Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Beyond Tumors: The Pivotal Role of TRIM Proteins in Chronic Non-Tumor Lung Diseases

Xiangfei Huang, Wen Yu, Aiping Wei, Xifeng Wang, Shibiao Chen

Department of Anesthesiology, The First Affiliated Hospital of Nanchang University, Nanchang, 330006, People's Republic of China

Correspondence: Shibiao Chen, Department of Anesthesiology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China, Email Chenlaoshi1111@163.com

Abstract: While TRIM proteins are extensively studied in the context of lung tumors, their roles in non-tumor chronic lung diseases remain underexplored. This review delves into the emerging significance of TRIM family proteins in the pathogenesis of idiopathic pulmonary fibrosis (IPF), asthma, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension (PH). TRIM proteins modulate key pathological processes, including inflammation, fibrosis, and cellular remodeling, contributing to disease progression. We highlight their potential as biomarkers and therapeutic targets, offering promising avenues for drug development in these debilitating respiratory disorders. However, the translation of these findings into clinical applications faces significant challenges. These include the dual functional nature of TRIM proteins, their context-dependent roles, the complexity of their downstream signaling networks, and the limitations of current therapeutic strategies in achieving tissue-specific targeting with minimal off-target effects. Addressing these challenges will require innovative approaches and interdisciplinary efforts to unlock the therapeutic potential of TRIM proteins in non-tumor chronic lung diseases.

Keywords: TRIM proteins, chronic lung diseases, idiopathic pulmonary fibrosis, COPD, asthma, pulmonary hypertension

Introduction

Chronic lung diseases continue to be a significant global health burden. According to a systematic analysis of data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, approximately 454.6 million people worldwide were affected by chronic lung diseases in 2019, marking a 39.8% increase since 1990.[1] These conditions were the third leading cause of death globally, with a 28.5% rise in mortality compared to 1990. Additionally, chronic lung disorders impose substantial economic burdens on society and individual families.[2,3] Traditional treatments primarily alleviate symptoms rather than alter the natural course of chronic lung diseases, highlighting the urgent need to better understand the mechanisms underlying these conditions and to develop novel targeted therapies.[4]

Protein homeostasis is critical for the proper functioning of all cell types and organs. The two primary systems responsible for regulating protein degradation are the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP).[5,6] Within the UPS, E3 ligases, including the TRIM family of proteins, play a pivotal role in maintaining cellular protein homeostasis by mediating substrate-specific ubiquitination.[7,8] This function makes E3 ligases critical determinants of the specificity of the UPS and key targets in various diseases.

The human genome encodes over 600 E3 ligases, which are categorized into three families: RING, HECT, and RING-between-RING (RBR).[9] RING-type E3 ligases facilitate the direct transfer of ubiquitin from E2 to substrates, while HECT and RBR ligases first bind ubiquitin before transferring it to the substrate. This highly regulated system ensures the precise selection of substrates, and E3 ligases play crucial roles in the regulation of multiple diseases, including cancer,[10–12] neurodegenerative diseases,[13–16] cardiovascular disease,[17–20] and autoimmune diseases.[21]

The tripartite motif (TRIM) family of proteins, a subfamily of RING finger E3 ligases, includes more than 80 members in humans.[22] TRIMs primarily function as canonical E3 ligases, promoting the UPS-mediated degradation of proteins. Interestingly, some TRIMs also act as deubiquitinases, preventing UPS-mediated degradation of proteins.[23–26]

Received: 2 October 2024
Accepted: 29 January 2025
Published: 7 February 2025

However, the dual role of TRIMs as both ubiquitinases and deubiquitinases is not unique; for example, A20 has been widely studied for its similar dual function.[27] The biological functions of TRIMs are therefore complex, and a deeper understanding could provide new perspectives for drug target development.

Chronic inflammation is a key driver in the pathogenesis of various chronic lung diseases, including COPD,[28] asthma,[29] pulmonary fibrosis,[30] and pulmonary fibrosis.[31] While TRIM family proteins have been widely recognized for their regulatory roles in mediating inflammation,[32] their specific contributions to chronic lung diseases remain intriguing and underexplored. Although much of the research on TRIM proteins has traditionally focused on their roles in cancer, emerging evidence suggests their significant involvement in non-tumor chronic lung diseases.[28] This review aims to shed light on the roles of TRIM proteins in these conditions (Table 1).

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial pneumonia of unknown origin that primarily affects adults.[50] Due to a limited understanding of its pathogenesis, effective treatment remains a significant challenge. The two antifibrotic drugs approved by the latest ATS/ERS/JRS/ALAT guidelines, pirfenidone, and nintedanib, only slow disease progression without offering a cure[51,52] Despite these treatments, IPF mortality rates continue to rise, with an estimated 17,000 deaths annually in Europe alone.[53] There is an urgent need to explore the underlying mechanisms of IPF and develop more effective therapies.

The TGF-β signaling pathway is a key driver of fibrosis, with receptor-Smad family transducers (R-Smads) forming complexes that activate target gene transcription.[54] TRIM33, also known as ectodermin, is a RING-type ubiquitin ligase that interacts with Smad4, serving as a potent endogenous antagonist of Smad signaling.[55] Interestingly, subsequent studies revealed that although TRIM33 acts as a Smad4 monoubiquitin ligase, it does not decrease Smad4 levels but instead promotes Smad4 K519 monoubiquitination, inhibiting the formation of the Smad2/3 complex and thus suppressing TGF-β gene responses.[56] Additionally, TRIM33 promotes TGF-β receptor 1 (Tgfbr1) polyubiquitylation and suppresses its expression in hematopoietic stem cells, blunting TGF-β signaling activation.[57] In the context of IPF,

Table 1 TRIM Family Proteins in Non-Tumor Chronic Lung Diseases

Disease	TRIMs	Substrates	References
IPF	TRIM33	Smad4	[33]
	TRIM47	PPM1A	[34]
	TRIM72	…	[35]
	TRIM21	…	[36]
	TRIM7/MEFV/TRIM45	…	[37]
Asthma	TRIM37	…	[38]
	TRIM33	Smad4	[39]
COPD	TRIM16	…	[40]
	TRIM63	…	[41–44]
	TRIM32	…	[45]
	TRIM25,	Keap1	[46]
PH	TRIM32	…	[47]
	TRIM24	…	[48]
	TRIM63/TRIM55	…	[49]

TRIM33 expression is increased in the lung tissue of IPF patients and rodent models, and its depletion exacerbates TGF-β1 signaling, leading to disease progression.[33]

TRIMs also modulate TGF-β1 signaling indirectly through other proteins involved in the pathway. For example, PPM1A, a phosphatase that interacts with Smad2 suppresses its phosphorylation and promotes nuclear export, thereby inhibiting TGF-β signaling.[58] In a lipopolysaccharide (LPS)-induced pulmonary fibrosis model, TRIM47 was shown to promote the ubiquitination and degradation of PPM1A, contributing to fibrosis[34] (Figure 1). Furthermore, TRIM72 expression is increased in IPF lungs and in mouse models subjected to various lung injuries, where it enhances the membrane repair of type II alveolar epithelial cells, protecting the epithelial layer integrity and reducing fibrosis.[35]

Several other TRIMs may also be involved in IPF, although their roles are less well studied. For instance, TRIM21 antibodies are among the most common autoantibodies detected in idiopathic interstitial pneumonia (IIP) patients.[36] Bioinformatic analyses have identified significant associations between TRIM7, MEFV, TRIM45, and TRIM47 with overall survival in IPF.[37] Additionally, machine learning studies have suggested TRIM2 as a potential gene signature for IPF,[59] with increased expression observed in bleomycin-induced pulmonary fibrosis in mice.[60]

Asthma

Asthma is a chronic respiratory disease marked by airway inflammation, bronchial hyperresponsiveness, and variable airflow limitation.[61] The condition arises from a complex interplay of genetic and environmental factors, including exposure to allergens, air pollution, and microbial products.[62] The pathogenesis of asthma involves immune cells, cytokines, and chemokines that drive chronic inflammation and remodeling of the airways. This results in symptoms such as wheezing, shortness of breath, chest tightness, and coughing, which can vary in severity and frequency among individuals.

