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衰老驱动细胞外基质稳态失衡在慢性阻塞性肺疾病中的作用机制及靶向干预研究进展

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摘要 衰老是慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)发生与发展的重要影响因素, 肺组织细胞外基质(extracellular matrix, ECM)稳态的失衡可能是连接衰老与COPD进展的关键病理环节, 包括ECM组分异常、基质金属蛋白酶(matrix metalloproteinases, MMPs)与其组织抑制剂(tissue inhibitors of metalloproteinases, TIMPs)平衡破坏、不同肺区的异常沉积或降解以及力学信号转导异常。这些变化共同损害肺组织的修复与再生能力, 加剧慢性气道炎症和结构重塑, 从而加速疾病进程。现有证据提示, 上游氧化应激与线粒体质量控制障碍、细胞衰老及衰老相关分泌表型、蛋白酶失衡和TGF-β/Wnt等通路共同构成多节点网络, 共同参与COPD肺组织中的ECM重塑。该综述旨在系统阐述“衰老-ECM轴”在COPD中的可能调控作用, 深入梳理衰老相关ECM重塑参与COPD的具体分子机制与潜在治疗靶点, 以期总结COPD防治研究的现有理论认识与潜在干预方向。

关键词 衰老; 细胞外基质; 慢性阻塞性肺疾病; 发病机制; 靶向治疗

Aging-Driven Dysregulation of Extracellular Matrix Homeostasis in Chronic Obstructive Pulmonary Disease: Mechanisms and Targeted Therapeutic Interventions

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Abstract Aging is an important factor associated with the onset and progression of COPD (chronic obstructive pulmonary disease). Dysregulation of ECM (extracellular matrix) homeostasis in lung tissue may represent a critical pathological link bridging aging and COPD progression, manifesting as aberrant ECM composition, imbalance between MMPs (matrix metalloproteinases) and TIMPs (tissue inhibitors of metalloproteinases), region-specific abnormal deposition or degradation, and impaired mechanotransduction. These alterations collectively impair the lung’s capacity for repair and regeneration, exacerbate chronic airway inflammation and structural remodel-

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ing, and ultimately accelerate disease progression. Accumulating evidence suggests that upstream oxidative stress, mitochondrial quality control defects, cellular senescence and the SASP (senescence-associated secretory phenotype), protease/antiprotease imbalance, and pathways such as TGF-β and Wnt collectively constitute a multi-nodal network that contributes to ECM remodeling in COPD lung tissues. This review aims to systematically elucidate the potential regulatory role of the "senescence-ECM axis" in COPD, comprehensively delineate the specific molecular mechanisms linking senescence-associated ECM remodeling to COPD pathogenesis, and identify potential therapeutic targets, thereby providing current theoretical insights and potential intervention strategies for COPD.

Keywords aging; extracellular matrix; chronic obstructive pulmonary disease; pathogenesis; targeted therapy

慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)是一种以持续性气流受限为特征的慢性炎症性疾病, 全球患病人数众多, 居死因顺位第三位, 疾病负担沉重[1]。除吸烟和粉尘等环境因素外, 衰老也是COPD发生与进展的重要危险因素, 两者在生理衰退与分子机制上存在广泛交集[2]。细胞外基质(extracellular matrix, ECM)的动态重塑已作为新的衰老标记物[3], 其稳态失衡构成了连接衰老与COPD结构性破坏的重要枢纽[2,4]。衰老通过多重机制驱动ECM紊乱: 累积的衰老细胞通过分泌衰老相关分泌表型(senescence-associated secretory phenotype, SASP), 持续释放促炎因子及基质降解酶, 直接破坏ECM稳态[5-6], 同时, 衰老相关的氧化应激、端粒损耗等事件共同加剧ECM成分的异常修饰与降解[7-8]。紊乱的ECM进而通过改变力学信号转导和释放生物活性片段, 反向促进局部炎症与细胞衰老、加重修复障碍, 形成自我强化的恶性循环[9]。研究表明, COPD患者肺组织中ECM组成谱的改变与肺功能下降及衰老标志物表达密切相关[10]。然而, 当前对"衰老-ECM轴"在COPD中的系统性调控网络仍缺乏完整认识。本综述旨在系统阐述衰老作为上游驱动因素, 通过影响ECM稳态参与小气道重塑、肺泡壁破坏和炎症微环境串扰的多重病理进程。重点剖析核心衰老信号通路与ECM重塑的交互作用, 并展望靶向该轴的多维治疗新策略, 以期总结COPD机制研究与干预的现有证据及研究方向。

