MAP3K3	Counteracting S122 phosphorylation effect	X	X	X	X	X	X	X	X	X	X	X	X

transcriptional programs specifically addressing cell proliferation and migration (Fig. 2).

Role in cell proliferation

A first indirect indication of the role of TFEB in cell proliferation was provided by a transcriptome analysis in a macrophage cell line lacking TFEB [43], which showed a marked downmodulation of genes involved in the cell cycle. This observation was later confirmed in endothelial cells [3]. However, this cellular model demonstrated that TFEB binds the cyclin-dependent kinase 4 (CDK4) promoter, and in the absence of TFEB, the CDK4 transcriptional rate and *in vitro* cell proliferation were reduced [3]. Interestingly, endothelial TFEB-null mice were characterized by reduced

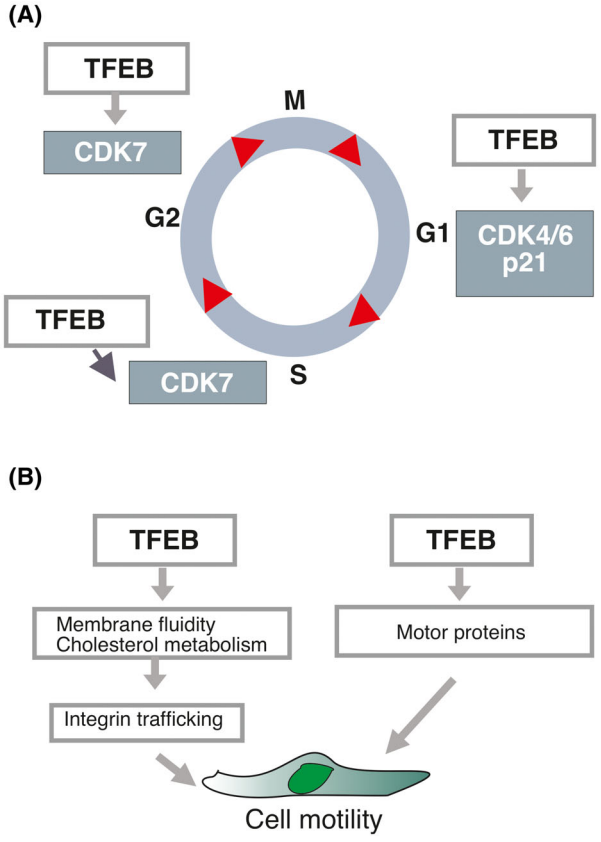

Fig. 2. Effects of TFEB on the cell cycle and cell migration. (A) TFEB promotes the transcription of CDK4 and CDK7: the former activity is restricted to the G1/S phase, the latter contributes to the regulation of the G2/M and S/G2 transitions. Furthermore, TFEB upregulates p21 (*CDKN1A) expression*, which inhibits the activity of the cyclin-CDK1, cyclin-CDK2, cyclin-CDK4, cyclin-CDK6 complexes. (B) TFEB regulates cell motility by an indirect effect on integrin trafficking mediated by its activity on lipid metabolism and by regulating the transcription of myosin motor proteins.

proliferation leading to defects in embryo angiogenesis [3]. In TFEB-silenced endothelial cells, the cell cycle was blocked at the level of the G1–S cycle transition, as also reported in hepatoblasts [44]. The reduced activity of CDK4 resulted in a lack of retinoblastoma protein phosphorylation, which interferes with the nuclear translocation of E2F, a key transcription factor that regulates the expression of genes involved in S-phase. A similar observation was made in HeLa cells: TFEB deletion resulted in reduced Rb phosphorylation, and a TFEBS142A active mutant increased the expression of CDK4 and CDK7 [43]. Interestingly, CDK4 itself and CDK6 phosphorylate TFEB on S142 in the nucleus, thereby favoring its nuclear export. Consequently, inhibition of CDK4/6 reduces the nucleocytoplasmic shuttling of TFEB and enhances its activation [38]. Collectively, these results indicate the integrating role of TFEB between the cell cycle and lysosome functions (Fig. 2A).

In addition to cyclin-dependent kinases, TFEB directly controls *CDKN1A* (p21 cyclin kinase inhibitor) by interacting with its promoter [45], and it has been reported that the genotoxic effect of doxorubicin results in TFEB activation, which contributes to cell cycle arrest by increasing the expression of *CDKN1A* [45].

A further interaction between the cell cycle and TFEB is mediated by CDK inhibitor 1B (p27). This protein can localize to the cytosolic surface of lysosomes and block mTORC1 activation, causing TFEB to translocate into the nucleus to exert its transcriptional function [46].

Role in cell motility

The data suggesting the role of TFEB in controlling cell movement are in their infancy but might provide interesting insights for deciphering the complexity of this process and its connection with metabolism. In endometrial, lung, pancreatic and prostate cancer cells, and in endothelial cells, it has been recently reported that overexpression and deletion of TFEB enhance and reduce cell motility, respectively [47–51]. These observations do not clearly tackle whether the effect of TFEB on migratory phenotype should be dependent on or independent of autophagy [52]. In endometrial cells, the effect of motility is likely mediated by the influence of TFEB on lipid metabolism and the subsequent changes in membrane fluidity contributing to the mesenchymal transition of these cancer cells [47]. According to these data, TFEB silencing in pancreatic cancer cell lines reduces motility induced by transforming growth factor β, promoting integrin α5β1 endocytosis and focal adhesion disassembly [50]. Similarly, in endothelial cells, TFEB connects mechano-contractive and metabolic signalling pathways that control integrin-mediated cell adhesion to the extracellular matrix. It has been reported that in the absence of TFEB, cell adhesion to the extracellular matrix is increased with defects in the turnover of focal adhesions. In addition, TFEB-silenced endothelial cells show defects in endogenous cholesterol synthesis and are characterized by inhibition of the cholesterol-dependent clustering of plasma membrane caveolin-1, the association of β1 integrins with caveolae and internalization of the caveolae [53] (Fig. 2B).

