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Review

TFEB is a central regulator of the aging process and age-related diseases

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ABSTRACT

Old age is associated with a greater burden of disease, including neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as other chronic diseases. Coincidentally, popular lifestyle interventions, such as caloric restriction, intermittent fasting, and regular exercise, in addition to pharmacological interventions intended to protect against age-related diseases, induce transcription factor EB (TFEB) and autophagy. In this review, we summarize emerging discoveries that point to TFEB activity affecting the hallmarks of aging, including inhibiting DNA damage and epigenetic modifications, inducing autophagy and cell clearance to promote proteostasis, regulating mitochondrial quality control, linking nutrient-sensing to energy metabolism, regulating pro- and anti-inflammatory pathways, inhibiting senescence and promoting cell regenerative capacity. Furthermore, the therapeutic impact of TFEB activation on normal aging and tissue-specific disease development is assessed in the contexts of neurodegeneration and neuroplasticity, stem cell differentiation, immune responses, muscle energy adaptation, adipose tissue browning, hepatic functions, bone remodeling, and cancer. Safe and effective strategies of activating TFEB hold promise as a therapeutic strategy for multiple age-associated diseases and for extending lifespan.

1. Introduction

Old age is associated with a greater burden of disease, including neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as chronic diseases such as hypertension, diabetes, and metabolic disorders (Wasay et al., 2016). In fact, a recent meta-analysis conducted across 195 countries showed that up to 92 diseases were more prevalent in older populations compared with younger age groups (Chang et al., 2017). Aging itself is associated with functional abnormalities similar to early-stage pathological disorders (Franceschi et al., 2018; Kubben and Misteli, 2017). For example, the eyes of older individuals without age-related macular degeneration can exhibit changes that resemble early stages of the disease (e.g., increased number of drusen, Bruch's membrane thickening, and retinal function loss) (Ardeljan and Chan, 2013; Ehrlich et al., 2008).

Extending lifespan or delaying aging has been shown to protect against degenerative diseases (Franceschi et al., 2018; Luu and Palczewski, 2018), and interventions that slow down the normal aging process can ameliorate multiple age-related pathologies and increase lifespan (López-Otín et al., 2023; McHugh and Gil, 2018). For this reason, age-related diseases may be viewed as organ-specific conditions of accelerated aging (Franceschi et al., 2018; MacNee et al., 2014). Therefore, slowing down the aging process is vital to prevent age-associated diseases.

Transcription factor EB (TFEB) is a key transcriptional regulator of autophagy and lysosomal biogenesis (Sardiello et al., 2009; Settembre and Ballabio, 2011). Laboratory experiments in model organisms demonstrated that TFEB overexpression promoted longevity and reduced the burden of diseases (Lapierre et al., 2013; Nakamura and Yoshimori, 2018; Sardiello, 2016). In rodents, healthy lifestyle interventions, such as caloric restriction and physical activity, were found to activate TFEB and upregulate autophagy, leading to a lower disease burden and extend lifespan (Huang et al., 2019; Kepp et al., 2020). Pharmacological activators of TFEB, such as metformin and trehalose, also promoted autophagy and therapeutic benefits similar to caloric restriction and physical exercise (Kepp et al., 2020; Morel et al., 2017). Trehalose is a two-sugar molecule that mimics the effects of caloric restriction by blocking glucose transport into cells (Mardones et al., 2016). The consumption of trehalose by mice activated TFEB and autophagy, protecting them against neurodegeneration in models of lysosomal

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storage disorder (Lotfi et al., 2018; Palmieri et al., 2017). Results from studies of other TFEB activators and caloric restriction mimetics, including spermidine and the flavonoids 3,4-dimethoxychalcone and 4, 4-dimethoxychalcone (Kepp et al., 2020; Zhang et al., 2019), indicate similar anti-aging and therapeutic benefits. In humans, the dysregulation of TFEB is implicated in aging and diseases (Lapierre et al., 2013; Nakamura and Yoshimori, 2018; Sardiello, 2016). Clinical trials are underway to test the safety and efficacy of caloric restriction mimetics known for their potent activation of TFEB and autophagy, such as metformin, trehalose, resveratrol, and spermidine (De Cabo et al., 2014; Madeo et al., 2019; Mohammed et al., 2021; Pekar et al., 2021; Turner et al., 2015).

Understanding the functional role of TFEB in the aging process and disease could help in the development of new therapeutic interventions for treating age-related diseases, which can extend lifespan. In this review, we provide up-to-date information on the contributions of TFEB activation in the modulation of the various hallmarks of aging and discuss the specific impact these may have on different tissues in the context of aging and age-related diseases. Furthermore, we argue that TFEB activation is a vital effector mechanism by which healthy lifestyle behaviors including caloric restriction, intermittent fasting, and exercise prevent diseases and extend lifespan.

2. TFEB: structure and activation

TFEB is a member of the microphthalmia (MiT) family of transcription factors; other members of the family include the *microphthalmia* transcription factor (MITF), transcription factor E3 (TFE3), and transcription factor EC (Napolitano and Ballabio, 2016). Structurally, the TFEB protein consists of approximately 490 amino acids and distinct protein domains. Its basic helix-loop-helix region has high DNA-binding affinity, promoting the recognition and interaction of the protein molecule with the E-box DNA sequence 5'-GTCA[T/C]GTGAC-3' in the promotor site of the target genes (Palmieri et al., 2011). TFEB activates downstream target genes, including the Coordinated Lysosomal Expression and Regulation (CLEAR) gene network, which regulates autophagy and lysosomal biogenesis (Palmieri et al., 2011; Sardiello et al., 2009). The leucine-zipper region facilitates dimerization, and the transactivation domain region regulates the transcriptional activation of TFEB (Napolitano and Ballabio, 2016).

The regulatory mechanisms behind the activation of TFEB in the cytosol and its translocation into the nucleus for binding to target genes may proceed via mammalian target of rapamycin (mTOR)-dependent and mTOR-independent pathways (Al-Bari and Xu, 2020). The complex regulatory mechanisms involved in TFEB activation have been the subject of many excellent reviews (Cui et al., 2023; Napolitano et al., 2022; Napolitano et al., 2020). Therefore, only a summary is given below. Under normal nutrient-rich conditions, the nutrient-sensitive mTOR complex 1 (mTORC1) pathway regulates TFEB depending on the availability of nutrients. In brief, under nutrient-rich conditions, recombination activating gene (RAG) GTPases activated by folliculin (FLCN) are anchored to the lysosomal surface where they interact with cytosolic TFEB, resulting in the retention of TFEB to lysosomes in an amino acid-dependent manner (Cui et al., 2023). Under normal rich-nutrient conditions, mTORC1 is active and induces the phosphorylation of TFEB and ULK1 resulting in the inhibition of autophagy (Vega-Rubin-de-Celis et al., 2017). Recent studies, however, have found that following mTOR activation and recruitment by RAG GTPases to the lysosomal surface, the phosphorylation and inhibition of TFEB occur through a non-canonical mTORC1 pathway involving the FLCN–RAG C/D axis (Napolitano et al., 2022; Napolitano et al., 2020). In contrast, the canonical mTOR pathway involves phosphorylation of mTORC1 substrates S6K and 4E-BP1 via the tuberous sclerosis complex 2 (TSC2)–Ras homolog enriched in brain (Rheb) axis. The phosphorylation of TFEB at multiple sites (including S211, 122, and 142) facilitates the binding of TFEB to 14–3–3 proteins and TFEB retention in the cytosol (Martina et al., 2012; Vega-Rubin-de-Celis et al., 2017). Thus, under nutrient-rich conditions mTORC1 is activated and TFEB is phosphorylated and retained in the cytosol, resulting in the transcriptional downregulation of autophagy and lysosomal biogenesis (Fig. 1). In amino acid-depleted conditions, however, mTORC1 is inactivated, leading to the dephosphorylation and dissociation of TFEB from RAG GTPases and the nuclear translocation of TFEB (Napolitano et al., 2022; Napolitano et al., 2020). Inside the nucleus, TFEB binds and activates target genes, including CLEAR network genes involved in autophagy induction and lysosomal biogenesis. Thus, TFEB links amino acid deficiency and mTORC1 to the transcriptional upregulation of autophagy (Settembre et al., 2012). However, because the mTORC1 pathway regulates many cellular processes, including ribosomal biogenesis, mRNA translation, lipid and nucleotide synthesis, and mitochondrial function, which promote cell growth and metabolism (Ardestani et al., 2018; Takei and Nawa, 2014). Hence, global TFEB activation, via mTORC1 inhibition, may cause undesirable effects (de la Cruz López et al., 2019).

For the mTOR-independent TFEB activation and nuclear localization, many unique regulatory mechanisms have also been proposed. A critical examination of these mechanisms reveals that they are mostly alternate pathways promoting the dephosphorylation of TFEB and increased nuclear translocation (Martina and Puertollano, 2018; Medina et al., 2015; Palmieri et al., 2017; Sha et al., 2017). Some of these mechanisms include AKT inhibition (Palmieri et al., 2017), calcineurin activation (Medina et al., 2015), protein phosphatase 2 A (PP2A) activation (Chen et al., 2017), STIP1 homology and U-Box-containing protein 1 (STUB1)-mediated selectively proteasome degradation (Sha et al., 2017), and Parkin-induced TFEB translocation (Nezich et al., 2015). Sirtuin 1 (SIRT1) was shown to promote the deacetylation of TFEB at lysine residue 116, increasing the binding affinity of nuclear TFEB to the promoter site of target genes in microglia (Bao et al., 2016). In addition, nuclear export proteins (e.g., XPO1) could act as a negative feedback loop to reduce TFEB accumulation in the nucleus (Li et al., 2018), and their inhibitors help stabilize and improve TFEB nuclear expression (Martin et al., 2019; Silvestrini et al., 2018). Moreover, eIF5A hypusination by the polyamine spermidine was found to facilitate TFEB translation and expression, but the underlying mechanism is still unclear (Zhang et al., 2019).

