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The important role of TFEB in autophagy-lysosomal pathway and autophagy-related diseases: a systematic review

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Abstract. – Autophagy is a main metabolic process in which eukaryotic cells use lysosomes to eliminate abnormal proteins and damaged organelles to maintain cell homeostasis. Studies have revealed that neurodegenerative diseases, tumor, hepatic diseases, etc. are related to abnormal autophagy processes in recent years. Recent studies have shown that TFEB is a major transcription regulator of autophagy-lysosomal pathway (ALP) transcriptional regulation, which positively regulates the expression of autophagy and lysosomal biogenesis-related genes, thereby promoting autophagosome formation, autophagosome-lysosome fusion, and degradation of autophagy substrates. It has also been found that TFEB promotes clearance of intracellular substrates through lysosomal exocytosis. Therefore, the study of biological functions and related regulatory mechanisms of TFEB will provide important clues and theoretical basis for further explaining its physiological pathogenesis and the treatment of related diseases.

Key Words:
TFEB, Regulator, Autophagy, Lysosome, Autophagosome, Pathway.

Introduction

Autophagy is an evolutionarily conserved degradation pathway through which cells can adapt to nutrient starvation, oxidative stress, lysosomal dysfunction as well as others. According to the delivery differences of cytoplasmic cargo to the lysosome, autophagy is typically categorized into macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA)[1]. Macroautophagy is the most common autophagy phenomenon, also known as the autophagy-lysosomal pathway (ALP), which mainly degrades abnormal proteins and damaged organelles and regulates many physiological and pathological processes. Under nutrient-rich conditions, autophagy remains at a basal level and mainly acts as a housekeeper responsible for degrading long-lived proteins and recycling damaged organelles. In conditions of starvation, autophagy is activated to provide energy supply to maintain cell survival[2]. Deficits in the ALP lead to protein aggregation, the generation of toxic protein species and accumulation of dysfunctional organelles, which are hallmarks of lysosomal storage disease, neurodegenerative diseases, nephrotic cystinosis, etc. Thus, correcting ALP defects and enhancing the activity of the pathway are potential therapeutic strategies[3]. As a major regulator of the ALP, TFEB is a potential target for the treatment of various autophagy-related diseases.

The transcription factor EB (TFEB) is a member of the MiTF/TFE (microphthalmia-transcription factor E) family of transcription factors of the leucine zipper bHLH-LZ (basic-helix-loop-helix leucine-zipper), which can bind to the promoter motif of autophagy genes to induce autophagosome formation, autophagosome-lysosome fusion, and degradation of autophagy substrates[4]. Studies have shown that TFEB is not only involved in autophagy but also lysosomal biogenesis and exocytosis. The lysosomes have shown a central role in cellular degradation and recycling processes, and its correct function is required to

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maintain cell homeostasis. The lysosomal genes network is called CLEAR (coordinated lysosomal expression and regulation)[5]. TFEB can recognize E-box and M-box sequences of the CLEAR network, activate downstream genes and promote their transcription, resulting in an increased number of lysosomes and higher levels of lysosomal enzymes, thereby enhancing lysosomal catabolic activity. It was also found that TFEB can cause calcium flow into cells by activating calcium channel protein MCOLN1, which promotes the fusion of lysosome and plasma membrane. Overexpression of TFEB in lysosomal storage diseases can promote the removal of metabolic wastes[6].

The Mechanism of TFEB Regulation

It is currently believed that the main signaling pathways that regulate the occurrence of autophagy include mTOR pathway and mTOR-independent pathway, the latter including AMPK, PI3K, TNFR, etc. signaling pathways. Among them, the mTOR signaling pathway is known to be the main way to negatively regulate autophagy. TFEB is a key transcription molecule regulating autophagy at the transcriptional level and it can promote the expression of multiple lysosomal genes, thereby regulating the production and efflux function of autolysosomes.

