•综述•

激活转录因子家族在炎症性肺病及肺纤维化中的研究进展

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摘要: 激活转录因子 (activating transcription factor, ATF) 家族是基本螺旋亮氨酸拉链 (basic leucine zipper, bZIP) 结构域转录因子家族的重要分支, 广泛参与应激、炎症、凋亡、代谢等多种生物学过程。在肺纤维化和炎症性肺病, 如急性肺损伤/急性呼吸窘迫综合征、慢性阻塞性肺病、哮喘的发生发展过程中, ATF 家族成员能够通过调控细胞应激、炎症反应及铁死亡等关键机制, 影响细胞免疫应答和组织重塑等过程, 表现出促病理与保护效应并存的双向调节特性。本文综述了 ATF 家族在炎症性肺病与肺纤维化中的表达变化、生物学功能及其潜在的分子机制, 旨在为基于肺部疾病发病机制的靶向治疗策略提供新的研究思路。

关键词: 激活转录因子; 炎症性肺病; 肺纤维化; 内质网应激; 炎症

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Advances of activating transcription factor family in inflammatory lung diseases and pulmonary fibrosis

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Abstract: The activating transcription factor (ATF) family, a key branch of the basic leucine zipper (bZIP) transcription factors, is widely involved in various biological processes including cellular stress responses, inflammation, apoptosis, and metabolism. In the pathogenesis and progression of pulmonary fibrosis and inflammatory lung diseases, such as acute lung injury/acute respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, ATF family members regulate critical mechanisms including cellular stress, inflammatory responses, and ferroptosis, thereby influencing immune responses and tissue remodeling. They exhibit bidirectional regulatory roles with both pathological promotion and protective effects. This review summarizes the expression changes, biological functions, and potential molecular mechanisms of ATF family members in inflammatory lung diseases and pulmonary fibrosis, aiming to offer novel research perspectives for developing mechanism-based targeted therapies for pulmonary diseases.

Key words: activating transcription factor; inflammatory lung disease; pulmonary fibrosis; endoplasmic reticulum stress; inflammation

近年来, 全球范围内肺部疾病的发病率持续上升, 涵盖急性呼吸窘迫综合征 (acute respiratory distress syndrome, ARDS)、慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD)、哮喘及肺纤维化 (pulmonary fibrosis, PF) 等多个主要类别[1-4]。值得注意的是, PF 的发生发展与多种持续性炎症密切相关, 如急性肺损伤 (acute lung injury, ALI)、COPD 及哮喘等引发的慢性炎症, 均可通过促纤维化因子的释放和成

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纤维细胞活化, 诱导细胞外基质 (extracellular matrix, ECM) 过度沉积, 推动肺组织纤维化的形成。其中, 特发性肺纤维化 (idiopathic pulmonary fibrosis, IPF) 作为一种进展性、致死率高的慢性间质性肺疾病[5,6], 临床预后差, 5年生存率仅为40%～50%。多数患者在确诊后数年内因呼吸衰竭而死亡, 严重威胁人类生命健康[7]。此外, 近年来, SARS-CoV、MERS-CoV及新型冠状病毒等感染引发的肺炎及继发性肺纤维化[8], 也进一步加剧了全球范围内的肺健康风险。当前, 多种肺部疾病的治疗仍面临显著挑战, 尤其是在PF领域, 尚缺乏能显著逆转疾病进程的有效疗法[9]。因此, 肺部疾病带来的公共健康负担亟需通过系统性研究与干预加以解决。

激活转录因子 (activating transcription factor, ATF) 家族因其在调控应激应答、免疫调控、代谢重编程等生物学过程中发挥着核心功能而受到了广泛关注。其家族成员已在多种肺部疾病中被发现具有动态表达变化, 并参与调控如内质网应激、TGF-β和NF-κB等关键信号通路[10-15]。通过介导上述信号, ATF家族成员能够影响下游靶基因的转录活性, 进而调节肺部细胞的炎症反应、凋亡、铁死亡及成纤维细胞增殖、活化等过程[16-18]。近年研究证实, 在炎性或纤维化肺病中, ATF家族不仅能推动疾病的病理过程, 还可在某些特定的病理条件下发挥保护作用, 呈现出双向调控功能。

ATF家族主要包括7个成员, 即ATF1～7[19], 其中, ATF3、ATF4与ATF6在肺部疾病研究中报道最为充分, 其作用机制也相对明确。因此, 本文将重点综述这3类ATFs在ALI、COPD、哮喘及PF中的表达情况、功能作用及调控机制, 旨在为肺病的分子机制研究及潜在靶向治疗策略提供理论支持与新思路。