2.1. TFEB dysregulation in aging and diseases

Data from immunohistochemistry investigations on donor tissues and model organisms revealed differential TFEB protein expression levels and subcellular localization, between younger versus older subjects and healthy versus diseased subjects, (Chao et al., 2018; Zhang et al., 2019). It is already recognized that an age-related decline in the immune response against pathogens and cancer cells may underlie the increased risk of infections and cancer (Feehan, Tripodi and Apostolopoulos, 2021; Weyand and Goronzy, 2016). Apart from this, a recent study has shed further insight into how the aging of the immune system, or immunosenescence, significantly contributes to the whole organism aging (Yousefzadeh et al., 2021). Mice with a selective deletion of *Ercc1, a* crucial DNA repair protein have hematopoietic cells with increased DNA damage and show accelerated aging not only in the immune system but also in every organ including immune-privileged sites (Yousefzadeh et al., 2021). Moreover, defective TFEB-mediated autophagy in mature lymphocytes of older individuals has been implicated in immune senescence (Zhang et al., 2019). Zhang and co-workers found that old B cells from both human subjects and mice were deficient in mounting immune response and showed reduced TFEB expression and autophagy. Importantly, TFEB expression through spermidine supplementation in mice led to improved autophagy and B cell responses in older mice (Zhang et al., 2019).

Numerous reports from studies investigating the molecular pathways underlying several human diseases, including hepatic disorders, kidney diseases, neurodegenerative diseases, and cancers point to the

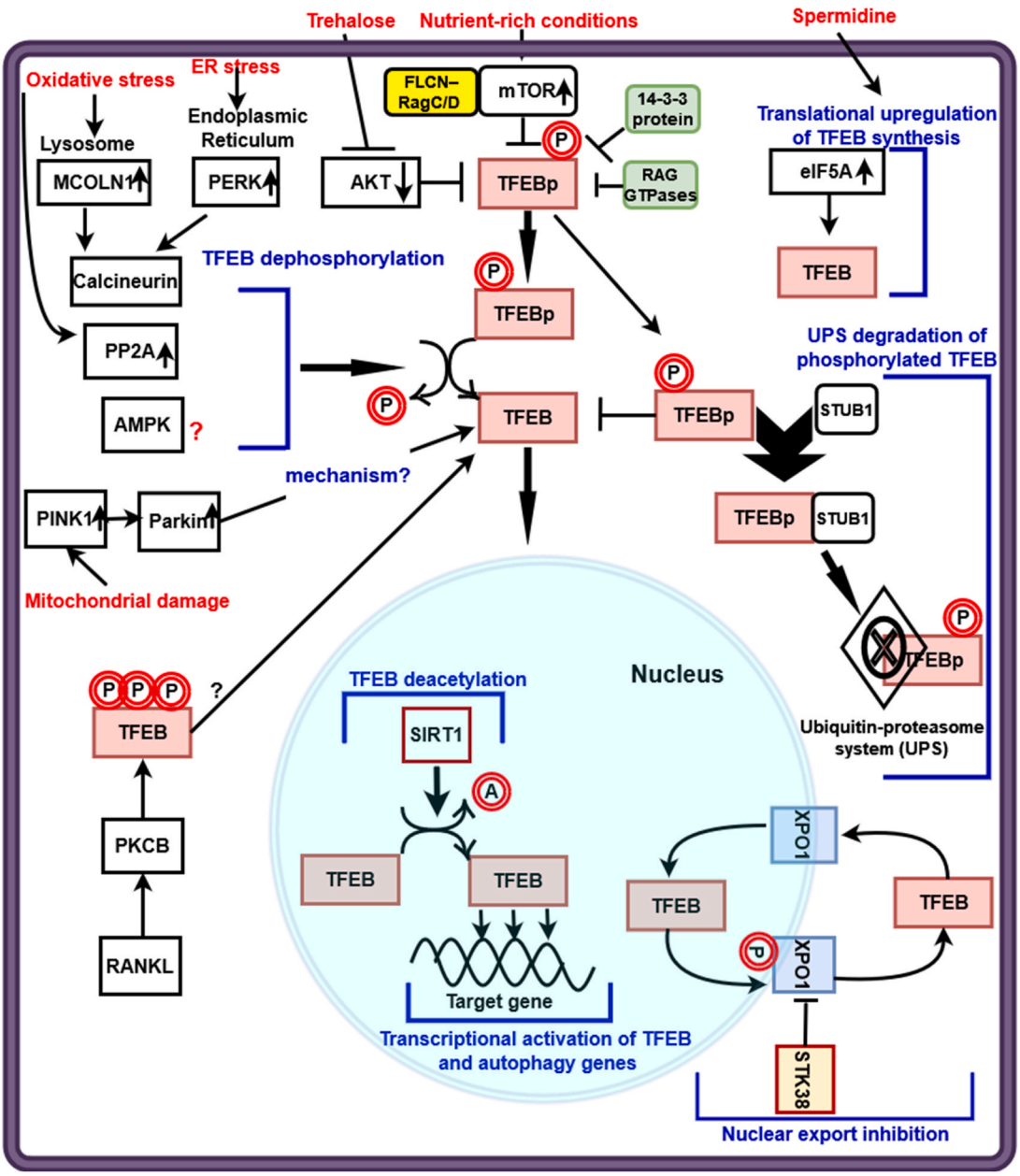

Fig. 1. . Targets for TFEB activation and nuclear translocation. Under normal nutrient-rich conditions, mTORC1 selectively phosphorylates TFEB (TFEBp) via a non-canonical signaling pathway mediated by FLCN–RagC/D axis, keeping it inactively bound to 14–3–3 proteins and RAG GTPases in the cytosol. However, stressful conditions, such as nutrient starvation, oxidative stress, ER stress, and mitochondrial dysfunction, or TFEB inducers activate TFEB, leading to TFEB nuclear translocation and induction of autophagy and other downstream survival genes. The main molecular mechanisms underlying TFEB activation are: 1) inhibiting the phosphorylation of TFEB (which may involve mTOR), or dephosphorylating TFEB; 2) inhibiting nuclear export; 3) TFEB deacetylation; 4) increasing translational synthesis of TFEB; and 5) selectively degrading TFEBp by the ubiquitin protein system (UPS).

involvement of TFEB and autophagy dysregulation in the development of those conditions. For instance, the liver tissue from patients with alcohol-induced hepatitis had lower TFEB levels in the nucleus compared to tissue from healthy donor controls (Chao et al., 2018). To ascertain TFEB's specific role in the disease, wild-type mice were fed a diet containing ethanol to induce liver damage. The histochemistry results revealed a decline in the total and nuclear TFEB levels and autophagy in the damaged liver of the mice. However, mice overexpressing *TFEB* were protected against ethanol-induced liver injury through mechanisms associated with increased lysosomal biogenesis and mitochondrial bioenergetics (Chao et al., 2018). In obese patients with chronic kidney disease (CKD), it was discovered that defective autophagy in the proximal tubule epithelial cells (the earliest site of injury in kidney disease) increased tubular vacuolar lesions and led to a decline in renal function (Yousefzadeh et al., 2021). Evidence from a mouse model of CKD revealed that TFEB-mediated autophagy was associated with tubulointerstitial fibrosis CKD progression (Yuan et al., 2021). In common age-related neurodegenerative disorders, including AD, PD, Huntington's disease, and amyotrophic lateral sclerosis, TFEB dysregulation may be evident at distinct stages of TFEB activation. Specifically, TFEB function is either affected at the initial cytosolic stage of activation, the intermediate stage of nuclear translocation, or the final transcriptional stage required for activation of target genes (including autophagy genes) and TFEB itself (Cortes and La Spada, 2019). Experimental studies in mice, nematodes, and flies have shown that inhibiting TFEB (or its ortholog HLH-30), genetically or pharmacologically, accelerated aging

and shortened lifespan, whereas TFEB overexpression had the opposite effect (Silvestrini et al., 2018). These pieces of evidence collectively implicate TFEB dysregulation as a commonly shared molecular pathway associated with aging and age-related diseases. In the next sections (i.e., ***Sections 3.0 and 4.0)***, we discussed the diverse molecular mechanisms by which TFEB dysregulation impacts aging and age-related diseases.

3. Impact of TFEB on the hallmarks of aging

Tackling aging and its health-related challenges necessitates an in-depth understanding of the cellular and molecular changes which underlie age-associated pathology. About a decade ago López-Otín and co-workers described the nine hallmarks of aging: genomic instability; telomere attrition; epigenetic alterations; loss of proteostasis; deregulated nutrient-sensing; mitochondrial and metabolic dysfunction; cellular senescence; stem cell exhaustion; and altered intercellular communication. However, recently up to five new hallmarks of aging have been added (López-Otín et al., 2023; Schmauck-Medina et al., 2022). Each of the hallmarks contributes to the aging phenotype in unique ways: (1) as a primary cause for the loss of cellular homeostasis/function (such as in the damage of the genome, telomeres, epigenome, proteome, and organelles; (2) as a maladaptive response to the cell damage with a negative impact in the long-term; or (3) as an integrative manifestation resulting from uncompensated upstream events (López-Otín et al., 2023; Schmauck-Medina et al., 2022). Hence, we present details on how targeting TFEB can reverse the different hallmarks of aging while bearing in mind the interplay among the hallmarks and their differential contributions to the aging process (Fig. 2).