Globally, asthma is a significant health concern, affecting approximately 4.3% of the population, with prevalence rates varying widely across different regions.[63] Despite advances in treatment, asthma remains a major cause of morbidity, and there is considerable global disparity in asthma-related mortality and years of life lost due to the

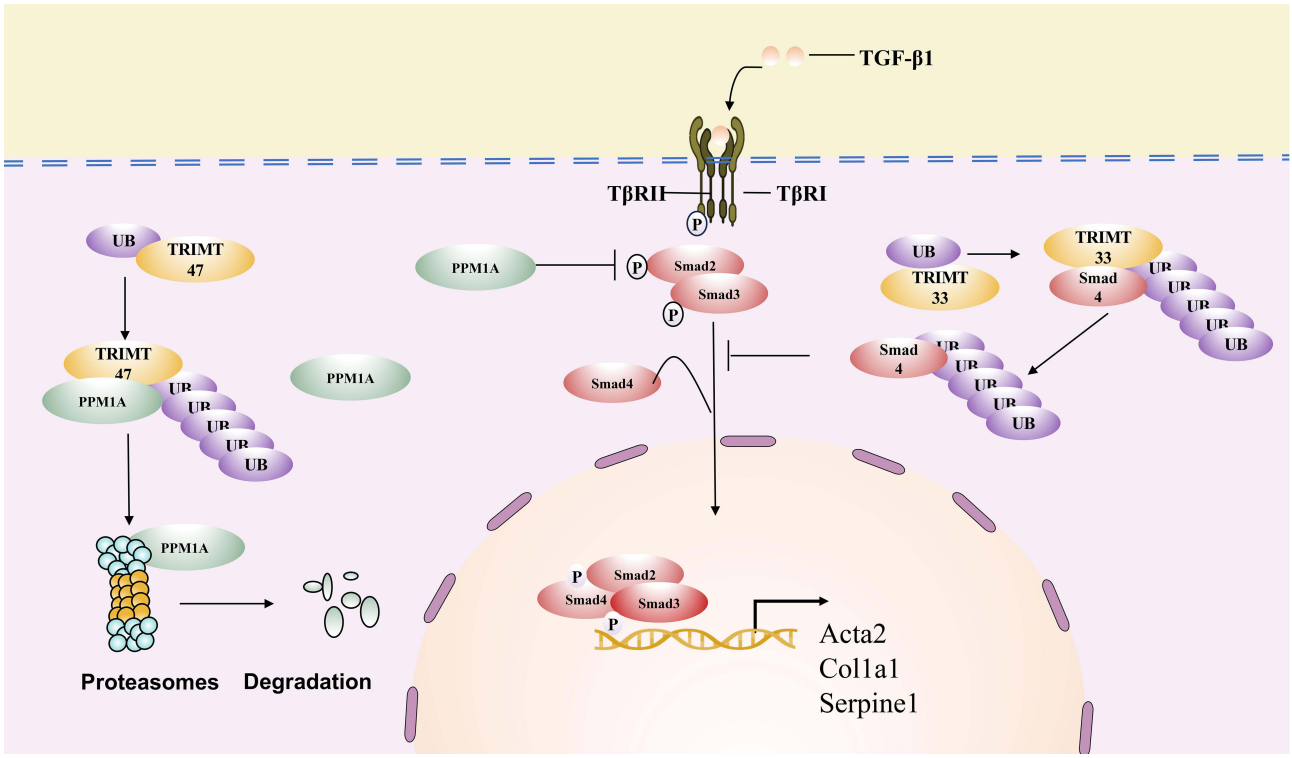

Figure 1 TRIM33 mitigates IPF by blunting TGF-β1 signaling through binding Smad4 and inhibiting its interaction with Smad2/3; TRIM47 alleviates pulmonary fibrosis by interacting with PPM1A and targeting it for UPS-mediated degradation.

https://doi.org/10.2147/JIR.S499029

disease.[61] While the overall mortality rate from asthma is relatively low compared to other respiratory conditions, the impact on quality of life and healthcare systems is substantial, particularly in low- and middle-income countries where access to effective treatments may be limited.

A key feature of asthma pathogenesis is the role of airway smooth muscle (ASM), which is composed of smooth muscle cells (ASMCs). ASMCs contribute to bronchoconstriction, airway hyperresponsiveness, and remodeling, making them a critical target for asthma treatment.[64] Recent research has highlighted the involvement of specific proteins, such as TRIM37 and TRIM33, in regulating the behavior of ASMCs.

TRIM37 has been shown to inhibit the proliferation and migration of ASMCs by suppressing the protein expression levels of β-catenin, c-Myc, and cyclin D1 in ASMCs stimulated by platelet-derived growth factor-BB (PDGF-BB).[38] This suppression interferes with the Wnt/β-catenin signaling pathway, a key regulator of cell growth and differentiation. The addition of LiCl, a Wnt/β-catenin pathway activator, can significantly reverse the inhibitory effects of TRIM37, underscoring its role in the regulation of ASMC function.

Similarly, TRIM33 has been found to play a crucial role in modulating ASMC activity. Consistent with findings in IPF, TRIM33 inhibits SMAD4, thereby suppressing the activation of the Wnt/β-catenin pathway (Figure 2). This action reduces PDGF-BB-induced proliferation and migration of ASMCs, suggesting that TRIM33 may have therapeutic potential in controlling airway remodeling in asthma.[39]

The role of these TRIM proteins in asthma highlights the importance of the Wnt/β-catenin signaling pathway in the disease's pathology. Targeting this pathway, and the regulatory proteins involved, could offer new therapeutic strategies for managing asthma, particularly in cases where traditional treatments are less effective. Given the chronic nature of asthma and the potential for severe exacerbations, ongoing research into the molecular mechanisms underlying the disease is essential for developing more effective and personalized treatment options.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a heterogeneous lung disease characterized by chronic respiratory symptoms and irreversible airflow limitation. The World Health Organization (WHO) predicts that COPD will become the third

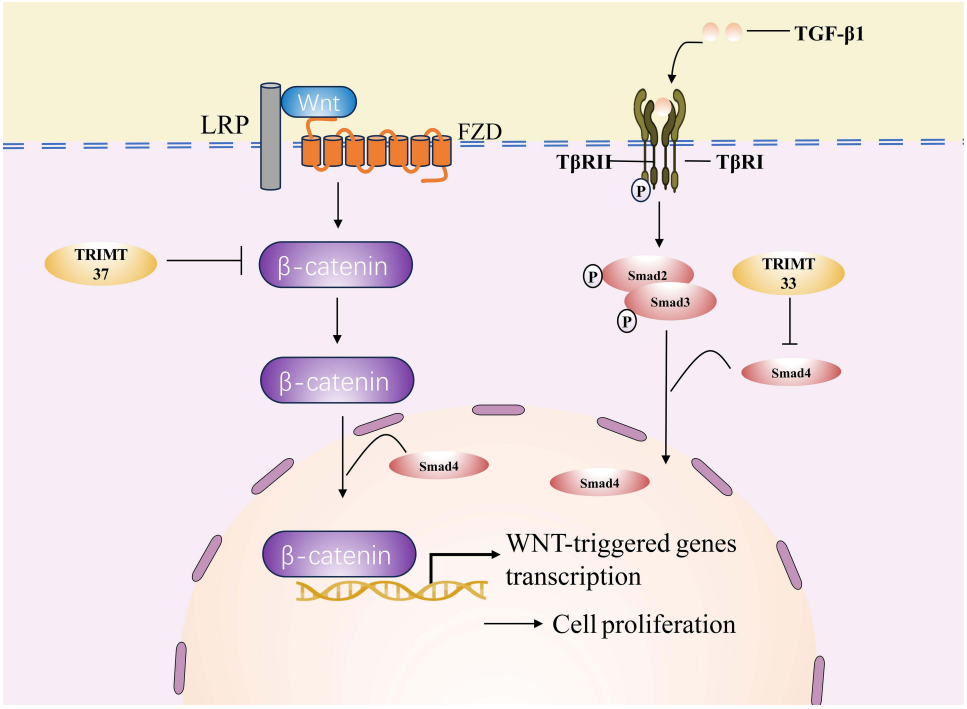

Figure 2 TRIM37 inhibits the proliferation and migration of ASMCs by suppressing Wnt/β-catenin pathway activation; TRIM33 blunts the proliferation and migration of ASMCs by inhibiting Wnt/β-catenin pathway activation through its interaction with Smad4.

