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GDF15 as a key disease target and biomarker: linking chronic lung diseases and ageing

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Abstract
Growth differentiation factor 15 (GDF15), a member of the transforming growth factor-beta superfamily, is expressed in several human organs. In particular, it is highly expressed in the placenta, prostate, and liver. The expression of GDF15 increases under cellular stress and pathological conditions. Although numerous transcription factors directly up-regulate the expression of GDF15, the receptors and downstream mediators of GDF15 signal transduction in most tissues have not yet been determined. Glial cell-derived neurotrophic factor family receptor α-like protein was recently identified as a specific receptor that plays a mediating role in anorexia. However, the specific receptors of GDF15 in other tissues and organs remain unclear. As a marker of cell stress, GDF15 appears to exert different effects under different pathological conditions. Cell senescence may be an important pathogenetic process and could be used to assess the progression of various lung diseases, including COVID-19. As a key member of the senescence-associated secretory phenotype protein repertoire, GDF15 seems to be associated with mitochondrial dysfunction, although the specific molecular mechanism linking GDF15 expression with ageing remains to be elucidated. Here, we focus on research progress linking GDF15 expression with the pathogenesis of various chronic lung diseases, including neonatal bronchopulmonary dysplasia, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and pulmonary hypertension, suggesting that GDF15 may be a key biomarker for diagnosis and prognosis. Thus, in this review, we aimed to provide new insights into the molecular biological mechanism and emerging clinical data associated with GDF15 in lung-related diseases, while highlighting promising research and clinical prospects.

Keywords GDF15 · Chronic lung disease · Mitochondrial dysfunction · Senescence · SASP

Introduction

Growth differentiation factor 15 (GDF15), initially termed macrophage inhibitory factor-1 in 1997, is a stress response cytokine that belongs to the transforming growth factor (TGF)-β superfamily. It is also known as non-steroidal anti-inflammatory drug induced gene (NAG-1), placenta transforming growth factor-β, prostate-derived factor, and placental bone morphogenetic protein [1–3]. GDF15 serves as a general biomarker for several diseases, with its serum level being used to predict all-cause mortality in conditions such as heart failure and cancer. GDF15 has also been reported to be a senescence-associated secretory phenotype (SASP) protein, indicating a role as an autonomic regulator of cellular senescence.

Chronic lung diseases, including bronchopulmonary dysplasia, idiopathic lung fibrosis, chronic obstructive pulmonary disease, and pulmonary hypertension, may be associated with an accelerated ageing of the lungs. Mounting evidence suggests that GDF15, senescence, and the pathogenesis of chronic lung diseases may be interlinked. Herein, we summarise the status of current research on the role and underlying mechanism(s) of GDF15 in chronic lung diseases.

Synthesis, secretion, and distribution of GDF15

Human *GDF15*, comprising 2 exons and 1 intron, is situated on chromosome 19p13.1–13.2 and comprises a total sequence length of 2746 base pairs [4, 5], as shown in Fig. 1. The GDF15 protein is approximately 35 kDa in size and includes a cysteine knot in the C-terminal domain

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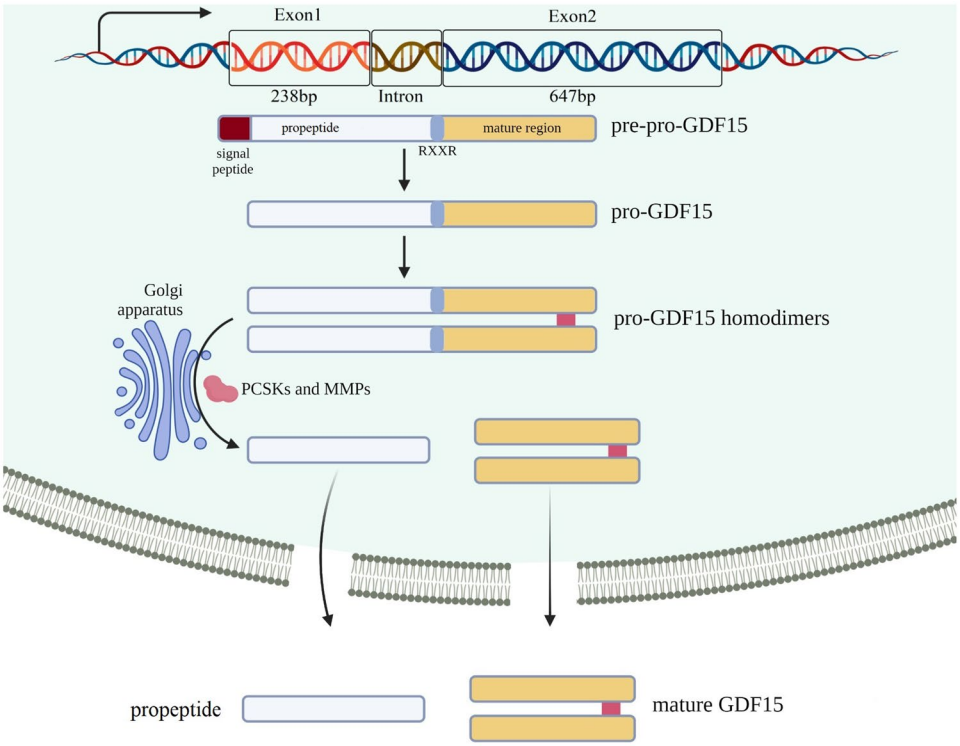