TFEB transcriptional activity and nuclear translocation are related to the TFEB phosphorylation status. mTOR is a more important kinase known to phosphorylate TFEB, which can inactivate TFEB and localize it in the cytoplasm. mTOR inhibitor can cause TFEB dephosphorylate and incorporate it into the nucleus, thereby exerting its transcriptional activity. After TFEB enters the nucleus, there are two ways to regulate autophagy. One is to activate the expression of various autophagy-related molecules (e.g., Ag molecules, LC3) through transcription to enhance cell autophagy so that the damaged organelles are degraded by autophagosomes and autolysosomes, which can recycle the degradation products (such as amino acids) for cells. The other is to combine the E-box element of CLEAR to transcriptionally activate the expression of lysosomal pathway-related molecules, especially the expression of lysosomal-associated membrane protein LAMP1, to promote lysosome formation *in vitro* (Figure 1).

Mammalian Target of Rapamycin Complex 1

TFEB subcellular localization and its transcriptional activity are strictly regulated by many protein molecules, which mainly affect the phosphorylation of TFEB specific serine. The mammalian target of rapamycin complex 1 (mTORC1) is the best regulator of mammalian autophagy, and its interaction with TFEB is regulated by the lysosomal nutrient-sensing (LYNUS) machinery. Under normal conditions (such as low lysosomal pH or high nutrients), the V-ATPase complex activates the small Rag GTPase (Rags), a component of the LYNUS machinery, which recruits mTORC1 to the lysosomal membrane. Then, mTORC1 directly phosphorylates TFEB at Ser142 and Ser211 sites and inactivate it. YWHA/chaperone proteins 14-3-3 also bind to phosphorylated TFEB to prevent its nuclear translocation, indirectly regulating autophagy[7]. However, in the context of external stimuli (such as starvation or oxidative stress), the amino acid content in the lysosomal lumen decreases, resulting in the inactivation of Rags. Accordingly, mTORC1 dissociates from the lysosomal membrane and cannot phosphorylate TFEB, then TFEB travels to the nucleus and activates its transcriptional program to adapt to cellular catabolic demands. The Rags constitutive active form remains TFEB in the cytoplasm, which is independent of the nutrient status of the cell[8].

Medina et al[9] found that lysosomal calcium in HeLa cells is released into the cytoplasm through calcium channel MCOLN1/TRPML1 upon nutrient deprivation, which can activate the phosphatase calcineurin, thereby promoting the dephosphorylation of TFEB and inducing it to translocate into the nucleus, activating transcriptional target genes. However, the consumption of MCOLN1 inhibits the release of lysosomal calcium and the activation of calcineurin, thereby preventing TFEB dephosphorylation during starvation. Upon chemically induced ER stress, TFEB nuclear translocation can also be promoted. Activation of TFEB through ER stress required a protein kinase RNA-like endoplasmic reticulum kinase (PERK, also known as EIF2AK3)-dependent mechanism, which can activate calcineurin to dephosphorylate TFEB[10]. Currently, it is known that TFEB is activated mainly by inhibiting the activity of mTORC1. For example, mTORC1 inhibitor-Torin1 can induce TFEB nuclear translocation, which is an important negative regulatory mechanism. However, mTORC1 is also involved in the regulation of cell growth and metabolism and has a wide range of biological functions. In the long run, inhibition of mTORC1 may bring unpredictable side effects. Therefore, activation

