Review

MiT/TFE (TFEB/TFE3) Pathways in Pulmonary Diseases: Current Evidence and Emerging Mechanisms

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Review

MiT/TFE (TFEB/TFE3) Pathways in Pulmonary Diseases: Current Evidence and Emerging Mechanisms

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Abstract

The MiT/TFE family transcription factors play a critical role in regulating lysosomal biogenesis, autophagy, mitochondrial turnover and lipid catabolism by regulating the CLEAR gene network. The dysregulation of MiT/TFE activity has been implicated in the onset and progression of cancer and neurodegeneration but its functions in association with pulmonary diseases remain poorly understood. Thus, elucidating the role of MiT/TFE proteins in cellular homeostasis in the lung is crucial for understanding the origin and progression of pulmonary diseases such as inflammation, disrupted repair mechanisms, and fibrosis. In this review we systematically summarize the findings from human pulmonary diseases and associated genetic disorders, such as asthma, cancer, Birt-Hogg-Dube (BHD) syndrome, and lung injury models that implicate MiT/TFE dysregulation in pathogenic progression. We also discussed MiT/TFE regulation and signaling through pathways involving mTORC1, AMPK, and lysosomal stress in different cellular contexts. Finally, we discussed significant mechanistic gaps, such as the absence of in vivo models targeting the combined activity of TFEB and TFE3 in disease progression and prevention. In conclusion, these insights seek to offer a comprehensive framework for understanding MiT/TFE signaling in human lung diseases and could present a promising opportunity for directing future mechanistic and translational research.

Keywords: MiTF; TFEB; TFE3; cancer; lung injury; asthma; lysosome-autophagy pathway; BHD

1. Introduction

The microphthalmia/transcription factor E (MiT/TFE) family comprises a small group of evolutionarily conserved transcription factors that play central roles in cellular adaptation to metabolic and environmental stress [1,2]. Members of this family belong to the basic helix-loop-helix leucine zipper (bHLH-LZ) superfamily of transcription factors, which includes regulators such as MYC, MAX, SREBP, USF, MLX, and AP4 [3–6]. In vertebrates, the MiT/TFE family consists of four closely related proteins: microphthalmia-associated transcription factor (MITF), transcription factor EB (TFEB), TFE3, and TFEC. These proteins form homo- or heterodimers via their leucine zipper domains and bind DNA through a conserved basic region that recognizes E-box motifs (CANNTG) and/or M-box motif (CATGTG) and modified E-box motif containing CLEAR (Coordinated Lysosomal Expression And Regulation) element, a palindromic 10-base-pair motif (GTCACGTGAC) within downstream target gene promoters [7–9].

TFEB was first identified as a transcriptional regulator of the CLEAR network, a discovery that established MiT/TFE proteins as master regulators of lysosomal biogenesis and autophagy[10]. Subsequent studies demonstrated that TFE3 and MITF can also bind CLEAR elements, highlighting functional redundancy and cooperation among family members [1,11–13]. These transcription factors coordinate a broad transcriptional program that extends beyond lysosomal gene expression to genes

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involved in autophagy initiation, autophagosome formation and trafficking, lysosome-autophagosome fusion, extracellular vesicle trafficking and selective degradation pathways such as mitophagy [11,12,14–17]. Through these functions, MiT/TFE proteins promote cellular catabolic and recycling processes, thereby supporting metabolic homeostasis under nutrient deprivation, organelle damage, and other stress conditions. In addition to this, MiT/TFE factors have also been implicated in nutrient sensing, energy metabolism, mitochondrial biogenesis, oxidative and endoplasmic reticulum stress responses, innate immunity and inflammation, cell fate determination, aging, and tissue-specific differentiation programs [18–34].