Fig. 1 Human *GDF15* includes 2 exons and 1 intron. Inactive human GDF15 pre-pro-protein in the cytoplasm is dimerised by a specific disulphide bond, cleaved at the RXXR cleavage site in the Golgi apparatus, and secreted as mature GDF15. *PCSK*: Proprotein convertase subtilisin/kexin; *MMP*: Matrix metalloproteinase

formed by eight intrachain disulphide bonds, which is the hallmark of the TGF-β superfamily. However, mature GDF15 is distinguished by a unique disulphide bonding configuration in its cysteine knot core [6] and is thus considered as a divergent member of the TGF-β superfamily. Human GDF15 pre-pro-protein contains 308 amino acid residues [7], comprising a 29-amino acid signal peptide, a 167-amino acid pro-peptide at the N-terminus, and a 112-amino acid mature region at the C-terminus [8]. The GDF15 precursor protein undergoes disulphide-linked dimerisation through a cysteine residue and is then cleaved at the RXXR cleavage site by proprotein convertase subtilisin/kexins and matrix metalloproteinases in the Golgi apparatus [7, 9].

In healthy individuals, GDF15 is expressed most abundantly in the placenta, followed by the prostate, kidney, colon, liver, and lung; it may also be expressed in the brain, heart, pancreas, gastrointestinal tract, and bone marrow at lower levels. In physiological states, GDF15 is only weakly expressed with a median circulatory level of 762 ng/L (interquartile range, 600–959) in healthy elderly individuals (median age of 65 years) [10]. However, GDF15 is highly expressed in the serum of pregnant women, with its concentration gradually increasing during pregnancy. GDF15 in the placenta and amniotic fluid may promote placental formation and help maintain pregnancy through its immunosuppressive effect [11]. The expression of GDF15 in other tissues may also increase under certain pathological states such as inflammation [12], tumorigenesis [7], oxidative

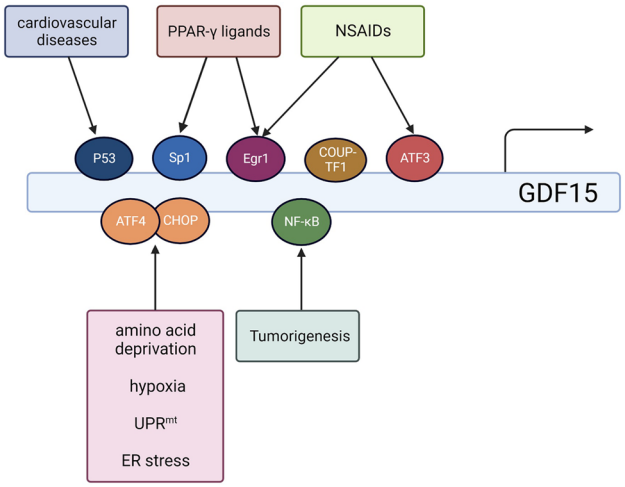

Fig. 2 Overview of regulation of GDF15 expression. *PPAR-γ*: Peroxisome proliferator-activated receptor γ; *NSAID*: Non-steroidal anti-inflammatory drugs; *P53*: Tumour protein 53; *Sp1*: Specificity protein 1; *COUP-TF1*: COUP transcription factor 1; *ATF*: Activating transcription factor; *CHOP*: C/EBP homologous protein; *NF-κB*: Nuclear factor-κB; *UPR^{mt}*: Mitochondrial unfolded protein response; *ER*: Endoplasmic reticulum

stress [13], ischaemia, anoxia, and hypoxia [14], as well as during ageing [15].

