

张震,邹吉宇,臧凝子,等. 特发性肺纤维化动物模型及中药干预作用的研究进展 [J]. 中国实验动物学报, 2025, 33(5): 704–720.

ZHANG Z, ZOU J Y, ZANG N Z, et al. Research progress in animal models of idiopathic pulmonary fibrosis and interventional effect of traditional Chinese medicine [J]. Acta Lab Anim Sci Sin, 2025, 33(5): 704–720.

Doi:10.3969/j.issn.1005-4847.2025.05.009

特发性肺纤维化动物模型及中药干预作用的研究进展

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【摘要】 特发性肺纤维化 (idiopathic pulmonary fibrosis, IPF) 是一种慢性进行性疾病, 确诊后生存期较短, 目前西药治疗效果欠佳, 且肺移植治疗价格高昂, 因此亟须寻求新的、安全有效的治疗手段。动物实验研究是验证药物作用机制的重要手段, 合理的 IPF 动物模型建立方法对 IPF 实验研究尤为重要。当前使用博来霉素 (bleomycin, BLM) 诱导 IPF 模型较为普遍。传统中药具有治疗靶点多、不良反应小等优点, 在 IPF 的治疗中正逐渐受到重视。通过中药干预 IPF 动物模型进而验证中药治疗 IPF 的具体作用靶点及作用机制是目前实验研究的中心内容。本文通过对 IPF 动物模型的选用、诱导方法、建立过程、评估方法及中药对模型的干预作用进行综述, 总结出 IPF 动物模型最佳建模方法及中药治疗现状, 以期 IPF 的科学研究和临床治疗提供依据。

【关键词】 特发性肺纤维化; 中药干预作用; 动物模型; 造模方法; 造模过程; 模型评价

【中图分类号】 Q95-33 **【文献标志码】** A **【文章编号】** 1005-4847 (2025) 05-0704-17

Research progress in animal models of idiopathic pulmonary fibrosis and interventional effect of traditional Chinese medicine

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【Abstract】 Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with a short survival time after diagnosis. Current treatments using western medicines have shown poor efficacy and lung transplantation is costly, highlighting the need to find new, safe, and effective treatments. Animal experiments are important for investigating the mechanisms of drug action, and suitable animal models of IPF are required for experimental research. Bleomycin is commonly used to induce IPF models. Traditional Chinese medicine (TCM) has the advantages of multiple therapeutic targets and few adverse reactions, and is gradually gaining attention for the treatment of IPF. Ongoing experimental research is being carried out to verify the specific targets and mechanisms of TCM in the

【基金项目】 国家自然科学基金面上项目 (82274440), 辽宁省教育厅高校基本科研项目储备项目 (2024-JYTCB-040)。

Funded by General Project of National Natural Science Foundation of China (82274440), Liaoning Provincial Department of Education University Basic Scientific Research Project Reserve Project (2024-JYTCB-040).

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treatment of IPF, utilizing animal models of IPF. This review considers the selection of animal models of IPF, the method used to induce, establish, and evaluate the models, and the interventional effects of TCM. We also summarize the best modeling method for animal models of IPF and the current status of TCM treatments to provide a basis for further scientific research and the clinical treatment of IPF.

【Keywords】 idiopathic pulmonary fibrosis; intervention of traditional Chinese medicine; animal model; modeling method; modeling process; model evaluation

Conflicts of Interest: The authors declare no conflict of interest.

特发性肺纤维化 (idiopathic pulmonary fibrosis, IPF) 是一种病因不明的慢性、进行性且无法逆转的间质性肺疾病^[1], 临床主要表现为咳嗽、咳痰、呼吸困难、肺通气功能下降, 患者生存质量严重受损, IPF 患病人群主要为老年人^[2], 确诊后中位生存期仅 2 ~ 3 年^[3]。IPF 的病因不明, 发病机制错综复杂^[4], 尚未完全阐释清晰, 主要包括氧化应激、上皮间质转化、巨噬细胞极化失衡及细胞凋亡等, 可能还存在其他机制, 因此进一步探寻 IPF 的具体发病机制对延缓 IPF 疾病进程、改善预后及提高生存率极为重要。