leading cause of death worldwide by 2030.[65] The annual prevalence of COPD in Germany is reported to be 5.8%, according to the Robert Koch Institute.[66] COPD also imposes a significant disease burden,[67] with comorbidities greatly impacting overall prognosis. For example, COPD-induced peripheral muscle fatigue not only leads to poor exercise performance but also contributes to reduced health status, increased healthcare utilization, and even mortality.[68]

TRIM16 has been found to play a critical role in autophagy.[69] Chauhan et al[70] revealed that TRIM16 is the key factor interacting with other autophagy regulators, including Galectin-3, ULK1, ATG16L1, and Beclin1, to protect cells from consequences of lysosome damage by assisting the formation of autolysosomes. In lung tissue and bronchial epithelial cells isolated from COPD patients, TRIM16 expression is decreased, accompanied by increased expression of galectin-3 and the accumulation of lysosomes with lysosomal membrane permeabilization. This indicates insufficient lysophagy, suggesting TRIM16's involvement in COPD pathogenesis[40] (Figure 3).

Beyond pulmonary pathological changes, COPD is also associated with several systemic effects, such as nutritional abnormalities, weight loss, and skeletal muscle dysfunction.[71] Cigarette smoke is a key risk factor for COPD, leading to pathological changes in the respiratory tract and lung parenchyma, which subsequently result in airflow limitation.[72] The inflammatory responses induced by cigarette smoke not only cause abnormalities in the lungs but are also linked to extrapulmonary pathophysiological changes, including malnutrition, weight loss, osteoporosis, and skeletal muscle wasting,[73] Among these, weight loss is particularly associated with peripheral muscle dysfunction and exercise intolerance, and is considered an independent risk factor for survival.[74,75]

TRIM63, also known as MURF1, and atrogin-1 are key E3 ubiquitin ligases involved in muscle protein degradation during acute skeletal muscle atrophy.[76] Although the expression of TRIM63 and atrogin-1 is not elevated in stable COPD patients,[41] Tim Crul et al[42] investigated the mRNA expression profile of the quadriceps muscle in COPD patients during acute exacerbations compared to stable COPD patients. Through gene ontology analysis, they identified upregulation of transcripts involved in ubiquitin-dependent protein catabolism in hospitalized COPD patients compared to those with stable disease. Given that TRIM63 is a muscle-specific atrophy-related E3 ubiquitin-protein ligase, subsequent Real-time PCR validated the increased expression of TRIM63 in hospitalized COPD patients. This increase is consistent with expression levels observed in COPD patients with muscle atrophy as well as in those with preserved muscle mass,[43] which may be partly driven by activation of the mitogen-activated protein kinases (MAPKs) pathway.[77]

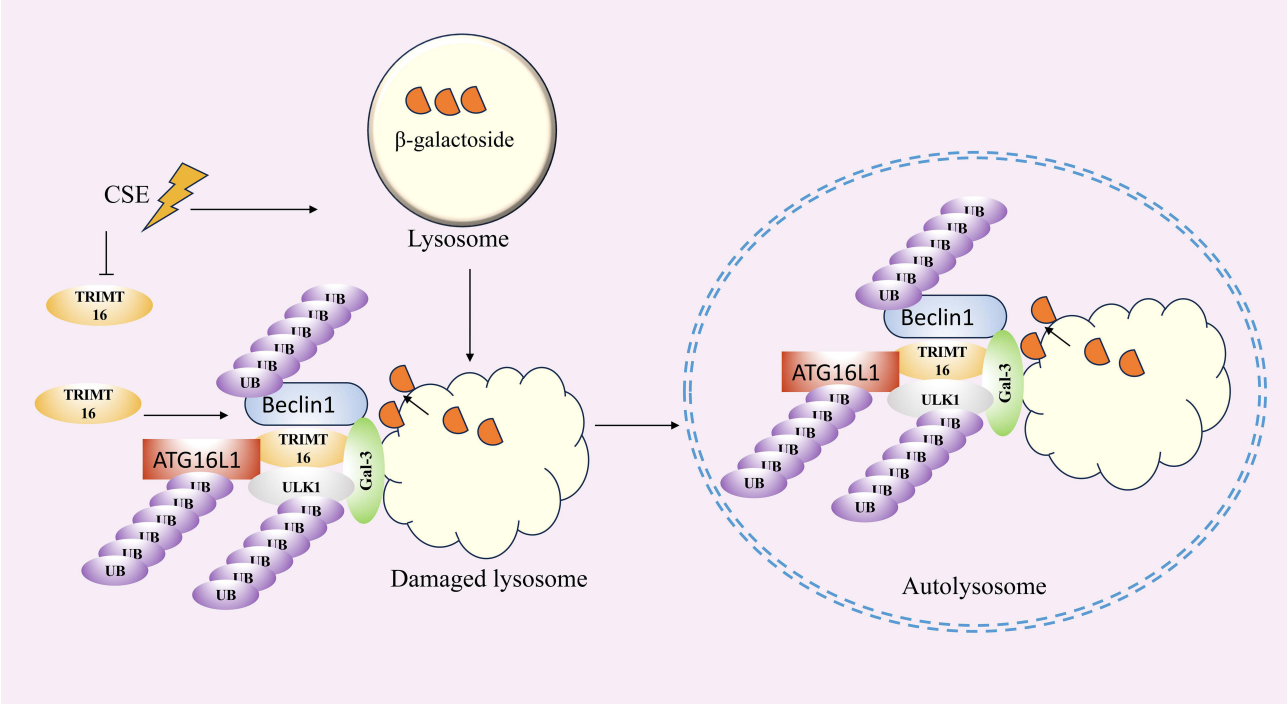

Figure 3 CSE enhanced lysosome damage while inhibiting autophagy by suppressing TRIM16 expression.

https://doi.org/10.2147/JIR.S499029

Barreiro et al[45] reported increased expression of TRIM32 and total ubiquitination levels in COPD patients, which might contribute to peripheral muscle weakness and mass loss. The use of the phosphodiesterase-4 inhibitor roflumilast was shown to reverse proteolysis in skeletal muscle cells, as evidenced by decreased TRIM32 expression and total protein ubiquitination levels.

Oxidative stress is another predominant mechanism implicated in muscle wasting in COPD patients.[78] Pomiès et al[44] demonstrated that the pro-oxidant molecule H2O2 activates TRIM63 expression, whereas the antioxidant molecule ascorbic acid reduces TRIM63 expression. Additionally, they found that the proteasome inhibitor MG132 not only restores basal atrophy levels in COPD myotubes but also suppresses pro-oxidant-induced myotube atrophy, suggesting that oxidative stress-induced TRIM63 overexpression may further promote atrophy via the proteasome pathway.