Expression and regulation of GDF15

GDF15 expression is up-regulated by various transcription factors, as shown in Fig. 2. The region upstream of the GDF15 promoter consists of several basic transcription factor-binding sites, including specificity protein 1, early growth response protein 1 (Egr-1), p53, and COUP transcription factor 1 [4]. In the promoter of GDF15, Egr-1 and specificity protein 1 bind to the same DNA sequence [16]. Known stress signals, such as amino acid deprivation, hypoxia, mitochondrial dysfunction, and endoplasmic reticulum stress, play a role in activating transcription factor 4 (ATF4) to form a heterodimer with C/EBP homologous protein (CHOP) via the phosphorylation of elF2α, resulting in the regulation of GDF15 transcription [17]. However, hypoxia- and anoxia-induced GDF15 expression during tumour growth depends on the level of promoter histone methylation rather than p53/hypoxia-inducible factor 1 (HIF-1) expression [15, 18]. Hypoxic exposure may drive the transcription of *GDF15* by activated pancreatic endoplasmic reticulum kinase–eukaryotic initiation factor 2 alpha signalling pathway; this triggers the up-regulation of CHOP, which binds to the GDF15 promotor directly [14]. Furthermore, the level of GDF15 has been shown to increase following treatment with non-steroidal anti-inflammatory drugs; hence, GDF15 has also been referred to as NAG-1, which is induced by Egr-1 and ATF-3 rather than cyclooxygenase/p53 [19–21]. In addition, peroxisome proliferator-activated receptor γ ligands act as positive regulators of GDF15 via interactions with Egr-1 and ATF-3/4 [22–24]. In cardiovascular diseases, GDF15 expression is stimulated by C-reactive protein through the p53 pathway in endothelial cells [25]. In addition, nuclear factor (NF)-κB can directly regulate GDF15 to evade macrophage surveillance during the early stages of tumour development [26].

However, the specific receptors and downstream mediators of the GDF15 signalling pathway in various tissues have not been identified to date. As a member of the TGF-β superfamily, GDF15 was initially considered to interact with a highly conserved receptor superfamily comprising type I and type II receptors. For example, GDF15 exerts its effects on food consumption and energy metabolism by interacting with the receptor TGF-β receptor II in the hypothalamus [27]. However, it has been demonstrated that glial cell-derived neurotrophic factor family receptor α-like protein (GFRAL), which is expressed only in the brain stem, is the only known orphan receptor that shows a high degree of affinity to GDF15 [6, 28–30]. As a transmembrane cell surface protein, GFRAL must interact with its RET receptor on the cell surface to initiate GDF15-specific signal transduction [6, 31]. The complex formed by the binding of GDF15 to GFRAL induces autophosphorylation of the intracellular domain of RET and activates signalling pathways, such as ERK1/2, Akt, FOS, and PLC-γ [32], while not affecting the Smad pathway [4]. GDF15 has been proposed to contribute to anorexia, cachexia, and body weight control via its interactions with these receptors. Moreover, Suriben et al. [33] recently demonstrated that suppression of GFRAL signalling with the therapeutic antagonistic monoclonal antibody 3P10 may reverse GDF15-induced excessive lipid oxidation and prevent cancer-related cachexia. This suggested that GDF15 may elicit lipolysis via the peripheral sympathetic axis, leading to reduced adipose, body, and tissue weights as well as muscle function [33].

The receptors for GDF15 in other tissues and organs remain unidentified. Although TGF-β receptors I and II are reportedly expressed in the lungs, it is unclear whether GDF15 interacts with them the same way as that observed in dendritic cells [34, 35]. GDF15 may be involved in promoting the senescence of respiratory epithelial cells induced by cigarette smoke exposure through the ALK1/Smad1 pathway [36]. GDF15 shows an anti-cardiac hypertrophy effect via the Smad2/3 pathway [37], whereas in cardiomyocytes cultured with GDF15, it exerted a pro-hypertrophic effect via the Smad1 pathway [38]. In cervical cancer, GDF15 binds to the ErbB2 receptor and promotes the proliferation of tumour cells by up-regulating cyclin D1 and cyclin E1 expression and down-regulating p21 expression through the PI3K/Akt and MAPK/ERK signalling pathways [39]. Therefore, future exploration and elucidation of receptor and signalling pathways in tissues other than the brain tissues, under different pathological conditions, might be important.

GDF15 and stress response

GDF15 acts as a stress-induced cytokine during tissue injury, hypoxia, and stimulation by pro-inflammatory cytokines as well as other stimuli or stressors to maintain cellular and tissue homeostasis. The most well-characterised stimuli include oxidised low-density lipoprotein, growth factors, interleukin (IL)-1β, tumour necrosis factor (TNF)-α, angiotensin II, macrophage colony-stimulating factor, and TGF-β [4, 40]. Hsiao et al. [41] reported that the expression of GDF15 in the liver apparently and swiftly increased in an animal model of partial hepatectomy and carbon tetrachloride-induced liver injury. Zimmers et al. [42] found up-regulated GDF15 expression in mouse models of kidney and pulmonary injury, suggesting that GDF15 induction is a broad cell injury response. GDF15 expression also increases rapidly with cardiovascular injuries, such as myocardial ischaemia/reperfusion [43], dilated cardiomyopathy [37], and heart failure. Xu et al. [44] reported that GDF15, as a newly identified sympathetic regulator, protects against

myocardial hypertrophy by inhibiting norepinephrine-induced epidermal growth factor receptor transactivation.