目前 IPF 的治疗手段较为局限, 美国食品药品监督管理局批准的药物为吡非尼酮与尼达尼布^[5], 但这两种药物的价格昂贵, 且作用有限、不良反应严重^[6]。肺移植作为唯一根治手段, 存在肺源不足、费用高昂、术后排斥反应大、并发症多等弊端^[7]。祖国传统医学中未提及肺纤维化这一病名, 现代中医根据辨证分型将其划归于“肺痿”“肺痹”“咳嗽”“肺胀”等范畴, 其中以“肺痿”最为普遍^[8]。“肺痿”的基本病机为肺虚损, 津气大伤导致肺叶枯萎, 病理性质属本虚标实。传统中药具有治疗靶点多、不良反应小、价格低等优势, 在 IPF 的治疗中逐渐受到关注。运用传统中医中药寻求 IPF 新的治疗方案是目前研究的一个重要方向。在现代生物医学研究中, 动物模型是一个不可或缺的环节。动物模型在模拟临床相关疾病、进行中医药干预及观察相应疗效的过程中尤为重要^[9]。本文梳理总结 IPF 动物模型的选用与建立方法、模型的评估方法及中医药对 IPF 动物模型的干预作用现状, 以期对 IPF 的相关科学研究与临床治疗提供参考价值。

1 IPF 动物模型的选用

选用合适的实验动物是成功建立动物模型

的基础, 动物的类别、年龄、性别、性格特点等均应加以考虑^[10]。当前用来诱导建立 IPF 模型的动物主要包括鼠、兔、马、犬、羊等^[11]。根据美国胸科协会 (American Thoracic Society, AST) 官方研讨会报告, 肺纤维化临床前测试的动物一线选择是小鼠, 其次是大鼠^[12]。鼠类与人类有大约 90% 的相似基因, 在众多的生理通路及病理过程中可能与人类极为相似^[13]。鼠类模型因其个体相似度高、造模周期短、实验效率高、价格低廉及可重复性好等优势, 是实验应用最多的造模动物^[14], 但鼠类同时也存在死亡率高、不能重复采样、体型小故不适用于放射影像学的研究等缺陷。目前 IPF 模型常用的有 SD、Wistar 大鼠; C57BL/6、ICR、BALB/c、KM 小鼠。Wistar 大鼠性格较为温顺, 抗病能力强且自发性肿瘤的发生率低; 而 SD 大鼠是用 Wistar 大鼠培育而成的, 其适应性和抗病能力更强, 尤其是对呼吸系统疾病抵抗力较强^[15]。小鼠中 C57BL/6 小鼠在造模过程中对博来霉素 (bleomycin, BLM) 和百草枯的敏感性均比 ICR 小鼠和 KM 小鼠高^[16-17]。与鼠类相比, 兔、犬、羊等动物体型大小适中, 心脏结构和血液循环系统与人类较为相似, 更适合心血管疾病的实验研究, 但兔、犬、羊等动物肺内结构显示清楚、高分辨率 CT (high resolution CT, HRCT) 等影像学形态与人类更接近, 更易观察肺内结构组织变化, 且可以大量采集组织样本, 减少因动物过小而带来的操作难度和组织样本误差^[18]。此外, 树鼯作为一种小型哺乳动物, 在基因、代谢、组织解剖学以及免疫系统等方面与灵长类动物关系密切, 且具有体型较小、饲养成本较低、繁殖周期短等优点。CHE 等^[19]通过气管内注射 BLM 导致树鼯肺部出现的病理特征较为符合人类 IPF 病理特征, 因此树鼯可能会成为新的 IPF 实验模型动物^[20-21]。

综合考量实验各方面要求及动物的优缺点,研究者在实验中应用最为广泛的模型动物为小鼠和大鼠,其中 Wistar 大鼠和 C57BL/6 小鼠是一般中药作用机制研究的最佳选择,兔、犬、羊等较大动物则更适合中药对 IPF 影像学改变的相关研究。