The Keap1-Nrf2 pathway is a well-established cellular stress response pathway to oxidative and electrophilic chemicals.[79] Keap1, part of an E3 ubiquitin ligase complex, normally binds to the transcription factor Nrf2 in the cytoplasm, targeting it for proteasomal degradation.[80] During oxidative stress, Nrf2 is released from Keap1, translocates to the nucleus, and activates the expression of key enzymes involved in cellular defense against oxidative stress, including HO1 and NQO1.[81] Notably, TRIM25, another E3 ubiquitin ligase, can directly bind to Keap1, targeting it for ubiquitination and proteasome-dependent degradation. This leads to Nrf2 activation and a reduction in oxidative stress.[82] Additionally, another study found that the increased expression of TRIM65, by regulating the Keap1-Nrf2 pathway, partly contributes to the protective effects of (−)-Epicatechin, a type of flavonoid, in COPD.[46]

Pulmonary Hypertension

Pulmonary hypertension is a multifaceted and progressively worsening condition marked by increased blood pressure within the pulmonary arteries, which can lead to right ventricular heart failure, along with significant morbidity and mortality.[83] PH is categorized into five groups based on distinct underlying pathophysiological mechanisms, with pulmonary arterial hypertension (PAH) being one of the most extensively researched subtypes.[84]

The pathogenesis of PH is driven by several factors, including endothelial dysfunction, vasoconstriction, excessive proliferation of pulmonary artery smooth muscle cells (PASMCs), and, in certain instances, thrombosis.[85] Genetic mutations, particularly in the BMPR2 gene, have been identified as major contributors to the development of PH.[86,87] In addition, inflammatory and autoimmune processes also contribute to the progression of the disease.[85]

Globally, PH affects approximately 1% of the population, with the prevalence rising to 10% among the elderly (over 65 years old).[88] Despite advancements in treatment options, the prognosis for PAH patients remains grim, with a reported 5-year mortality rate of about 34% in PAH patients,[89] This underscores the critical importance of early diagnosis and intervention.

Current treatment approaches for PAH focus on alleviating symptoms, slowing disease progression, and enhancing the quality of life. Therapeutic strategies include three main classes of pulmonary vasodilators: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin analogs.[83] The choice of therapy is often tailored to the severity of the disease and the patient's response to initial treatments. Lung transplantation is considered a definitive treatment for patients with advanced disease.[90] However, there remains a pressing need for a deeper understanding of PAH and the identification of more effective therapeutic targets.

Pulmonary vascular remodeling, driven by an imbalance between PASMC proliferation and apoptosis, is a primary cause of PAH.[91,92] Hu et al[47] found that TRIM32 expression was reduced in plasma samples from PAH patients compared to healthy controls, which exacerbated hypoxia-induced PASMC proliferation and migration. Conversely, overexpression of TRIM32 inhibited PASMC proliferation and migration while promoting apoptosis under hypoxic conditions. TRIM32 exerted these effects by suppressing the PI3K/Akt signaling pathway. In contrast, Jingwen Xu et al[48] reported that TRIM24 expression was decreased in a chronic hypoxia-induced pulmonary arterial hypertension mouse model and hypoxia-treated PASMCs. Knockdown of TRIM24 inhibited hypoxia-induced PASMC proliferation and migration by blocking the AKT/mTORC1 axis. The distinct functions of these TRIM proteins may be due to their interaction with different downstream substrates, despite both functioning as E3 ubiquitin ligases (Figure 4).

Similar to chronic lung diseases such as COPD, PAH can also lead to skeletal muscle atrophy and contractile dysfunction.[93] Thanh et al[49] discovered that knockdown of TRIM63 and TRIM55, which are key proteins involved in muscle protein degradation, protected against peripheral myopathy in a monocrotaline-induced pulmonary hypertension

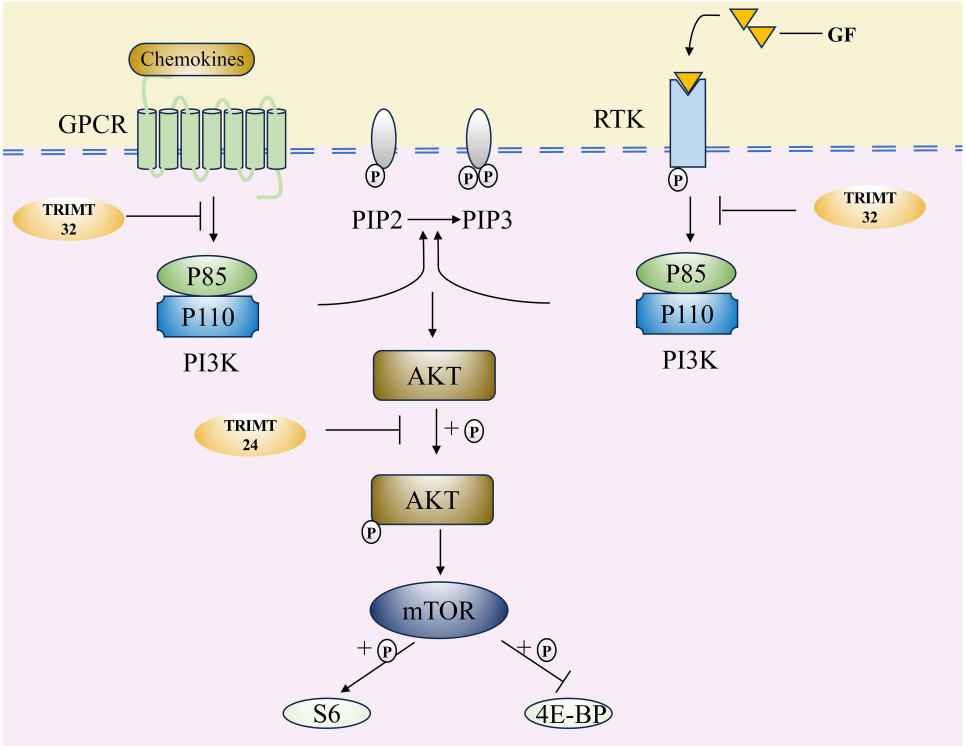

Figure 4 TRIM32 inhibited PASMC proliferation and migration by inhibiting the PI3K/AKT signaling pathway; TRIM24 promoted PASMC proliferation and migration via AKT/mTOR axis.

mouse model. They also observed that TRIM55 expression was lower in TRIM63 knockout mice compared to wild-type C57BL/6 mice, highlighting the close regulatory relationship between TRIM63 and TRIM55. While TRIM63 and TRIM55 are crucial regulators of skeletal muscle, their role in muscle protein degradation in lung diseases is not exclusive but extends to other conditions such as cancer cachexia,[94,95] cardiac cachexia[96] chronic kidney disease,[97] diabetes,[98] and sarcopenia,[99] underscoring their significant role in muscle atrophy associated with chronic diseases.

Therapeutic Targeting of TRIM Proteins: Opportunities and Challenges

Potential of TRIM Proteins as Therapeutic Targets

Targeting TRIM proteins as therapeutic interventions has gained considerable interest, with several strategies emerging to achieve selective modulation of these multifunctional proteins. However, the complexity of TRIM-mediated pathways necessitates precise and innovative approaches to minimize off-target effects and enhance therapeutic efficacy.