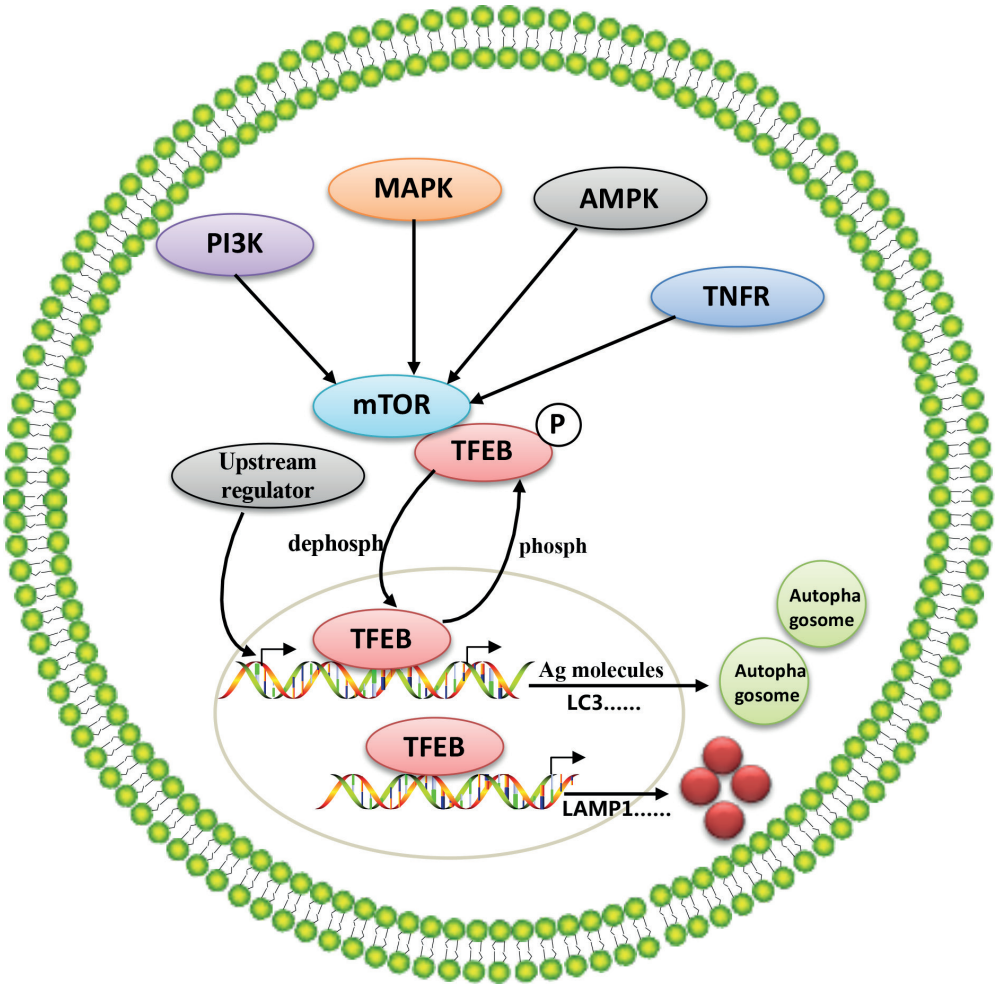

Figure 1. The regulation of TFEB activity.

of TFEB by the mTOR non-inhibitory pathway may be less deleterious to cells.

Extracellular Signal-Regulated Kinase 2

Extracellular signal regulated kinase 2 (ERK2), which is a member of the mitogen-activated protein kinase 1 (MAPK1), can phosphorylate TFEB at serine 142 site and regulate its subcellular localization. ERK2 phosphorylates TFEB and sequester it in the cytoplasm in the presence of sufficient cellular nutrients. In starvation conditions, ERK2 does not interact with TFEB, resulting in TFEB dephosphorylates and enters into the nucleus to promote the expression of autophagy-related genes[11].

Protein Kinase

Protein kinase B (AKT) phosphorylates TFEB at Ser467 by the mTOR-independent mechanism to inhibit TFEB nuclear translocation. Studies have demonstrated that mTOR-independent autophagy activator trehalose activates TFEB by inhibiting AKT activity and increases TFEB nuclear accumulation[12]. For example, when trehalose is given to a mouse model of Batten's disease, it can promote the clearance of cellular protein aggregates, reduce neuropathology and prolong the survival time of diseased mice, suggesting the broad applicability of this method. These findings collectively open up a new idea for the removal of cellular protein aggregates in TFEB-mediated neurodegenerative storage diseases.

Protein kinase C (PKC) is a crucial controller of activating TFEB by mTOR-independent pathway. PKC has many subtypes, including alpha, beta, delta, and other subtypes. It is reported[13] that PKC can activate the transcription factor TFEB while inactivating the transcriptional repressor ZKSCAN3 through two parallel signal cascades.

Table I. Regulatory proteins and modes of action of TFEB.