Therefore, GDF15 appears to exert different effects under different conditions. For example, GDF15 exerts anti-inflammatory effects by evading macrophage activation and NF-κB activity, although the mechanism is still not fully understood [45]. Transgenic mice overexpressing GDF15, which were injected with a lipopolysaccharide (LPS), showed lower mortality than wild-type mice, whereas *Gdf15*-knockout mice presented a higher mortality than wild-type mice [46]. Furthermore, GDF15 treatment reduced the mortality rate in the model of inflammation induced by LPS, poly(I:C), or D-galactosamine [12, 47]. Moreover, several lines of evidence suggest that GDF15 may play a protective role under septic conditions. Luan et al. [12] found that GDF15 induced by acute inflammatory injury drives the metabolism of hepatic triglycerides by directing sympathetic outflow to the liver, which was presumed to be mediated by GFRAL-expressing neurons. Conversely, the knockout of *Gdf15* protected mice from caecal ligation and puncture-induced abdominal sepsis [48]. GDF15 also blocks various cytokines, including interferon-γ, IL-6, monocyte chemoattractant protein-1, and TNF-α [4, 43]. In human nasal epithelial cells, GDF15 is regulated by ATF-4 and inhibits the LPS-induced secretion of inflammatory cytokines and mucin 5AC through the PI3K/Akt pathway [24].

GDF15 and ageing

Senescence is a cellular stress response to molecular damage, characterised by irreversible cell cycle prolongation. Senescent cell arrest results in the formation of a complex secretome, known as the senescence-associated secretory phenotype (SASP). In recent years, a link between GDF15 and senescence has become more evident. A Swedish cohort study, involving a group of 876 male patients aged 35–80 years and a group of 324 twins aged 63–93 years, found that the serum GDF15 level may serve as an independent indicator of all-cause mortality [49]. The authors of that study showed that the serum GDF15 level, similar to telomere length, could predict lifespan independent of the genetic background of an individual. Pence et al. conducted a study which investigated the relationship between circulating GDF15 levels in older adults and indices of age-related monocyte dysfunction, suggesting a potential causal link between GDF15 and age-related decline in immune function [50].

GDF15, the core SASP protein known in humans, is one of the most highly secreted proteins by fibroblasts or epithelial cells among secretory SASPs [51]; however, the specific molecular mechanism underlying its involvement in ageing remains unclear. By activating the ALK1/Smad1 pathway, GDF15 promotes cellular senescence induced by radiation via the reactive oxygen species-mediated p16 pathway in human endothelial cells [52] and facilitates the senescence of airway epithelial cells as induced by cigarette smoke exposure [36]. Another study showed that female transgenic mice overexpressing GDF15 lived longer than wild-type mice [53].

Furthermore, GDF15 is associated with mitochondrial dysfunction [54, 55]. The mitochondria play a key role in the process of ageing, and mitochondrial dysfunction is one of the distinguishing features of senescence. Unfolded or misfolded proteins may accumulate in mitochondrial compartments under cellular stress, resulting in the up-regulation of mitochondrial chaperone protein expression as encoded by nuclear genes. The mitochondrial unfolded protein response (UPR^{mt}) is a retrograde transcriptional response that helps misfolded proteins return to normal conformation and ensures that newly synthesized proteins fold correctly. Therefore, the UPR^{mt} is a compensatory mechanism that helps identify, combat, and recover from mitochondrial dysfunction, and it maintains mitochondrial homeostasis together with other mitochondrial stress response pathways, such as mitophagy or mitochondrial dynamics [56, 57]. During mitochondrial stress, UPR^{mt} not only regulates the transcription of mitochondrial genes, such as *ATF4, ATF5*, and *CHOP* [56, 58–60], but also influences the production of stress-responsive molecules known as mitokines, which include GDF15, fibroblast growth factor 21 (FGF21), and mitochondrial-derived peptides [61]. In a *Crif1*(mitoribosomes)-knockout mouse model, aberrant mitochondrial oxidative phosphorylation induces the CHOP-dependent transcription of *Gdf15* after UPR^{mt} activation [62, 63]. However, recent studies have also demonstrated that activation of 5´AMP-activated protein kinase, a key protein for regulating mitochondrial function, can lead to an increase in circulating and hepatic GDF15 levels, independently of CHOP [64]. It has also been suggested that GDF15 may play a protective role by restoring metabolic homeostasis [65, 66]. GDF15 alleviates steatosis of hepatocytes by inhibiting mitochondrial damage and reducing the release of dsDNA from mitochondria to cytosol [67]. In SH-SY5Y cells exposed to rotenone, up-regulated GDF15 affects PGC1α by regulating p53 and then reduce mitochondrial damage and apoptosis, and this process depends on the phosphorylation of Akt/mTOR [68]. GDF15 may also protect mitochondrial function by regulating mitochondrial membrane potential and oxygen consumption of immortalized mouse hippocampal neuronal cells through the PI3K-Akt signal pathway [66]. In addition, the level of GDF15 decreased in the subcutaneous adipose tissue and in vitro-differentiated adipocytes of elderly women, which was negatively correlated with the mRNA expression level of lipogenic genes and was related to mitochondrial dysfunction [68]. Therefore, it can be inferred that GDF15 may be an indicator of