Small-molecule inhibitors remain a foundational strategy for targeting TRIM proteins. These compounds typically disrupt protein-protein interactions or inhibit enzymatic activity, such as the ubiquitin ligase function of TRIM proteins. For instance, recent research has demonstrated that inhibitors targeting TRIM24, such as IACS-9571 and dTRIM24, effectively suppress glioblastoma stem cell (GSC) proliferation and invasion. Additionally, the dual TRIM24/BRPF1 inhibitor 20L (Y08624) demonstrated significant tumor growth suppression in prostate cancer (PC) xenograft models, highlighting its therapeutic potential.[100] These findings highlight the therapeutic potential of TRIM24 inhibitors in mitigating the progression of tumors.[101] Similar approaches might be applicable in chronic non-tumor diseases. For example, studies have shown that melittin-induced down expression of TRIM47 or siRNA-mediated knockdown of TRIM47 in lung fibrosis models alleviates fibrotic processes by restoring the anti-fibrotic PPM1A and suppressing TGF-β signaling.[34]

RNA-based strategies, such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), offer high specificity by targeting unique mRNA sequences. In addition to their success in modulating TRIM47 in fibrosis,[34] RNA-based methods have been explored for downregulating other TRIM proteins implicated in chronic diseases.[102–104] However, delivery challenges and off-target effects remain barriers to their broader application in vivo. There are two

https://doi.org/10.2147/JIR.S499029

other technologies for targeted degradation based on the UPS-mediated protein degradation. These might also hold promise for the targeted degradation of E3 ligase themselves.

The development of proteolysis-targeting chimeras (PROTACs) has revolutionized the targeted degradation of proteins.[105] PROTACs are bifunctional molecules that recruit target proteins to E3 ligases for ubiquitination and subsequent proteasomal degradation. Although not yet explored extensively in chronic non-tumor diseases, PROTAC-based strategies hold promise for selectively degrading pathogenic TRIM proteins such as TRIM33 or TRIM47, both of which are implicated in pulmonary fibrosis.[33]

An emerging strategy for selective protein modulation is TRIM-away technology, which leverages TRIM21's ability to degrade specific proteins. By combining TRIM21 with antibodies against a target protein, TRIM-away directs the target for rapid proteasomal degradation.[106] This technology has been successfully applied in preclinical models of cancer and neurodegeneration,[107,108] showcasing its flexibility and efficiency. The application of TRIM-away in chronic lung diseases might enable precise degradation of pathogenic TRIM proteins, such as TRIM72 or TRIM63, thereby mitigating fibrosis or systemic muscle wasting.

Challenges in Developing TRIM-Targeted Therapies

Despite the growing recognition of TRIM proteins as critical modulators in various diseases, significant challenges remain in translating these findings into clinical therapies. One major obstacle is the dual functional nature of TRIM proteins, which act not only as ubiquitin ligases but also, in some cases, as deubiquitinases. This duality complicates the development of highly specific inhibitors or activators, as targeting one function may inadvertently affect the other, leading to unforeseen outcomes.[23,109] Additionally, TRIM proteins often exhibit context-dependent roles; the same TRIM protein can act as a tumor suppressor in one tissue while promoting malignancy in another, further complicating therapeutic applications.[19,22]

Another hurdle is the intricate network of downstream substrates regulated by TRIM proteins. Identifying and selectively targeting these substrates remains a daunting task due to the extensive crosstalk between signaling pathways. For instance, TRIM25 is known to ubiquitinate multiple substrates involved in antiviral immunity, inflammation, and oxidative stress, raising concerns about off-target effects.[41] Furthermore, TRIM proteins lack a catalytic cysteine residue, thus targeting their activity cannot rely on directly inhibiting the catalytic (nucleophilic) sites through covalent modification.[110] Instead, modulating TRIM functions requires a comprehensive analysis of their multidomain characteristics, which hinders rational drug design and the development of specific small-molecule modulators.[9]

The challenges of drug delivery and bioavailability must also be addressed. Small-molecule inhibitors or activators targeting TRIM proteins need to effectively reach intracellular compartments where TRIM proteins exert their functions, such as the nucleus or cytoplasmic aggregates. This is particularly critical for diseases like IPF or COPD, where the affected tissues are localized deep within the respiratory system.[9]

Moreover, safety concerns related to off-target effects and systemic toxicity pose additional barriers. Given the broad expression and diverse functions of TRIM proteins, systemic inhibition or activation could lead to deleterious effects in non-diseased tissues. For example, TRIM16 is involved in COPD pathogenesis by enhancing cellular senescence, yet targeting TRIM16 for its role in autophagy might inadvertently affect lysophagy processes critical for cellular homeostasis in other organ systems.[40,70] Therefore, achieving tissue-specific delivery and ensuring a favorable therapeutic index are essential for successful clinical translation.

Addressing these challenges will require an interdisciplinary approach combining advanced structural biology, high-throughput screening, and innovative drug delivery systems. Furthermore, integrating single-cell technologies and patient-derived organoid models could provide more precise insights into TRIM protein functions and their therapeutic potential.

Conclusion and Perspective

This review underscores the critical importance of TRIM family proteins in non-tumor chronic lung diseases, including IPF, asthma, COPD, and PH. By modulating inflammation, fibrosis, and cellular remodeling, TRIM proteins emerge as pivotal regulators of disease progression and potential biomarkers or therapeutic targets. These findings highlight an

important transition from tumor-centered research to exploring TRIM proteins in broader pathological contexts, offering new avenues for addressing unmet clinical needs.

Despite these advancements, the clinical application of TRIM-targeted therapies remains in its early stages, with several challenges still to be resolved. Key hurdles include the dual functional nature of TRIM proteins, their context-dependent effects, and the complexity of their interactions within extensive signaling networks. These challenges necessitate innovative approaches to ensure tissue-specific targeting, minimize off-target effects, and effectively deliver therapeutics to the intracellular compartments where TRIM proteins exert their functions.

Looking ahead, future research should emphasize a deeper mechanistic understanding of TRIM protein functions in specific disease contexts. Cutting-edge methodologies such as single-cell technologies, patient-derived organoids, and advanced computational modeling can shed light on the intricate roles of TRIM proteins and guide therapeutic design. Emerging strategies, including PROTACs and TRIM-away technology, hold promise for addressing the unique challenges of targeting TRIM proteins. Additionally, exploring the role of TRIM proteins in currently underrepresented areas of chronic lung disease may uncover new therapeutic opportunities.

Realizing the clinical potential of TRIM proteins will require collaborative, interdisciplinary efforts that integrate molecular biology, pharmacology, and clinical expertise. By fostering such collaborations, we can accelerate the translation of basic research into impactful therapies, ultimately improving the lives of patients affected by chronic lung diseases worldwide.

Funding

This work was supported by the National Natural Science Foundation of China [82060023 and 82360385]; and the Graduate Innovative Special Fund of Jiangxi Province [Yc2023-B072].

Disclosure

The authors report no conflicts of interest in this work.