3.1. Regulating cellular clearance pathways and proteostasis in aging

Autophagy, a lysosomal degradation pathway involved in the recycling of intracellular components and removal of pathogens, is essential, for maintaining cellular homeostasis and function (Aman et al., 2021; Kaushik et al., 2021). The growing understanding of the role of autophagy in aging has led to the recent inclusion of dysfunctional autophagy as one of the unique hallmarks of aging. This marked a dramatic change from the previously held view that dysfunctional autophagy was only triggered by other more relevant hallmarks of aging, including

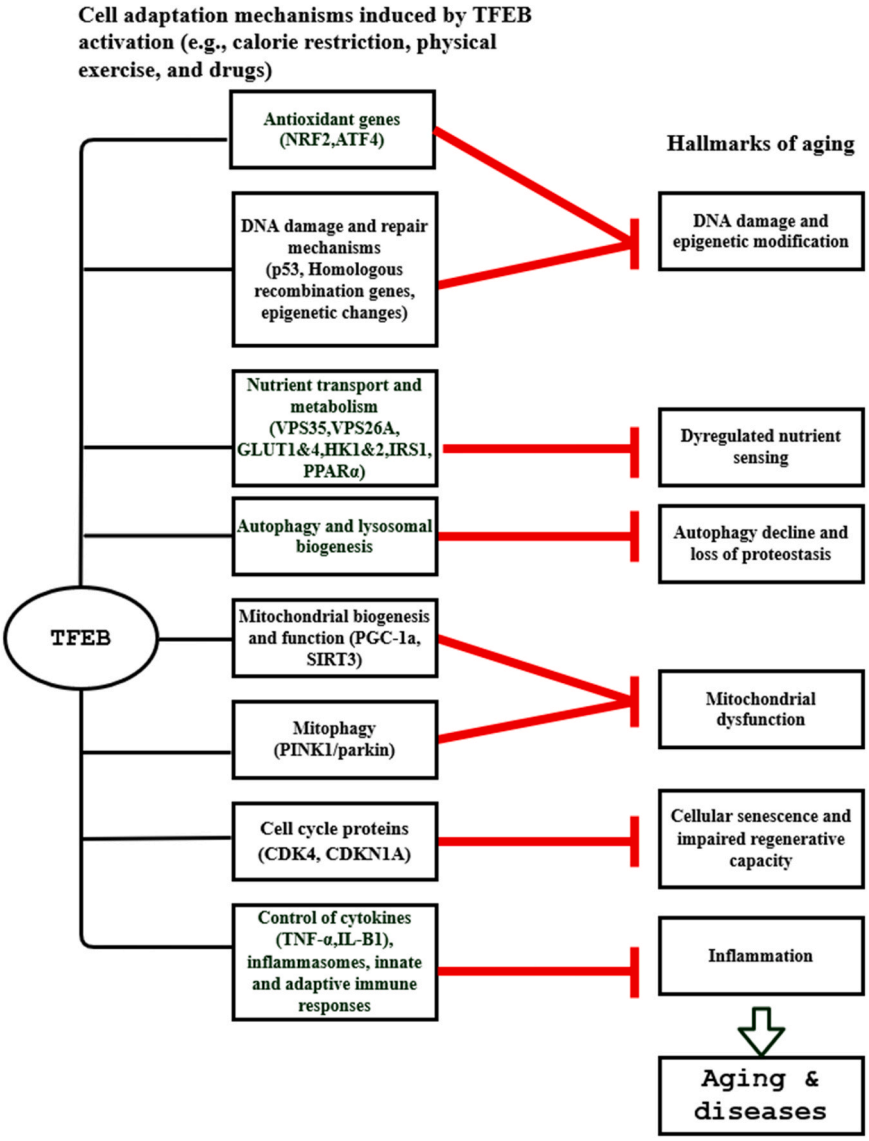

Fig. 2. . TFEB activation counteracts the hallmarks of aging. The activation of TFEB induces various cellular adaptation mechanisms involving the activation of transcriptional factors and genes that regulate DNA damage and repair, energy metabolism and nutrient homeostasis, autophagy, mitochondrial quality control, cell cycle, senescence, and inflammation.

altered proteostasis, deregulated nutrient-sensing, DNA damage, and mitochondrial dysfunction (López-Otín et al., 2023; Schmauck-Medina et al., 2022). In contrast to this previously held view, the evidence now highlights the central role of autophagy in aging, and that many geroprotective interventions with the potential to slow aging and extend healthspan may work through increasing autophagy (Aman et al., 2021; Kaushik et al., 2021). Current data implicate all three major types of autophagy – macroautophagy, microautophagy, and chaperone-mediated autophagy– as relevant in aging, suggesting coordinated crosstalk among the autophagic processes (Kaushik et al., 2021).

Dysfunctional autophagy in aging could arise from either transcriptional changes or epigenetic regulatory modifications (Füllgrabe et al., 2016; Lapierre et al., 2015). Impaired TFEB activity in aging partly accounts for the transcriptional downregulation of autophagy in older and diseased persons (Di Malta, Cinque and Settembre, 2019). It is understood that following TFEB activation and nuclear translocation, TFEB binds directly to the CLEAR motifs (GTCACGTGAC) at the promoter regions of target genes. TFEB promotes autophagy through the activation of various autophagy-related genes critical for early-stage autophagy processes, including autophagy initiation (*BECN1, WIPI1, ATG9B*, and *NRBF2*), cargo delivery to autophagosomes (*SQSTM1*), autophagosome membrane elongation (*GABARAP, MAP1LC3B*, and *ATG5*), up to final-stage autophagosomes trafficking and fusion with lysosomes (*UVRAG, RAB7*) (Di Malta, Cinque and Settembre, 2019). Also, the involvement of epigenetic mechanisms, such as histone modifications induced by enzymatic reactions causing phosphorylation, methylation, acetylation, and ubiquitination, have been observed to affect autophagy gene expressions, leading to impaired autophagy (Baek and Kim, 2017). Histone modifications have been implicated in the repression of autophagy genes by serving as decoy sites for transcriptions factors, including TFEB, other MiT family members, or Forkhead box O proteins (FOXOs) (Baek and Kim, 2017; Shi et al., 2021).

The therapeutic potential of TFEB-induced autophagy in aging and age-related diseases are linked to the recycling of the damaged intracellular molecules, which restores protein homeostasis (e.g., lipofuscin, α-synuclein, tau, and huntingtin), provide energy and building blocks for the biosynthesis, and inhibits oxidative stress (Cortes and La Spada, 2019; Menzies et al., 2017). Autophagy is particularly important in post-mitotic cells, like the retinal pigment epithelium and neurons, which cannot dilute protein aggregates and reduce the burden of cytosolic waste through cell division and, therefore, are vulnerable to degeneration triggered by accumulation of toxic protein waste (Sánchez-Vidaña et al., 2023). As such, TFEB-induced autophagy has been found to have therapeutic potential in many neurodegenerative diseases (Cortes and La Spada, 2019). Also, TFEB regulates exocytotic transportation of intralysosomal content across the lipid bilayer membrane of cells to their external environment, by promoting lysosomal biogenesis and coordinating the docking of lysosomes to the plasma membrane for fusion (Buratta et al., 2020; Medina et al., 2011; Singh and Haka, 2016; Tancini et al., 2020). Hence, through exocytosis, TFEB activates cellular clearance, cell secretions (including hormones and neurotransmitters), and plasma membrane repair (Singh and Haka, 2016). TFEB's role in the regulation of bile acid synthesis and secretion was found to affect hepatic cholesterol homeostasis in mice (Wang et al., 2020a, 2020b). It is worth noting too that the autophagy machinery could be recruited for unconventional protein secretion, to dispose of toxic protein aggregates and pathogens by a process called secretory autophagy (Buratta et al., 2020). By promoting phagocytosis in specialized cells like the retinal pigment epithelium, TFEB facilitates the recycling of rhodopsin and the proteins important for phototransduction, promoting retinal homeostasis (Kwon and Freeman, 2020). Increasing evidence supports that TFEB-induced autophagy has far-reaching effects on the aging process, through the modulation of intercellular communication, such as in gap junction protein degradation, or crosstalk with extracellular vesicular systems (Kaushik et al., 2021). These physiological roles of autophagy and exocytosis on cellular survival and organismal homeostasis make TFEB a promising target in many age-related diseases, including endocrine disorders, kidney disease, and neurodegenerative diseases (Nakamura et al., 2023; Tancini et al., 2020; Xu et al., 2021).

3.2. *Enhancing mitochondrial function and energy metabolism in aging*

Mitochondria are no longer only recognized as the powerhouse of cells, but also as a signaling hub for the regulation of redox homeostasis, calcium transport, hormonal biosynthesis, inflammation, cell survival, and death signaling (Dard et al., 2020). In mice with premature aging, a distinct type of senescence state caused by mitochondrial dysfunction occurs, through the nicotinamide adenine dinucleotide (NAD)-AMP-activated protein kinase (AMPK)-p53 pathway (Korolchuk et al., 2017; Wiley et al., 2016). Hence, mitochondrial homeostasis and quality control are pivotal for cell adaptation to stress and healthy aging. While the age-related decline in mitochondrial function and energy metabolism affects all kinds of cell types– from undifferentiated stem cells to matured differentiated and postmitotic cells– the functional impact may differ between cell types (Sun et al., 2016). In stem cells, mitochondrial dysfunction affects the ability to self-renew or differentiate (Khacho et al., 2019; Papa et al., 2019). This is because the transition from quiescence to proliferation, and from a primitive stem-like state to a differentiated state requires a metabolic change from predominant glycolysis to mitochondrial oxidative phosphorylation and adenosine triphosphate (ATP) generation, to meet the higher energy requirement of proliferating and differentiated cells (Papa et al., 2019). Mitochondrial regulation of stem cell fate in aging has implications on the repair and regenerative potential of tissues, including promoting neuroplasticity in aging (Khacho et al., 2019). Also, mitochondrial reactive oxygen species (ROS) production may affect stem cell fate, as stem cells have been shown to exhibit low levels of ROS, which increase upon the commitment to differentiate, possibly to activate nuclear factor erythroid 2-related factor 2 (NRF2) for the transcriptional upregulation of antioxidant gene expression profile (Khacho et al., 2016).

Mitophagy, a selective mitochondrial degradative pathway, serves two purposes in mitochondrial quality control: (1) preventing the accumulation of dysfunctional mitochondria, and (2) promoting mitochondrial biogenesis to meet the changing metabolic demand (Palikaras and Tavernarakis, 2014). Ivankovic and co-workers demonstrated, using human neuroblastoma SH-SY5Y cells, that TFEB activation and nuclear translocation were induced by mitophagy, leading to TFEB protein overexpression, activation of autophagy and lysosomal genes, and *PGC-1α,* which was responsible for mitochondrial biogenesis (Ivankovic et al., 2016). Similarly, it was shown that the activation of TFEB by carbon monoxide in hepatocytes enhanced both mitophagy and mitochondrial biogenesis, preventing inflammatory liver damage (Kim et al., 2018). These observations support that TFEB activation tightly couples mitochondrial biogenesis and mitophagy for mitochondrial quality control and maintenance of cellular homeostasis (Palikaras and Tavernarakis, 2014; Wang et al., 2020a). Peroxisome proliferator-activated receptor-gamma (PPARγ) coactivator-1 alpha (PGC-1α) is a key transcriptional coactivator of the nuclear receptor PPARγ which controls diverse genes involved in energy metabolism (Wang et al., 2020a, 2020b). Settembre and co-workers (2013) demonstrated that in hepatocytes, *PGC-1α* upregulated lipid catabolism following starvation-induced TFEB activation (Settembre et al., 2013). In that study, it was shown that TFEB delivery to the liver, using adenoviral vector injection, prevented obesity and metabolic syndrome caused by dietary or genetic factors in mice (Settembre et al., 2013). Accordingly, TFEB overexpression induced the catabolic lipid pathways while downregulating the anabolic lipid pathway genes (Settembre et al., 2013). Despite the relevance of TFEB-mediated autophagy in lipid catabolism in mice, the study found that the TFEB-PGC-1α pathway also regulated lipogenesis (Settembre et al., 2013). The implication, therefore, is PGC-1α activation by TFEB is critical in maintaining lipid

homeostasis not only through autophagy but also through lipid biosynthesis.