2 IPF 动物模型的诱导方法和建立过程

2.1 模型的诱导方法

IPF 动物模型的诱导方法众多,现阶段用于构建 IPF 动物模型的诱导方法标准不一,主要包括 BLM 诱导、石棉/二氧化硅诱导、百草枯诱导、异硫氰酸荧光素 (fluorescein isothiocyanate, FITC) 诱导、辐射诱导和基因修饰技术诱导等^[18]。BLM 诱导的 IPF 大鼠肺部病理变化早期以肺泡炎症改变为主,晚期以肺间质纤维化为主^[22]。石棉的主要成份为二氧化硅,长时间暴露于二氧化硅,会导致二氧化硅在肺中沉积,引起炎症细胞浸润、肺泡破坏等病理改变,最终形成纤维化结节^[23]。二氧化硅诱导产生的肺纤维化结节类似于暴露于粉尘或微小颗粒的肺纤维化结节,更接近于矽肺模型^[24]。百草枯作为一种毒性较强的除草剂,进入机体后会导致机体出现氧化应激、炎症损伤等表现,最终引起多器官的衰竭甚至死亡^[25],因其造模死亡率高,现已多用于百草枯毒性的研究^[26]。FITC 可以用于气道,作为半抗原与其他的肺组织蛋白结合,通过趋化因子受体 2 与趋化因子配体 12 的相互作用使纤维细胞进入肺,诱导肺纤维化^[27]。由于超声处理的 FITC 颗粒的大小不一,致使其诱导的纤维化反应程度可变性过大,已经很少应用于 IPF 模型建立。辐射诱导具有依赖性,具体机制是辐射通过使 DNA 损伤直接诱导肺泡上皮细胞死亡、巨噬细胞涌入进而激活单核细胞产生炎症因子、促纤维化细胞因子等促使肺纤维化发生^[28-29]。基因修饰技术通过在模型动物基因组中删除或者插入内源基因而建成^[18],是近些年较为新式的造模方法,但是价格昂贵。此外,异种移植是将人细胞、组织或器官移植到免疫缺陷动物体内的方法,在 IPF 特异性病理机制和个性化治疗策略方面具有独特价值。

不同诱导手段都存在各自的优点与局限性。

综上,BLM 诱导方法最为实用,其操作简便、造模成功率高、可重复性好、病理表现与人类 IPF 最为相似。美国 ATS 的一份报告证实,BLM 诱导模型是最佳特征动物模型^[30]。在使用 BLM 诱导模型时,相较于雌鼠,雄鼠对 BLM 的反应更为强烈,是更加理想的模型动物^[31]。具体造模方法选择的优点和局限性总结,见表 1。

2.2 模型的建立过程

截至目前,如何构建一个与人类 IPF 相似的实验动物模型依然面临重大考验,造模方法选择的不同和操作的差异均会影响模型的最终情况。在各种 IPF 模型中,BLM 诱导模型目前应用最多、特性最好^[32]。BLM 诱导包括无创气管插管滴注^[33]、有创气管滴注^[34]、气管内雾化吸入^[35]、滴鼻吸入^[36]、腹腔注射^[37]、尾静脉注射^[38]。此外,还有一些研究者选择腹腔注射百草枯^[39]、X 射线诱导^[40]及口咽滴注 SiO₂ 混悬液^[41]等方法诱导建立 IPF 动物模型。造模具体操作总结,见表 2。

3 IPF 动物模型的评估方法

动物模型建立后,要明确模型是否建立成功,因此模型建立后评估指标的选择同样是不可忽视的重点。目前的研究者使用的评估指标主要包括动物一般体征、肺系数、肺功能、肺组织病理、肺组织羟脯氨酸 (hydroxyproline, HYP) 含量等,其中肺组织病理学检查和肺组织 HYP 含量是检查 IPF 动物模型成功与否的主要指标。

3.1 一般体征及肺系数评估

模型建立后,动物的一般体征可通过肉眼直接观察记录。一般情况下,造模后动物会出现活跃度下降、精神萎靡、弓背抱头、反应迟钝、摄食及饮水量减少、体质量减轻、呼吸困难、毛色干枯或脱毛甚至动物死亡等现象,存活的实验动物在造模后 7 ~ 10 d 生活状态开始恢复^[42]。处死动物,分离出完整肺,使用 PBS 缓冲液清洗肺血迹,吸干表面水分后马上称量肺湿重并计算肺系数,在造模成功的状况下,与空白组比较,模型组动物的肺湿重及肺系数会升高^[43]。