1 衰老-ECM轴对COPD进展的重要影响

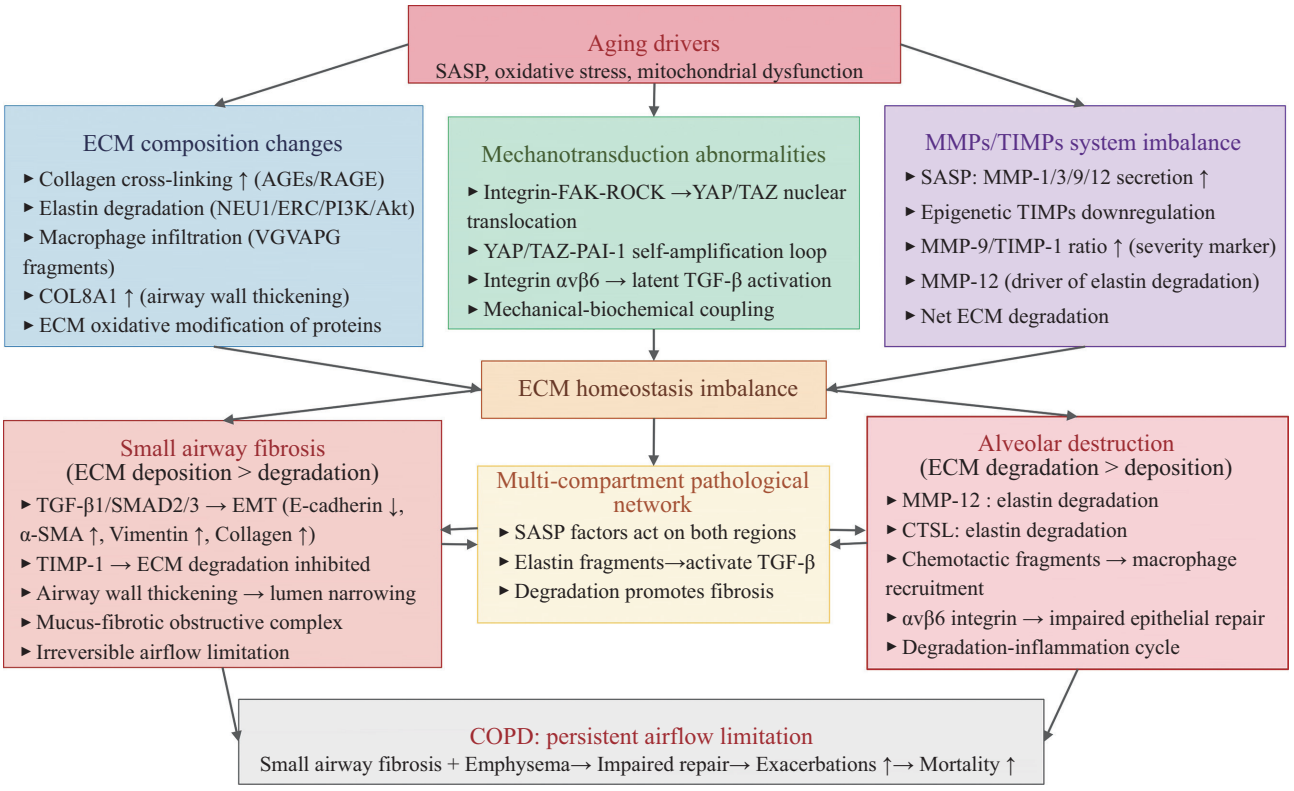
年龄是COPD发病的独立危险因素, 流行病学研究显示, 70岁以上人群的COPD患病率为27.4%~32.6%, 较40~49岁组(2.7%~4.2%)增长8倍, 且≥70岁是与COPD关联最强的因素[校正比值比(adjusted odds ratio, aOR)=17.86, 95% CI 14.16~22.52][11]; 增龄还与COPD的影像学风险表型及烟雾暴露下的疾病严重程度相关[12-13], 提示年龄增长与疾病风险密切相关。需要注意的是, 年龄、累积吸烟量、职业暴露和并发症相互交织, 上述关联并不等同于自然衰老的独立因果效应。生理学角度, 衰老伴随肺弹性下降、肺泡表面积减少及小气道所受的支撑力减弱, 这些结构性改变在微观层面与ECM的增龄性重塑密切相关, 共同导致气流受限[13]。COPD患者肺组织中可观察到与细胞衰老相关变化, 如衰老相关β-半乳糖苷酶(SA-β-gal)活性升高、细胞周期抑制蛋白p16与p21表达上调, 以及线粒体DNA损伤水平升高[14]。这些变化提示肺组织中细胞衰老表型增加, 但单一标志物不足以证明个体衰老加速或其对COPD进展的独立因果作用。

2 ECM稳态失衡的表现与肺区异质性

肺ECM是由胶原蛋白、弹性蛋白、糖胺聚糖、蛋白聚糖及糖蛋白等构成的动态三维网络, 不仅为肺组织提供结构支撑, 更是调控细胞行为、力学信号转导和组织稳态的核心微环境。衰老相关改变可能扰动ECM平衡, 通过成分改变、基质金属蛋白酶(matrix metalloproteinases, MMPs)及其组织抑制剂(tissue inhibitors of metalloproteinases, TIMPs)失衡和力学性能异常, 参与COPD的结构性病理改变(图1)。

2.1 ECM成分的年龄相关性改变

衰老导致肺ECM发生结构和功能的改变。胶原与弹性纤维增粗、变直, 同时晚期糖基化终末产物(advanced glycation end-products, AGEs)的积累使胶原交联增加、弹性纤维降解加速, 共同提升基质刚度, 并伴随组织弹性丧失[15-16]。AGEs通过其受体RAGE激活炎症与氧化应激, 该过程与COPD患



衰老通过SASP、氧化应激、线粒体功能障碍等途径, 引发ECM成分改变、力学信号转导异常及MMPs/TIMPs系统失衡, 导致ECM稳态失衡。该失衡在小气道区域表现为ECM过度沉积与纤维化(TGF-β1/SMAD通路驱动), 在肺泡区域则表现为弹性蛋白被过度降解与肺泡破坏(MMP-12/CTSL介导); 二者通过SASP因子及弹性蛋白降解片段相互串扰, 共同导致持续性气流受限。ECM降解产生的生物活性片段进一步促进细胞衰老与慢性炎症发生, 形成正反馈恶性循环, 推动COPD持续进展。图中实线箭头(→)表示促进或驱动作用, 双向箭头(⇔)表示病理环节间的相互串扰; ↑表示升高或增加, ↓表示降低。

Senescence triggers ECM homeostasis imbalance through SASP, oxidative stress, and mitochondrial dysfunction, leading to altered ECM composition, aberrant mechanotransduction signaling, and dysregulated MMPs/TIMPs system. This imbalance manifests as ECM hyperdeposition and fibrosis in small airways (driven by the TGF-β1/SMAD pathway) and excessive elastin degradation with alveolar destruction in alveolar regions (mediated by MMP-12/CTSL); the two pathological processes interact via SASP factors and elastin-derived bioactive fragments, collectively contributing to persistent airflow limitation. Bioactive fragments generated from ECM degradation further promote cellular senescence and chronic inflammation, forming a self-perpetuating positive feedback vicious cycle that drives the sustained progression of COPD. In the figure, solid arrows (→) indicate promoting or driving effects, double-headed arrows (⇔) indicate mutual crosstalk between pathological processes, ↑ indicates an increase, and ↓ indicates a decrease.

图1 衰老介导的ECM稳态失衡导致COPD进展示意图

Fig.1 Schematic illustration of senescence-mediated ECM homeostasis imbalance driving COPD progression

者肺功能下降呈正相关[17]。这些改变形成促衰老的反馈循环: 弹性蛋白降解片段[如弹性蛋白来源六肽VGVAPG(Val-Gly-Val-Ala-Pro-Gly)]作为信号分子, 通过结合含神经氨酸酶1(neuraminidase 1, NEU1)的弹性蛋白受体复合体(elastin receptor complex, ERC), 激活PI3K/Akt信号通路, 驱动单核/巨噬细胞浸润和慢性炎症发生, 形成“降解–炎症–再降解”的恶性循环[18]。线粒体腺嘌呤核苷酸转位酶1(adenine nucleotide translocase 1, ANT1)蛋白表达水平随年龄增长在气道上皮细胞中进行性下降, 其敲除可诱导气道上皮细胞衰老并特异性上调VIII型胶原α1链(collagen type VIII alpha 1 chain, COL8A1)表达[19]。然而, 香烟烟雾提取物可通过线粒体氧化应激和caspase相关过程抑制人肺成纤维细胞胶原a1及纤维连接蛋白的生成与释放[20]。这表明COPD中的ECM改变具有肺区和细胞类型异质性。增龄性的ECM氧化修饰还可改变蛋白沉积谱并损害成纤维细胞功能[21]。