1 ATF家族概述

1.1 ATF家族的发现

ATF家族是亮氨酸拉链 (basic leucine zipper, bZIP) 结构域转录因子家族的重要分支, 其发现始于1987年Lee等[20]的研究。作为能识别并结合腺病毒早期启动子区域中保守核心序列“CGTCA”的潜在蛋白, 因而被命名为ATF。同年, 研究人员在解析细胞内cAMP响应元件 (cAMP response element, CRE) 结合蛋白的过程中, 识别出一类可结合该顺式作用元件并激活转录的蛋白, 后被命名为CREB (CRE-binding protein)[21]。后续研究证实, ATF和CREB家族蛋白均属于结构相似的bZIP转录因子超家族, 能共同识别并结合“TGACGTCA”这一核心序列[22]。

由于ATF与CREB在结构和DNA结合特性上具有高度相似性, 早期研究并未对两类亚家族进行明确区分, 一度导致其命名和分类混淆。但随着研究的深入, 二者在结构域细节、功能特征及组织表达谱等方面的差异逐渐显现。CREB家族成员 (CREB1、CREM) 主要参与生理稳态维持、代谢及神经功能调控等[23]; 而ATF家族则在细胞应激反应、凋亡和组织纤维化等生理病理过程中扮演关键角色[24]。为系统展示ATF家族成员的组织与亚细胞分布情况, 下表根据人类蛋白质图谱 (Human Protein Atlas) 数据库 (https://www.proteinatlas.org) 的数据进行总结, 以期为理解其功能提供参考 (表1)。

1.2 ATF家族的结构特点

尽管在整体氨基酸序列上差异较大, ATF家族各成员仍保留了高度同源的核心结构区域, 即典型的bZIP结构, 构成其发挥转录调控的功能基础。该结构由两个功能区组成: 位于N端的碱性区域, 主要负责识别并特异性结合DNA上的顺式作用元件, 如CRE; 而位于C端的bZIP结构[25], 则通过疏水性相互作用介导蛋白二聚化, 实现DNA结合与转录调控功能的激活[26](图1)。

由于识别的序列高度相似, ATFs与其他bZIP家族成员 (AP-1、C/EBP) 存在潜在的DNA结合竞争及靶基因调控重叠。研究表明, ATF家族蛋白除通过形成同源二聚体发挥作用外, 还常与其他转录因子如CREB、JUN、FOS等形成异源二聚体, 拓展其转录调控谱[26,27]。因此, bZIP这一保守结构不仅是ATF家族成员行使转录调控功能的关键基础, 更赋予了其在细胞不同状态下实现功能多样性与调控灵活性的能力。

Table 1 Subcellular localization and distribution of activating transcription factor (ATF) family members. ER: Endoplasmic reticulum; ERS: Endoplasmic reticulum stress

Member	Subcellular localization	Distribution
ATF1	Nucleus	Widely expressed, low tissue specificity
ATF2	Nucleus, mitochondria	Widely expressed, relatively high in the nervous system
ATF3	Nucleus, cytoplasm	Widely expressed in various tissues; significantly upregulated under stress stimulation
ATF4	Nucleus, cytoplasm, ER	Highly expressed under ERS; widely distributed
ATF5	Nucleus, cytoplasm	Primarily expressed in the liver
ATF6	ER, Golgi apparatus, nucleus	Widely expressed, relatively high in the pancreas
ATF7	Nucleus, cytoplasm	Widely expressed in multiple tissues

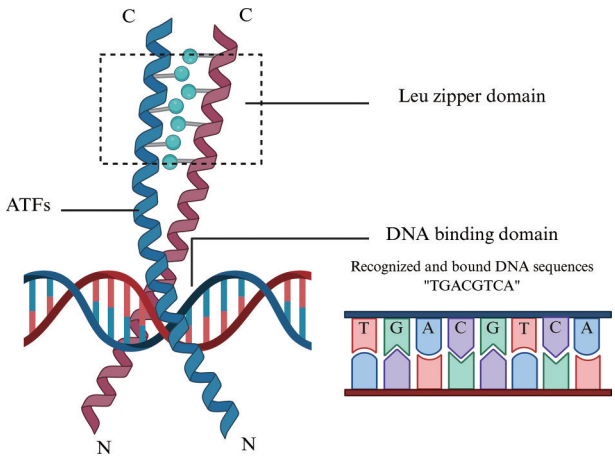


Figure 1 ATF family members regulate gene transcription through the formation of homo- or heterodimers, which specifically recognize and bind to the "TGACGTCA" DNA sequences

