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Research Progress of Transcription Factor TFEB

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Abstract: ***Transcription factor TFEB belongs to MIT-TFE subfamily of the bHLHZIP transcription factor family. Currently, the function of transcription factor TFEB has been found to mainly regulate the biogenesis autophagosomes and lysosomes, and play an important role in biological functions including metabolism, angiogenesis, immunity, and inflammation. This paper reviews the structure physiological functions of TFEB, and provides support for further understanding the role of TFEB in disease.***

Keywords: TFEB, Autophagy, Lysosome, Physiological function.

1. Introduction

Transcription factor EB (TFEB) belongs to the basic helix-loop-helix Leucine zipper (HLH-LZ) family members, and the function of transcription factor TFEB has been found to mainly regulate the biogenesis of autophagosomes and lysomes, and plays an irreplaceable role in the occurrence and development of lipid metabolism, sugar metabolism, phagocytosis, neurodegenerative diseases and tumors.

2. Structure and Characteristics of TFEB

TFEB belongs to the MIT-TFE subfamily of the bHLHZIP transcription factor family. The MIT-TF transcription factor family mainly includes four members, including microphthalmia-associated transcription factor (MITF), TFEB, TFE3 and TFEC [1]. Transcription factors of MIT-TFE family are highly conserved in structure, and all include basic helix-loop-helix leucine zipper (bHLHZIP structure, transcription activation domain and Heterodimer or homodimer NDA binding structure, but they all have high variability in the regions outside the conserved structure [2]. TFEB contains 476 amino acid residues, and its structure mainly includes leucine zipper, helix-loop-helix, glutamine-rich and line-rich structural domains. Currently, the function of transcription factor TFEB has been found to mainly regulate the biogenesis of autophagosomes, lysosomes and also play an important role in biological functions including metabolism, angiogenesis, immunity and inflammation. TFEB is the first member of the MiTF/TFE family to found to regulate lysosomal biogenesis. TFEB overexpression in HeLa cells can induce the transcriptional activation of multiple genes of lysosomes, several subunits of V-ATPase, lysosomal membrane proteins and lysosomal hydrolases, and lead to a significant increase in the total number ofysosomes [3]. Whole-genome chromatin immunoprecipitation sequencing (ChIP-seq) analysis found that lysosomal genes were highly enriched when TFEB was overexpressed, and further demonstrated that TFEB could directly bind to the conserved sequence of the CLEAR motif (GTCACGTGAC) [4]. The conserved binding sites were found in the promoters of 96 genes related to lysosomes. TFEB also binds to the promoters of many genes involved in lysosome-related processes, such as endocytosis, phagocytosis and autophagy. TFEB can regulate the transcription initiation of genes related to lysosomal biogenesis, lysosomal acidification, lysosomal exocytosis, endocytosis, phagocyosis, autophagy and membrane repair, and the expression of lysosomal membrane proteins, lysosomal hydrolases, and autophagy-related [3]. At the same time, TFEB also plays an important role in the extracellular secretion of lysosomes [5].

3. Subcellular Localization of TFEB

TFEB depends on its phosphorylation status to change subcellular localization, thereby playing an important role in a variety of physiological processes. Typically, TFEB is phosphorylated and localized in the cytoplasm. In state of starvation or abnormal lysosomal function, TFEB is dephosphorylated and transferred from the cytoplasm to the nucleus, where it plays role in activating the autophagy-lysosome pathway for substrate recognition, phagosome formation, vesicle fusion, and substrate degradation. For example, TFEB overexpression can cause the biogenesis of autophagosomes to be activated [6]. In addition, it was found that post-translational of TFEB contributes to its transcriptional activity. Methyl benzamide hydroxyl amide (inhibitor of histone deacetylase) can the transcriptional activity of TFEB, thereby activating lysosomal function [7]. At the same time, it was also found that TFEB can be by a small ubiquitin-like modification, sumoylation, which affects its transcriptional activity [8]. The subcellular localization of TFEB usually determines function, and its phosphorylation state at the key serine sites is closely related to its function. Current research has found that mTOR kinase can phosphorylate specificine residues in TFEB and play a major role in regulating the subcellular localization of TFEB. At least three serines in TFEB, including S22, S142, and S211, are phosphorylated by mTORC1 [9, 10]. After phosphorylation TFEBS211, it can bind to 14-3-3 protein, which masks the nuclear localization signal (NLS) of TFEB, inhibiting the nuclear translocation of TFEB [9, 11, 12]. In addition to mTOR, it was found that other kinases, ERK, AKT, GSK, etc., can also phosphorylate TFEB. For example, ERK2 phosphorylation of TFEBS142 causes TFEB to be localized in the cytoplasm. TFEBS134 and TFEBS138 can also be phosphorylated by GSK, which causes TFEB to be localized in the cytoplasm, and the use of GSK3 inhibitors can cause TFEB nuclear localization [13]. In addition, the phosphorylation of TFEB may also enhance its nuclear localization. TFEB serine residue S467 is phosphorylated by AKT, treatment of cells with AKT inhibitors promotes TFEB nuclear translocation [14]. In addition, trehalose (a known autophagy activator) can AKT activity, thereby promoting TFEB nuclear translocation. Compared with wild-type TFEB, TFEB with a S467A mutation in normally cult cells has significantly increased nuclear localization [15]. A recent

study found that TFEBS142 and TFEBS211 are phosphorylated and bind to the E3 ubiquitin ligase STUB1, thereby mediating the degradation of TFEB by the ubiquitin-proteasome system [1], which suggests that the phosphorylation state of TFEB can not only regulate its subcellular localization to regulate its biological function, but can also affect its function by its stability.