At the molecular level, MiT/TFE proteins activity is tightly regulated by post-translational modifications, most prominently phosphorylation, which integrates upstream signals from nutrient-, stress- and growth factors- sensing pathways. Under nutrient- replete condition, the mechanistic target of rapamycin complex 1 (mTORC1) act as a central negative regulator of TFEB and TFE3 by phosphorylating conserved serine residues that promote 14-3-3 mediated cytoplasmic retention [35–37]. Conversely, nutrient starvation, lysosomal dysregulation, mitochondrial dysfunction, or calcium signaling induces MiT/TFE dephosphorylation, nuclear translocation, and transcriptional activation of downstream transcriptional program. Other post-translational modifications include ubiquitination, acetylation, SUMOylation, and dephosphorylation that also implicate in the fine tuning of MiT/TFE stability and activity as mTORC1-independent mechanisms in a tissue- and context-dependent manner.

Dysregulation of MiT/TFE signaling is associated with a wide spectrum of human diseases. Aberrant activation of TFEB and TFE3 contributes to tumorigenesis, neurodegenerative disorders and lysosomal storage diseases. Owing to their central role in coordinating lysosomal and autophagic pathways, MiT/TFE transcription factors have emerged as attractive therapeutic targets. Here, we review the emerging role of MiT/TFE proteins in pulmonary disease and summarize recent progress in defining the mechanisms that regulate their activity in the lung.

2. Regulation of MiTF/TFE Transcription Factors

2.1. MITF

The microphthalmia-associated transcription factor (MITF) is a highly conserved transcription factor that plays a critical role in melanocyte development, differentiation, and survival, as well as in melanoma pathology. MITF gene is located on chromosome 3 (approximately 230,000 bp) in human and chromosome 6 (approximately 215,000 bp) in mouse, respectively [38]. Multiple protein isoforms of MITF with different N-terminal regions are generated by using alternative promoters and splicing, allowing tissue specific regulation [39,40]. For example, In melanocytes, MITF-A [41], and MITF-M [42,43] are key isoforms associated with distinct biological functions ranging from melanocyte differentiation to the survival and invasion of melanoma cells [44]. MITF expression and activity are regulated at transcriptional, post-transcriptional, and post-translational levels. At the transcriptional level, MITF is primarily regulated by transcription factors such as SOX10, PAX3, ATF4, GLI2 and BRN2 (POU3F2), which either activate or repress MITF expression depending on the tissue- or cellular- context. For example, PAX3 and SOX10 enhances MITF transcription, linking it to melanocyte viability [45–47], while BRN2 and GLI2 represses MITF in specific melanoma subpopulations [48,49]. MITF promoter contains multiple cis-acting elements and cAMP-responsive elements (CREs) where various signaling pathways including Wnt/β-catenin, BRAF/MAPK/ERK, PI3K/AKT/mTOR, Notch, cAMP/PKA Pathway and TGF-β signaling converge to modulate its expression and activity [37,50–53]. Post-translational modifications, such as phosphorylation [39] , SUMOylation [54,55] and acetylation [56], affect MITF driven transcriptional programs, MITF stability, and target selectivity [44].

2.2. TFEB

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TFEB is the most extensively studied and best characterized member of the MiT/TFE family, due to its central role in coordinating autophagy and lysosomal biogenesis and ubiquitous expression pattern. The human *TFEB* locus spans approximately 51,000 bp on chromosome 6, whereas mouse *Tfeb* is located on chromosome 17, and extends over 55,000 bp [57]. TFEB is expressed as multiple alternatively spliced transcript isoforms, such as TFEB-A, TFEB-B, TFEB-C, TFEB-D, TFEB-E, TFEB-F, and TFEB-G, have distinct tissue distribution profile [58]. Several transcription factors such as XBP1, PGC-1α, PPARα, and MYC regulate TFEB expression and regulate its downstream pathways. XBP1, PGC-1α and PPARα activates TFEB expression by directly binding to TFEB promoter [59–61] whereas MYC acts as a repressor by directly binding on MYC response elements on TFEB promoter [62,63]. TFEB activity is also regulated through a self-regulatory positive feedback mechanism under nutrient starvation where TFEB binds to CLEAR elements of PGC-1α and PPARα, in response inducing TFEB expression [64].