2.2 ECM结构改变介导的力学信号转导异常

COPD肺组织的ECM结构改变产生显著的力学微环境改变: 小气道纤维化区域因胶原沉积及交联而硬度升高, 肺泡破坏区域则因弹性纤维断裂导致柔顺性异常增高, 两者共同构成不可逆气流受限的物理基础[15]。升高的基质硬度被整合素感知后, 经FAK-ROCK轴传递至细胞骨架, 驱动YAP/TAZ

核转位, 促进成纤维细胞活化, 并上调PAI-1抑制纤溶酶活性, 维持整合素黏附及自身核定位, 形成硬度-YAP/TAZ放大环路[22]。此外, 机械应力通过整合素αvβ6激活潜伏态的TGF-β, YAP/TAZ稳定SMAD复合体增强其促纤维化效应, 构成机械–生化信号耦合[23]。但YAP/TAZ-PAI-1和机械激活TGF-β的直接证据主要来自成纤维细胞及纤维化模型, 其在COPD不同肺区中的因果地位仍需空间分辨的人体研究验证。

2.3 ECM紊乱参与COPD的多重病理网络

ECM稳态失衡在COPD不同肺区呈现病理异质性, 这些变化构成相互联系的多重网络。小气道以ECM异常沉积、重新分布和管壁增厚为主要表现: 慢性炎症激活TGF-β1/SMAD2/3信号通路, 诱导气道上皮细胞发生上皮–间质转化(epithelial-mesenchymal transition, EMT)[24], 同时黏液栓、肺泡附着丢失及终末细支气管减少共同加重管腔狭窄[25]。在肺泡区域, 巨噬细胞来源的MMP-12及嗜酸性粒细胞来源的组织蛋白酶L(cathepsin L, CTSL)降解弹性蛋白, 产生趋化片段招募炎症细胞, 形成“降解–炎症”自我放大循环[26-27]。弹性蛋白降解片段(elastin degradation products, EDPs)作为ECM来源的致病介质, 通过激活TLR4受体、抑制Wnt/β-catenin再生信号, 阻碍AT2细胞介导的肺泡修复[28]。小气道重塑以TGF-β/SMAD通路驱动的ECM合成为主, 肺泡破坏以MMP-12/CTSL介导的弹性蛋白降解为主, SASP因子可同时作用于气道、肺泡和免疫微环境[2]。因此, 多个机制节点在不同肺区持续串扰, 共同形成复杂调控机制。

综上, 衰老通过改变ECM成分、干扰力学信号及打破蛋白酶系统平衡, 破坏肺基质的稳态, 构成小气道重塑和肺泡壁破坏的结构基础; ECM降解产生的生物活性片段, 又可加剧细胞衰老与慢性炎症, 推动COPD持续进展(图1)。

3 衰老驱动ECM紊乱的分子调控网络

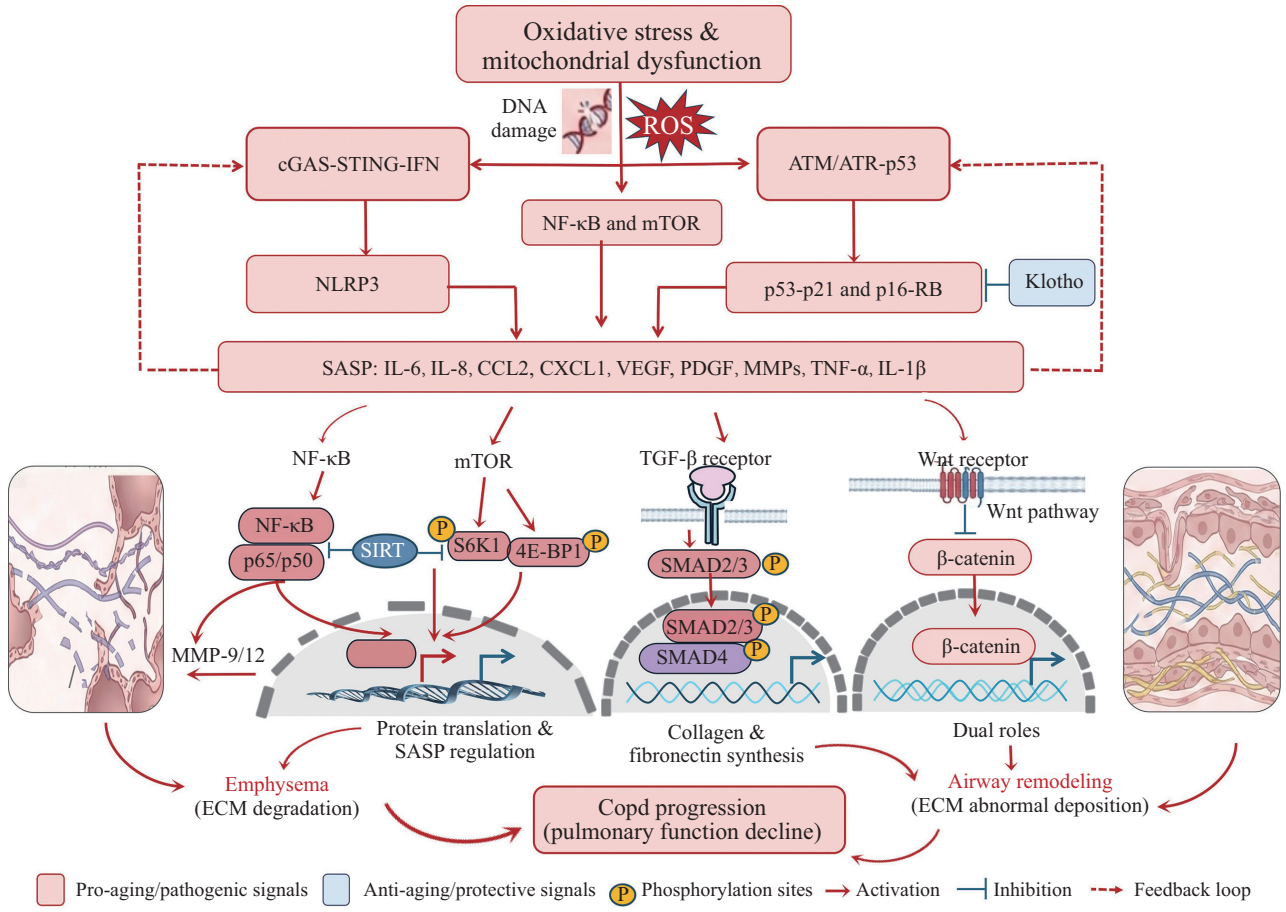
衰老细胞通过SASP重塑ECM微环境并加速COPD进展。SASP包含促炎细胞因子(如IL-6、IL-8)、趋化因子(CCL2、CXCL1)、生长因子(VEGF、PDGF)及基质降解酶(如MMPs), 构成破坏ECM稳态的效应库[29]。该过程涉及相互关联的多条信号通路。上游的氧化应激与线粒体损伤首先激活p53-p21和p16-RB等核心衰老调控通路, 再经NF-κB与mTOR两大枢纽启动SASP的转录与翻译, 并通过TGF-β与Wnt/β-catenin等效应通路将衰老信号转化为ECM重塑指令。各节点之间可交互放大, 形成自我强化的多节点网络(图2)。