4. Physiological Functions of TFEB

It was reported that when Tfeb was knocked out whole body, mice died at embryonic (E) 9.5–10.5 days due to placental vascular defects [17]. Therefore, it was further confirmed by using several conditional knockout animal models at present. Researchers found that TFEB played an important role in hepatic lipid metabolism when it was specifically missing the liver or when it was expressed in the liver by virus mediation [18]. Articles reported that TFEB could control the lipid catabolism and directly regulate the of PGC1α. The specific deletion of Tfeb in the mouse liver would destroy the catabolism function of the liver in the obese mice and further lead to metabolic disorders imbalance, and the symptoms of obesity and related abnormal metabolic diseases could be improved if TFEB was overexpressed. [19]. In C. elegans, functional abnormal mutant of HLH-30 (the TFEB homolog in worms) could cause the absence of important enzymes expressed in the process of fat metabolism and decomposition, led to the abnormal lipid metabolism function, which showed that the function of transcription factor TFEB in the lipid metabolism process in different species was conservative to some extent [2]. At the same time, in several longevity models of C. elegans, the overexpression of HLH-30 could induce the activation of the autophy pathway and aggravate the process of lipid catabolism, and extend its life span, while the C. elegans lacking HLH-30 showed a shortened life [21]. The activity of TFEB in osteoclasts is controlled by RANKL, a key regulator of osteoclast function. Osteoast-specific deletion of TFEB can destroy the normal function of osteoclasts, thus causing an increase in bone mass [22], which implies that TFE may also play a role in regulating bone absorption. Also, by using Drosophila melanogaster, it was found that the TFEB homolog Mitf played important role in regulating lysosomal genes, especially the subunits of the v-ATPase proton pump, which induced the reduction of intracellular clearance rate and proteinates [23]. Currently, in a variety of animal models, TFEB plays an important role in inflammation, immunity, hepatic lipid metabolism and sugar metabolism

4.1 TFEB and Tumorigenesis

At present, there are relatively few studies on the relationship between TFEB and the progression of tumors, and they are in renal cancer, melanoma and pancreatic ductal adenocarcinoma. However, studies have found that it may play different roles in different types of and at different stages of tumor progression. Epithelial-mesenchymal transition (EMT) plays an indispensable role in the process of tumor transformation and metastasis [4]. The balanced role of TFEB in epithelial cells and mesenchymal cells was first proposed in 2005, but it has not been deeply [25]. It was found that TFEB could directly activate the E-cadherin promoter when it was overexpressed in 3T3 and mouseonic fibroblasts, and TFEB was found to be essential for the endogenous E-cadherin expression in these cells [26]. However, it was found that the expression of E-cadherin in epithelial cell lines does not depend the expression of TFEB. The above indicates that TFEB is closely related to its source in the process of tumor metastasis. The above findings suggest that TFEB inhibit the transformation process of EMT, thereby inhibiting the metastasis and invasion of tumors. It was found that BRAFV600E can phosphorylate TFEB through ERK, which will localize it in the cytoplasm and inhibit it from playing a transcriptional regulatory role in lysosome biogenesis. It found that inhibition of TFEB-induced activation of the autophagic lysosome pathway can promote the development of melanoma and enhance the resistance of BF inhibitors, which may be related to the epithelial-mesenchymal transition mediated by TGF-β [27]. At the same time, interestingly in metastatic melanoma, the expression of TFEB is positively correlated with the expression of genes required for the immune response [28], which may suggest that TB may also play an important role in tumor immunotherapy. At the same time, it was found that in colorectal cancer (CRC), the protein levels and of TFEB in CRC tissues were significantly lower than those in adjacent normal tissues [29], which may imply that the deep mucosal infiltration, lymph dissemination, aggressive clinical characteristics and poor prognosis of CRC are related to the low expression of TFEB in CRC samples. However, some scientists also found that pancreatic ductal adenocarcinoma (PDAC) cell lines and patient tumor tissues, the mRNA and protein expression of TFEB, MITF and T3 increased, which in turn increased the autophagy flux, which may enhance the utilization efficiency of amino acids for tumor cell growth [30, 31].TGF-β signaling pathway is an important regulator of pancreatic ductal adenocarcinoma, and it was found that TGF-β signaling pathway can activate TB-mediated autophagy process, thereby promoting the migration and metastasis of PDAC cells [32]. In sporadic clear cell renal cell carcinoma TFEB and TFE3 gene fusions often occur [33]. The most common variant is the fusion of TFEB with the non-protein-c metastasis-associated lung adenocarcinoma transcript 1 gene (MALAT1) on chromosome 11q13 [34-36], causes the persistent increase of TFEB protein levels, which can translocate into the nucleus. At the same time, when MALAT1-TFEB is overepressed in renal cancer cell lines, it will increase cell proliferation, invasion and in vivo tumorigenicity [37].

5. Summary

TFEB is a key factor regulating autophagic lysosomes, and its main function is to regulate the biogenesis of lysosomes, which plays an irreplaceable role in the and progression of neurodegenerative diseases, glycometabolism, lipid metabolism and tumor.

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