mitochondrial dysfunction associated with senescence and age-related diseases.

Role of GDF15 in chronic lung diseases

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease (CLD) in premature infants of gestational age < 28 weeks or birth weight < 1200 g, especially those who require oxygen inhalation or mechanical ventilation during treatment. Since BPD was first described in 1967, advances in integrated management techniques for this condition have effectively improved the survival rate of premature infants. However, its incidence has not declined, and BPD survivors are at risk of a variety of chronic sequelae, including persistent respiratory symptoms, pulmonary function injury, neurodevelopmental disorders, pulmonary hypertension, and post-neonatal death [69].

The primary pathological features of BPD are a reduction in alveolar number, increase in alveolar volume, simplification and irregularity of the alveolar structure, narrowing of the alveolar septum, and abnormal morphology of the pulmonary micro-vessels, which may in turn lead to an abnormal alveolar structure. It is speculated that these changes may be due to arrested development of lung tissue during the vesicular to alveolar phase, thus highlighting the characteristics of a new type of BPD, namely pulmonary stagnation and pulmonary microvascular dysplasia [70]. Current research on the pathogenesis of BPD mainly focuses on the damage and abnormal repair of the pulmonary epithelial barrier following lung injury, DNA damage, and the role of epigenetics in the pathogenesis of BPD, mainly involving mechanisms such as apoptosis and autophagy.

Early damage to the neonatal lung, such as that caused by BPD, can affect different ageing pathways, such as DNA damage, telomere attrition, epigenetic alterations, proteostatic imbalance, mitochondrial dysfunction, cellular senescence, and altered intercellular communication, thereby resulting in premature lung ageing in adults and the early onset of chronic lung disease later in life [71]. Various ageing-related molecular pathways are also associated with neonatal BPD, including TGF-β1-induced connective tissue growth factor expression, the ataxia telangiectasia-mutated/p53-dependent pathway, the insulin-like growth factor 1/Akt/mTOR signalling axis, and hyperoxia-induced DNA methylation and histone acetylation changes [71–77]. Hyperoxia can induce the senescence of lung cells, including lung epithelial cells [75, 78], smooth muscle cells of the airways [79, 80], and fibroblasts [81]. As previously described, GDF15 participates in the cellular stress response pathway, which can be induced by hyperoxia exposure, whereas ageing is a protective response to stress, leaving cells in a non-proliferative state that triggers the development of a harmful pro-inflammatory SASP [71]. Hyperoxia has been shown to considerably induce GDF15 expression in the lung [82], especially in epithelial and endothelial cells [83] (Table 1). In addition, the increase in GDF15 expression under hyperoxic conditions may be a response to oxidative stress, and GDF15 knockout could also decrease cell survival and increase reactive oxygen species production [83, 84]. The level of GDF15 in the umbilical cord blood of full-term neonates (3095 ± 191 pg/mL) accounts for 25% of maternal blood levels in the third trimester of pregnancy; however, it is several times higher than that in adults [85], and it is now evident that neonatal GDF15 is derived from the new-born rather than the placenta [85, 86]. Almudares et al. showed that the level of GDF15 negatively correlated with gestational age (i.e., decreased with age) and that the level of GDF15 is directly or indirectly associated with adverse respiratory outcomes in premature infants [87]. Therefore, exploring the role of GDF15 in the pathogenesis of the alveolarisation and lung development dysfunction in BPD has high research value.