TFEB activity is strictly regulated by its nucleocytoplasmic localization, controlled by nutrient-sensing signaling at the lysosomal surface and post-translational modifications. TFEB has more than 20 phosphorylation sites, including multiple residues phosphorylated by mTORC1, act as major regulator of TFEB. However, this control is not uniform across systems and appears complex and context dependent. Under nutrient-replete conditions, mTORC1 phosphorylates TFEB at S211 and also at S142 [65,66]. Phosphorylation at Ser211 promotes TFEB binding to 14-3-3 proteins, which retain TFEB in the cytoplasm [66,67]. Under nutrient limiting condition or impaired lysosomal function, TFEB gets dephosphorylated, disengages from 14-3-3, and translocate to the nucleus. Nuclear TFEB activates CLEAR target genes to restore lysosomal homeostasis and cellular clearance capacity [66–69]. Studies also suggest that loss of phosphorylation only at S211 is not sufficient to drive TFEB import into the nucleus, as S211A TFEB mutant remains responsive to mTORC1 [70]. Celis et al identified S122 as a direct mTOR phosphorylation site, and a phosphomimetic S122 substitution largely attenuates the response of TFEB to MTORC1 inhibition [70]. Together, these findings support a multistep model in which MTORC1 regulates TFEB through coordinated phosphorylation at multiple sites, rather than through S211 alone.

Growth factors, mitogens, nutrients (such as amino acids), and stress signals integrate at the lysosomal surface, and this integration tightly regulates mTORC1-TFEB rheostat. RTK signaling (such as insulin or IGF) activates the PI3K–AKT pathway [71–74], and mitogens activate the RAS–RAF–MEK–ERK pathway [75,76]. Both signaling pathways converge at the TSC1–TSC2–TBC1D7 complex upstream to mTORC1, ultimately releases TSC-mediated inhibition of Rheb [77,78]. This reduction allows Rheb-GTP to directly activate mTORC1 [79,80]. Concurrently, amino acids regulate mTORC1 by influencing their recruitment to lysosomes through RagA/B-RagC/D GTPases and the Ragulator-v-ATPase platform [81–83]. This process is further modulated by GATOR1/GATOR2 and nutrient sensors like Sestrins for leucine, CASTOR for arginine, and SAMTOR for methionine/S-adenosylmethionine, along with lysosomal amino acid transport and sensing components such as SLC38A9 [84–89]. Glucose and energy sensor AMPK promote TFEB pathway activation through upstream remodeling of the Rag–mTORC1 via AMPK-mediated phosphorylation of FNIP1 suppresses FLCN–FNIP function [90]. Starvation and lysosomal stress also release lysosomal Ca^{2+} via MCOLN1/TRPML1 and activates calcineurin that dephosphorylates TFEB [91,92]. Because TFEB is a critical substrate associated with lysosomes downstream to mTORC1, the combined effects of Rheb-driven activation and Rag-mediated lysosomal positioning determine TFEB's phosphorylation and 14-3-3 binding. This, in turn, dictates whether TFEB remains in the cytosol or enters the nucleus to activate CLEAR genes involved in lysosomal function and autophagy.

2.3. TFE3

TFE3, or transcription factor E3 (Transcription Factor binding to IGHM Enhancer 3) is another MiT/TFE family transcription factor that shares significant similarities with TFEB in terms of protein structure and function. TFE3 is expressed ubiquitously with highest expression pattern in placenta, lung, and adrenal gland [58]. The TFE3 gene is located on the short arm of the X-chromosome in both

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mouse and human (Xp11.2) [93]. Through the use of alternative transcription start sites, TFE3 is expressed as two main isoforms, a long and a short form [93,94]. Both isoforms utilize the same Rags/mTORC1-dependent regulatory mechanism and have a similar ability to trigger the expression of lysosomal and autophagic genes when activated. However, the short isoform is missing the N-terminal 105 amino acid residues, which include a phosphorylation-ubiquitin ligase recognition site that targets it for degradation by the proteasome, known as a phosphodegron. As a result, this short isoform is consistently expressed at high levels in most cells [94].