3.2 肺功能评估

通过肺功能检测,可以评估动物有无气流受

表 1 IPF 动物造模方法优点、局限性和适用情况

Table 1 Advantages, limitations and applicability of IPF animal modeling methods

诱导方式 Induction methods	建立途径 Establishing pathways	优点 Advantages	局限性 limitations	适用情况 Applicability
博来霉素 BLM	气管内滴注/雾化吸入、腹腔注射、尾静脉注射、滴鼻吸入等 Intratracheal instillation/nebulized inhalation, intraperitoneal injection, tail vein injection, nasal drip inhalation, etc	操作简便,建模时间短,可重复性高,能复制出 IPF 典型肺组织病变,多次重复气管滴注和雾化吸入效果更为理想 Easy to operate, short modeling time, high reproducibility, and reproduce lung tissue lesions typical of IPF, repeated tracheal drops and nebulization work better	纤维化改变存在自限性和可逆性,缺少间质性肺炎进行性和不可逆性的特征,存在自愈倾向,不同给药途径所导致的纤维化病变部位及病理特点不一 Fibrotic changes are self-limited and reversible, and lack the progressive and irreversible characteristics of interstitial pneumonia, self-healing tendency, the fibrotic lesions and pathological features caused by different routes of administration vary	广泛适用于潜在抗纤维化药物的筛选及药物治疗靶点的研究 Widely applicable to the screening of potential anti-fibrosis drugs and the research of drug treatment targets
二氧化硅/石棉 Silica/asbestos	气管内滴注/雾化吸入、口咽滴注等 Intratracheal instillation/nebulized inhalation, oropharyngeal instillation, etc	操作简便,沉积肺部的二氧化硅/石棉粒子难以清除,会形成一个持久性的刺激因素 Easy to operate, silica/asbestos particles that deposit in the lungs are difficult to remove and can form a persistent irritant	建模时间长,肺叶病变分布不均匀,缺少间质性肺炎典型特征,建立的模型与矽肺/石棉肺模型更为相似,石棉可能引起人罕见的间皮瘤发生 Long modeling time, uneven distribution of lobar lesions, lack typical features of interstitial pneumonia, and the created model is more similar to the silicosis/asbestosis model	适合矽肺/石棉肺治疗药物相关研究 Suitable for research on drugs related to silicosis/asbestosis treatment
百草枯 Paraquat	腹腔注射、灌胃给药等 Intraperitoneal injection, intragastric administration, etc	操作简便,模型成功率高 Easy to operate, high model success rate	致死率高,会引起各脏器损伤,影响动物生理状态,缺少间质性肺炎的典型特征,纤维化病理特点更符合百草枯致人肺纤维化病理特点 High lethality, cause damage to various organs, affect animal physiological state, lack typical features of interstitial pneumonia, the pathological features of fibrosis are more in line with the pathological characteristics of lung fibrosis caused by paraquat	适合于百草枯致人肺纤维化研究 Suitable for research on paraquat-induced pulmonary fibrosis
异硫氰酸荧光素 Fluorescein isothiocyanate	气管内滴注 Intratracheal instillation	可用免疫荧光的方法定位肺纤维化的具体位置 Locate the specific location of pulmonary fibrosis using the immunofluorescence method	稳定性较差,造模动物会出现急性中毒或死亡,标准化和重复性较难实现,无临床相关性 Poor stability, modeling animals can be acutely poisoned or die, difficult to achieve standardization and repeatability, no clinical relevance	现已很少用于 IPF 治疗药物研究 Now rarely used in drug research for IPF
辐射 Radiation	X 线照射 X-ray irradiation	有多种相关因子参与纤维化病变过程,纤维化病变持续时间较长 Multiple related factors are involved in the fibrotic lesion process, the fibrotic lesions last for a relatively long time	建模时间长,辐射量难以把控,价格高昂,个体差异大,有剂量依赖性,射线不正确使用会对动物和操作人员造成伤害 Long modeling time, difficult to control radiation levels, expensive, great individual differences, dose-dependent and improper use of the rays can harm animals and operators	早期可作放射性肺炎模型,晚期可作放射性肺纤维化模型 Early-stage can be used as radiation pneumonia model, late-stage can be used as radiation-induced pulmonary fibrosis model