3.1 氧化应激与线粒体功能障碍是衰老级联的上游触发器

氧化应激与线粒体功能障碍位于衰老-ECM轴的最上游, 作为初始触发器启动后续级联反应[30]。线粒体损伤是连接外界刺激(如香烟烟雾)与细胞衰老的核心环节[31]。一方面, ROS过量产生可直接造成DNA损伤, 通过ATM/ATR传感器激活p53-p21和p16-RB通路; 另一方面, 受损线粒体释放的线粒体DNA(mitochondrial DNA, mtDNA)作为损伤相关分子模式(damage-associated molecular patterns, DAMPs), 可激活cGAS-STING通路并与NLRP3炎症小体交互作用, 放大炎症反应与组织损伤[32]。同时, ROS能直接激活NF-κB和AP-1等转录因子, 促进炎性介质和MMPs的表达[33]; 在巨噬细胞中, 线粒体功能障碍依赖的ROS水平升高可通过PPIA-NF-κB轴驱动持续性肺部炎症[34], 并能激活TGF-β通路, 促进纤维化进展[35]。在代谢层面, 线粒体功能障碍驱动的代谢重编程与mTOR信号异常激活相互协同, 进一步加剧细胞衰老与炎症反应的恶性循环[31]。Klotho蛋白对IGF-1R/mTOR信号具有抑制作用; 其表达减少后这一抑制作用减弱, PINK1/Parkin介导的线粒体自噬亦受损, 导致受损线粒体不断累积并释放更多ROS; 在人COPD肺组织中已观察到PINK1与Klotho蛋白水平显著降低[36]。此外, ROS通过调控miR-377-3p等miRNA影响细胞衰老与ECM稳态[6]。氧化应激诱导的DNA损伤除激活ATM/ATR-p53轴外, 还可经由cGAS-STING通路放大衰老信号。Guo等[37]对COPD患者支气管上皮细胞的单细胞测序显示, COPD中cGAS-STING通路显著激活, 且与IFN-β、IFN-γ表达水平升高密切相关; STING抑制剂C-176可降低p16、p21表达水平及SASP因子(IL-6、IL-8、GM-CSF)分泌水平。氧化应激与线粒体损伤通过ROS爆发、mtDNA释放及代谢重编程, 激活p53-p21/p16-RB核心衰老轴, 构成衰老-ECM级联反应的第一层级。

3.2 p53-p21和p16-RB通路的转录与表观遗传重编程是衰老的核心

承接上游氧化应激与DNA损伤信号, p53-p21和p16-RB通路通过细胞周期阻滞与表观遗传重编程,



氧化应激与线粒体功能障碍作为上游触发因素, 通过ROS/mtDNA释放并行激活ATM/ATR-p53轴与cGAS-STING-IFN轴; p53-p21/p16-RB核心衰老轴经细胞周期阻滞及表观遗传重编程(DNA甲基化、组蛋白修饰)建立衰老状态; NF-κB与mTOR作为并行枢纽全局性调控SASP转录与翻译(SIRT1/SIRT6形成负向制衡); 下游TGF-β/SMAD驱动小气道纤维化, Wnt/β-catenin依配体类型与靶细胞身份呈现促再生/促纤维化双重角色; 各层级间通过SASP因子及ECM降解片段形成正反馈放大环路, 共同参与COPD进展。

Oxidative stress and mitochondrial dysfunction serve as upstream triggers, activating the ATM/ATR-p53 axis and the cGAS-STING-IFN axis in parallel via ROS/mtDNA release. The p53-p21/p16-RB core senescence axis establishes cellular senescence through cell cycle arrest and epigenetic reprogramming (DNA methylation, histone modification). NF-κB and mTOR function as parallel hubs to globally regulate SASP transcription and translation (counterbalanced by SIRT1/SIRT6). Downstream, TGF-β/SMAD signaling drives small airway fibrosis, whereas the Wnt/β-catenin pathway exhibits a dual role in epithelial regeneration versus fibrogenesis depending on ligand type and target cell identity. These hierarchical nodes form self-amplifying positive feedback loops via SASP factors and ECM-derived bioactive fragments, collectively contributing to COPD progression.

图2　COPD中衰老驱动ECM重塑的多节点分子调控网络

Fig.2　Multi-node molecular regulatory network of senescence-driven ECM remodeling in COPD

建立并维持衰老细胞的异常表型。活化的p53通过上调p21(*CDKN1A*), 导致视网膜母细胞瘤蛋白(retinoblastoma protein, RB)持续低磷酸化, 阻滞细胞周期[38-39]。p53还可直接抑制胶原合成并上调MMPs表达, 使ECM的降解速率大于其合成速率[40]。p16-RB轴通过抑制CDK4/6活性维持细胞周期阻滞状态[41]。p21以依赖于CDK4/RB的方式直接调控ECM成分表达, 将细胞周期阻滞与ECM病理重塑紧密耦联[42]。表观遗传重编程是衰老细胞稳定异常表型、确保SASP持续释放的关键。衰老细胞表现出全基因组DNA甲基化格局改变, ECM相关基因启动子的异常甲基化可导致其表达失调[43]。COPD中*Klotho*基因常因启动子区高甲基化而被抑制, 香烟烟雾暴露通过上调DNA甲基转移酶3A(DNA methyltransferase 3 alpha, DNMT3A)促使*Klotho*启动子高甲基化并降低*Klotho*基因的表达水平[44]。这些表观遗传改变使得衰老细胞的异常分泌和ECM重塑稳定且难以被逆转, 是连接上游衰老信号与下游SASP效应的关键桥梁。