2 ATF家族参与的关键生物学过程

ATF家族通过与CREB、JUN、FOS等转录因子形成功能性复合物, 在炎症、代谢稳态、细胞命运决定及应激应答等多种核心生理病理过程中发挥关键调控作用。

2.1 细胞应激反应

内质网应激 (endoplasmic reticulum stress, ERS) 是指未折叠或错误折叠蛋白在内质网内积累, 引发细胞通过增强折叠、清除错误蛋白和自噬等机制来恢复稳态的过程[28]。然而, 持续或过度的ERS可导致细胞功能障碍甚至凋亡[29]。ERS在PF和COPD等疾病中广泛存在, 与肺组织损伤、炎症和修复过程密切相关[30]。在此过程中, ATFs发挥了重要的调控作用。如ERS激活的ATF4能参与成纤维细胞的活化, 推动PF的发生[31]; ATF6激活后能够上调内质网稳态相关基因, 如XBP1的表达, 有助于减轻细胞压力、恢复组织功能[32]; 而ATF3在受到ERS刺激后表达上调, 作为细胞应激的重要调节因子, 调控细胞存活与凋亡之间的平衡, 维持肺组织稳态[33]。此外, 不同ATF成员在ERS调控网络中也具有复杂的协同关系, 如ATF4与ATF6可协同上调下游靶基因CHOP, 介导细胞凋亡或适应性反应[34,35]; 而ATF3作为ATF4的下游靶基因, 可通过ATF4-ATF3-CHOP通路协同增强CHOP的表达[36], 这对于ERS信号的维持具有重要意义。

氧化应激 (oxidative stress) 是由活性氧 (reactive oxygen species, ROS) 和活性氮 (reactive nitrogen species, RNS) 等自由基生成与清除失衡引发的细胞损伤过程[37], 是多种疾病发病和进展的核心机制之一。ATF家族成员在调控细胞对氧化应激的防御机制中发挥重要作用。如ATF4促进抗氧化关键转录因子NRF2的表达[38], 进而诱导包括HO-1和NQO1等在内的抗氧化相关基因的表达, 增强自由基清除和细胞保护能力[39,40]。在缺血再灌注损伤、肿瘤应激反应等模型中也观察到ATF4对氧化还原稳态的关键调控作用[38,41]。ATF3则作为氧化应激的早期应答因子, 在不同细胞环境中呈现出双向调控特点: 既可通过负反馈抑制ROS过度积聚, 也可参与促凋亡通路, 影响组织修复或病理损伤进程[42,43]。

2.2 炎症反应

ATF家族成员在炎症反应中发挥关键调控作用。ATF3作为关键的炎症抑制因子, 在外源性炎症刺激物 (香烟烟雾) 的刺激下迅速上调, 并通过负向调控IL-6、IL-1β等促炎因子的表达[44], 限制炎症反应的过度激活; 此外, ATF3还可与NF-κB/p65相互作用并招募HDAC1, 降低p65的乙酰化水平, 抑制其转录活性, 发挥抗炎功能[45]。*Atf3*缺失小鼠在内毒素刺激下表现出炎症因子释放增加和致死率上升, 同样提示ATF3在遏制炎症反应中具有重要保护性作用[46]。与之相反, ATF4激活后可单独或与NF-κB协同作用增强IL-6等因子的表达, 在代谢紊乱或慢性刺激下放大炎症信号[47]; 激活PI3K-AKT信号通路, 增强LPS刺激产生的鼻上皮细胞的炎症反应, 并增加黏蛋白的分泌[48]; 此外, ATF4还可通过调控靶基因SMPD3的表达, 介导巨噬细胞M1极化, 增强机体的炎症反应[49]。同样地, ATF6也被发现参与促进炎症。研究表明, ATF6能上调小鼠肠上皮细胞及类器官中TNF-α、CXCL1等炎症因子的表达, 在炎症性肠病的进展中起促进作用[50]; 抑制ATF6还能下调巨噬细胞中IL-6和TNF-α的释放, 从而减轻肝脏缺血–再灌注损伤中的炎症水平。

2.3 铁死亡

铁死亡 (ferroptosis) 是一种以铁离子依赖性脂质过氧化物积累为特征的细胞死亡机制[51]。近年来, 铁死亡被证实与多种肺部疾病密切相关。如在ARDS中, 铁死亡可破坏肺泡–毛细血管屏障, 加剧炎症与肺水肿[52]; 在PF中, 铁死亡则能通过促进上皮损伤、炎症反应及成纤维细胞活化推动纤维化进程[53]; 而在COPD和吸烟相关肺损伤中, 铁死亡则因抗氧化防御受损而加重气道上皮细胞损伤[54]。ATF家族成员ATF3、ATF4在调控细胞铁死亡程序中发挥着关键作用, 且通常表现出双重调控特性。