Moreover, TFEB activation also controls glucose metabolism, the most efficient form of energy transfer, independent of PGC1α (Chen et al., 2019a; Mansueto et al., 2017). TFEB activation during physical exercise enhanced glucose uptake by skeletal muscles and promoted metabolic adaptation in mice, through upregulation of the genes involved in glucose transport (i.e., *GLUT1* and *GLUT4)*, oxidative phosphorylation (*hexokinase 1* and *2*), and mitochondrial biogenesis (Mansueto et al., 2017). A study by Heckel et al. (2022) found that inhibiting TFEB in photoreceptor cells decreased the expression of SIRT3, one of the mitochondrial sirtuins that regulate mitochondrial protein networks, and metabolic adaptation, and provides protection against age-related diseases (van de Ven et al., 2017). The sirtuins (SIRT3–5) are conserved from bacteria to humans. In model organisms, supplementation with NAD improved healthspan and restored mitochondrial homeostasis via activation of mitochondrial sirtuins (SIRT3–5) (Ji et al., 2022; van de Ven et al., 2017). Hence, elucidating how TFEB controls mitochondrial sirtuins, in general, will have a considerable influence on aging and age-related diseases.

3.3. Regulating DNA damage and repair and epigenetic modifications in aging

Genome integrity and stability are compromised by exogenous factors and endogenous physiological processes, UV radiation, viral infection, DNA replication errors, chromosome segregation defects, and oxidative events. These may cause point mutations, deletions, translocations, telomere shortening, single- and double-strand breaks, chromosomal rearrangements, and disruption of the nuclear and mitochondrial genome (López-Otín et al., 2023). Damage accumulated over time in both nuclear DNA and mitochondrial DNA (mtDNA) can trigger cell death and senescence, which in turn may cause inflammation, loss of organ function, and pathological aging (Schumacher et al., 2021). To counteract DNA damage, cells recruit tightly controlled, specific DNA repair mechanisms to restore cellular homeostasis (Chen et al., 2020). Because of the mitochondria's oxidative internal milieu, their limited DNA repair mechanisms, and the absence of histones for the protection of DNA molecules, mtDNA is more susceptible to damage accumulation than nuclear (López-Otín et al., 2023). Also, epigenetic changes, commonly caused by histone modifications, or methylation, affect the DNA or the proteins that package and regulate the DNA, resulting in changes in gene expression. Recent research has shown that epigenetic modifications affect the regulation of autophagy, and vice versa (Baek and Kim, 2017). For example, histone modifications may downregulate the expression of genes that are involved in autophagy by serving as a decoy for binding to transcriptions factors, including TFEB, other MiT family members, or forkhead box O proteins (Baek and Kim, 2017; Shi et al., 2021). However, some interventions that activate autophagy, such as caloric restriction and exercise, also promote beneficial epigenetic modifications and improve overall healthspan (Gensous et al., 2019).

TFEB is an important target in the modulation of DNA damage and DNA repair mechanisms, especially under stress and in cancers, where it inhibits apoptosis and leads to chemoresistance (Brady et al., 2018; Gomes, Menck and Leandro, 2017; Slade et al., 2020). In aged macrophages with defective mitophagy, damaged mitochondrial accumulates, and mtDNA leaks into the cytosol, activating the simulator of interferon gene (STING) signaling, and thereby contributing to sterile liver inflammation (Zhong et al., 2022). This evidence further highlights the essential role of mitophagy in mtDNA homeostasis. Besides autophagy, TFEB and TFE3 also regulate DNA damage and cell cycle arrest in mouse embryonic fibroblasts, through stabilization of the p53 tumor suppressor (Brady et al., 2018). The transcription factor p53 integrates cellular stress with cell proliferation, DNA repair, and apoptosis (Pitolli et al., 2019). TFEB-mediated activation of p53 in response to DNA damage induced the transcriptional upregulation of DNA repair factors and Cyclin-dependent kinase inhibitor 1 CDKN1A (also known as p21), which promoted cell cycle arrest and senescence (Juretschke and Beli, 2021). Using transcriptomic analysis in breast cancer cells, TFEB was shown to modulate DNA repair and apoptosis by regulating genes involved in homologous recombination, cell cycle, and interferon-gamma signaling (IFNγ) (Slade et al., 2020). Slade and coworkers observed that TFEB activation enhanced DNA repair and inhibited apoptosis in breast cancer cells subjected to doxorubicin treatment to cause DNA double-strand breaks, independent of autophagy. Conversely, the inhibition of TFEB-phosphatase calcineurin enhanced doxorubicin-induced apoptosis, by downregulation of the cell cycle and homologous recombination genes that promoted DNA repair, and the upregulation of IFNγ and death receptor signaling genes (Slade et al., 2020). A recent investigation into rare variants in 1667 genes associated with PD, by whole-exome sequencing in a cohort of 32 patients with PD and 30 age-matched controls, identified an increased prevalence of mutations in TFEB target genes regulating mitochondrial and lysosomal function (Segur-Bailach et al., 2022). Postmortem data show reduced brain TFEB nuclear expression and retention of TFEB in Lewy bodies in the brain tissues of patients with PD (Decressac et al., 2013). These findings connect mtDNA mutations with TFEB dysregulation in the pathogenesis of PD (Segur-Bailach et al., 2022).

In addition, TFEB's critical role in protecting against oxidative damage to DNA, proteins, lipids, and organelles, through transcriptional upregulation of antioxidant genes, has been demonstrated (Abokyi et al., 2020; Martina and Puertollano, 2017; Wortel et al., 2017). Potent antioxidant pathways, such as NRF2 and activating transcription factor 4 (ATF4) cellular adaptation (Tonelli et al., 2018), are induced following TFEB activation in response to heat and oxidative stress (Lin et al., 2018; Wortel et al., 2017). Using mRNA-sequencing in *Caenorhabditis. elegans*, Lin and coworkers identified several TFEB-regulated antioxidant genes which were upregulated under oxidative stress and heat stress for stress resistance and longevity (Lin et al., 2018). TFEB overexpression in neuroglioma cells increased levels of the autophagy adaptor p62, stabilized and activated NRF2, leading to the transcriptional activation of downstream antioxidant genes (Park et al., 2019). Also, through the transcriptional upregulation of ATF4 by TFEB under stress (Martina et al., 2016), TFEB acts as a master regulator of the integrated stress response. Given the relevance of DNA damage and the interconnections with most of the hallmarks of aging, including proteostasis, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion, TFEB activation in DNA damage is an attractive strategy for counteracting aging and age-related dysfunction (Schumacher et al., 2021).

3.4. Modulating of nutrient-sensing and nutrient homeostasis in aging

Nutrient homeostasis, the tight control of nutrients like sugars, amino acids, lipids, and surrogate metabolites, is essential for cell and organismal survival (Efeyan, Comb and Sabatini, 2015). Nutrient-sensing pathways, involving the insulin (I)/insulin-like growth factor 1 (IGF-1), mTOR, sirtuins, and AMPK, are, necessary to detect nutrient abundance and nutrient scarcity, and also play a role in determining whether cells engage anabolism and storage, or mobilize internal stores through autophagy and catabolism (Hadem, Majaw and Sharma, 2020; Johnson, 2018; Templeman and Murphy, 2018). Specifically, nutrient abundance activates both insulin/IGF-1 and mTORC1 signaling, which promotes growth and energy expenditure (anabolic response), whereas nutrient depletion activates AMPK signaling to generate energy and promote cellular longevity (catabolic response) (Templeman and Murphy, 2018). Deregulation of the nutrient-sensing pathways is associated with aging and many metabolic disorders (Kioussis et al., 2021). It has been implicated in impaired autophagy, altered mitochondrial function and energy metabolism, and increased oxidative stress in aging (Parmar et al., 2022; Tomtheelnganbee et al., 2022). Consistently, studies have found the inhibition of IGF-1 or MTORC1

signaling, by either genetic manipulation or drugs, to enhance health and lifespan in flies, worms, and mice, highlighting the crucial impact of the nutrient-sensing pathways on the aging process (Johnson, 2018; Leontieva and Blagosklonny, 2016).

Autophagy is a key effector mechanism for maintaining nutrient homeostasis with an enormous impact on nutrient recycling and energy metabolism, as well as other hallmarks of aging (Moreno et al., 2022; Parmar et al., 2022). This is backed by data demonstrating impaired autophagy in age-related pathologies associated with the deregulation of mTOR, IGF-1, and AMPK, such as diabetes, kidney diseases, and neurodegenerative disorders (Parmar et al., 2022; Rahimi et al., 2019; Zha and Wu, 2023). Also, laboratory experiments have supported the efficacy of TFEB-induced autophagy in reversing age-related metabolic disorders and extended lifespan in model organisms and mice (Wang et al., 2017). In humans, healthy lifestyles, such as caloric restriction and physical exercise, alter the nutrient-sensing pathways and activate TFEB-induced autophagy. Fasting in mice promoted the release of an important metabolic hormone, fibroblast growth factor 21 (FGF21), which activated TFEB through dephosphorylation mechanisms mediated by PP2A in the hepatocyte of mice, leading to the induction of autophagy and lipid metabolism (Chen et al., 2017). FGF21 acts as an autocrine and endocrine signal on different tissues, fasting-induced FGF21 stimulation of TFEB may impact metabolic health and aging of multiple tissues (Tezze et al., 2019). Besides autophagy, TFEB regulates transmembrane proteins which function as signaling receptors, nutrient and solute transporters, or adhesion molecules for cell-to-cell interaction (Cullen and Steinberg, 2018). It was recently discovered that TFEB regulated the retromer complex and, therefore, influenced the sorting and recycling of transmembrane proteins in endosomes (Curnock et al., 2019). Endosomes are intracellular membrane-bound vesicles that control the sorting of different transmembrane proteins either for degradation or for egress and recycling to compartments such as the Golgi and the plasma membrane (Chen et al., 2019a, 2019b). Endosomal protein sorting (EPS) of transmembrane cargoes relies upon protein-specific recognition and transport mechanisms that are regulated by the retromer complex (Chen et al., 2019a, 2019b). In an investigation of the role of the retromer complex in the retrieval and recycling of glutamine transporters, it was found that glutamine or amino acid deprivation-induced TFEB activation upregulated transcriptions of retromer genes (VPS35 and VPS26A) and the glutamine transporter sodium-coupled neutral amino acid transporter 2, by binding to CLEAR elements in their promoters (Curnock et al., 2019). Thus, TFEB links the sensing of nutrient availability to the retromer complex–EPS mechanism. Targeting TFEB, therefore, might offer an opportunity to control signaling receptors, and nutrient and solute transport. Furthermore, TFEB was found to regulate glucose metabolism through transcriptional and miRNA upregulation of insulin receptor substrate (IRS) 1 in vascular endothelial cells, (Sun et al., 2021), suggesting that TFEB is a potential molecular target in endothelial cells for the treatment of vascular and metabolic diseases. Mice deficient for IRS-1 develop insulin resistance and suggesting that it may play a crucial role in obesity and type-2 diabetes (Kubota et al., 2016; Kulkarni et al., 2003). Additionally, TFEB regulates other cellular processes, such as mitochondrial biogenesis, and glucose and lipid homeostasis, that are essential in the mobilization and utilization of nutrients in an autophagy-independent manner (*for details, refer to* ***subsection 3.2***). Thus, nutrient-sensing involves the coordination of different cellular and extracellular pathways, including hormonal signaling, cell surface receptors, and the anabolic and catabolic cellular pathways (Johnson, 2018), in which TFEB is involved.