Table 1 Functional role of GDF15 in response to diverse lung diseases

Disease	Cell type	Functional role	References
Bronchopulmonary dysplasia	Epithelial and endothelial cells	Responds to oxidative stress	[82–84]
Idiopathic lung fibrosis	Epithelial cells	Exerts protective effect in lung fibroblasts/promotes epithelial cell ageing/telomere dysfunction/promote ferroptosis	[35, 87, 95]
Chronic obstructive pulmonary disease	Epithelial cells	Induces cellular senescence/promotes lung inflammation after cigarette smoke exposure/activates EMT after cigarette smoke exposure	[36, 110, 111]
Pulmonary hypertension	Vascular endothelial cells	Induces angiogenesis/prevents endothelial cell apoptosis/causes muscle atrophy	[112, 114, 115, 116]
COVID-19	Endothelial cells	Causes iron metabolism disorder/endothelial inflammation	[127, 129, 133]

Idiopathic lung fibrosis

Idiopathic pulmonary fibrosis (IPF) remains an irreversible and progressive fatal disease. It is characterised by the accumulation of extracellular matrix proteins and fibroblast proliferation, leading to chronic pulmonary remodelling and respiratory failure [88]. Studies have revealed that IPF is an ageing-related disease in which the senescence of lung cells plays a major role in the pathogenesis, and the senescence of alveolar epithelial cells promotes fibrosis by generating an SASP [89]. The expression of GDF15 in the human IPF lung is increased, along with increased levels in the bronchoalveolar lavage fluid and plasma, with pulmonary epithelial cells proven to be the main source of GDF15 in this condition [35, 88]. A study involving 108 patients with IPF and 31 healthy controls in China [90] found that the serum level of GDF15 in patients with acute exacerbation of IPF was elevated and that the protein and mRNA levels of GDF15 in IPF lung tissues were significantly increased. Additionally, immunohistochemical staining showed that GDF15 expression in the cytoplasm of type II alveolar epithelial cells was moderately positive. Radwanska et al. co-stained GDF15 with AT II cells marker ProSurfactant protein C (PSPC) in human IPF and healthy lungs [91], and their results also confirmed that GDF15 is expressed in alveolar epithelial type II (ATII) cells. In addition to being involved in promoting epithelial cell ageing, GDF15 exerts a protective effect on lung fibroblasts. Zhang et al. [35] found a connection between up-regulated GDF15 expression in alveolar epithelial type 2 cells and telomere dysfunction in IPF. Thus, GDF15 may play different roles in different lung cell types.

Lambrecht et al. [92] reported that GDF15 can also serve as a marker for the degree of lung damage in systemic sclerosis and that it is associated with the occurrence of fibrosis via the activation of fibroblasts and M2 macrophages. Moreover, the level of GDF15 in vivo is associated with the number of diseased organs in addition to the lung and is thus linked to the severity of the disease. GDF15 participates in immune recruitment in the lungs, activates fibroblasts, and ultimately leads to fibrosis via its direct involvement in the expression of pro-inflammatory cytokines and chemokines (such as IL-6 and CCL2). Additionally, low expression of caveolin-1 in the IPF lung weakens the inhibitory effect of the TGF-β receptor, thereby activating the TGF-β signalling pathway, leading to the excessive production of extracellular matrix and eventually the occurrence of pulmonary fibrosis [93–95]. GDF15 may aggravate the inflammatory response of the lung tissue and accelerate the process of pulmonary fibrosis by promoting ferroptosis, which may be related to the ability of members of the TGF-β superfamily to promote ferroptosis in tumour cells [96]. However, GDF15 has also been proposed as a potential therapeutic agent for IPF, as it could ameliorate pulmonary fibrosis by inhibiting the TGF-β signalling pathway [97]. Therefore, although the mechanism of GDF15 in pulmonary fibrosis is not yet clear, current evidence and technology enable its application as a biomarker for the diagnosis and prognosis of IPF and show its potential as a therapeutic target for IPF.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) accounts for more than 3 million reported deaths globally each year, and the associated morbidity and mortality are expected to rise in the future. Persistent respiratory symptoms and progressive airflow obstruction are the hallmarks of COPD [98]. As a sensitive marker of cardiopulmonary stress, GDF15 has no known specific diagnostic function in different diseases such as heart failure, pneumonia, COPD, nephropathy, and septicaemia [99], although its expression is markedly increased in patients with acute exacerbations of COPD [100, 101]. Compared with healthy subjects and patients with asthma, patients with COPD show a high GDF15 level in the serum, which is negatively correlated with exercise levels [102]. In a 9-year study of 413 patients with COPD, a high level of plasma GDF15 was independently associated with higher exacerbation rates, higher mortality, and a more significant decrease in the forced expiratory volume in 1 s and forced vital capacities [103]. Therefore, the GDF15 level may be correlated with the severity, deterioration, and prognosis of COPD. In a cohort study of 694 smokers without clinical cardiovascular disease, the level of GDF15 in the plasma independently contributed to the risk of subclinical coronary atherosclerosis [104].