TFE3 and TFEB share several overlapping functions. TFE3 and TFEB are partially redundant in certain functions such as inducing lysosomal biogenesis [95] and controlling CD40 ligand expression [96]. Additionally, both factors play a role in helping cells cope with stress in the endoplasmic reticulum (ER) by promoting the expression of ATF4 and other genes involved in the unfolded protein response (UPR) [27,97,98]. However, if ER stress persists, the activation of TFEB and TFE3 may lead to cell death. This occurs either by directly triggering pro-apoptotic genes like CHOP and PUMA or indirectly by increasing ATF4 levels, which can subsequently induce CHOP and PUMA expression. Collectively, these findings indicate that the TFEB/TFE3–ATF4 signaling pathway can either support cell survival or lead to apoptosis, depending upon the stress intensity and duration. MiT/TFE factors (including TFEB/TFE3) have also been linked to selective autophagy programs such as ER-phagy, where TFEB/TFE3 can induce the ER-phagy receptor FAM134B during prolonged starvation [99]. However, they also have their unique functions. For example, global deletion of Tfeb results in early embryonic lethal in mice due to placental defects whereas Tfe3 knockout has no abnormal phenotypes under physiological conditions. In addition to the common target gene set, they may also have their unique target genes in different cellular context [100].

2.4. TFEC

TFEC is the only member in the family that lacks the transactivation domain. The human TFEC gene maps to chromosome 7q31.2, while the mouse Tfec gene is on chromosome 6. TFEC has 3 isoforms, TFEC-A, TFEC-B and TFEC-C. TFEC-A and TFEC-B are generated by alternative transcription start sites. Using 5′-RACE in human kidney cDNA, a third transcript (TFEC-C) was identified that starts from a distinct 5′ exon (exon 1c) located between exons 3 and 4. TFEC have restricted, tissue-specific expression, with each variant displaying a distinct distribution pattern across organs. For example, TFEC-A is enriched in testis, thymus, trachea, colon, and prostate, TFEC-B is more broadly expressed (largely absent from heart and liver), and TFEC-C is restricted to kidney and small intestine [58].

TFEC has been reported to heterodimerize with TFE3 and antagonizes TFE3-driven transactivation and transcriptional programs [101]. TFEC is expressed strongly and selectively in macrophages [102], and TFEC-knockout mice develop normally without obvious abnormalities [103]. Rehli et al have further shown IL-4 dependent TFEC expression through STAT6 in macrophages, and loss of TFEC reduces a small set of IL-4–responsive genes, including Csf3r (the G-CSF receptor) [103]. Another study using OVA-induced allergic asthma mice model showed that IL-4 induced TFEC can bind the IL-4Rα promoter and boost IL-4Rα expression, creating an IL-4–TFEC–IL-4Rα positive feedback loop that supports M2 macrophage polarization [104,105]. Altogether, TFEC and its associated functions remain poorly characterized. Therefore, additional studies are needed to define TFEC's roles across different human tissues and cell types.

3. Role in Human Pulmonary Diseases

MiT/TFE transcription factors (TFEB, TFE3, MITF, and TFEC) have been studied mainly in neurodegeneration, cancer, and immune regulation, where MiT/TFE proteins control lysosome–autophagy programs, cellular metabolism, and innate immune gene responses. In contrast, their roles in pulmonary biology and lung diseases remain less defined. Most lung-focused work to date has centered on lung cancer and asthma/allergic airway inflammation, where TFEB-linked lysosomal programs and TFEB regulation in airway/immune compartments have been implicated in disease

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mechanisms. Together, these emerging findings highlight a growing need to systematically investigate MiT/TFE signaling across a wider range of pulmonary diseases.