Recently, caloric restriction and intermittent fasting have become extremely popular and are practiced by many people who are health conscious or have certain diseases because of the numerous health benefits and lifespan extension properties as seen in humans, mice, and model organisms (de Cabo and Mattson, 2019; Madeo et al., 2019). Caloric restriction, describing the reduction of calorie intake (15–30%) without causing malnutrition or nutrient deficiency, sharply contrast nutrient deprivation strategies (like low protein intake and fasting), where cells are deprived of certain nutrients, such as amino acids or glucose (Hwangbo et al., 2020). Both dietary strategies, however, activate TFEB and increase autophagy in various tissues and organs, including the liver, brain, and muscle (Hwangbo et al., 2020). The nutrient-sensing signaling pathway mediates TFEB activation by caloric restriction and nutrient deprivation through various pathways, including (1) phosphorylation of TFEB by activated AMP-activated protein kinase (AMPK) or mTOR inhibition; (2) deacetylation of TFEB for enhanced transcriptional activity by sirtuins; (3) inhibition of insulin and insulin-like growth factor 1 (IGF-1) signaling (de Cabo and Mattson, 2019; Madeo et al., 2019). In obese healthy adults, caloric restriction and fasting induce weight loss, improve insulin sensitivity, and reduce inflammation, which improves general health. Also, the Okinawa population in Japan with reduced calorie intake has the highest number of centenarians, associating caloric restriction with lifespan extension. Moreover, physical exercise, another effective intervention antiaging with therapeutic implications for treating a range of diseases, including neurodegenerative disorders, metabolic diseases, and cancer, was shown to activate TFEB and autophagy in skeletal muscle, through signaling pathways, including AMPK-SIRT1 and calcium-calcineurin activation (Huang et al., 2019; Morais et al., 2023). Apart from the skeletal muscles, TFEB activation by exercise has been proposed to affect brain health and protect against neurodegenerative diseases such as AD, through the induction of autophagy and mitochondrial biogenesis possibly by TFEB-PGC-1α activation (Morais et al., 2023). Exercise improves cognitive functions in AD mice by reducing Aβ accumulation in the hippocampus and cortex of AD mice in a TFEB-induced autophagy-dependent manner (Wang et al., 2022). The involvement of nutrient-sensing pathways and TFEB activation as key mechanisms behind healthy lifestyle interventions support their relevance as therapeutic targets to revert or at least prevent pathogenic age-associated deterioration.

3.5. *Modulation of inflammation in aging*

Inflammaging, describing the low-grade elevated levels of blood inflammatory markers in older persons, is implicated in a wide range of age-related diseases, supporting the influence of chronic inflammation in healthy aging and diseases (Ferrucci and Fabbri, 2018; Franceschi et al., 2017). Pro-inflammatory mediators in the blood, such as IL-1, IL-6, C-reactive protein, IFNα, and several others become elevated with aging, contributing to organ damage and chronic morbidity, and frailty in old age (Ferrucci and Fabbri, 2018). Inflammaging is influenced by other hallmarks of aging, including cellular senescence, gut microbiota, and autophagy. For example, an accumulation of cell waste coupled with a decline in autophagy and/or mitophagy can trigger an autoimmune response by receptors of the innate immune system (Franceschi et al., 2017). Tumour necrosis factor (TNF)-α inhibition in mice or rats partially reversed the aging phenotype caused by defective T cells lacking the mitochondrial transcription factor A (López-Otín et al., 2023).

Available data suggests that TFEB expression level is affected by inflammation whereas TFEB also regulates the inflammatory process. This is supported by the finding that TFEB mRNA and protein levels vary in macrophages during sustained exposure to lipopolysaccharide, a component of the outer membrane of most Gram-negative bacteria that induces immune dysregulation and inflammation (Page et al., 2022). It was shown that the changes in TFEB expression under chronic inflammation contribute to cellular adaptation (Pastore et al., 2016). The regulatory effect of TFEB activation on the immune response and inflammation is mediated by diverse mechanisms that could be autophagy- dependent or -independent. For instance, the endothelial lining of blood vessels is constantly exposed to shear stress from blood pressure and blood flow, which induce inflammation (Lu and Kassab, 2011). As

an adaptive mechanism to shear stress, endothelial cells overexpressed TFEB, resulting in the induction of autophagy-independent anti-inflammatory responses and vasoprotection (Lu et al., 2017). TFEB overexpression in endothelial cells reduced leukocyte recruitment and decreased atherosclerosis in mice on a high-fat diet (Lu et al., 2017). These anti-inflammatory and vasoprotective effects of TFEB were found to be, at least, partly due to reduced oxidative stress (Lu et al., 2017), although the direct regulation of chemotactic factors, promoting the adhesion and migration of leukocytes through the endothelium, was not ruled out. Also, TFEB/TFE3 was found to regulate the transcriptional activation of antimicrobial genes and inflammatory cytokines such as TNF/TNF-α and IL-1β in murine macrophages, which enhanced an innate immune response against pathogen infections (El-Houjeiri et al., 2019; Pastore et al., 2016).

Another way by which TFEB modulates the adaptive immune response is through the regulation of antigen presentation by dendritic cells (DCs) (Samie and Cresswell, 2015). DCs determine the specific T cell responses based upon whether they will present an antigen on either the major histocompatibility complex (MHC) class I or MHC class II molecules. When exogenous antigens are presented on MHC class I molecules, known as cross-presentation or cross-priming, it activates cytotoxic CD8 + T cell responses against tumour cells and pathogens. It has been demonstrated that TFEB regulates T-cell response through the inhibition of cross-presentation (Samie and Cresswell, 2015). Additionally, TFEB modulates humoral immunity by promoting CD40 ligand expression in CD4 + T cells, critical for T cell-dependent antibody responses (Huan et al., 2006). Moreover, TFEB controls cell-mediated immunity by regulating the release of lytic granules from cytotoxic T-lymphocytes and natural killer cells, which is dependent on lysosomal Ca^{2+} release and exocytosis (Liu et al., 2005). Thus, these examples highlight the varied mechanisms through which TFEB affects inflammaging and age-related diseases. While numerous studies have profiled the regulatory role of TFEB activation in immune modulation, more research is needed to elucidate the mechanisms underlying TFEB-mediated pro-inflammatory and/or anti-inflammatory tissue response.

3.6. Inhibiting senescence and promoting regenerative capacity in aging

Aging tissues show a progressive decline in regenerative capacities due to age-dependent deterioration of stem cell function (i.e., stem cell survival, self-renewal, quiescence, proliferation, and commitment to specific differentiation) (Oh et al., 2014). Cellular senescence, a state of growth cycle arrest induced in response to stressors (e.g., DNA damage, telomere attrition, oncogene activation) is implicated in stem cell exhaustion and other hallmarks of aging (Di Micco et al., 2021). The cell cycle arrest state inhibits tumour growth and the regenerative capacity of aging cells, while the pro-inflammatory senescence-associated secretory phenotype (SASP)– comprising pro-cytokines, chemokines, proteases, bioactive lipids, inhibitory molecules, and other factors– induces chronic inflammation and tissue dysfunction which drives age-related diseases (Di Micco et al., 2021; Zhang et al., 2023). With increasing age, senescent cells accumulate in all tissues, but at various levels; affecting mitotic cells (e.g., blood cells) more than post-mitotic/slow proliferating cells (e.g., neurons and cardiocytes) (Sapieha and Mallette, 2018). Senescence of immune cells, or immunosenescence, plays a crucial role in inflammaging, vulnerability to infections, and auto-immunity, which underlie many diseases associated with aging (Feehan, Tripodi and Apostolopoulos, 2021). In neural tissue, age-related microglia senescence promotes neuroinflammation and neurodegeneration (Ng et al., 2023). In several disease models, senolytics and senomorphics have shown therapeutic benefits leading to an improvement in the Healthspan and lifespan (Kim and Kim, 2019; Zhang et al., 2023).

TFEB activation has been reported as an effective therapeutic remedy for reversing or alleviating the senescence phenotype in several age-related disease models (Hu et al., 2020; Wang et al., 2021). Recently, the rejuvenation of senescent stem cells, using embryonic stem cell-derived extracellular vesicles (EVs), has been demonstrated to be an effective regenerative therapy for the restoration of tissue structure and function (Hu et al., 2020). In rats generated to exhibit signs of vascular dementia, including progressive cognitive impairment, hippocampal neural stem cell (H-NSC) senescence, and reduced neurogenesis, it was demonstrated that EVs therapy reversed H-NSC through miRNAs promoting mTOR-dependent TFEB activation (Hu et al., 2020). Similarly, another study showed that TFEB expression was reduced in neuronal cells from the frontal cortex and hippocampus of older mice (18-month-old), whereas TFEB overexpression inhibited neuronal senescence and improved cognitive memory (Wang et al., 2021). Thus, these studies emphasize the role of TFEB in promoting neuroplasticity and inhibiting neurodegeneration.