Knockdown of the microRNA let-7 in migrating neuroblasts prevents radial migration, and this effect is blunted by TFEB overexpression [54]. The activation of TFEB has also been demonstrated to restore the migration of neural stem cells impaired by the deletion of tuberous sclerosis complex 1 (*TSC1*) [55]. Finally, it has been reported that AdipoRon, a small molecule that activates the adiponectin receptor, inhibits vascular smooth muscle cell migration and *in vitro* angiogenic sprouting. These effects are abrogated by deletion of TFEB, supporting its role in cell migration [56].

Mechanistically, in endothelial cells, TFEB binds to the promoter and enhances the transcription of myosin 1c (MYO1C) [3], which contributes to G-actin delivery to the leading edge and optimal cell migration [57]. Furthermore, TFEB promotes the activation of myosin light-chain kinase, which is responsible for phosphorylation of the motor protein myosin II at the dendritic cell rear, triggering directional motility [58,59].

The role of TFEB in controlling cell motility has also been supported by recent observations [60] that oestradiol analogues block the Ca^{++} channel mucolipin 1 and consequently block calcineurin-mediated TFEB nuclear translocation [20]. Interestingly, these molecules inhibit breast cancer cell invasion and migration by a mechanism strictly dependent on the inhibition of mucolipin 1 on the surface of lysosomes [60]. The relationship between mucolipin 1-mediated mechanisms and cell migration is further suggested by results showing that the small GTPase Rab7b interacts with mucolipin1, allowing the localization of the motor protein myosin II at the surface of lysosomes accumulated at the migrating cell rear [59].

Furthermore, a role of TFEB in controlling cell motility activity can be inferred from emerging evidence of the activity of TFEB in epithelial–mesenchymal transition (EMT), a process characterized by the transition of static and polarized epithelial cells to a

motogenic and mesenchymal phenotype [61]. The role of TFEB in establishing the equilibrium between epithelial and mesenchymal phenotypes was discovered in 2005 [62] but has not been studied in depth since. Transcription factor EB overexpression in fibroblasts directly activates the E-cadherin promoter. Transcription factor EB also increases the expression of WNT [62], which regulates both EMT and the inverse process, mesenchymal-epithelial transition [63]. Finally, in gastric cancer, TFEB regulates EMT and cell migration through the Wnt pathway [64].

Conclusions

This short review summarizes new perspectives on the genetic programs regulated by TFEB, envisaging novel functions relevant to many chronic and degenerative diseases, such as cancer, ischaemic diseases, and immune disorders. For many years, transcription factors were considered to be without any significant pharmacological properties of interest. However, recent discoveries on the mechanisms of DNA–protein interactions, post-translational modifications of transcription factors, and their epigenetic control have led to the generation of specific inhibitors, including some for TFEB [11]. Answers to relevant open questions are clearly required to better understand the roles of TFEB in cell motility and proliferation and to consider this molecule a putative and realistic therapeutic target. The most crucial issue is defining the tissue-specific genetic programs regulated by TFEB. While strong overexpression of TFEB is certainly able to promote transcription of genes involved in lysosome functions and autophagy in all tissues, it is relevant to understand the impact of subtle variations in TFEB activation on the control of gene transcription. Elucidation of this crucial issue will support an improved understanding of the biochemical mechanisms regulating the synthesis, degradation, activation, and nuclear import–export of TFEB, as well as the tissue specificity thereof. While it is well established that posttranslational modifications, such as phosphorylation of certain Ser residues, are crucial for preventing nuclear translocation of TFEB, further questions remain. What are the mechanisms mediating TFEB degradation? What are the roles of speficic phosphorylated residues in the nuclear activity of TFEB [12]? In addition to phosphorylation, are there other biologically relevant posttranslational modifications? Furthermore, the cellular stress conditions that lead to TFEB activation need to be understood in more detail. For instance, which molecular sensors connect extracellular cues to TFEB-mediated cellular responses? How do they modify TFEB cellular homeostasis? Finally, TFEB activation is a promising target for the treatment of lysosomal storage diseases [9,10] and pathological conditions involving the aggregation of abnormal proteins [11]. This relies on TFEB's ability to increase autophagic flux and to favor clearance of engulfed molecules. Interpretation of the data showing that mucolipin 1 is associated with TFEB in both the regulation of autophagy [20] and cell migration [58–60] requires understanding of how the motogenic and mitogenic activity of TFEB interferes with therapeutic strategies aimed at increasing the autophagic flux. In summary, TFEB is likely to be a promising therapeutic target, but additional research is needed to firmly establish this fact.

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Author contributions

All authors equally contributed to the preparation of this review. FB wrote the final version.

Data accessibility

Summarized data of this review are available in the quoted papers.

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