3.1. Lung Tumors and Cancer Progression

The role of MITF in lung tumor and cancer progression vary depending on the types of cancer cells studied. In lung adenocarcinoma-derived A549 cells, an increase in MITF activity has been associated with resistance to cisplatin (DDP) chemotherapy, as well as enhanced lysosomal biogenesis and autophagy. This indicates a stress-tolerance mechanism that may mitigate the effects of cytotoxic treatments [106]. Hsiao et al have demonstrated higher expression of MITF in low-invasive CL1-0 lung adenocarcinoma cells. Both xenograft mouse model and in vitro studies showed *MITF* knockdown enhances metastasis and tumorigenesis [107]. Whole-transcriptome analyses and ChIP assays in lung adenocarcinoma suggest that MITF directly binds to promoter of FZD7, PTGR1, and ANXA1 and act as transcriptional repressor to attenuates cell cycle progression, invasion and WNT signaling [107].

Elevated levels of TFEB are linked to poor prognosis in non-small cell lung cancer (NSCLC) through its role in autophagy-lysosome pathway (ALP) that enhances tumor cell survival and migration, and confers resistance to therapeutic interventions [108,109]. In vitro studies using human lung cancer cells (393P) showed knockdown of TFEB entirely and significantly reversed overexpression of CLEAR genes and Cathepsin D activity caused by the induction of TMEM106B, a lysosomal transmembrane protein as a critical driver of lung cancer metastasis [110]. A recent study examining lung adenocarcinoma cohorts has identified TFEB as a key factor influencing therapy sensitivity, rather than serving as a consistent pro-resistance lysosomal driver. Elevated levels of TFEB were correlated with improved patient survival rates and a transporter profile (high ABCA1 and low ABCC1 expression) that increase sensitivity to chemotherapy drug cisplatin [111]. In contrast, loss of TFEB led to increased ABCC1-dependent drug efflux and maintenance of mitochondrial ATP/OXPHOS under stress and therefore promotes resistance to platinum-based therapies. Additionally, TFEB was found to support a SREBP2-cholesterol/isoprenoid (IPP) pathway, which enhanced the activation and immune-killing capabilities of Vγ9Vδ2 T-cells through ABCA1-associated metabolite efflux [111]. Thus, in NSCLC, TFEB level seems to affect sensitivity of cancer cells to treatment. When TFEB levels are low, there is a decreased response to chemotherapy and immune system attacks. A specific transcriptional signature, marked by low TFEB, low ABCA1, and high ABCC1, has been suggested as an indicator of poor outcomes to both chemotherapy and immunotherapy. To counteract this resistance in tumors with low TFEB, it might be possible to restore their vulnerability by targeting the pathways regulated by TFEB.

TFE3 can directly promote pro-proliferative programs by binding the hTERT promoter to support telomerase expression and cell-cycle progression [112]. Simultaneously, TFE3 gene fusions characterize rare yet significant subsets of pulmonary tumors where TFE3 is under abnormal regulatory control or form chimeric transcriptional proteins. The YAP1-TFE3 fusion is notably recurrent in clear cell stromal tumor of the lung (CCST-L) [113], Perivascular epithelioid cell tumor (PEComas) [114] and pulmonary epithelioid hemangioendothelioma [115] as evidenced by numerous studies and case reports, establishing it as a molecularly distinct entity. Additionally, TFE3 rearrangements appear in exceedingly rare conditions such as pulmonary alveolar soft part sarcoma [116], where molecular confirmation of the ASPSCR1-TFE3 fusion and TFE3 by immunohistochemistry and fluorescence in situ hybridization (IHC/FISH) prove diagnostically valuable. Within epithelioid hemangioendothelioma (EHE), cases positive for YAP1-TFE3 fusions have been identified as a distinct molecular subset. Moreover, the spectrum of these fusions is expanding with the discovery of non-canonical TFE3 fusions, such as RREB1-TFE3 [117]. Therapeutic treatment of D-mannose enhanced TFE3-driven lysosomal biogenesis, accelerating wild type EGFR and mutant EGFR (E746-A750 deletion, L858R and T790M mutations) degradation in lysosomes and suppressing NSCLC progression in vitro and in xenograft tumor mouse model [118].