References

1. Momtazmanesh S, Moghaddam SS, Ghamari S-H. Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the global burden of disease study 2019. *EClinicalMedicine*. 2023;59:101936. doi:10.1016/j.eclinm.2023.101936
2. Flewett R, Flewett R. How IPF has changed our lives. *Lancet Respir Med*. 2021;9(3):232–233. doi:10.1016/S2213-2600(20)30563-4
3. Xie M, Liu X, Cao X, et al. Trends in prevalence and incidence of chronic respiratory diseases from 1990 to 2017. *Respir Res*. 2020;21(1):49. doi:10.1186/s12931-020-1291-8
4. Wang W, Zhou K, Wang L, et al. Aging in chronic lung disease: will anti-aging therapy be the key to the cure? *Eur J Pharmacol* 2024;980:176846. doi:10.1016/j.ejphar.2024.176846
5. Zhou -Q-Q, Xiao H-T, Yang F, et al. Advancing targeted protein degradation for metabolic diseases therapy. *Pharmacol Res*. 2023;188:106627. doi:10.1016/j.phrs.2022.106627
6. Pohl C, Dikic I. Cellular quality control by the ubiquitin-proteasome system and autophagy. *Science*. 2019;366(6467):818–822. doi:10.1126/science.aax3769
7. Zheng N, Shabek N. Ubiquitin ligases: structure, function, and regulation. *Annu Rev Biochem*. 2017;86(1):129–157. doi:10.1146/annurev-biochem-060815-014922
8. Sun-Wang JL, Ivanova S, Zorzano A. The dialogue between the ubiquitin-proteasome system and autophagy: implications in ageing. *Ageing Res Rev*. 2020;64:101203. doi:10.1016/j.arr.2020.101203
9. Toma-Fukai S, Shimizu T. Structural diversity of ubiquitin E3 ligase. *Molecules*. 2021;26(21). doi:10.3390/molecules26216682
10. Cabana VC, Lussier MP. From drosophila to human: biological function of E3 ligase godzilla and its role in disease. *Cells*. 2022;11(3):380. doi:10.3390/cells11030380
11. Behera A, Reddy ABM. WWP1 E3 ligase at the crossroads of health and disease. *Cell Death Dis*. 2023;14(12):853. doi:10.1038/s41419-023-06380-0
12. Ji F, Zhou M, Sun Z, et al. Integrative proteomics reveals the role of E3 ubiquitin ligase SYVN1 in hepatocellular carcinoma metastasis. *Cancer Commun*. 2021;41(10):1007–1023. doi:10.1002/cac2.12192
13. Covill-Cooke C, Howden JH, Birsa N, et al. Ubiquitination at the mitochondria in neuronal health and disease. *Neurochem Int*. 2018;117:55–64. doi:10.1016/j.neuint.2017.07.003
14. Parolini F, Ataie Kachoie E, Leo G, et al. Site-specific ubiquitination of tau amyloids promoted by the E3 ligase CHIP. *Angew Chem*. 2023;62(50):e202310230. doi:10.1002/anie.202310230
15. Zhang Z-Y, Harischandra DS, Wang R, et al. TRIM11 protects against tauopathies and is down-regulated in Alzheimer's disease. *Science*. 2023;381(6656):eadd6696. doi:10.1126/science.add6696
16. Liu Y, Zhu M, Lin L, et al. Deficiency of Trim27 protects dopaminergic neurons from apoptosis in the neurotoxin model of Parkinson's disease. *Brain Res*. 2014;1588:17–24. doi:10.1016/j.brainres.2014.09.018

17. Zhang Y, Qian H, Wu B, et al. E3 Ubiquitin ligase NEDD4 family-regulatory network in cardiovascular disease. *Int J Bio Sci*. 2020;16 (14):2727–2740. doi:10.7150/ijbs.48437
18. Goto J, Otaki Y, Watanabe T, et al. The role of HECT-type E3 ligase in the development of cardiac disease. *Int J mol Sci*. 2021;22(11):6065. doi:10.3390/ijms22116065
19. Chen SN, Czernuszewicz G, Tan Y, et al. Human molecular genetic and functional studies identify TRIM63, encoding muscle RING finger protein 1, as a novel gene for human hypertrophic cardiomyopathy. *Circ Res*. 2012;111(7):907–919. doi:10.1161/CIRCRESAHA.112.270207
20. Brauner S, Jiang X, Thorlacius GE, et al. Augmented Th17 differentiation in Trim21 deficiency promotes a stable phenotype of atherosclerotic plaques with high collagen content. *Cardiovasc Res*. 2018;114(1):158–167. doi:10.1093/cvr/cvx181
21. Wu J, Li Y, Feng D, et al. Integrated analysis of ATAC-seq and RNA-seq reveals the transcriptional regulation network in SLE. *Int Immunopharmacol*. 2023;116:109803. doi:10.1016/j.intimp.2023.109803
22. Hatakeyama S. TRIM family proteins: roles in autophagy, immunity, and carcinogenesis. *Trends Biochem Sci*. 2017;42(4):297–311. doi:10.1016/j.tibs.2017.01.002
23. Lin Z, Lin X, Zhu L, et al. TRIM2 directly deubiquitinates and stabilizes Snail1 protein, mediating proliferation and metastasis of lung adenocarcinoma. *Can Cell Inter*. 2020;20(1):228. doi:10.1186/s12935-020-01316-6
24. Yang X, Zhang Y, Xue Z, et al. TRIM56 promotes malignant progression of glioblastoma by stabilizing cIAP1 protein. *J Exp Clin Cancer Res*. 2022;41(1):336. doi:10.1186/s13046-022-02534-8
25. Zhang S, Cao M, Yan S, et al. TRIM44 promotes BRCA1 functions in HR repair to induce cisplatin chemoresistance in lung adenocarcinoma by deubiquitinating FLNA. *Int J Bio Sci*. 2022;18(7):2962–2979. doi:10.7150/ijbs.71283
26. Lyu L, Lin T-C, McCarty N. TRIM44 mediated p62 deubiquitination enhances DNA damage repair by increasing nuclear FLNA and 53BP1 expression. *Oncogene*. 2021;40(32):5116–5130. doi:10.1038/s41388-021-01890-7
27. Wertz IE, O'Rourke KM, Zhou H, et al. De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. *Nature*. 2004;430(7000):694–699. doi:10.1038/nature02794
28. Qian H, Chen L. TRIM proteins in fibrosis. *Biomed Pharmacother*. 2021;144:112340. doi:10.1016/j.biopha.2021.112340
29. Habib N, Pasha MA, Tang DD. Current understanding of asthma pathogenesis and biomarkers. *Cells*. 2022;11(17):2764. doi:10.3390/cells11172764
30. Heukels P, Moor CC, von der Thüsen JH, et al. Inflammation and immunity in IPF pathogenesis and treatment. *Respir Med*. 2019;147:79–91. doi:10.1016/j.rmed.2018.12.015
31. Racanelli AC, Kikkers SA, Choi AMK, et al. Autophagy and inflammation in chronic respiratory disease. *Autophagy*. 2018;14(2):221–232. doi:10.1080/15548627.2017.1389823
32. Yang L, Xia H. TRIM proteins in inflammation: from expression to emerging regulatory mechanisms. *Inflammation*. 2021;44(3):811–820. doi:10.1007/s10753-020-01394-8
33. Boutanquoi PM, Burgy O, Beltramo G, et al. TRIM33 prevents pulmonary fibrosis by impairing TGF-β1 signalling. *Eur Respir J*. 2020;55 (6):1901346. doi:10.1183/13993003.01346-2019
34. Li L, Zhang S, Wei L, et al. Anti-fibrotic effect of melittin on TRIM47 expression in human embryonic lung fibroblast through regulating TRIM47 pathway. *Life Sci*. 2020;256:117893. doi:10.1016/j.lfs.2020.117893
35. Cong X, Nagre N, Herrera J, et al. TRIM72 promotes alveolar epithelial cell membrane repair and ameliorates lung fibrosis. *Respir Res*. 2020;21(1):132. doi:10.1186/s12931-020-01384-2
36. Tahara M, Sakamoto N, Satoh M, et al. Clinical characteristics of idiopathic interstitial pneumonias with anti-Ro52/tripartite motif-containing 21 antibodies. *Sci Rep*. 2022;12(1):11122. doi:10.1038/s41598-022-15321-4
37. Zhou M, Ouyang J, Zhang G, et al. Prognostic value of tripartite motif (TRIM) family gene signature from bronchoalveolar lavage cells in idiopathic pulmonary fibrosis. *BMC Pulm Med*. 2022;22(1):467. doi:10.1186/s12890-022-02269-4
38. Dai Y, Li Y, Cheng R, et al. TRIM37 inhibits PDGF-BB-induced proliferation and migration of airway smooth muscle cells. *Biomed Pharmacother*. 2018;101:24–29. doi:10.1016/j.biopha.2018.02.057
39. Li J, Wang X, Su Y, et al. TRIM33 modulates inflammation and airway remodeling of PDGF-BB-induced airway smooth-muscle cells by the wnt/β-catenin pathway. *Int Arch Allergy Immunol*. 2022;183(10):1127–1136. doi:10.1159/000524574
40. Araya J, Saito N, Hosaka Y, et al. Impaired TRIM16-mediated lysophagy in chronic obstructive pulmonary disease pathogenesis. *J Immunol*. 2021;207(1):65–76. doi:10.4049/jimmunol.2001364
41. Natanek SA, Riddoch-Contreras J, Marsh GS, et al. MuRF-1 and atrogin-1 protein expression and quadriceps fiber size and muscle mass in stable patients with COPD. *COPD*. 2013;10(5):618–624. doi:10.3109/15412555.2013.781577
42. Crul T, Testelmans D, Spruit M, et al. Gene expression profiling in vastus lateralis muscle during an acute exacerbation of COPD. *Cell Physiol Biochem*. 2010;25(4–5):491–500. doi:10.1159/000303054
43. Doucet M, Russell AP, Léger B, et al. Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176(3):261–269. doi:10.1164/rccm.200605-704OC
44. Pomiès P, Blaquière M, Maury J, et al. Involvement of the FoxO1/MuRF1/Atrogin-1 signaling pathway in the oxidative stress-induced atrophy of cultured chronic obstructive pulmonary disease myotubes. *PLoS One*. 2016;11(8):e0160092. doi:10.1371/journal.pone.0160092
45. Barreiro E, Puig-Vilanova E, Salazar-Degracia A, et al. The phosphodiesterase-4 inhibitor roflumilast reverts proteolysis in skeletal muscle cells of patients with COPD cachexia. *J Appl Physiol*. 2018;125(2):287–303. doi:10.1152/japplphysiol.00798.2017
46. Tian X, Xue Y, Xie G, et al. (-)-Epicatechin ameliorates cigarette smoke-induced lung inflammation via inhibiting ROS/NLRP3 inflammasome pathway in rats with COPD. *Toxicol Appl Pharmacol*. 2021;429:115674. doi:10.1016/j.taap.2021.115674
47. Hu Z, Song Q, Ma H, et al. TRIM32 inhibits the proliferation and migration of pulmonary artery smooth muscle cells through the inactivation of PI3K/Akt pathway in pulmonary arterial hypertension. *J Bioenerg Biomembr*. 2021;53(3):309–320. doi:10.1007/s10863-021-09880-w
48. Xu J, Zhong Y, Wang Z. Decrease in Tripartite Motif Containing 24 suppresses hypoxia-induced proliferation and migration of pulmonary arterial smooth muscle cells via the AKT/mammalian target of rapamycin complex 1 pathway. *Bioengineered*. 2022;13(5):13596–13606. doi:10.1080/21655979.2022.2080423
49. Nguyen T, Bowen TS, Augstein A, et al. Expression of MuRF1 or MuRF2 is essential for the induction of skeletal muscle atrophy and dysfunction in a murine pulmonary hypertension model. *Skelet Muscle*. 2020;10(1):12. doi:10.1186/s13395-020-00229-2

50. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192(2):e3–19. doi:10.1164/rccm.201506-1063ST
51. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18–e47. doi:10.1164/rccm.202202-0399ST
52. Martinez FJ, Collard HR, Pardo A, et al. Idiopathic pulmonary fibrosis. *Nat Rev Dis Primers*. 2017;3(1):17074. doi:10.1038/nrdp.2017.74
53. Podolanczuk AJ, Raghu G. Idiopathic pulmonary fibrosis mortality: update on trends in the modern treatment era. *Europ resp J*. 2024;64 (2):2401305. doi:10.1183/13993003.01305-2024
54. Massagué J, Sheppard D. TGF-β signaling in health and disease. *Cell*. 2023;186(19):4007–4037. doi:10.1016/j.cell.2023.07.036
55. Dupont S, Zacchigna L, Cordenonsi M, et al. Germ-layer specification and control of cell growth by Ectodermin, a Smad4 ubiquitin ligase. *Cell*. 2005;121(1):87–99. doi:10.1016/j.cell.2005.01.033
56. Dupont S, Mamidi A, Cordenonsi M, et al. FAM/USP9x, a deubiquitinating enzyme essential for TGFbeta signaling, controls Smad4 monoubiquitination. *Cell*. 2009;136(1):123–135. doi:10.1016/j.cell.2008.10.051
57. Quéré R, Saint-Paul L, Carmignac V, et al. Tif1γ regulates the TGF-β1 receptor and promotes physiological aging of hematopoietic stem cells. *Proc Natl Acad Sci USA*. 2014;111(29):10592–10597. doi:10.1073/pnas.1405546111
58. Lin X, Duan X, Liang -Y-Y, et al. PPM1A functions as a Smad phosphatase to terminate TGFbeta signaling. *Cell*. 2006;125(5):915–928. doi:10.1016/j.cell.2006.03.044
59. Zhou X, Tan F, Zhang S, et al. Combining single-cell RNA sequencing data and transcriptomic data to unravel potential mechanisms and signature genes of the progression of idiopathic pulmonary fibrosis to lung adenocarcinoma and predict therapeutic agents. *Funct Integrat Genomics*. 2023;23(4):346. doi:10.1007/s10142-023-01274-y
60. Yi H, Luo D, Xiao Y, et al. Knockdown of long non-coding RNA DLEU2 suppresses idiopathic pulmonary fibrosis by regulating the microRNA-369-3p/TRIM2 axis. *IntJ Mol Med*. 2021;47(5). doi:10.3892/ijmm.2021.4913
61. Papi A, Brightling C, Pedersen SE, et al. Asthma. *Lancet*. 2018;391(10122):783–800. doi:10.1016/S0140-6736(17)33311-1
62. Miller RL, Grayson MH, Strothman K. Advances in asthma: new understandings of asthma's natural history, risk factors, underlying mechanisms, and clinical management. *J Allergy Clin Immunol*. 2021;148(6):1430–1441. doi:10.1016/j.jaci.2021.10.001
63. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12(1):204. doi:10.1186/1471-2458-12-204
64. Camoretti-Mercado B, Lockey RF. Airway smooth muscle pathophysiology in asthma. *J Allergy Clin Immunol*. 2021;147(6):1983–1995. doi:10.1016/j.jaci.2021.03.035
65. Kahnert K, Jörres RA, Behr J, et al. The diagnosis and treatment of COPD and its comorbidities. *Deutsches Arzteblatt int*. 2023;120 (25):434–444. doi:10.3238/arztebl.m2023.027
66. Steppuhn H, Kuhnert R, Scheidt-Nave C. 12-month prevalence of known chronic obstructive pulmonary disease (COPD) in Germany. *J Health Monit*. 2017;2(3):43. doi:10.17886/RKI-GBE-2017-065
67. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science*. 1996;274(5288):740–743. doi:10.1126/science.274.5288.740
68. Man WDC, Kemp P, Moxham J, et al. Skeletal muscle dysfunction in COPD: clinical and laboratory observations. *Clin Sci*. 2009;117 (7):251–264. doi:10.1042/CS20080659
69. Fraiberg M, Elazar Z. A TRIM16-Galactin3 complex mediates autophagy of damaged endomembranes. *Dev Cell*. 2016;39(1):1–2. doi:10.1016/j.devcel.2016.09.025
70. Chauhan S, Kumar S, Jain A, et al. TRIMs and galectins globally cooperate and TRIM16 and galectin-3 co-direct autophagy in endomembrane damage homeostasis. *Dev Cell*. 2016;39(1):13–27. doi:10.1016/j.devcel.2016.08.003
71. Agustí AGN, Noguera A, Sauleda J, et al. Systemic effects of chronic obstructive pulmonary disease. *Europ resp J*. 2003;21(2):347–360. doi:10.1183/09031936.03.00405703
72. Calverley PMA, Walker P. Chronic obstructive pulmonary disease. *Lancet*. 2003;362(9389):1053–1061. doi:10.1016/S0140-6736(03)14416-9
73. Kamiide Y, Furuya M, Inomata N, et al. Chronic exposure to cigarette smoke causes extrapulmonary abnormalities in rats. *Environ Toxicol Pharmacol*. 2015;39(2):864–870. doi:10.1016/j.etap.2015.02.016
74. Agustí AGN, Sauleda J, Miralles C, et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166(4):485–489. doi:10.1164/rccm.2108013
75. Schols AM, Slangen J, Volovics L, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(6 Pt 1):1791–1797. doi:10.1164/ajrccm.157.6.9705017
76. Foletta VC, White LJ, Larsen AE, et al. The role and regulation of MAFbx/atrogin-1 and MuRF1 in skeletal muscle atrophy. *Pflugers Archiv*. 2011;461(3):325–335. doi:10.1007/s00424-010-0919-9
77. Lemire BB, Debigaré R, Dubé A, et al. MAPK signaling in the quadriceps of patients with chronic obstructive pulmonary disease. *J Appl Physiol*. 2012;113(1):159–166. doi:10.1152/japplphysiol.01518.2011
78. Pomiès P, Blaquière M, Gouzi F, Mercier J, Préfaut C, Hayot M. Atrophic phenotype of cultured COPD myotubes can be reversed by an antioxidant treatment. *Eur Respir J*. 2014;44(Suppl 58):P3686.
79. Liu S, Pi J, Zhang Q. Signal amplification in the KEAP1-NRF2-ARE antioxidant response pathway. *Redox Biol*. 2022;54:102389. doi:10.1016/j.redox.2022.102389
80. Motohashi H, Yamamoto M. Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med*. 2004;10 (11):549–557. doi:10.1016/j.molmed.2004.09.003
81. Vriend J, Reiter RJ. The Keap1-Nrf2-antioxidant response element pathway: a review of its regulation by melatonin and the proteasome. *Cardiovasc ResCardiovasc Res*. 2015;401:213–220. doi:10.1016/j.mce.2014.12.013
82. Liu Y, Tao S, Liao L, et al. TRIM25 promotes the cell survival and growth of hepatocellular carcinoma through targeting Keap1-Nrf2 pathway. *Nat Commun*. 2020;11(1):348. doi:10.1038/s41467-019-14190-2
83. Humbert M. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618–3731.

84. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Europ resp J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018
85. Thenappan T, Ormiston ML, Ryan JJ, et al. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ Clin Res*. 2018;360: j5492. doi:10.1136/bmj.j5492
86. Aldred MA, Vijayakrishnan J, James V, et al. BMPR2 gene rearrangements account for a significant proportion of mutations in familial and idiopathic pulmonary arterial hypertension. *Human Mutation*. 2006;27(2):212–213. doi:10.1002/humu.9398
87. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *Europ resp J*. 2019;53(1):1801899. doi:10.1183/13993003.01899-2018
88. Hoeper MM. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;4(4):306–322.
89. Thenappan T, Shah SJ, Rich S, et al. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Europ resp J*. 2010;35(5):1079–1087. doi:10.1183/09031936.00072709
90. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Europ resp J*. 2019;53 (1):1801889. doi:10.1183/13993003.01889-2018
91. Hu P, Xu Y, Jiang Y, et al. The mechanism of the imbalance between proliferation and ferroptosis in pulmonary artery smooth muscle cells based on the activation of SLC7A11. *Eur J Pharmacol*. 2022;928:175093. doi:10.1016/j.ejphar.2022.175093
92. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122(2):156–163. doi:10.1161/CIRCULATIONAHA.109.911818
93. Kosmas K, Michael Z, Papathanasiou AE, et al. Skeletal muscle dysfunction in experimental pulmonary hypertension. *Int J mol Sci*. 2022;23 (18):10912. doi:10.3390/ijms231810912
94. Bilgic SN, Domaniku A, Toledo B, et al. EDA2R-NIK signalling promotes muscle atrophy linked to cancer cachexia. *Nature*. 2023;617 (7962):827–834. doi:10.1038/s41586-023-06047-y
95. Tisdale MJ. Cancer cachexia. *Curr Opin Gastroenterol*. 2010;26(2):146–151. doi:10.1097/MOG.0b013e3283347e77
96. Bowen TS, Adams V, Werner S, et al. Small-molecule inhibition of MuRF1 attenuates skeletal muscle atrophy and dysfunction in cardiac cachexia. *J Cachexia Sarcopenia Muscle*. 2017;8(6):939–953. doi:10.1002/jcsm.12233
97. Huang M, Yan Y, Deng Z, et al. Saikosaponin A and D attenuate skeletal muscle atrophy in chronic kidney disease by reducing oxidative stress through activation of PI3K/AKT/Nrf2 pathway. *Phytomedicine*. 2023;114:154766. doi:10.1016/j.phymed.2023.154766
98. Song J, Liu J, Cui C, et al. Mesenchymal stromal cells ameliorate diabetes-induced muscle atrophy through exosomes by enhancing AMPK/ ULK1-mediated autophagy. *J Cachexia Sarcopenia Muscle*. 2023;14(2):915–929. doi:10.1002/jcsm.13177
99. Gumucio JP, Mendias CL. Atrogin-1, MuRF-1, and sarcopenia. *Endocrine*. 2013;43(1):12–21. doi:10.1007/s12020-012-9751-7
100. Xiang Q, Luo G, Zhang C, et al. Discovery, optimization and evaluation of 1-(indolin-1-yl)ethan-1-ones as novel selective TRIM24/BRPF1 bromodomain inhibitors. *Eur J Med Chem*. 2022;236:114311. doi:10.1016/j.ejmech.2022.114311
101. Han M, Sun Y. Pharmacological targeting of tripartite motif containing 24 for the treatment of glioblastoma. *J Transl Med*. 2021;19(1):505. doi:10.1186/s12967-021-03158-w
102. Wu L, Jia M, Xiao L, et al. TRIM-containing 44 aggravates cardiac hypertrophy via TLR4/NOX4-induced ferroptosis. *J Mol Med*. 2023;101 (6):685–697. doi:10.1007/s00109-023-02318-3
103. Liu C, Huang X, Hou S, et al. Silencing of tripartite motif (TRIM) 29 inhibits proliferation and invasion and increases chemosensitivity to cisplatin in human lung squamous cancer NCI-H520 cells. *Thoracic Cancer*. 2015;6(1):31–37. doi:10.1111/1759-7714.12130
104. Xie X, Li H, Pan J, et al. Knockdown of TRIM26 inhibits the proliferation, migration and invasion of bladder cancer cells through the Akt/ GSK3β/β-catenin pathway. *Chem Biol Interact*. 2021;337:109366. doi:10.1016/j.cbi.2021.109366
105. Sakamoto KM, Kim KB, Kumagai A, et al. Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. *Proc Natl Acad Sci USA*. 2001;98(15):8554–8559. doi:10.1073/pnas.141230798
106. Clift D, McEwan WA, Labzin LI, et al. A method for the acute and rapid degradation of endogenous proteins. *Cell*. 2017;171(7):1692–1706. e18. doi:10.1016/j.cell.2017.10.033
107. Zeng J, Santos AF, Mukadam AS, et al. Target-induced clustering activates Trim-Away of pathogens and proteins. *Nat Struct mol Biol*. 2021;28 (3):278–289. doi:10.1038/s41594-021-00560-2
108. Wang M, et al. Trim-Away in adult animals through Nano-ERASER and its application in cancer therapy. *Res Square*. 2023;2023:1.
109. Xie S, Zhang L, Dong D, et al. HDAC6 regulates antibody-dependent intracellular neutralization of viruses via deacetylation of TRIM21. *J Biol Chem*. 2020;295(42):14343–14351. doi:10.1074/jbc.RA119.011006
110. Zhang Y, Zhang W, Zheng L, et al. The roles and targeting options of TRIM family proteins in tumor. *Front Pharmacol*. 2022;13:999380. doi:10.3389/fphar.2022.999380