ATF4作为参与铁死亡调控的核心转录因子, 一方面能抑制铁死亡过程, 如ATF4可通过诱导SLC7A11, 阻断应激相关的铁死亡[55]; AHR-ATF4轴的激活则通过介导溶酶体内的半胱氨酸代谢反应, 降低细胞对铁死亡的敏感性[56]。另一方面, ATF4在某些病理状态下

也可促进铁死亡, 如镉可通过EIF2AK3-ATF4-CHOP信号通路诱导肾小管上皮细胞发生铁死亡[57]; ATF4还可激活CHAC1的表达, 参与胱氨酸缺乏诱导的肿瘤细胞铁死亡过程[58]。

而作为ATF4下游应激相关基因的ATF3, 对铁死亡的调控同样展现出双重作用。一方面, ATF3能通过调节铁死亡相关基因, 如GPX4、FANCD2等转录, 抑制缺血/再灌注引起的心肌细胞铁死亡[59]。另一方面, ATF3能通过与SLC7A11启动子结合并抑制其表达, 进而促进erastin诱导的铁死亡过程[60]。

3 ATF家族在肺部疾病中的研究进展

尽管不同类型的肺部疾病在病因和临床表现上存在差异, 但其病理机制往往具有一定共性。如持续性的炎症反应、氧化应激、细胞凋亡及异常的纤维化重塑, 均在COPD、ALI/ARDS、PF及病毒感染相关肺炎中普遍存在[61-63]。因此, 探讨ATF家族在这些核心病理环节中的调控作用, 有助于理解其在多种肺部疾病中的广泛关联。

ATF3、ATF4和ATF6作为ATF家族中的核心成员, 在肺部疾病的炎症反应和组织修复中发挥着关键作用。近年来, 随着这3种亚型的研究不断深入, 它们在ALI、COPD、哮喘及PF等病理过程中的关键作用机制逐步得到揭示 (表2)[44,46,64-85]。

3.1 ATF3

ATF3基因通过可变剪接可产生多种转录本异构体, 主要包括全长型ATF3 (ATF3-FL) 和缺失bZIP结构域的剪接变体 (ATF3*Δ*Zip)。ATF3-FL保留了完整的DNA结合及二聚化能力, 能直接结合靶基因启动子区域, 发挥转录激活或抑制作用; 而ATF3*Δ*Zip则丧失DNA结合能力, 主要通过与其他转录因子相互作用而间接影响转录活性[86]。这些异构体在不同的细胞类型和应激环境中呈现差异性表达, 为其在肺损伤、炎症及纤维化等病理过程中的双向调控特性提供了分子基础。

3.1.1 ALI ATF3在ALI中发挥着双向调控作用: 一方面通过抑制炎症反应减轻组织损伤, 另一方面能诱导铁死亡加剧肺泡上皮损伤, 推动疾病进展。

在炎症调控方面, Qian等[46]利用全身性*Atf3*敲除小鼠构建LPS诱导的肺损伤模型, 发现*Atf3*缺失会显著加剧肺组织水肿和血浆渗漏, 并降低小鼠生存率。ATF3还可通过抑制*Ilf3*的转录及表达, 降低NEAT1 mRNA的稳定性, 促进M2型巨噬细胞极化, 在脓毒症相关肺损伤中发挥抗炎和免疫调节功能[66]。

此外, 在呼吸机相关性肺损伤 (VILI) 模型中, 全身性*Atf3*缺失小鼠对机械通气诱导的肺损伤更敏感, 表现为支气管肺泡灌洗液 (BALF) 中炎症细胞浸润增多, 炎症因子水平升高, 以及肺水肿和组织损伤加重[87]。

另一方面, ATF3也被证实能通过促进铁死亡途径加重ALI。作为ALI/ARDS最常见诱因, 脓毒症能引发全身炎症反应、破坏肺泡−毛细血管屏障, 进而导致肺组织水肿与损伤[88], 而铁死亡是ATF3导致肺损伤的重要机制之一[89]。研究发现, RNA结合蛋白AUF1能上调*Nrf2*和下调*Atf3*, 对抗弹性蛋白酶诱导的肺泡上皮细胞铁死亡, 从而减轻细胞损伤[67]。此外, ATF3在氧化镍纳米粒子 (NiONPs) 的暴露模型中的表达显著

Table 2 Functions of ATF family members in pulmonary diseases. ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; PF: Pulmonary fibrosis; AT2: Alveolar type II epithelial cell; EMT: Epithelial-mesenchymal transition