3.3　NF-κB与mTOR通路是SASP表达的枢纽

NF-κB和mTOR并非简单承接上游p53-p21/p16-RB的下游信号, 而是与DNA损伤、氧化应激和细胞

周期停滞并行交叉的SASP调节枢纽。在COPD患者肺组织中, DNA损伤、氧化应激或炎性信号通过ATM/NEMO/IKK等复合物激活IKK激酶, 进而磷酸化并降解IkB, 释放NF-κB(主要为p65/p50二聚体)入核[45]。持续的NF-κB激活导致IL-1、IL-6、TNF-α等促炎细胞因子及CCL2、CXCL8等因子高表达[46]。这些因子募集炎症细胞的同时, 进一步正反馈式地激活NF-κB, 并强力诱导MMP-9、MMP-12等基质降解酶的表达, 形成炎症与ECM降解的恶性循环[47]。mTOR信号是SASP的代谢调控中心。衰老细胞中mTORC1常处于过度激活状态[48], 通过磷酸化4E-BP1和S6K1增强核糖体生物合成和蛋白质翻译效率, 全局性地促进SASP的大量合成与分泌[49-50]。mTOR还能通过调控自噬和代谢重编程影响细胞的衰老状态和分泌能力[51]。抑制mTOR的药物Senomorphics可靶向SASP, 抑制其有害分泌而非清除衰老细胞, 为治疗COPD提供了新思路, 但其可能同时影响免疫防御和组织修复, 尚需COPD特异性验证[52]。Sirtuins家族(SIRT1、SIRT6)对上述通路形成制衡: SIRT1/FOXO3和SIRT6下降可加重烟雾诱导的氧化损伤、上皮衰老并促进肺泡腔扩大[53-54]。SIRT1通过去乙酰化p53, 抑制*TP53*的转录活性, 延缓p21介导的衰老[55]。SIRT6通过去乙酰化组蛋白H3K9抑制NF-κB靶基因的转录, 保护细胞免受衰老相关的ECM过度降解[56]。因此, NF-κB/mTOR作为信号转导网络的关键节点, 通过调控SASP在COPD中的表达水平, 发挥重要病理生理功能。

3.4 衰老相关的MMPs/TIMPs系统失衡

MMPs和TIMPs的平衡是调节ECM稳态的核心。衰老可通过SASP持续分泌MMP-1、MMP-3、MMP-9和MMP-12等蛋白酶及炎症介质的释放, 直接降解ECM成分[57]; 同时衰老相关的表观遗传改变可下调TIMPs表达, 削弱其对MMPs的抑制能力[58]。MMP-12是驱动肺气肿的关键蛋白酶, 其切割弹性蛋白产生的趋化活性片段招募更多巨噬细胞浸润, 而*Mmp-12*基因敲除小鼠可抵抗香烟烟雾诱导的肺气肿[59]。MMP-9主要由中性粒细胞和巨噬细胞分泌, 可降解基底膜IV型胶原。香烟烟雾提取物通过激活PI3K/Akt信号通路, 同时驱动细胞衰老和MMP-2/MMP-9的高表达[60]。COPD患者血清MMP-9水平与第1秒用力呼气容积占预计值百分比(forced expiratory volume in the first second as a percentage of the predicted value, FEV1%pred)呈独立负相关[61]。MMP-9/TIMP-1值升高与肺气肿严重程度和急性加重风险呈正相关, 是预测COPD严重程度的独立危险因素[62]。总体而言, 衰老相关SASP、炎症细胞负荷和蛋白酶–抗蛋白酶失衡共同决定ECM净降解, 而非单一路径所致。

3.5 TGF-β与Wnt/β-catenin通路介导ECM紊乱

TGF-β与Wnt/β-catenin作为下游效应通路, 将上游衰老信号转化为具体的ECM重塑指令。TGF-β/SMAD通路是介导肺纤维化的核心效应器。COPD患者小气道中TGF-β通路过度激活, 通过磷酸化SMAD2/3并使其转位入核, 直接上调胶原蛋白、纤维连接蛋白等ECM成分的基因表达[63]。衰老增强细胞对TGF-β的反应: 衰老细胞通过SASP分泌PAPP-A增强IGF信号, 与TGF-β协同创造促纤维化微环境[64]。衰老与TGF-β信号之间存在双向正反馈循环[65]。与之拮抗的是, BMP4可通过激活SMAD1/5/9信号抑制TGF-β通路, 为纠正失衡提供了潜在靶点[66]。

Wnt/β-catenin通路在COPD的ECM紊乱中扮演双重角色。适当的Wnt信号促进肺泡上皮再生[67], 而持续性激活则驱动纤维化进程[68]。这种双重性由配体类型、靶细胞身份及微环境背景共同决定。配体类型是首要决定因素。Canonical配体Wnt3a通过激活β-catenin/TCF/LEF程序促进上皮细胞增殖与再生[67]; 然而当Wnt3a作用于成纤维细胞时, 可诱导Wnt5a表达并触发noncanonical信号转换, 促进胶原沉积[68]。Noncanonical配体Wnt5a在COPD患者肺组织中水平升高, 既抑制上皮修复, 又直接诱导成纤维细胞α-SMA表达驱动纤维化进展[69]。靶细胞身份是另一关键变量。不同细胞类型表达差异化的Frizzled受体谱, 决定了“相同配体–不同细胞–相反效应”[70]。综上所述, Wnt/β-catenin通路的双重角色由配体类型、靶细胞、信号强度及微环境共同决定。未来研究需利用单细胞空间转录组技术精确解析其动态时空特征, 以实现精准调控。

在COPD的进程中, 衰老驱动ECM重塑涉及相互交织的调控网络(图2)。氧化应激与线粒体功能障碍作为上游触发器, 通过DNA损伤激活p53-p21/p16-RB核心衰老轴; 该轴通过细胞周期阻滞和表观遗传重编程建立并维持衰老细胞状态; NF-κB与mTOR作为枢纽节点调控SASP; 最终,

TGF-β/SMAD与Wnt/β-catenin作为下游效应通路，将衰老信号转化为ECM重塑指令，分别驱动小气道纤维化与肺泡结构破坏。这种网络化的调控意味着，靶向单一通路可能不足以完全阻断衰老驱动的ECM紊乱，需要着眼于关键网络节点或采用联合干预策略。

4 靶向衰老-ECM轴的干预策略

随着对“衰老-ECM轴”紊乱参与COPD进展机制的认识加深，治疗正从单纯对症管理拓展至上游损伤控制和网络枢纽调节[71]。需要说明的是，目前尚无直接靶向衰老-ECM轴的药物获批用于COPD。因此，治疗策略聚焦于COPD临床试验、特异性临床前研究，以及具有转化前景的新技术，按证据等级进行论述。