No	Regulatory proteins	Modes of action
1	mTOR	Phosphorylation
2	Rag GTPases	Phosphorylation
3	MAPK	Phosphorylation
4	P38	Phosphorylation
5	GSK3β	Phosphorylation
6	Erk 1/2	Phosphorylation
7	Calcineurin	Dephosphorylation
8	AMPK	Dephosphorylation
9	PKCβ	Dephosphorylation
10	STUB1	Dephosphorylation
11	Protein phosphatase 2A(PP2A)	Dephosphorylation
12	PIAS3	SUMO
13	Acetyltransferase GCN5	Acetylation
14	Suberoylanilide hydroxamic acid (SAHA)	Acetylation

The ingenol analogue HEP14 activates PKCα and PKCδ, which can inactivate glycogen synthase kinase-3β (GSK3β) by phosphorylation, resulting in the reduced phosphorylation of GSK3β on the serine 134 and 138 sites of TFEB, thereby promoting TFEB activation and its nuclear translocation. In addition, PKCδ can activate JNK2 (c-Jun N-terminal kinase 2) and p38 MAPK (p38 mitogen-activated protein kinase), which can phosphorylate transcription inhibitors ZKSCAN3 (zinc finger protein with KRAB and SCAN3 domains) at Thr153, and results in its inactivation and sequesters it in the cytoplasm, relieving the inhibitory effect of ZKSCAN3 on lysosomal synthesis. PKC activators can promote the clearance of cellular protein aggregates and lipid droplets. Therefore, they are viable in the treatment of lysosomal-related diseases. In osteoclasts, TFEB is activated by another mechanism. Studies have shown that[14] selective deletion of TFEB can reduce the resorption of bone matrix in mouse osteoclasts. Stimulated by the osteoclast differentiation factor RANKL, PKCβ phosphorylates the serine region at the C-terminus of TFEB, which promotes the expression of lysosomal biogenesis, and increases the resorption function of differentiated osteoclasts.

AMP-Activated Protein Kinase

Under nutrient-rich conditions, the stability of co-activator-associated arginine methyltransferase 1 (CARM1) is regulated by the SKP2-containing E3 ubiquitin ligase in the nucleus. Under the condition of nutrient deficiency (co-activator-associated arginine methyltransferase 1) CARM1-dependent histone arginine methylation plays an important role in the process of autophagy. Adenylate-activated protein kinase (AMPK) can increase the protein levels of CARM1 and the dimethylation of histone H3 Arg17, which is mediated by the AMPK-SKP2-CARM1 signal axis. CARM1 acts as a transcriptional co-activator by

Table II. Downstream regulatory factors and functions of TFEB.

No	Downstream regulator factors	Functions
1	The coordinated lysosomal expression and regulation (CLEAR) network, E-box and M-box sequences	Promoting the expression of lysosomal genes.
2	Lysosomal genes network: ARSA, ARSB, ATP6V0E1, ATP6V1H, CLCN7, CTSA, CTSB, CTSD, CTSF, GALNS, GBA, GLA, GNS, HEXA, LAMP1, MCOLN1, MAGLU, NEU1, PASP, SCPEP1, SGSH, TMEM55B, TPP1	Increasing lysosomal population
3	Acid hydrolases, lysosomal acidification machinery, membrane proteins	Raising the levels of lysosomal enzymes and promoting degradation of lysosomal substrates

forming a complex with TFEB[15]. Increasing evidence has demonstrated that AMPK deficiency leads to a partial reduction of SKP2-mediated nuclear CARM1, which causes cardiac autophagy dysfunction in the elderly.

Small Ubiquitin-Like Modifier SUMO

The small ubiquitin-like modifier SUMO can also modify TFEB. Miller et al[16] found that PIAS3 can induce SUMO-1 to modify TFEB at Lys316 in COS-7 cells (monkey kidney fibroblasts). Indeed, it has been recently reported that[17] SUMO modification of TFEB can promote the expression of genes related to autophagy and lysosomal biosynthesis, inducing autophagy and lysosome formation in macrophages, thereby hydrolyzing lipids in macrophages to cholesterol and promoting its efflux, and ultimately inhibiting the formation of macrophage foam cells.