Member			Function in pulmonary disease	Ref.
ATF1			Involved in the proliferation, migration, and drug resistance of lung cancer cells	[64]
ATF2			Promotes proliferation and migration of lung cancer cells	[65]
ATF3	ALI/ARDS	Protective	Suppresses inflammation, reduces pulmonary edema and inflammatory cell infiltration	[46,66]
		Detrimental	Promotes cellular ferroptosis	[67]
	COPD	Protective	Suppresses inflammatory cytokine expression, oxidative stress, and immune cell infiltration	[68]
		Detrimental	Promotes goblet cell mucus secretion, contributing to airway remodeling and possibly worsening pathology	[44,69]
	Asthma		Alleviates airway inflammation and hyperresponsiveness	[70]
	PF		Induces apoptosis of AT2 cells and activating fibroblasts	[71,72]
ATF4	ALI/COPD		Mediates ERS, promotes apoptosis and ferroptosis	[73-76]
	PF		Induces AT2 cell apoptosis, fibroblast activation and EMT	[77,78]
ATF5			Associated with radio-resistance in lung cancer therapy	[79]
ATF6	ALI		Promotes inflammatory cell infiltration and cytokine expression	[80]
	Asthma		Regulates airway smooth muscle contraction and inflammatory responses	[81,82]
	PF	Protective	Protects against AT2 cell apoptosis	[83,84]
		Detrimental	Promotes fibroblast activation and exacerbates fibrosis	[85]
ATF7			The role in pulmonary diseases remains unclear	

上调, 而 *Atf3* 的缺失可缓解 NiONPs 所诱发的肺泡上皮细胞凋亡与铁死亡, 提示 ATF3 在此过程中加剧了肺泡上皮损伤[90]。

3.1.2 COPD 在 COPD 中, ATF3 的功能同样呈现出复杂的双重特性。一方面, ATF3 被证实具有显著的抗炎保护功能。Wu 等[44]研究发现, 抑制 *Atf3* 可增强香烟烟雾提取物诱导人支气管上皮细胞中 IL-6 和 IL-8 等促炎因子的表达, 显著加重小鼠 BALF 中性粒细胞的浸润。进一步机制研究显示, ATF3 通过抑制 NF-κB 的激活与磷酸化, 负向调控香烟烟雾诱导的炎症反应, 发挥抗炎保护作用。在香烟烟雾暴露的小鼠模型中, *Atf3* 缺失加剧了肺部炎症反应, 并伴随着肺气腔扩大、氧化应激标志物 8-oxo-dG 表达升高、巨噬细胞浸润增加, 以及 BALF 中 IL-6 和 TNF-α 水平显著升高[68]。

另一方面, ATF3 也可能参与推动 COPD 疾病的进展。香烟烟雾暴露后的小鼠肺组织中 ATF3 表达上调, 并伴随杯状细胞分泌的黏蛋白 5AC (MUC5AC) 增加, 而 *Atf3* 缺失则显著抑制 MUC5AC 的上调[69], 提示 ATF3 可能通过调控杯状细胞功能, 参与香烟烟雾诱导的黏液分泌过程, 从而促进 COPD 的气道重塑。

3.1.3 哮喘 ATF3 在哮喘的发病过程中发挥重要的抗炎调节功能, 可抑制哮喘中的气道炎症与气道高反应性。在卵清蛋白诱导的哮喘小鼠模型中, ATF3 表达上调, 并参与对 Th2 细胞因子释放的转录调控。*Atf3* 缺失则会导致气道高反应性增强、肺部嗜酸性粒细胞浸润增加, Th2 细胞因子与趋化因子水平升高, 加重炎症反应[70]。此外, 在二异氰酸酯诱导哮喘患者的全基因组测序结果中鉴定出位于 *ATF3* 基因调控区的 7 个变异位点, 且在高通量筛选中排名靠前, 提示 ATF3 可能作为关键因子参与转录失衡的调控[91]。

3.1.4 PF 在 IPF 患者及博来霉素 (bleomycin, BLM) 诱导的 PF 小鼠的肺组织中, ATF3 的表达水平显著升高[92]。ATF3 能上调长链非编码 RNA LINC00941 的表达, 诱导成纤维细胞向肌成纤维细胞的分化, 并增强其增殖和迁移能力, 从而加速 PF 进程[71]。过表达 *Atf3* 可抑制线粒体稳态调节因子 *Pink1* 的转录, 导致线粒体 ROS 积聚和细胞功能障碍。而在 II 型肺泡上皮细胞 (alveolar type II epithelial cell, AT2) 中条件性敲除 *Atf3* 可显著缓解 BLM 诱导的小鼠 PF 表型[72]。

抗纤维化药物吡非尼酮 (pirfenidone) 可下调 PF 小鼠肺组织中 ATF3 的表达水平[92]。此外, 一些天然产物也可通过调控 ATF3 相关通路缓解纤维化。如柚皮苷[93]和柑橘提取物[94]能通过调控 ATF3-PINK1 信号轴, 降低 ERS 水平, 增强线粒体自噬, 减轻 BLM 诱导的小鼠 PF 表型。