4.1 靶向衰老细胞及衰老分泌的干预

衰老细胞是驱动“衰老-ECM轴”的源头，直接干预这些细胞成为根本性策略。干预策略主要分为两类：选择性诱导衰老细胞凋亡的药物Senolytics和抑制SASP分泌的Senomorphics[72]。

4.1.1 选择性清除衰老细胞的Senolytics 达沙替尼与槲皮素(D+Q)是经典的Senolytics组合。Justice等[73]在特发性肺纤维化(IPF)患者中开展的首次人体、开放标签先导试验(NCT02874989)证实了D+Q间歇给药的可行性与安全性，但该证据尚不能直接被外推至COPD；Nambiar等[74]随后进行的随机、安慰剂对照I期试验进一步验证了其耐受性。Baker等[75]的最新研究则为此提供了更直接的临床前依据：在COPD患者支气管上皮细胞(气–液界面分化培养)中，D+Q显著降低了衰老标志物p16INK4a及SASP因子(CXCL8、MMP-2、IL-33等)水平，并改善了上皮屏障完整性；在11天香烟烟雾暴露小鼠中，D+Q治疗性给药可降低肺组织衰老负荷和支气管肺泡灌洗液(bronchoalveolar lavage fluid, BALF)中CXCL1水平，并减少炎症细胞浸润。这提示D+Q可能通过清除衰老上皮细胞减轻COPD气道炎症，但向临床转化仍需COPD患者试验验证。

BCL-xL的蛋白水解靶向嵌合体(PROTAC)药物在临床前研究中能高效降解BCL-xL蛋白，特异性诱导COPD患者来源的衰老小气道上皮细胞凋亡，同时降低p21和纤溶酶原激活物抑制剂-1(PAI-1)水平，并促进周围细胞增殖[76]，这代表了通过PROTAC技术提高Senolytic选择性的新方向。Navitoclax(ABT263)通过抑制Bcl-2家族蛋白诱导衰老细胞凋亡[77]，在肺纤维化动物模型中已显示疗效。这些策略尚处于临床前阶段，向COPD临床转化需进一步验证其安全性和有效性。

4.1.2 抑制SASP分泌的Senomorphics 烟酰胺核苷(NR)是在COPD中完成随机对照临床试验的Senomorphic策略。Norheim等[78]的随机、双盲、安慰剂对照试验(n=40)显示，稳定期COPD患者口服NR六周后痰液中IL-8水平下降、全血NAD^+水平升高，并呈现延缓表观遗传衰老的趋势。该研究为NAD^+补充作为COPD辅助治疗提供了首个临床证据。核因子E2相关因子2(Nrf2)激活可恢复COPD巨噬细胞氧化代谢和功能[79]，研究证实，在COPD模型中，Nrf2激活剂(如莱菔硫烷)可减少衰老支气管上皮细胞聚集，降低SASP因子表达水平，并改善肺功能与病理损伤[80]。需要注意的是，口服莱菔硫烷的II期随机双盲安慰剂对照试验并未显著提高COPD患者Nrf2靶基因表达水平，也未改善炎症指标与肺功能[81]，提示Nrf2激活剂的临床转化仍面临挑战。二甲双胍通过激活AMPK并调节mTOR/NF-κB通路，减轻氧化应激并抑制SASP释放，在理论上具有Senomorphic潜力。然而，Hitchings等[82]在重度AECOPD患者(n=52)中开展的随机双盲安慰剂对照试验显示，二甲双胍未降低C反应蛋白(CRP)水平，也未改善患者的临床结局，提示目前尚无明确临床证据支持其用于COPD急性加重治疗。mTOR抑制剂雷帕霉素在COPD相关模型中显示出抗衰老潜力。Houssaini等[83]证实，COPD肺组织和细胞中mTOR通路活化与细胞衰老密切相关；低剂量雷帕霉素可抑制mTORC1，降低衰老标志物及促炎SASP因子表达水平，还可预防*TSC1*条件性敲除小鼠的肺气肿样改变。但mTOR抑制剂可能同时影响免疫防御和组织修复，其COPD临床价值尚需验证。SIRT2抑制剂AK-7在烟雾相关COPD模型中可抑制NF-κB/MAPK信号、减轻气道炎症和氧化损伤，并降低TGF-β、α-SMA、MMP-9水平和减少胶原沉积[84]，为靶向表观遗传调控的Senomorphic策略提供了新思路。

4.2 靶向上游信号通路的生物制剂

针对驱动衰老或SASP的特异性通路是新药研发热点，与Senolytics和Senomorphics策略形成互补。靶向IL-33/ST2通路的单克隆抗体9MW1911已完成

首次人体研究。Zhao等[85]报道的I期研究显示其具有良好的安全性与耐受性。目前针对COPD患者的Ib/IIa期临床试验(NCT06175351)正在进行, 旨在评估其阻断IL-33/ST2轴对COPD急性加重的预防作用。同时靶向TSLP和IL-13的双特异性抗体CM512已进入治疗中重度COPD的II期临床试验(NCT06980142)[86], 通过同时阻断上游警报素与Th2炎症信号, 抑制气道重塑。这些生物制剂代表了从传统多靶点调节到精准多靶点设计的演变, 但其核心机制更偏向炎症调控而非直接清除衰老细胞。

4.3 天然化合物与中药复方的多靶点调节

天然产物因其多组分、多靶点特性, 在调节复杂的“衰老–炎症-ECM紊乱”网络中具有独特优势。其作用并非针对单一环节, 而是通过协同调节多条信号通路, 系统性干预疾病网络。

4.3.1 *天然多酚及皂苷类成分* 临床前研究显示, 部分天然多酚及皂苷类成分具有调节衰老-ECM紊乱的潜力。槲皮素、白藜芦醇等多酚兼具Senolytic和Senomorphic活性[87]。咖啡酸与二甲双胍联用可有效抑制IL-6、IL-8等SASP因子; 表儿茶素单独或与抗纤维化药尼达尼布联用, 可抑制胶原蛋白生成[88]。山柰酚可能通过抑制PI3K/Akt信号通路, 减轻COPD相关的炎症反应与ECM损伤[89]。上述化合物目前均处于临床前研究阶段, 向临床转化需解决生物利用度和靶点选择性等关键问题。