Smoking and occupational exposure to smoke are the leading causes of COPD [98]. Cigarette smoke exposure increases GDF15 expression in airway epithelial cells and induces cellular senescence by activating the ALK1/Smad1 pathway, with significant increases in early senescence marker p21, late senescence marker p16, and HMGB1 levels [36]. This is consistent with the observation of increased cellular senescence in Clara cells, alveolar type II cells, endothelial cells, and leukocytes from smokers or cigarette smoke-exposed mice [72, 105–108], suggesting that the accumulation of senescent cells in the lungs may play a key role in the pathogenesis of COPD. GDF15 was found to regulate MUC5AC expression in respiratory epithelial cells exposed to cigarette smoke by activating the PI3K/Akt signalling pathway [109]. Another study using a mouse model of cigarette smoke exposure showed that the knockout of *Gdf15* could reduce pulmonary inflammation, and that an increase in T and B lymphocytes in the airway and lung tissue was considerably attenuated after 4 weeks of cigarette smoke exposure [110]. The human rhinovirus (HRV) is the most common virus causing acute exacerbations of COPD. HRV-induced lung inflammation in mice can be increased by

the overexpression of human GDF15 protein, which results in heightened viral replication and release in airway epithelial cells [111]. Collectively, these results demonstrate that GDF15 promotes lung inflammation after cigarette smoke exposure. In addition, persistent active epithelial–mesenchymal transition (EMT) has been observed in the airway epithelial cells of patients with COPD; specifically, IL-17A markedly up-regulated the expression of GDF15 in cigarette smoke-treated HSAEpiC cells in a dose-and time-dependent manner, and IL-17A combined with GDF15 activated EMT in HSAEpiC cells after cigarette smoke exposure [112].

Pulmonary hypertension

In animal models of hypoxia, GDF15 overexpression in pulmonary vascular endothelial cells in pulmonary arterial hypertension (PAH) is accompanied by an elevated circulating GDF15 level, reflecting the process of pulmonary vascular remodelling [113, 114]. GDF15 promotes HIF-1α activation through p53 degradation, followed by the induction of angiogenesis in hypoxia-induced human umbilical vein endothelial cells (HUVECs) [115]. GDF15 could also prevent high glucose-induced endothelial cell apoptosis in HUVECs by inhibiting the phosphorylation of the PI3K/Akt/eNOS pathway and attenuating the activation of the NF-κB/JNK pathway [116]. An elevated systemic GDF15 level is associated with the risk, progression, and severity of pulmonary hypertension by increasing atrial and pulmonary capillary wedge pressure, which are caused by hypoxia and laminar shear stress in pulmonary vascular endothelial cells [114, 117]. GDF15 is also associated with left ventricular dysfunction as induced by pulmonary hypertension, especially in the case of persistent heart disease. As left heart disease leads to an increase in cell death and remodelling at the myocardial level, elevated GDF15 level can be used as a marker for the evaluation of post-capillary pulmonary hypertension [117]. In a study of children with congenital heart disease complicated by pulmonary hypertension, the GDF15 serum level was found to be considerably increased, which was positively associated with the level of N-terminal pro-brain natriuretic peptide (NT-proBNP). Furthermore, the addition of GDF15 to NT-proBNP as a diagnostic marker showed slightly higher specificity and positive predictive value than the use of NT-proBNP alone when diagnosing PAH [118]. In 2019, Larissi et al. [119] reported that patients with sickle cell disease had a high level of serum GDF15, with clinical manifestations of vascular occlusion, chronic haemolytic anaemia, and frequent infection, and the GDF15 level in the serum positively correlated with the mean pulmonary artery pressure. Tantawy et al. confirmed through echocardiography that young patients with thalassemia intermedia may have endothelial dysfunction present before the appearance of obvious clinical cardiovascular abnormalities, and this was accompanied by an increase in circulating GDF15 levels. They suggested using 1500 pg/mL GDF15 as a baseline to assess the presence of cardiovascular disease [120]. As a severe complication of systemic sclerosis, PAH is characterized by a high incidence and mortality rate, and GDF15 is significantly elevated in the remodelled pulmonary arteries and serum of systemic sclerosis-PAH patients [114].