Most studies attribute the impact of TFEB in senescence to mechanisms including (1) activation of cell clearance pathways, such as autophagy, exocytosis, and phagocytosis, to restore protein homeostasis, (2) restoration of lysosomal homeostasis (3) promoting mitochondrial biogenesis and energy metabolism, and (4) regulation of DNA repair (Hu et al., 2020; Wang et al., 2021; Zhang et al., 2019). It was recently discovered that senescent cells increased the lysosomal content via TFEB activation as an adaptation mechanism for their survival and the inhibition of TFEB caused the death of senescent cells (Curnock et al., 2023). This finding supports the targeting of TFEB as a senolytic intervention. In addition, studies have demonstrated that GATA binding protein 4 (GATA4) expression regulates NF-κB activation and SASP in human fibroblasts and mice (Kang et al., 2015; Lee et al., 2018). They showed that p62-mediated selective autophagy degradation in infra-red light--induced senescent mice was crucial in the maintenance of GATA4 homeostatic levels, preventing the development of SASP (Kang et al., 2015). In human mesenchymal stem cells with DNA damage, GATA4 levels are elevated leading to the activation of NF-κB and release of monocyte chemoattractant protein-1 (MCP-1), supporting the relevance of GATA4 and autophagy in regulating SASP (Lee et al., 2018). Endothelial senescence, a significant biomarker of vascular aging, contributes to deregulated angiogenesis and vascular repair and increased vascular permeability, implicated in age-associated cardiovascular diseases (Jia et al., 2019). TFEB has been found to upregulate the expression of genes involved in endothelial cell proliferation, including cyclin-dependent kinase 4 (CDK4) which controls cell division and transitions through the cell cycle (Doronzo et al., 2019). Moreover, TFEB depletion by small hairpin RNA silencing inhibited CDK4 activity, resulting in cell cycle arrest at the G1-S transition and higher vascular endothelial growth factor receptor 2 expression (Doronzo et al., 2019). This is consistent with an earlier report about the relevance of TFEB activation in post-ischemic angiogenesis, although they attributed the effect partly to autophagy (Fan et al., 2018). Moreover, senescence mitigation by TFEB activation may also involve crosstalk with the molecular pathways mediating growth arrest (e.g., p53 and $p16^{INK4a}$/Rb tumour suppressor, or over-expression of Cdc2/cdk1 and survivin) or SASP (e.g., NF-κB) (Brady et al., 2018; Chakradeo et al., 2015). These experimental data, demonstrating the potential impact of TFEB on the senescence phenotype in undifferentiated stem cells and mature postmitotic cells, have implications for the treatment of age-related diseases, supporting the targeting of TFEB as an effective regenerative strategy in aging.

4. Tissue-specific therapeutic and anti-aging roles of TFEB

The various functional roles of TFEB and its impact on aging and lifespan extension have already been examined. Some of the TFEB functions are, however, cell-type specific, such as its role in vascular development, immunity, and adipose tissue browning (Doronzo et al., 2019; Evans et al., 2019; Samie and Cresswell, 2015). This may be important because mature specialized cells are unique in terms of the stressors they encounter and the cell adaptation required for survival

(Cornish et al., 2015; Fulda et al., 2010). TFEB is differentially expressed in various body tissues, possibly reflecting the adaptation needs of different cell types (Murray et al., 2004). Analysis of the human proteome in 32 different tissues revealed higher TFEB mRNA and protein expressions in the brain, endocrine tissues, skeletal muscles, spleen, lymph nodes, B-cells, and granulocytes (Uhlén et al., 2015; Uhlen et al., 2010). The body parts with lower TFEB levels included the liver, natural killer cells, T-cells, the pancreas, the lungs, and the eyes (Uhlén et al., 2015; Uhlen et al., 2010). Details about the effect of TFEB activation in body tissues are reviewed to shed light on TFEB's contribution to aging and diseases, and the potential therapeutic benefits of modulating TFEB (Fig. 3).

4.1. Immune system and infectious diseases

A meta-analysis conducted on the global burden of diseases has established that age is a significant risk factor for various infectious and chronic inflammatory diseases (Chang et al., 2017). As already discussed, autophagy upregulation by TFEB is crucial for innate and adaptive immune responses, promoting pathogen clearance and effector cell priming (Nabar and Kehrl, 2017). Lymphocytes face multiple stressors throughout development, which threaten their survival unless they adapt accordingly (Mcleod et al., 2012). Autophagy upregulation by TFEB is, therefore, necessary for lymphocyte adaptation and survival (Mcleod et al., 2012). In mice, age-related decline in TFEB expression decreased lymphocyte autophagy and induced lymphocyte senescence, which compromised the immune response and led to poor vaccination efficacy and increased infections (Zhang et al., 2019). However, increasing the expression of TFEB using spermidine upregulated autophagy and reversed senescence in mice and lymphocytes (Zhang et al., 2019). Also, TFEB activation was found to be necessary for murine macrophages exposed to *Staphylococcus aureus* (*S. aureus*) infection to induce cytokine and chemokine genes, supporting TFEB-induced autophagy in immune response activation during infection and the maintenance of immune system homeostasis (Visvikis et al., 2014). In model organisms, such as *C. elegans*, the TFEB ortholog HLH-30 mediated transcriptional upregulation of close to 80% of the host response, including antimicrobial and autophagy genes that were essential for host tolerance of infection (Visvikis et al., 2014). The above examples elucidate the proinflammatory role of TFEB and autophagy in both

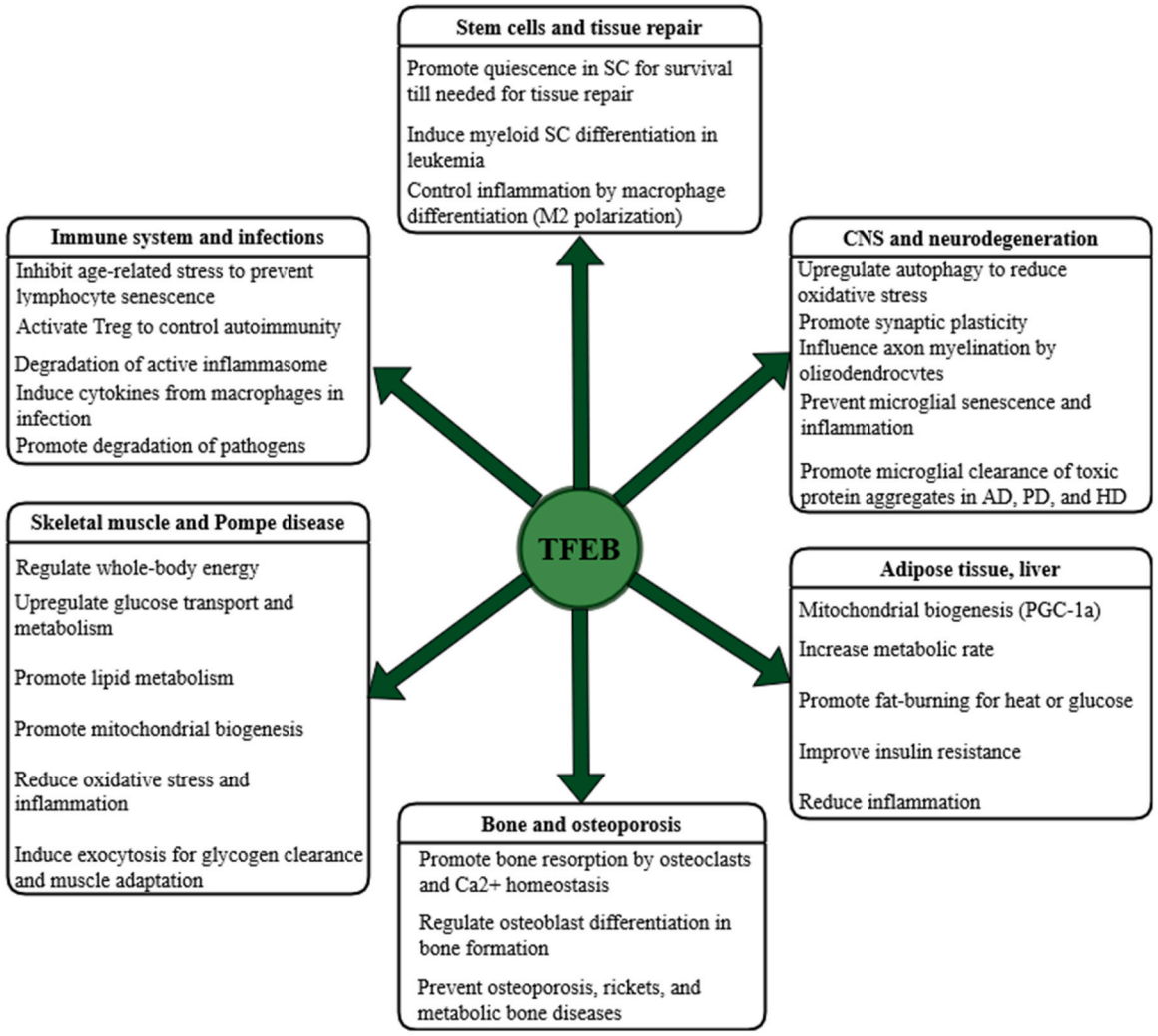

Fig. 3. . Tissue-specific therapeutic and anti-aging roles of TFEB. Targeting TFEB in the body offers diverse therapeutic advantages in various diseases and anti-aging benefits, contingent upon the specific tissue type. TFEB regulates tissue repair, regeneration, and inflammation by stem cells (SC) through modulation of differentiation and quiescence. In the central nervous system (CNS), TFEB regulates microglial activity, axon myelination, synaptic plasticity, and neuroinflammation. By enhancing adipose tissue browning and gluconeogenesis in the liver, TFEB controls fat-burning, thermogenesis, metabolic rate, insulin sensitivity, weight loss, and inflammation. In specialized bone cells, TFEB regulates bone formation and Ca^{2+} homeostasis. In skeletal muscles, TFEB regulates muscle adaptation and whole-body glucose and lipid homeostasis. TFEB affects the innate and adaptive immune responses in infection and inflammation control. (N.B.: The therapeutic role of TFEB in cancer is currently controversial and was deliberately left out in the diagram).

adaptive and innate immunity.