综上, ATF3 在多种肺部疾病中展现出显著的双向调控特性。一方面, ATF3 能通过抑制炎症因子表达、调节免疫细胞功能、维持细胞氧化还原稳态与内质网功能的稳定性, 从而发挥保护作用; 另一方面, 在某些病理刺激下, ATF3 也可能介导细胞功能障碍与组织重塑, 促进疾病的发生发展。尤其在肺纤维化中, ATF3 可通过调控线粒体稳态、非编码 RNA 表达等途径, 参与纤维化进程的调控。基于这一点, 针对 ATF3 的特异性调控策略有望成为未来开发 PF 靶向药物的关键突破口。

3.2 ATF4

ATF4 同样存在多种转录本变体, 其差异主要集中在 N 端结构域, 这可能影响其转录调控特性和蛋白稳定性。另外, ATF4 的表达还受到上游开放阅读框 (uORFs) 介导的选择性翻译机制的严格调控[95], 使得 ATF4 能在不同的疾病背景下呈现出多样化的生物学功能。

3.2.1 ALI ATF4 作为 ERS 途径中的核心转录因子, 在 ALI 的发生与发展中扮演着重要角色。研究显示, ERS 抑制剂能够抑制 LPS 诱导的小鼠 ALI 模型中 *Atf4* 的表达, 阻断铁死亡的发生, 减少肺泡上皮细胞的凋亡[73]。重组小鼠中脑星形胶质细胞来源的神经营养因子也可通过抑制 GRP78/PERK/ATF4 信号轴, 降低 LPS 诱导的脓毒症相关 ALI 模型中的铁死亡, 从而减轻肺损伤[74]。此外, 中药半夏可有效抑制 LPS 诱导的 ALI 小鼠中 Bip/ATF4/CHOP 通路的过度激活, 改善内质网稳态并减轻肺组织损伤[96]。

3.2.2 COPD 目前关于 ATF4 在 COPD 中的研究相对有限, 现有研究表明, ATF4 可能通过调控 ERS 反应参与 COPD 的发病过程。PM2.5 能通过激活经典的 PERK/eIF2α/ATF4/CHOP 通路, 加剧 COPD 中的气道炎症和细胞凋亡, 而使用 ERS 抑制剂可有效逆转由 PM2.5 诱导的炎症反应和细胞损伤[75]。人参皂苷 Rg1 也可通过调控 PERK/ATF4 轴, 抑制 ERS 及其介导的体内外铁死亡过程, 从而减轻由香烟烟雾引起的 COPD 小鼠模型中的肺气肿病变和炎症反应[76]。

3.2.3 PF ERS 及其触发的未折叠蛋白反应 (unfolded protein response, UPR) 已被揭示在 PF 的发生发展中发挥着关键作用。具体而言, ERS 不仅能诱导 AT2 细胞的凋亡, 还参与调控成纤维细胞的活化、上皮–间质转化及炎症反应的启动等一系列关键病理过程[97-99]。Korfei 等[77]最早报道, 在 IPF 患者的外周肺组织及 AT2 细胞中, ATF4 及其下游靶基因 CHOP 的表达显著上调, 这可能与 AT2 细胞的凋亡增加密切相关。进一步研究证实, ERS 诱导产生的 ATF4 能激活 AT2 中的线粒

体未折叠蛋白反应 (mitochondrial unfolded protein response, UPR mt), 导致线粒体功能障碍, 从而加重肺损伤[100]。ATF4还可通过转录激活*α*-平滑肌肌动蛋白来促进成纤维细胞的活化, 推动纤维化反应[78]。另一方面, TGF-*β*可激活PI3K-AKT-mTORC1通路, 上调ATF4的表达, 进而增加肺成纤维细胞中丝氨酸−甘氨酸合成通路相关酶的表达, 促进细胞内甘氨酸的从头合成。而甘氨酸作为胶原蛋白合成的重要前体物质, 在成纤维细胞活化和细胞外基质积聚过程中发挥关键作用[101,102]。因此, ATF4在PF中能通过多种机制介导AT2损伤及成纤维细胞活化等过程, 在PF的发生与进展中占据重要地位。

综上, ATF4能通过多条下游通路驱动疾病的发生发展, 在肺部疾病中表现较强的促病理特性, 体现其作为潜在干预靶点的应用价值。

3.3 ATF6

ATF6存在两种主要异构体, 即ATF6*α*和ATF6*β*[103]。ATF6*α*作为典型的UPR激活因子, 在肺损伤、慢性炎症和纤维化等疾病中的关键作用得到了广泛研究。相比之下, ATF6*β*的研究相对有限, 现有证据表明其可能通过抑制ATF6*α*的活性, 在ERS反应中发挥负向调控作用, 从而精细调节UPR信号通路的强度和时序[104]。