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3.2. Asthma

In asthma or allergic airway inflammation, the lysosomal-autophagic machinery could act either as a protective mechanism or a harmful one, depending upon the specific cell type, the trigger involved, and the stage of the disease. TFEB is emerging as important regulator of stress responses in asthma. Using severe asthma mouse model by intranasal administration of house dust mite (HDM)/c-di-GMP, elevated TFEB activity, achieved by pre-treatment with dexamethasone or trehalose intraperitoneally, dampen NLRP3-dependent inflammatory responses in monocytes and improve disease features [119]. A recent study showed reduced TFEB and other lysosomal gene expressions in airway epithelial cells of ovalbumin induced and HDM-induced asthma mouse models. It also showed that the expression of inflammatory cytokines (*nlrp3*, *IL-1β*, and *tslp)* was enhanced. Further, microscopy imaging from tissue sections of OVA treated mice demonstrated SUMO1 expression in airway epithelial cells and in vitro co-immunoprecipitation experiment supported the increased TFEB SUMOylation upon ovalbumin treatment in BEAS-2B cells. Thus, TFEB SUMOylation inhibits lysosomal biogenesis and promotes asthma development in airway epithelial cells [120]. TFEB have also been reported to influence adaptive immunity by regulating dendritic-cell antigen presentation, including effects on MHC II and co-stimulatory molecules, with downstream consequences for immune balance [121]. Another study using OVA- and papain-induced asthma model demonstrated increased TFEB-mediated autophagy with higher ATG5 and LC3 II expressions. Neuropeptide S/NPS receptor expression was found to be high in asthma mouse model. Further, in vitro studies showed NPS/NPSR expression induces TFEB expression activity in airway epithelial cells. Thus, NPS/NPSR signaling has been shown to aggravate asthma via a TFEB-dependent autophagy pathway in bronchial epithelial cells, highlighting stimulus- and context-specific outcomes [122].

3.3. COPD/Emphysema

Limited studies have been performed to examine the roles of MiTF/TFE family transcription factors in COPD/emphysema. In longitudinal lung tissue sections from patients with COPD-emphysema, nuclear localization of TFEB decreases with severity of the disease while perinuclear localization of TFEB increases in samples with severe emphysema compared to non-emphysema and mild emphysema [123]. Increased perinuclear TFEB was also observed in smokers compared to non-smokers. Interestingly, cigarette smoke-induced emphysema-like lung histopathology and the associated autophagy impairment, inflammation, and apoptosis in mice can be rescued by gemfibrozil-mediated TFEB induction. Separate studies also show that TFEB alteration may mediate cigarette smoke-induced lung emphysematous pathology by a variety of mechanisms including increased TFEB oxidation and nuclear localization, TFEB expression [124], and autophagy impairment [125].

3.4. Interstitial Lung Diseases

3.4.1. Birt–Hogg–Dubé (BHD) Syndrome

BHD syndrome is an autosomal-dominant disease characterized by facial fibrofolliculomas, renal tumor, and cystic lung disease. Up to 90% of individuals with BHD develop pulmonary cysts, with pneumothorax occurring in ~30% [126,127]. Mechanistically, under nutrient starvation, the FLCN-FNIP complex functions as a GTPase-activating protein, leading to the inactivation of RagC/D. A major advance came from the demonstration of a substrate-selective mTORC1 pathway in which TFEB phosphorylation depends strongly on RagC/D–mediated amino-acid signaling explaining how FLCN loss can preferentially dysregulate TFEB control and drive disease phenotypes [4]. In vivo studies showed that constitutive TFEB activation is a key driver of the kidney cyst/cancer-like phenotype in BHD mou[126,127se models and that TFEB depletion rescues the renal disease features, positioning TFEB as a central effector downstream of FLCN–Rag–mTORC1 signaling in BHD [16].