Autophagy also plays a critical role in limiting excessive inflammation. During inflammation, autophagy is induced in macrophages to regulate the inflammatory process by targeted elimination of active inflammasomes and inhibiting IL-1β production (Shi et al., 2012). Additionally, autophagy regulates DC maturation and antigen presentation, which are crucial for the priming of naïve T cells and regulatory T cells (Treg) that help control autoimmune and inflammatory responses (Deretic, Saitoh and Akira, 2013). Thus, TFEB-induced autophagy impacts different components of the immune system, acting both proinflammatory and anti-inflammatory in infections and autoimmune diseases.

Coxsackievirus B3 (CVB3), a common cause of viral myocarditis and neurological disorders in infants and young children, was found to disrupt autophagy by targeting TFEB with the CVB3 viral proteinase 3 C (Mohamud et al., 2021). TFEB is digested by the proteinase into lower-molecular mass (~63 kDa) fragments, which despite retaining the ability to translocate into the nucleus and bind TFEB target genes, had lower transcriptional activity. *Salmonella* and *S. aureus* are two common disease-causing bacteria in humans. While macrophages recognize and phagocytose these bacteria, they escape from digestion and can survive causing infectious diseases (Rao et al., 2020). *Salmonella* adapts by activating caspase-1 to inhibit TFEB activation and impair lysosome degradation. In *S. aureus* infection, however, the expression and activation of TFEB in macrophages were enhanced early but later dysregulated following mTOR activation (Rao et al., 2020). This is a clear indication that targeting TFEB can be an effective strategy for fighting pathogens, including viral and bacterial infectious diseases.

4.2. Stem cell and dysfunctional tissue repair and regeneration

Normal healthy aging requires growth and the repair of damaged tissue, which involves stem cell division and differentiation (Goodell and Rando, 2015). In embryos, embryonic stem cells divide and differentiate into specialized cells that form different tissues, organs, and organ systems (Fuchs and Segre, 2000). Adult stem cells are also found in various body organs, including the brain, eyes, blood, heart, liver, bone marrow, skin, and muscle. The type of cell an adult stem cell differentiates into after division is defined by its location. For instance, an adult stem cell in the bone marrow usually differentiates into a blood or immune cell, but rarely other cell types (Fuchs and Segre, 2000).

In adult neural stem cells, TFEB-mediated autophagy plays a crucial role in promoting quiescence to maintain the cells over extended periods until they are needed for regeneration (Kobayashi et al., 2019). TFEB activation in *C. elegans* under starvation maintains a long-lived quiescent state by increasing protein synthesis and mitochondrial fusion via other signaling pathways, suggesting that besides autophagy other TFEB-mediated mechanisms also contribute to stem cell quiescence and preservation (Gerisch et al., 2020). Thus, TFEB activation may be a strategy for overcoming stem cell dysfunction and decreased tissue repair and regeneration in aging.

Tissue-resident stem cells possess anti-inflammatory properties, which have been linked to their influence on macrophage polarization (Yuan et al., 2020). Activated macrophages differentiate into two subtypes, M1 and M2, with M1 macrophages involved in pro-inflammatory responses and M2 macrophages involved in anti-inflammatory responses (Yuan et al., 2020). TFEB activation in mesenchymal stem cells of mice polarizes macrophages towards the M2 phenotype and suppresses inflammation, protecting against diabetic nephropathy. Mesenchymal stem cells also have a widespread effect on innate and adaptive immunity through the modulation of immune cells, direct cell-cell interactions, and the secretion of cytokines, growth factors, and chemokines (Wang et al., 2018). Therefore, TFEB expression in mesenchymal stem cells may contribute to regulating tissue inflammation.

Myeloid stem cells normally differentiate into various types of blood cells. In acute myeloid leukemia, these stem cells do not fully differentiate into functional blood cells, resulting in the accumulation of abnormal myeloblasts in the bone marrow and blood. This leads to a decrease in normal blood cell production, including white and red blood cells, platelets, and mature granulocytes (Siveen et al., 2017). Differentiation therapy, which targets the differentiation block in the myeloblast cells, has been proposed as a potential intervention for this condition (Gocek and Marcinkowska, 2011). A recent in vitro study found that TFEB-induced autophagy promoted myeloid differentiation in primary leukemia cells and the NB4 leukemia cell line (Orfali et al., 2020), suggesting that TFEB expression may have a significant impact on myeloid stem cell differentiation, which underlies blood cancers. Due to these regulatory functions of TFEB in stem cells, its targeting may have therapeutic benefits in a variety of diseases, including blood cancers and disorders, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases, and aging.

4.3. CNS, neuroplasticity, and neurodegeneration

Age-associated decline in neuroplasticity and neurogenesis, contribute to neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and schizophrenia (Jellinger and Attems, 2013). Besides the neural stem cell decline, oxidative stress and glial-mediated inflammation also play a crucial role (Cohen and Torres, 2019; Spittau, 2017). Microglial autophagy-assisted phagocytosis in the CNS is beneficial, as it reduces oxidative stress through the removal of toxic protein aggregates (like lipofuscin, amyloid-beta), damaged mitochondria, and dead cells (Bao et al., 2016; Plaza-Zabala et al., 2017). In glial cells, it was shown that a decline in autophagy increased oxidative stress and induced senescence and the SASP in the CNS (Alirezaei et al., 2011; Wang and Xu, 2020). TFEB activation in microglia plays a pivotal role in the clearance of Aβ deposits in AD (Bao et al., 2016). Autophagy upregulation in neurons also achieves similar results in reducing oxidative stress, clearance of toxic protein aggregates, and protecting against neurodegeneration (Cortes and La Spada, 2019; Sánchez-Vidaña et al., 2023). Another vital role of autophagy in microglia is its involvement in synaptic development and plasticity, which regulate signal transmission across the neural circuitry (Andoh and Koyama, 2021). Mice with a specific knockout of the autophagy-related 7 gene in microglia and bone marrow cells had altered connectivity between brain regions and an increase in synapse-related proteins in the sensory cortex, indicating poor recycling of synaptic material phagocytosed by microglia (Kim et al., 2017). However, autophagy may also contribute to synaptic growth and neuronal plasticity independently of microglia, as demonstrated in flies (Collins et al., 2006). In *Drosophila melanogaster* larva, autophagy upregulation promoted neuromuscular junction development by controlling levels of an E3 ubiquitin ligase (called highwire) which inhibited synaptic growth (Collins et al., 2006). Given the well-established role of TFEB in promoting autophagy, it is a reasonable target for interventions aimed at improving microglia functions in neurodegenerative diseases.

Additionally, TFEB regulates neural signaling and anatomy in the CNS through the control of axon myelination by oligodendrocytes (Sun et al., 2018). TFEB becomes highly expressed in the oligodendrocytes during developmental myelination in specific regions of the murine brain (Sun et al., 2018). It was shown that in a region of the premyelinating oligodendrocytes, TFEB induced PUMA and Bax/Bak-dependent apoptotic cell death to selectively eliminate oligodendrocytes from typically unmyelinated brain regions (Sun et al., 2018). Since axon myelination determines the velocity of action potential propagation, oligodendrocyte-specific TFEB activation plays a key role in neural signal transmission (Suminaite et al., 2019). Taken together, TFEB expression in the CNS may have different effects, depending on which cell type expresses TFEB. Particularly the autophagy-enhancing effect in microglia may be beneficial in multiple neurodegenerative diseases (Cortes and La Spada, 2019).

4.4. Skeletal muscle

Skeletal muscles comprise 30–40% of the total body mass. Glycogen is synthesized in the liver and skeletal muscles, and muscle glycogen is used for energy production. Skeletal muscles release amino acids that stimulate glycogen conversion to glucose in the liver to maintain blood glucose homeostasis (Kanungo et al., 2018; Pedersen and Febbraio, 2012). As already discussed, physical exercise promotes skeletal muscle activity and activates TFEB which has therapeutic benefits in chronic diseases such as diabetes, obesity, and metabolic syndrome, by improving mitochondrial function, energy metabolism, and reducing oxidative stress and inflammation (Holloszy and Coyle, 2016; Mansueto et al., 2017; Sallam and Laher, 2016). During physical exercise, TFEB activation mediated by Ca^{2+}-dependent phosphatase, calcineurin, upregulates glucose uptake, glycogen synthesis, insulin sensitivity, and glucose and fatty acid metabolism, showing that TFEB is the central regulator of the beneficial effects of exercise on metabolism in skeletal muscles in an autophagy-independent manner (Mansueto et al., 2017). A similar result on exercise-induced TFEB activation is observed in the brain, although mediated by AMPK-SIRT1 signaling (Huang et al., 2019; Morais et al., 2023). TFEB-mediated activation of autophagy and exocytosis are, however, particularly critical in skeletal muscle metabolic adaptation (Sato et al., 2016). For example, TFEB-mediated exocytosis of dysfunctional autolysosomes and promotion of glycogen clearance can ameliorate progressive muscular weakness in models of Pompe disease, which is caused by lysosomal enzyme (α-glucosidase) deficiency (Sato et al., 2016). However, constitutive TFEB activation may promote muscle wasting (Du Bois et al., 2015), indicating that TFEB activation in skeletal muscles is necessary for muscle glycogen utilization and glucose transport, but when overactivated under healthy conditions, it may have adverse effects. Altogether, the fact that most age-related diseases are associated with physical inactivity and reduced TFEB expression supports the need for targeting TFEB in skeletal muscles as an antiaging strategy.

4.5. Adipose tissue, the liver, and metabolic diseases

Adipose tissue plays a critical role in converting excess carbohydrates to fat and vice versa, as well as in the synthesis and secretion of hormones and cytokines that regulate energy metabolism and inflammation. Therefore, adipose tissue modulates insulin sensitivity and fat storage, which are linked to various metabolic disorders, such as obesity, diabetes, atherosclerosis, and metabolic disorders (Choe et al., 2016; Coelho et al., 2013). Recently, it was found that TFEB activation in adipose tissue leads to the transformation from white adipose tissue into brown adipose tissue (BAT) that has fat-burning and therapeutic properties (Evans et al., 2019; Maixner et al., 2016). Adipocyte-specific TFEB overexpression in mice fed on a Western diet increased their metabolic rate and reversed obesity, insulin resistance, and other associated metabolic issues whereas TFEB knockout did the opposite (Evans et al., 2019; Sass et al., 2021). The therapeutic benefits of TFEB activation were mediated by the regulator of mitochondrial biogenesis PGC-1α. Similarly, during prolonged fasting, the liver synthesizes glucose from non-carbohydrate sources including fat through TFEB-PGC-1α signaling. In the murine liver, TFEB overexpression during starvation upregulates lipid metabolism via the PGC1α target gene and its downstream effector PPARα, promoting gluconeogenesis (Settembre et al., 2013). Thus, promoting TFEB expression in the liver and adipose tissue has the potential to be used as an intervention for weight loss, insulin resistance, and treating metabolic diseases, due to their unique fat catabolic properties.