3.3.1 ALI 在ALI模型中, ATF6的激活可加剧肺组织中炎症因子的表达与结构损伤, 而维生素D可通过上调miR-149-5p, 抑制*Atf6*及其下游靶基因*Chop*的表达, 显著改善由LPS诱导的小鼠ALI模型中的肺水肿、中性粒细胞浸润及组织结构破坏[80], 这表明ATF6可能是维生素D发挥抗炎保护作用的重要靶点。

3.3.2 COPD与哮喘 ATF6除在急性应激反应中发挥作用外, 也可能参与慢性肺部疾病的持续进展过程。Martin等[105]发现, 缺氧条件下COPD患者肺成纤维细胞中ATF6与其他ERS因子 (IRE1、PERK) 及氧化应激相关分子 (SOD3、HIF-1*α*) 显著上调, 提示缺氧可能通过激活ATF6介导的应激通路, 参与肺成纤维细胞功能重塑与气道重构。

在哮喘方面, ATF6主要通过调控气道平滑肌 (airway smooth muscle, ASM) 的增殖和收缩能力, 促进气道高反应性形成。体内外研究均表明, ATF6在哮喘的气道结构改变中发挥重要调控作用, 其缺失可显著减轻过敏原所致的ASM增生与气道高反应性增强[81]。近期研究发现, ATF6在哮喘中可通过增强Th2和Th17细胞的分化与细胞因子表达, 促进混合型粒细胞炎症的发生。敲除T细胞中的ATF6或使用ATF6抑制剂可显著减轻气道炎症和细胞浸润。在慢性哮喘模型中, 靶向ATF6同样具有良好效果, 因而有望成为治疗激素抵抗型或T2低型哮喘的潜在策略[82]。

3.3.3 PF ATF6在PF中的作用同样表现出复杂的双重性。ATF6可通过与mTOR信号通路的协同作用, 驱动AT2细胞的衰老样表型, 并促进在应激与损伤状态下过渡细胞的异常积累, 加速AT2细胞的凋亡过程[83]。香烟烟雾可通过诱导肺成纤维细胞中的ERS反应, 促进其向肌成纤维细胞分化, 在这一过程中, ATF6表达显著上调, 可能作为促病理因子在气道重塑和纤维化过程中发挥作用[84]。此外, ATF6在TGF-*β*1刺激下活化增加, 促进肺成纤维细胞中硫氧还蛋白结构域蛋白5 (TXNDC5) 的表达上调, 进而增强TGF*β*1的信号活性, 推动PF的进展[106]。

然而, 另有研究指出, ATF6也可能在特定病理条件下发挥保护性作用。ATF6可通过调节UPR/ERS信号, 抑制促凋亡通路中IRE1*α*的过度活化及其下游的促炎JNK信号, 同时促进与AT2细胞蛋白质稳态相关的调节机制, 有助于维持肺组织在损伤/修复过程中的功能稳定性[85]。

综上, ATF6在急性与慢性肺部疾病中能参与肺组织炎症、损伤与结构重塑, 并在不同病理背景下展现出其作为关键调控节点的潜力。ATF6在不同肺部疾病中表现出的双向效应, 可能与其两种异构体 (ATF*α*与ATF6*β*) 的功能差异有关。未来的研究应系统比较两种异构体在肺损伤、纤维化及肺癌等多种疾病中的表达和功能, 以明确其作为治疗靶点的潜在价值, 并为靶向UPR通路的干预策略提供依据。

3.4 其他家族成员研究现状

ATF3、ATF4和ATF6是目前在肺部疾病研究中报道最为广泛的ATF家族成员, 其他成员 (ATF1/2/5/7) 在不同类型肺疾病中的功能尚未被系统阐明。研究提示, ATF1和ATF2在肺癌中可能通过调控细胞增殖、迁移和耐药性发挥作用[64,65]。ATF5则在多种肿瘤中表现出促生存和致癌作用, 其在肺癌中高表达, 并与细胞增殖、侵袭和放射抗性密切相关。体内外研究显示, ATF5过表达促进肿瘤生长, 而抑制其表达可增强肺癌细胞对放化疗的敏感性[79], 此外, 研究表明ECM刚度可激活ATF5, 进而推动肺癌进展[107], 提示其发挥作用可能受到ECM机械信号的调控。而ATF7的功能尚不明确。有研究表明, ATF7可通过抑制促炎性衰老表型的分泌, 抑制细胞衰老并减轻炎症[108], 提示其在“衰老−炎症轴”上发挥调控作用, 可能影响肺部慢性炎症与纤维化进展, 其作用和机制仍需进一步研究。另外, 部分研究提示其与肿瘤分期及预后相关。