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Upon FLCN inactivation, TFE3 becomes dephosphorylated shuttles to nucleus and activates its downstream signaling relevant to tumorigenesis [128]. While pulmonary cyst formation in BHD remains an active area of investigation, current models emphasize that FLCN loss disrupts mesenchymal homeostasis and mechanobiology in the lung [129]. In vitro studies using human fetal lung fibroblasts (MRC-5) demonstrate FLCN inactivation with ~ 100-fold decrease in Wnt2 expression and a 33-fold decrease in Wnt7b expression, indicating that abnormalities in the WNT pathway's developmental signals. Upon silencing the transcription factor TFE3 in FLCN deficient cells completely reversed this phenotype. Thus, FLCN via TFE3 might play a role in the development of pulmonary cysts associated with BHD [130].

3.4.2. Lymphangioleiomyomatosis (LAM)

LAM is a rare cystic lung disorder characterized by the infiltration of the lung by abnormal, smooth-muscle–like LAM cells, associated with a gradual disruption of the tissue architecture. LAM occurs in two forms, sporadic LAM (S-LAM) [131] [132] and tuberous sclerosis complex-associated LAM (TSC-LAM) also known as familial LAM (F-LAM) [133,134]. In S-LAM, LAM cells or niche cells usually harbor somatic mutations in the TSC2 gene, whereas in F-LAM, the underlying issue involves germline disruptions in TSC1 or TSC2 genes [135]. LAM predominantly affects women due to risk factors associated with elevated estrogen levels, such as during pregnancy or with external estrogen exposure [136–138]. The critical involvement of the mTOR pathway in LAM is highlighted by findings that sirolimus (an mTORC1 inhibitor) can help stabilize lung function and enhance clinical outcomes during treatment [139–141]. Currently there is no direct evidence reporting MITF/TFE protein involvement in LAM progression. Paradoxically, despite high mTORC1 in LAM cells, TFEB is often nuclear and active. TFEB also promotes mTORC1 activation via Rag GTPases, creating a feedback loop for mTORC1 activation [142]. Recent single cell RNAseq [143] and spatial transcriptomics studies [144–146] using LAMS patient samples also showed GPNMB, PMEL, and CTSK as differentially expressed genes in LAM core niche cells. Thus, investigating MITF/TFE proteins role in LAM could provide insights into how dysregulation of mTORC1 and TFEB/TFE3 alters lysosome-autophagy pathways and metabolic processes in LAM cells, and associated niche cells.

3.4.3. Pulmonary Lysosomal Storage Diseases (LSDs)

Pulmonary lysosomal storage diseases (LSDs) are a group of inherited disorders characterized by the accumulation of lysosomal substrates in lung cells due to lysosomal dysfunction [147,148]. This accumulation can lead to patterns such as interstitial lung disease (ILD) and the "storage" phenotypes of alveolar macrophages, with Gaucher disease and Niemann–Pick diseases serving as classic examples [149]. In these disorders, lung involvement may manifest as ILD features observable through imaging, necessitating clinical awareness as part of the disease spectrum [149–151]. Mechanistically, TFEB and TFE3 play a crucial role, as TFEB acts as the primary transcriptional regulator of a coordinated lysosomal gene network, known as CLEAR, and becomes activated (translocating to the nucleus) in response to lysosomal stress or storage conditions. In LSD models, enhancing TFEB activity by treating with sulforaphane, a small molecule TFEB agonist promotes lysosomal exocytosis and facilitates cellular clearance, thereby ameliorating storage phenotypes both in vitro and in vivo, which supports the role of TFEB as a functional "lysosomal capacity" switch [152]. Additionally, TFEB and TFE3 influence innate immune cells by promoting lysosomal biogenesis and autophagy, thereby shaping inflammatory responses—an important consideration for pulmonary LSDs, where alveolar macrophages are key drivers of storage and inflammation. Collectively, these studies suggest that profiling and functionally testing TFEB/TFE3 pathways in lung macrophages and epithelial cells from pulmonary LSD patients could elucidate disease variability and aid in developing therapeutic strategies.