Curcumin Analog C1

Zhang et al[18] have shown that curcumin is non-toxic and has a wide spectrum of pharmacological activities, which can inhibit the PI3K-AKT-mTOR signaling pathway to enhance autophagy. However, curcumin has poor water solubility and low oral bioavailability, restricting its clinical development. Curcumin analog C1 has been considered as a new orally effective activator of TFEB, which can specifically bind to the N-terminal glycine and alanine-rich region of TFEB in an mTOR-independent manner, thereby promoting TFEB nuclear translocation, and it is possibly achieved by reducing the interaction of TFEB and YWHA/14-3-3[19]. This finding has an important implication for the treatment of many autophagy-related diseases.

The upstream and downstream regulatory factors related to TFEB signaling pathway are shown in Table I and Table II.

TFEB as a Therapeutic Target for Diseases

We observed human and animal models, suggesting[20] that impaired TFEB signaling pathways can contribute to a variety of diseases. Indeed, the regulation of TFEB activity has become an effective means in the development of related diseases.

Lysosomal Storage Disease

Lysosomal storage disease (LSD) is a group of hereditary metabolic diseases whose pathogenesis is that genetic mutations lead to defects of related acid hydrolases or accessory proteins in the lysosome; as a result, the metabolites in the body cannot be degraded normally and accumulate in the lysosome, causing tissue or organ dysfunction. The lysosome is a central component of cellular catabolism. Most processes based on lysosomes – including macromolecular degradation, autophagy, lysosomal exocytosis, etc. – are regulated by TFEB transcription. Pompe disease[21] is a lysosomal storage disorder in which glycogen accumulates abnormally in muscle, whereby AAV (adeno-associated virus)-mediated TFEB delivery can induce exocytosis of lysosomes, which is beneficial to remove excess glycogen. This overexpression also improves overall autophagy and lysosomal function. Fraldi et al[22] performed in autophagy-deficient muscles also indicate that the clearance of accumulative substances requires a functional autophagy degradation pathway.

Neurodegenerative Storage Diseases

Increasing evidence focuses on the autophagy-lysosomal pathway because its activity regulation is closely related to the pathogenesis of neurodegenerative diseases. Arotcarena et al[23] have shown that lysosomal biogenesis and function have provided a suitable target for manipulating lysosomal degradative pathways. TFEB participates in the intracellular clearance process mainly by enhancing lysosomal biosynthesis, cellular exocytosis, the expression of degradative enzymes, and lysosomal proteostasis to act as a cellular clearance regulator. In rodent models of neurodegenerative diseases (including Alzheimer's disease, Parkinson's disease, and Huntington's disease), heterologous expression of TFEB is beneficial to improve the disease phenotype and promote lysosomal clearance.

The main pathological features of Alzheimer 's Disease (AD) are neurofibrillary tangles (NFT) formed by extracellular β-amyloid (Aβ) plaque deposition and intracellular Tau protein hyperphosphorylation (p-Tau). Xiao et al[24] have shown that ALP can regulate the metabolism of Aβ. Acting as a major activator of ALP, TFEB-mediated beneficial effects have been confirmed in Aβ and Tau pathology in multiple AD mouse models. Polito et al[25] found that in the rTg4510 mouse model of Tau lesions, TFEB delivery can effectively reduce neurofibrillary tangles and improve neurodegenerative behavior. Furthermore, TFEB overexpression can selectively target p-Tau protein, but does not exert harmful effects on normal Tau protein.

Parkinson's disease (PD) is a common neurodegenerative disease. The typical pathologi-

cal feature is the selective deletion of substantia nigra-striatum dopaminergic neurons and the discovery of Lewy bodies formed by abnormally folded α-synuclein aggregation in the remaining neurons. The overall animal and isolated cell research[26] support that aggregated α-synuclein can affect the transcriptional activity of TFEB, causing damage to the autophagy-lysosomal degradation pathway. However, using drugs or transgenic technology to increase the activity of TFEB can restore lysosomal biosynthesis and improves disease phenotype. For example, AAV-mediated delivery of TFEB in the brain of a PD rat model obtained by overexpressing α-synuclein can reduce the accumulation of α-synuclein and improve neurodegenerative behavior deficits.