尽管相关研究仍处于起步阶段, 但这些成员在其

他组织器官中参与应激、炎症、分化等过程的作用表明, 它们在肺部疾病中亦具有潜在的研究价值。未来应加强对整个ATF家族功能谱的系统解析, 进一步揭示其在肺病发生发展中的协同调控机制。

4 ATF家族作为疾病治疗靶标的前景

4.1 靶向ATF的直接干预策略

尽管目前尚缺乏针对ATF家族成员的特异性小分子调节剂, 但已有大量研究通过敲除或干扰ATFs的表达, 逐步明确了其在肺部疾病中发挥的功能。这不仅为ATF家族成员作为潜在治疗靶点提供了理论依据, 也为其药物开发提供了新思路。针对传统“不可成药”靶点的挑战, 近年来, 如PROTAC等蛋白降解技术的应用, 或对ATFs与泛素系统的相互作用进行干预, 均有望用于实现对ATF家族成员功能的精准调控。

4.2 ATF相关信号通路的间接调控策略

ATF家族成员多作为应激通路中的下游转录因子参与调控。因此, 已有研究尝试通过抑制相关上游通路来间接降低ATF蛋白的表达与活性, 缓解肺组织的损伤与纤维化。如使用ERS抑制剂 (4-PBA) 可通过阻断PERK通路下调ATF4和CHOP的表达[109], 减轻高氧诱导的ALI。此外, JNK、PI3K-AKT等应激相关信号在内的通路也可调控ATF家族成员的表达[110,111]。通过转录调节、翻译调控或蛋白稳定性影响ATFs水平, 提示调控ATFs表达不仅限于单一路径阻断, 而是一种多靶点、多通路协同的治疗策略。

4.3 ATF家族作为潜在诊断/预后生物标志物

ATF家族蛋白在肺部疾病中常呈现动态且特异性的表达模式。如在ALI中, ATF3在肺泡上皮细胞、内皮细胞或巨噬细胞中均上调, 并与炎症因子释放、组织损伤程度相关[112-114]。部分研究还发现, ATF4和CHOP的表达水平可反映ERS的强度[115], 可能作为应激状态的分子指征。随着单细胞测序及空间转录组等技术的发展, ATF家族成员在不同细胞群体中的表达分布与功能特征将被进一步解析, 为其在疾病分型、疗效评估与预后判断中提供支持。

4.4 联合或个体化治疗的潜力

ATFs常与NF-κB、AP-1等多种信号通路交叉调控, 在调控免疫应答、细胞应激和细胞命运决策方面具有桥梁作用。因此, ATFs可作为多条信号通路的协同调控节点, 在联合治疗策略中作为辅助性靶点。如在使用抗纤维化药物 (尼达尼布) 治疗时, 适度调控ATF3的表达可能进一步增强疗效。此外, ATF蛋白在不同病理阶段和细胞类型中发挥的功能具有明显差异, 未来可基于患者肺组织ATF表达谱制定个体化干预策略, 从而实现靶向精准治疗。

5 总结与展望

近年来, 随着对转录调控网络深入解析, ATF家族成员在多种肺部疾病中的作用逐渐被揭示。无论是在ALI/ARDS、COPD、哮喘还是在PF中, ATF家族成员ATF3、ATF4和ATF6均在炎症应答、ERS、细胞凋亡及铁死亡调控等关键病理环节中发挥着重要的调节能力, 具有重要的生物学意义与潜在的靶向价值。

现有研究提示ATF家族成员不仅参与疾病的启动过程, 也可在损伤修复阶段发挥保护作用, 呈现出时空依赖性与细胞类型特异性的复杂调控特点。然而, 目前针对ATF家族成员在肺部疾病中作用的研究仍存在诸多不足。一方面, 尚缺乏对ATF家族成员功能的系统比较及其上下游机制的深入解析, 尤其是家族成员之间的相互作用尚未得到系统阐明; 另一方面, 多数研究仍停留在动物模型或体外验证层面, 临床相关性与转化应用研究仍较薄弱。此外, ATF蛋白广泛参与多通路交叉调控, 其在不同细胞群体中可能存在“二元调控”效应, 亟需借助空间转录组、单细胞组学及遗传编辑工具进行精细化探究。

未来研究应聚焦于ATF家族成员的功能异质性与信号整合机制, 系统性解析其在肺部微环境中的动态调控网络, 并结合药物筛选和靶点验证, 探索其作为肺部疾病预后标志物与治疗靶点的应用潜力。随着组学技术和转化研究的不断推进, ATF家族有望成为连接基础研究与临床干预的关键桥梁。

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