4.3.2 *中药复方* 中药复方研究仍是重要的干预方向。临床前研究提示, 二陈汤加味可调节MMP-1、MMP-9及TIMP-1表达水平, 减少细支气管ECM中胶原的异常沉积[90]。参芪补肺汤则可能通过抑制肺气虚证COPD大鼠的肺内ECM过度沉积, 从而干预气道重构进程[91]。通塞颗粒在COPD急性加重期模型中, 能抑制肺组织ECM成分的降解与气道重塑[92]。连花清咳可通过调节Sp1/SIRT1/HIF-1α通路, 减轻烟雾诱导的COPD小鼠模型中的细胞衰老[93]。

临床研究中, 肺苏颗粒可显著提高临床总有效率, 并改善患者生活质量和免疫功能[94-95]。温阳润肺膏方对COPD西北寒燥证患者显示出明确的临床疗效, 其机制可能与降低ECM及黏附分子水平有关[96]。这些RCT为中药复方的临床应用提供了初步证据, 但样本量较小, 需进行大规模多中心试验验证。

4.4 先进递送技术

临床前研究: 纳米技术为提高药物靶向性和生物利用度提供了新途径[97]。负载槲皮素的Fe_3O_4磁性纳米颗粒兼具清除衰老细胞(Senolytic)和抑制SASP(Senostatic)的双重活性[98]。Cu-NAD@CM纳米系统则尝试同时补充NAD^+、清除ROS并抑制NF-κB相关SASP[99], 支持“靶向衰老+代谢重编程”的概念验证, 但尚无COPD患者研究。Zhao等[100]开发了一种可吸入式、低炎症反应的mRNA脂质纳米颗粒(NIF-LNP)。该团队将天然产物熊果酸整合入磷酰胺类可电离阳离子脂质PL32, 形成P-UA LNPs; 在机制上, 熊果酸通过激活V-ATPase促进内体酸化, 增强mRNA表达的同时抑制IL-6、IL-1β、TNF-α等炎症因子释放。利用该载体递送*NR1D1* mRNA, 在肺纤维化模型中显示出显著疗效, 且已完成冻干与雾化工艺优化, 为COPD等慢性肺病的mRNA治疗提供了可行路径。传统药材沉香制备的纳米乳剂也被发现具有调控TGF-β诱导气道重塑的潜力[101](表1)。

5 展望

衰老与COPD发生发展密切相关, 其重要驱动在于肺组织细胞外基质稳态的系统性失衡。这种失衡并非单一组分改变, 而是涉及胶原交联、弹性纤维降解、基质刚度异常及蛋白酶系统紊乱的多维病理重构, 最终在小气道形成纤维化闭塞、在肺泡区域造成结构破坏, 构成COPD不可逆气流受限的核心病理基础。与此同时, 靶向衰老-ECM轴的干预策略已从概念验证走向临床前乃至临床转化阶段, Senolytics、Senomorphics及抗纤维化药物的开发为疾病修饰治疗提供了新路径。

未来研究需在以下方面取得实质性突破。在机制解析层面, 当前对ECM重塑的认识多基于组织匀浆后的整体组学分析, 即将整块肺组织消化提取后进行RNA测序或蛋白质检测, 所得信号为多种细胞类型的平均表达水平, 无法区分成纤维细胞、上皮细胞、免疫细胞各自对ECM沉积或降解的贡献, 更无法定位这些事件在纤维化小气道与肺气肿区域的空间差异。单细胞空间转录组与蛋白质组技术的整合应用, 可在保留组织切片空间信息的前提下, 精确绘制成纤维细胞活化状态、上皮细胞衰老表型及免疫细胞浸润在肺组织中的三维分布图谱, 识别驱动ECM异常沉积或过度降解的关键细胞状态与分子开关。在靶点发现层面, 衰老-ECM调控网络涉及p53-p21、p16-RB、NF-κB、mTOR、TGF-β、Wnt

表1 靶向衰老-ECM轴的COPD干预策略证据图谱

Table 1 Evidence mapping of COPD interventions targeting the senescence-ECM axis

类别 Category	药物/干预策略 Drug/intervention strategy	作用机制 Mechanism of action	研究阶段(截至2026年8月) Research phase (as of August 2026)	主要证据 Primary evidence	证据等级 Evidence level
Clinical Research	NR (nicotinamide riboside)[78]	NAD^+ supplementation; regulates Sirtuin/DNA repair and SASP-related inflammation	COPD randomized double-blind placebo-controlled trial	Stable COPD (n=40); after 6 weeks of treatment, sputum IL-8 decreased by 52.6% vs.placebo; whole-blood NAD^+ increased >2-fold	Level I
	Sulforaphane[81]	Activates Nrf2 antioxidant pathway; inhibits oxidative stress and cellular senescence	Phase II (COPD)	In a COPD randomized double-blind placebo-controlled trial, it did not significantly increase Nrf2 target gene expression, nor improve inflammation or lung function	Level I
	Metformin[82]	Activates AMPK and regulates mTOR/NF-κB, oxidative stress, and SASP	COPD randomized double-blind placebo-controlled trial	Severe AECOPD (n=52); did not improve CRP or clinical outcomes, suggesting current clinical evidence does not support definite benefit	Level I
	Feisu Granule[94-95]	Multi-target anti-inflammatory and immunomodulatory effects; indirectly influences airway remodeling	COPD randomized controlled clinical study	Small-sample studies suggest improved clinical response rate, quality of life, and partial inflammatory/immune markers	Level I
	Wenyang Runfei Formula[96]	Multi-target regulation; may reduce ECM and adhesion molecule levels	COPD randomized controlled clinical study	Demonstrated symptom and related ECM marker improvement in Northwest Cold-Dry syndrome COPD patients; limited sample size	Level I
	9MW1911 (anti-ST2 monoclonal antibody)[85-86]	Blocks IL-33/ST2 axis; inhibits epithelial injury-related inflammatory amplification	Phase Ib/IIa (COPD)	NCT06175351: randomized, double-blind, placebo-controlled; registry shows active, not recruiting; no results posted yet	Level II
	CM512 (TSLP/IL-13 bispecific antibody)[86]	Simultaneously blocks TSLP and IL-13; inhibits upstream inflammation and airway remodeling signals	Phase II (COPD)	NCT06980142: multi-center randomized double-blind placebo-controlled study; registry last recorded as not yet recruiting; no results yet	Level II
Preclinical Research	BCLXL-PROTAC[102]	Selectively degrades BCL-XL; induces senescent cell apoptosis	COPD patient-derived cells/lung tissue slices	Reduced p21, p16, and SA-β-gal and promoted cell proliferation; precision-cut lung slices also showed decreased senescence markers	Level III
	Navitoclax (ABT-263)[77]	Inhibits BCL-2 family proteins; exerts senolytic effects	Pulmonary fibrosis animal/cell models	Can clear senescent cells and alleviate pulmonary fibrosis; lacks COPD-specific clinical validation	Level IV
	Rapamycin[83]	mTOR inhibitor; inhibits cellular senescence and SASP	COPD patient-derived cells/animal mechanistic studies	mTOR activation is associated with senescence in COPD lung tissue and cells; low-dose rapamycin can inhibit senescence and pro-inflammatory SASP	Level III
	Cu-NAD@CM Nanoplatform[99]	Targets senescent cells and promotes NAD^+ cycling; clears ROS, inhibits NF-κB and SASP	Preclinical nanodrug research	Supports the concept of "targeting senescence + metabolic reprogramming"; no COPD patient studies yet	Level IV
	AK-7 (SIRT2 inhibitor)[84]	Regulates neuro-immune interaction and TGF-β fibrotic signaling	COPD animal model	In cigarette smoke COPD mice, reduced TGF-β, α-SMA, MMP-9, and collagen deposition	Level III