In recent years, PAH has been increasingly regarded as a systemic disease. GDF15 has been linked to muscle atrophy in malignancy and anorexia nervosa. GDF15 inhibits appetite through its central receptor GFRAL, resulting in weight and muscle mass loss, and accelerates muscle protein degradation by up-regulating the expression of ubiquitin ligase atrogin-1, TAK1-NF-κB, and MuRF1 [113, 121]. The main muscle-related complications in PAH are declines in muscle strength, endurance, contractility, and capillary density along with the impaired oxygenation of microcirculation and a transition to type 2 muscle fibres [122]. GDF15 has been shown to contribute to muscle atrophy by increasing the phosphorylation of TAK1 and its target protein, NF-κB, and this process could be antagonised by treatment with TAK1 inhibitors [113]. This finding not only indicates that GDF15 is implicated in the pathogenesis of PAH vascular lesions but also shows that the pulmonary circulation affects the muscle mass of patients with PAH through a GDF15-mediated endocrine mechanism. In conclusion, GDF15 may participate in the pathogenesis of PAH vascular lesions and may be a powerful and promising biomarker for disease risk, progression, and a poor prognosis.

GDF15 and other lung diseases

GDF15 is also involved in the aetiology of other lung diseases. It has been found to promote and maintain T helper cell 2 immunity in the lung. In an asthma model mediated by allergens and environmental pollutant particles, NOTCH4 signalling up-regulated the expression of GDF15 in regulatory T cells, which promoted ILC2 expansion and activation through the Notch4-Wnt-GDF15 pathway [123] and provided a new therapeutic prospect for restoring lung immune tolerance and homeostasis [124].

In a retrospective cohort study of patients with acute respiratory distress syndrome, a higher level of GDF15 was strongly associated with a poor prognosis [125]. Herter et al. [126] found that GDF15 could protect the lungs of patients with acute lung injury by reducing the platelet count and suppressing neutrophil extracellular trap formation via the activation of αIIBβ3 on platelets. GDF15 also improved lung injury by up-regulating SIRT1 in an LPS-induced acute lung injury mouse model [127]. In addition, GDF15 has been found to affect the recruitment of neutrophils in the

post-capillary venules of the cremaster muscle in a ventilator-induced lung injury model.

Dynamic changes in the GDF15 level are furthermore closely associated with COVID-19 progression, and they are used as a useful marker for identifying patients with poor respiratory function [128, 129]. Therefore, GDF15 may be used as an index to evaluate disease severity in patients with COVID-19. The pathogenesis of severe COVID-19 involves an overactive immune response, leading to a 'cytokine storm' characterised by haemophagocytosis and elevated serum cytokine levels [130]. Moreover, as SARS-CoV-2 directly targets endothelial cells, endothelial dysfunction is a trait of COVID-19 that is related to oxidative stress [129]. Considering its capacity to induce hypoxia and characteristic high expression in endothelial cells, GDF15 may also participate in COVID-19 endothelial inflammation [114, 129, 131]. Another possible mechanism underlying the oxidative stress and inflammation in COVID-19 involves a disorder of iron metabolism [132]. GDF15 has been reported as an upstream negative regulator of hepcidin, being associated with hepcidin levels and/or regulation of hepcidin expression. The plasma GDF15 level is higher in thalassemia and other diseases with ineffective erythropoiesis [119, 133]. The negative correlation between GDF15 and hepcidin [134], which may be associated with the Smad signal pathway, results in iron overload [135]. In addition, inhibition of GDF15 can also promote erastin-induced ferroptosis by attenuating the expression of SLC7A11. Therefore, GDF15 may play a key role in regulating ferroptosis and iron metabolism [136].

Conclusions

In cells, GDF15 is present in different forms, with mature GDF15 being distributed in various human organs. As a molecule closely associated with stress and the ageing process, GDF15 is linked to the pathogenesis of several lung diseases, particularly chronic lung diseases; however, several inconsistencies remain with the molecular mechanism underlying GDF15 function at the cellular level. Although other lung cells may also secrete GDF15 under different disease or stress conditions, pulmonary epithelial cells, which are the most likely source of GDF15 in the lungs, play a role in subsequent immune responses, such as oxidative stress and inflammation. GDF15 is considered a core SASP protein and mitokine that is strongly associated with mitochondrial dysfunction. Furthermore, GDF15 has been identified as a potential biomarker for assessing the degree of mitochondrial dysfunction in ageing and age-related diseases. As a secreted protein, GDF15 can be used as not only a predictor of all-cause mortality but also a biomarker for the diagnosis, progression assessment, and prognosis of various lung diseases. Future research may be required on the pathogenesis of GDF15 in chronic lung diseases, such as the identification of (i) the upstream molecules involved in regulating GDF15 expression, (ii) receptors in lung tissues that directly bind GDF15, and (iii) mechanisms underlying the association between GDF15 and ageing, as well as mitochondrial dysfunction in the development of chronic lung diseases.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare that they have no competing interests.

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