Huntington's disease (HD) is a neurodegenerative disease. Due to the abnormal expansions of the CAG trinucleotide sequence in the coding region of the Huntington (HTT) gene, the HTT protein misfolds into a pathogenic conformation, accelerating the degeneration of neurons. Based on the HD mouse model study, Tsunemi et al[27] found that the expression of TFEB and its downstream genes were significantly decreased. Through peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) overexpression corrected the defects of TFEB, thereby promoting the degradation pathway of autophagolysosome. Eventually, the accumulated HTT protein in the mice was reduced. In addition, experiments conducted by TFEB silencing and PGC1α overexpression, as well as TFEB overexpression and PGC1α silencing, demonstrated that PGC1α acts upstream of TFEB, thus, targeting the PGC1α-TFEB axis is highly attractive for the treatment of this disease.

Hepatic Disease

Accumulating evidence shows that autophagy plays an important role in maintaining the homeostasis of the liver. Autophagy is involved in the process of recycling cellular nutrients and quality control of subcellular organelles. Defects in autophagy and lysosomal function can lead to various liver pathologies. TFEB regulates lysosomal biosynthesis. Chao et al[28] found that the levels of total TFEB and nuclear TFEB in the ethanol-induced mouse liver injury model were lower than in the normal group, and the biosynthetic capacity of lysosomes was reduced. However, Torin-1 (mTOR activity inhibitor) or adenovirus vector-mediated overexpression of TFEB can increase TFEB levels in liver tissue, reduce ethanol damage to liver and steatosis, and increase lysosomal biosynthesis and mitochondrial bioenergy, indicating that increasing TFEB levels can protect alcoholic fatty liver caused by ethanol. Quercetin can also reverse the inhibitory effect of ethanol on the nuclear translocation of TFEB and show a similar effect to Torin 1, which can promote the nuclear translocation of TFEB and improve the autophagy-lysosomal dysfunction caused by ethanol[29].

Spinobulbar Muscular Atrophy

The pathological features of spinobulbar muscular atrophy (SBMA) are due to the repeat morbid expansion of the trinucleotide (CAG) sequences in the genes encoding the androgen receptor (AR) protein, which ultimately leads to polyQ-AR formation. In the spinal cord of SBMA mice[30], it was found that polyQ-AR reduced the expression of TFEB by chelating nuclear factor YA (NF-YA), thereby reducing ALP activity and enhancing polyQ-AR toxicity. Treating SBMA mice with paeoniflorin can promote the nuclear translocation of TFEB and the expression of the ubiquitin-protease complex system by increasing the expression of nuclear factor-YA (NF-YA), thereby promoting the clearance of polyQ-AR and improving the disease phenotype. Cortes et al[31] also found that both AR and polyQ-AR can directly interact with TFEB, but AR is a TFEB co-activator that promotes its transcriptional activity, while polyQ-AR reduces the activity of TFEB in SBMA motor neurons and neuron precursor cells from patients, resulting in decreased expression of TFEB target genes and defects in autophagy flux. The above research results indicate that polyQ-AR causes tissue-specific dysregulation of TFEB and suggest that it can be treated by enhancing autophagy.

Nephropathic Cystinosis

Nephropathic cystinosis is caused by mutation of the *CTNS* biallelic genes, resulting in the lack of cystine lysosomal transporter-cystinosin, which is a proton-cystine symporter responsible for the excretion of cystine and protons from the lysosomal lumen, and the accumulation of cystine into lysosomes, consequently causing proximal tubular dysfunction (such as Fanconi syndrome), which eventually develops into end-stage renal disease. Rega et al[32] have shown that[32] the lack of cystinosin can reduce the total expression of TFEB. Andrzejewska et al[33] detected that the mTOR signaling pathway in cystinotic cells has changed. The lack of cystinosin inhibits the mTOR signaling pathway, as well as the lysosomal stress

response caused by cystine accumulation, which can lead to TFEB compensatory nuclear translocation, but it is still insufficient. Overexpression of TFEB can promote lysosomal exocytosis and lower the levels of cystine, which brings new hope for the treatment of nephropathic cystinosis.