续表1

类别 Category	药物/干预策略 Drug/intervention strategy	作用机制 Mechanism of action	研究阶段(截至2026年8月) Research phase (as of August 2026)	主要证据 Primary evidence	证据等级 Evidence level
	Dasatinib+Quercetin (D+Q)[75]	Senolytic; interferes with senescent cell survival pathways and promotes apoptosis	COPD patient-derived cells/animal model	In COPD patient-derived bronchial epithelial cells (air-liquid interface differentiation), D+Q significantly reduced senescence markers (p16INK4a, p21WAF1) and SASP factors (CXCL8, CCL5, MMP-2, IL-33, etc.), and improved epithelial barrier integrity (increased TEER); in 11-day cigarette smoke-exposed mice, D+Q reduced lung tissue senescence burden, BALF CXCL1 levels, and inflammatory cell (neutrophil, macrophage) infiltration	Level III
	Natural Polyphenols (Quercetin, Resveratrol, Caffeic acid, Epicatechin)[87-88]	Possess antioxidant, senolytic/senomorphic, and anti-fibrotic effects	*In vitro*/other pulmonary disease preclinical	Can reduce SASP or collagen production in senescent human lung fibroblasts; limited direct COPD evidence	Level IV
	Kaempferol[89]	Inhibits PI3K/Akt signaling; reduces inflammation and ECM damage	COPD cell model	Can reduce inflammatory response and ECM damage in COPD model cells	Level III
	Modified Erchen Decoction[90]	Regulates MMP-1, MMP-9, and TIMP-1; improves ECM metabolic imbalance	COPD animal model	Reduced abnormal collagen deposition in bronchiolar walls and improved ECM remodeling	Level III
	Shenqi Bufei Decoction[91]	Inhibits excessive ECM deposition in lungs; intervenes in airway remodeling	COPD animal model	Improved abnormal pulmonary ECM deposition in lung-qi deficiency syndrome COPD rats	Level III
	Tongse Granule[92]	Inhibits abnormal ECM degradation and airway remodeling	AECOPD animal model	In AECOPD rats, regulated pulmonary tissue ECM and alleviated airway remodeling	Level III
	Lianhua Qingke[93]	Regulates Sp1/SIRT1/HIF-1α; inhibits cellular senescence and inflammation	COPD animal model	In cigarette smoke COPD mice, alleviated cellular senescence, inflammation, and lung tissue damage	Level III
	Quercetin-Fe3O4 Magnetic Nanoparticles[98]	Possesses both senolytic and senostatic activity, involving AMPK-related regulation	*In vitro* cell model	Demonstrated anti-senescence activity in oxidative stress-induced senescent human fibroblasts; non-COPD specific	Level IV
	NIF-LNP/P-UA LNP delivery of NR1D1 mRNA[100]	V-ATPase activation promotes endosomal acidification, increases mRNA expression, and reduces LNP inflammatory response	Chronic lung injury animal model	Improved pathology in pulmonary fibrosis and other models; completed lyophilization/nebulization process validation; no COPD clinical evidence yet	Level IV
	Agarwood Nanoemulsion[101]	Regulates TGF-β-induced oxidative stress, inflammation, and airway remodeling	Bronchial epithelial cell in vitro model	In BEAS-2B model, reduced TGF-β-induced remodeling-related changes	Level IV

研究阶段以目标适应证COPD为主标注; 证据等级为本文按转化成熟度设置的分层: I级, COPD患者随机/对照临床证据; II级, COPD早期或进行中临床试验,或其他肺病人体临床证据; III级, COPD患者来源细胞/组织或COPD动物模型证据; IV级, 其他肺病、非COPD或体外机制性临床前证据。该分层用于描述证据直接性, 不等同于GRADE证据质量评级。

The research phase is annotated primarily for the target indication COPD. The evidence level is a stratification defined in this review according to translational maturity: Level I, randomized or controlled clinical evidence in patients with COPD; Level II, early-phase or ongoing clinical trials in COPD, or clinical evidence in patients with other pulmonary diseases; Level III, evidence from COPD patient-derived cells/tissues or COPD animal models; Level IV, preclinical mechanistic evidence from other pulmonary diseases, non-COPD settings, or *in vitro* studies. This stratification describes the directness of evidence and is not equivalent to the GRADE evidence quality rating.

等多通路交叉，传统单一靶点筛选策略难以把握网络动态特性。结合肺组织生物力学表征(如原子力显微镜测定的基质刚度分布、数字体积相关技术追踪的形变场)与机器学习算法，可建立“力学微环境–分子信号-ECM表型”的关联模型，预测网络脆弱节点并指导联合干预方案设计。在药物递送层面，Senolytics(如达沙替尼–槲皮素组合)及基因治疗药物(如编码NR1D1的mRNA)的系统给药存在脱靶毒性风险，而肺部吸入制剂可实现病灶局部富集。需重点解决可电离脂质纳米颗粒的炎症反应控制、雾化过程中的颗粒稳定性保持及肺泡上皮有效穿透等关键技术问题，近期基于磷酰胺脂质库与天然产物修饰的低炎症LNP已展现较好前景。在临床转化层面，当前缺乏可预测衰老-ECM靶向治疗响应的标志物体系。整合肺功能参数、血清SASP因子谱、高分辨率CT影像组学特征及单细胞测序分子分型，构建多维度预测模型，是筛选优势人群、评估疗效动态及指导个体化用药的必由之路。

作者贡献

周立文完成主要文献搜集、论文撰写；谢依桐负责绘图和查阅写作方法；高越负责文章初次修改；张录梅和王转弟负责文稿校对；杜改焕确定题目和写作具体思路。

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