3.5. Acute Lung Injury and Fibrosis

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In acute lung injury (ALI) and fibrotic remodeling, mainly TFEB and TFE3, act as stress-response regulators that adjust autophagy/lysosome function, inflammation, and cellular metabolism. Increasing TFEB activity is protective against injury as demonstrated in LPS induced ALI mouse models and in vitro experiments. For example, TFEB overexpression reduced inflammation and mitochondrial damage by boosting mitophagy [153]. In silica-induced lung injury mouse model, where alveolar macrophages develop lysosomal stress and impaired autophagy flux, trehalose induced TFEB activity improves lysosomal function and autophagy flux and thus reduces fibrotic progression [154]. Another study using mouse model of elastase- and cigarette smoke-induced emphysema (PiZ model) showed that increased TFEB activity via lung-directed TFEB gene transfer and treatment with autophagy enhancer drug (FLU and CBZ) significantly reduced lung collagen deposition and leukocyte infiltration in mice [155] [156]. Thus, TFEB can be protective by restoring cellular clearance and organelle quality control, but their impact on fibrosis and remodeling can vary depending on tissue and cellular context and yet to be studied. In mechanically stiff environments, TFE3 displays enhanced nuclear localization and transcriptional activity, potentially through altered phosphorylation dynamics and interactions with mechanosensitive signaling pathways [157]. This mechano-regulation positions TFE3 as a transcriptional responder not only to metabolic and lysosomal cues but also to physical properties of the cellular microenvironment.

4. Discussion and Conclusions

MiT/TFE transcription factors act as central regulators of cellular homeostasis by coordinating lysosome biogenesis and autophagy. They are mainly considered as nutrient responsive on/ and off switches but emerging regulatory mechanisms that control their stability, subcellular localization, and transcriptional activity. For example, TFEB has been also shown to be involved in ferritinophagy-mediated iron metabolism and contributing to ferroptosis in injured hepatocytes [158]. TFEB is also able to interact with acetyl-CoA synthetase 2 to locally produce acetyl-CoA for histone H3 acetylation in the TFEB-binding promoter region [158]. This epigenetic modification further promotes its activity in lysosomal biogenesis, autophagy, cell survival, and brain tumorigenesis. This review summarized the findings from the pulmonary diseases where MiT/TFE factors continue to emerge as critical drivers in pulmonary disorders including acute lung injury, chronic inflammatory airway disease, pulmonary vascular remodeling, and fibrotic interstitial lung disease. Therefore, more mechanisms and functional roles of MiTF/TFE in pulmonary physiology and diseases remain to be explored. Recent single cell RNA seq, spatial transcriptomics, and proteomics studies have demonstrated mTORC1 hyperactivation and/or higher expression of CLEAR genes (GPNMB, CTSK, PMEL) in LAMS, sarcoidosis and other ILD diseases also suggests the dysregulation of MITF/TFE activity which could have implications in disease progression.

MiT/TFE proteins driven differential transcriptional activity could mainly be due to different post translational modifications (PTMs) in different cellular context (not discussed) can be found in previously published studies [37,159] . Thus, future work should prioritize cell-type–resolved and time-controlled interrogation of MiT/TFE biology in lung disease models by combining inducible, lineage-traced gain- and loss-of-function models for TFE3 and TFEB across key cell compartments (airway epithelium, alveolar macrophages, endothelium, and fibroblast lineages).

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