Atherosclerosis

In the development of atherosclerosis (AS), macrophages phagocytose excess cholesterol derived from extracellular or obtained from the conversion of oxidized low-density lipoprotein in lysosomes, which causes macrophage lysosomal dysfunction, and the vascular wall locally produces an inflammatory response, thereby promoting the formation of macrophage foam cells and AS plaques[34]. Thus, enhancing lysosomal function and promoting cholesterol efflux from macrophages are effective means to treat atherosclerosis. Related research has shown[35] that TFEB is a major regulator of lysosomal biogenesis, which increases lysosomal lipids catabolism and oxidation pathways while inhibits the biosynthesis of it. TFEB can hydrolyze lipids into cholesterol through PGC-1α-PPARα signaling pathway, whereby ABCA1-mediated cholesterol efflux from cells to reduce lipid load. Simultaneously, it can reduce the secretion of pro-inflammatory cytokines (interleukin-1β) and inhibit excessive activation of inflammatory bodies, improving the progression of AS.

Immune Response

The main feature of the immune response is to use the inflammatory reaction to eliminate pathogens and other foreign bodies, thereby helping tissue regeneration and repair. The disorder of inflammatory response can cause a variety of diseases. Brady et al[36] have shown that the ALP plays an anti-inflammatory role in the inflammatory response, mainly through its negative feedback regulation of the inflammatory body and indirectly reduces inflammation. As the main regulator of autophagy and lysosomal function, TFEB can link autophagy and lysosomal dysfunction with inflammatory diseases. The autophagolysosome system plays a key role in the immune response by regulating various aspects of antigens presentation. TFEB can regulate the immune function by inducing the activation of lysosomes. After TFEB is activated, it can inhibit the expression of exogenous antigens mediated by (major histocompatibility complex) MHCI, and at the same time enhance antigens presentation of MHCII, thereby affecting the process of dendritic cells and T cells binding through the MHC pathway to present exogenous antigens, ultimately affecting the immune response[37].

Tumor

In the process of tumorigenesis, autophagy has a dual role. When cells are stimulated by environmental factors, they can remove toxic proteins and damaged organelles through the autophagy pathway to inhibit cell carcinogenesis; but once tumors form, autophagy can provide nutrients for cancer cells and contribute to the development of a tumor. Cancer cells have a higher energy requirement than normal cells to support accelerated cell growth[38]. When nutrient supply is limited, cancer cells can mobilize energy by scavenging nutrients through autophagy-lysosomal pathways. Gomes et al[39] have shown that excessive lysosomal activity is a characteristic of cancer recurrence. TFEB can control the transcription process of autophagy and lysosomal biogenesis and has become an important regulator of tumor energy metabolism. For example, in renal cell carcinoma (RCC), chromosomal translocation involving TFEB, increased expression, and easy translocation into the nucleus can initiate the transcription of downstream genes and promote the formation of autophagolysosomes[40]. Calcagnì et al[41] treatment with Wnt signaling pathway inhibitors significantly inhibited tumor growth, indicating that targeting Wnt signaling may be used for the treatment of TFEB-associated RCC. Overexpression of TFEB can activate the Wnt pathway, induce the occurrence of kidney cancer and the proliferation and invasion of cancer cells. Therefore, blocking the downstream pathway of TFEB activation can provide an important target for the production of anticancer agents.

Conclusions

TFEB is an important transcription factor in the cell and occupies an important position in the process of lysosome and cell autophagy. In this review, we have highlighted the role of TFEB in the successful completion of autophagy and autophagy-related diseases. TFEB is just like a master switch of the autophagy-lysosome pathway. Blocking the transcriptional activity of TFEB will affect the production and clearance of lysosome. Thus, the regulatory mechanism of TFEB and its role in autophagy-related diseases are worthy of

study, which can provide a theoretical basis for the treatment of diseases caused by ALP dysfunction and the development of new drugs.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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