4.6. Bone remodeling and osteoporosis

The age-dependent loss of bone mass, or osteoporosis, is partly dependent on the dysregulation of the bone remodeling process involving continuous resorption and replacement of new bone extracellular matrix (Demontiero et al., 2012). Bone remodeling is vital for bone repair and the maintenance of calcium homeostasis, through the exchange of minerals between bones and blood (Hadjidakis, Androulakis II, 2006). Osteoclasts are the bone cells that resorb bone and release Ca^{2+} while the osteoblasts are bone cells that form a new bone matrix (Hadjidakis, Androulakis II, 2006).

Bone resorption by osteoclasts, however, depends on proteolytic enzymes released into the resorption lacuna to lower the pH (~4.5) (Lacombe et al., 2013). Hence, lysosomal biogenesis is essential for bone resorption due to its involvement in lowering the pH of resorption lacuna (Lacombe et al., 2013). The osteoclast differentiation factor receptor activator of nuclear factor kappa-B ligand found in osteoclasts recruits protein kinase C beta, which promotes the phosphorylation and overexpression of TFEB (Ferron et al., 2013). Consequently, TFEB is activated which results in lysosomal biogenesis (Ferron et al., 2013). As the master regulator of lysosomal biogenesis, therefore, TFEB controls the bone resorption process. Additionally, TFEB regulates osteoblastic differentiation, by changing the expression levels of ATF4 and CCAAT/enhancer-binding protein homologous protein (Tsukuba et al., 2017). These findings explicitly demonstrate the modulatory role of TFEB on both bone formation and resorption, which are the determinants of bone mass. With these roles of TFEB in bone resorption by osteoclasts and osteoblastic differentiation, TFEB could be a therapeutic target for osteoporosis and other common metabolic bone diseases including, rickets, osteomalacia, osteogenesis imperfecta, Paget disease of bone, and fibrous dysplasia.

4.7. Cancer development, chemoresistance, and metastasis

Cancer development, chemoresistance, and metastasis are relevant topics for promoting healthy aging and extending lifespan. In 2020 alone, it was estimated that 19.3 million new cancer cases occurred worldwide and approximately 10.0 million deaths, calling for preventive and therapeutic measures for cancer control (Sung et al., 2021). Literature indicates that somatic genetic alterations influence cancer onset, but cancer progression is also dependent on the tumor microenvironment, which may favor or halt the expansion of cancer cells and confer resistance to the therapies (Astanina et al., 2021). Using whole-genome sequencing, somatic mutations in the *TFEB* gene were identified in some human melanomas, and renal and pancreatic cancers, implicating TFEB in the onset of these tumors (Astanina et al., 2021). Interestingly, oncology investigations demonstrate the involvement of both upregulated and downregulated TFEB-induced autophagy in cancer, and each could have tumor-suppressing or tumor-promoting roles depending on the context (Levy et al., 2017; White, 2015). For instance, impaired autophagy might promote genome instability and oncogene-induced senescence, leading to tumor initiation (White, 2015). Conversely, established cancers can upregulate autophagy to survive microenvironmental stress and growth, by suppressing the p53 tumor suppressor protein and enhancing nutrient recycling, DNA repair, and antiapoptotic mechanisms (White, 2015). The pro-survival role of autophagy may increase resistance of cancers, including solid tumor glioma, osteosarcoma, and non-solid tumor acute myeloid leukemia, against chemotherapy treatment (Li et al., 2019). The effect of targeting autophagy in cancer therapy, therefore, has been demonstrated to be context-dependent (Levy et al., 2017; Li et al., 2019). It is argued that to address whether to induce or inhibit autophagy as a cancer therapy, it is needed to establish if it is a premalignant lesion, or the results of mutation accumulation in more advanced cancer stages, because enhancing autophagy is protective in the former stage, whereas in the latter, the reports are inconsistent (Galluzzi et al., 2015; Levy et al., 2017).

Lysosomal degradation of mutated cells is crucial for eliminating damaged or mutated cells and preventing tumor growth. However, lysosome dynamics, in terms of motility and positioning, are of importance in the regulation of tumor invasion and metastasis (Pu et al.,

2016). A recent study discovered that unique changes in the lysosomal landscape occur in bladder cancer to promote the disease (Mathur et al., 2023). Using a cellular bladder cancer model, Mathur and coworkers identified a phenotype of peripheral lysosome positioning prevailing in bladder cancer cell lines but not normal urothelium. It was demonstrated that TFEB controlled endomembrane phosphatidylinositol-3-phosphate levels which recruit FYVE-domain containing proteins for lysosomal dispersion, through VPS34 activation in aggressive bladder cancer cells (Mathur et al., 2023). These results highlight a novel, special mediatory role of TFEB in on tumor invasion and metastasis. In pancreatic cancer, TFEB was shown to be overexpressed, and TFEB inhibition suppressed tumor growth by downregulating glutaminase transcription and glutamine metabolism independent of autophagy (Kim et al., 2021). EGR1, a newly discovered transcriptional regulator of TFEB, was found to alter TFEB overexpression and several cell cycle regulators in Birt-Hogg-Dubé syndrome (an inherited cancer associated with TFEB activation) (Cesana et al., 2023). Collectively, targeting TFEB in cancer can modulate diverse cell mechanisms, including lysosomal positioning, autophagy, cell cycle, epithelial-mesenchymal transition, energy metabolism, angiogenesis, and inflammation, contributing to cancer cell proliferation (Astanina et al., 2021). However, further research is necessary to determine if in specific cases and stages of cancer TFEB activation cmay have therapeutic potential. However, this is unlikely in certain cancers with constitutive activation of TFEB which may trigger mTORC1 activity and promote tumor growth (Cesana et al., 2023; Di Malta et al., 2017).

5. Perspectives and conclusion

Aging and age-related diseases pose significant challenges for a globally aging population. Presently, strategies aimed at TFEB overexpression or activation, including caloric restriction/intermittent fasting, physical exercise, and caloric restriction mimetics, have shown promising therapeutic in extending lifespan and treating a range of diseases, including neurodegenerative disorders, metabolic diseases, and cancer in model organisms, mice primates, and humans (de Cabo and Mattson, 2019; Madeo et al., 2019). Here, we analyzed results from several studies to support the roles of TFEB in modulating the hallmarks of aging and age-related disorders, beyond just the perspective of autophagy and lysosomal biogenesis. Hence, in the review, we illustrated the impact of TFEB activation on cellular processes including mitochondrial biogenesis and energy metabolism, DNA repair, nutrient homeostasis, oxidative stress, inflammation, vascular development, cellular senescence, and cell regenerative capacity.

A major concern, however, with TFEB activation is the potential for adverse side effects which may arise from the crosstalk with mTOR. Studies have reported adverse side effects, such as wound-healing complications, hyperglycemia, dyslipidemia, proteinuria, nephrotoxicity, pneumonitis, anemia, hypertension, and gonadal dysfunction, observed following TFEB activation induced by inhibiting mTOR (Kaplan et al., 2014; Pallet and Legendre, 2013), suggesting that there may be the need for utilizing alternate pathways for TFEB activation that circumvent mTOR as an antiaging strategy. This is because the mTORC1 pathway regulates many cellular processes, including ribosomal biogenesis, mRNA translation, lipid and nucleotide synthesis, and mitochondrial function, which promote cell growth and metabolism (Ardestani et al., 2018; Takei and Nawa, 2014). Also, it is worth noting that there is feedback regulation from TFEB activation to increased mTORC1 activity in cancer cells from donors tissue and murine models, which is mediated by the transcriptional upregulation of the Rag GTPase component Rag D (Di Malta et al., 2017; Ramirez Reyes et al., 2021). This mechanism is responsible for cell hyper-proliferation and cancer growth after starvation and physical exercise. The implication is that while starvation-induced TFEB activation may be beneficial to cancer in the short term by managing energy metabolism in a nutrient-starved environment, once nutrient levels are restored in patients with cancer, tumors are likely to grow when normal feeding is resumed because of the increased mTOR activation (Di Malta et al., 2017). Another challenge is related to the issue-specific effects of TFEB, in that TFEB activation can have different effects in different tissues and cell types. Therefore, it is possible that activating TFEB in one tissue could have unintended consequences in other tissues or organs.

Studies in model organisms, such as planaria and hydra, led to the understanding that the preservation of tissue regenerative capacity is important for avoiding the gradual decline in fitness and ultimately death (Rando and Jones, 2021). Experimental studies using strategies targeted at reversing senescence and expanding the stem cell pool, such as heterochronic parabiosis and cellular reprogramming, have proven the efficacy of tissue regeneration in countering degenerative diseases and age-related tissue dysfunction (Rando and Jones, 2021). Interestingly, a current regenerative technology using exosomes from embryonic stem cells to rejuvenate neuronal stem cells was found to be dependent on TFEB activation (Hu et al., 2020). A role of TFEB in cell reprogramming and tissue regeneration is also supported by others (Wang et al., 2021; Zhang et al., 2019), and may hold the key to overcoming the aging menace. Overall, the evidence of TFEB activation being an important regulatory pathway induced by healthy lifestyle interventions, such as calorie restriction and exercise, supports TFEB as a promising avenue for promoting health and longevity. TFEB activation affects the cellular functions in nearly every cell type from the undifferentiated stem cells up to the highly specialized postmitotic cells in the body. This warrants future research into the development of safe and effective methods for activating TFEB in humans and its long-term effects on health and aging.

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CRediT authorship contribution statement

Conceptualization, data curation, and the writing of the original draft were done by S.A.; S.A. and D.Y.T. were responsible for formal analysis, funding acquisition, and methodology; G.K. edited the original draft. All authors reviewed the revised draft and approved the submission.

Declaration of Competing Interest

The authors declare no known financial/personal interest that constitutes a potential conflict in the publication of this article.

Data availability

Data will be made available on request.

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Declarations of interest

None.

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