续表 1

诱导方式 Induction methods	建立途径 Establishing pathways	优点 Advantages	局限性 limitations	适用情况 Applicability
基因修饰 Gene modification	转基因、基因点突变、 基因敲除等 Genetic modification, gene point mutation, gene knockout, etc	靶点明确,可诱导多种基 因模式模型,可观察疾病 自然进程,利于对 IPF 特 定机制进行探索和研究 Clear target, inducible multiple gene pattern models, able to observe the natural course of the disease, beneficial for exploring and researching specific mechanisms of IPF	建模时间长、价格高昂,有 种属依赖性,介导转基因用 的病毒载体本身具有潜在 危害性,单一基因模型与 人多基因相关的 IPF 存在 一定差异 Long modeling time, expensive, species-dependent, the viral vectors used for mediating transgenes inherently possess potential hazards, and differences between single-gene model and human multi-gene-related IPF	适合筛选特定抗纤维化药 物的具体成分相关研究 Suitable for research on the specific components of specific anti-fibrotic drugs in screening
异种移植 Xenotrans plantation	移植人类细胞、组织 或器官至免疫缺陷动物 体内 Transplanting human cells, tissues or organs into immunodeficient animals	更贴近临床病理,保留了 人类基因和表型特征,可 针对特定患者亚群 More clinicopathologically, preserving human genetic and phenotypic signatures, allowing for specific patient subpopulations	建模时间长,价格高昂,仅 模拟局部纤维化病灶,移植 细胞存活率低,依赖高免疫 缺陷宿主,存在伦理问题 Long modeling time, expensive, only simulating localized fibrotic lesions, low survival rate of transplanted cells and rely on highly immunodeficient hosts, ethical issues exist	适合探索人类特异性病理 机制和个性化治疗策略 Suitable for exploring human-specific pathological mechanisms and personalized treatment strategies

表 2 IPF 动物造模过程
Table 2 IPF animal modeling process

造模方法 Modeling methods	动物选择 Animal selection	造模过程 Modeling process	参考文献 References
气管内滴注 BLM Intratracheal instillation of BLM	雄性, C57BL/6J 小鼠, 7 ~ 8 周 龄, 20 ~ 22 g Male, C57BL/6J mice, 7 ~ 8 weeks, 20 ~ 22 g	腹腔注射 1% 戊巴比妥钠 (70 μg/kg) 麻醉小鼠, 经声门裂 气管插管, 滴入 BLM 溶液 (5 mg/kg) 后悬垂旋转小鼠, 使 药物均匀分布肺组织 Intraperitoneal injection of 1% sodium pentobarbital (70 μg/kg) anesthetized the mice, intubated through the tracheal cleft of the glottic cleft, and then draped and rotated the mice after dropping BLM solution (5 mg/kg) to evenly distribute the drug in the lung tissue	[33]
	雄性, SD 大鼠, 6 ~ 7 周龄, 180 ~ 210 g Male, SD rat, 6 ~ 7 weeks, 180 ~ 210 g	腹腔注射 2% 戊巴比妥钠 (0.04 mg/g) 麻醉大鼠固定, 沿颈 正中切开皮肤, 暴露气管, 经气管缓慢滴入 BLM 溶液 (5 mg/kg) 后直立旋转大鼠, 使药物均匀分布肺组织 Intraperitoneal injection of 2% sodium pentobarbital (0.04 mg/g) anesthetized the rat for fixation, incision of the skin along the median of the neck, exposure of the trachea, and slow instillation of BLM solution (5 mg/kg) through the trachea and upright rotation of the rat to evenly distribute the drug to the lung tissue	[34]
气管内雾化吸入 BLM Endotracheal nebulized inhalation of BLM	雄性, SD 大鼠, 6 ~ 8 周龄, (253.18 ± 5.37) g Male, SD rat, 6 ~ 8 weeks, (253.18 ± 5.37) g	雾化吸入 BLM 溶液 (40 mmol/L) 30 min, 连续 3 d Atomized inhalation of BLM solution (40 mmol/L) for 30 min for 3 days	[35]
滴鼻吸入 BLM Nasal inhalation BLM	雌性, ICR 小鼠, 6 ~ 8 周龄, (16 ± 2) g Female, ICR mice, 6 ~ 8 weeks, (16 ± 2) g	麻醉小鼠后, 用微量移液器将 BLM 溶液 (15 mg/kg) 经鼻腔缓缓滴入小鼠气管内 After anesthetized the mice, BLM solution (15 mg/kg) was slowly dripped into the trachea of the mice through the nasal cavity with a micropipette	[36]

续表 2

造模方法 Modeling method	动物选择 Animal selection	造模过程 Modeling process	参考文献 References
腹腔注射 BLM Intraperitoneal injection of BLM	雄性, C57BL/6 小鼠, 8 周龄 Male, C57BL/6 mice, 8 weeks	在第 1、5、8、11 和 15 天分别腹腔内注射 BLM 溶液 (5 mg/kg) BLM solution (5 mg/kg) was injected intraperitoneally on the 1st, 5th, 8th, 11th, and 15th days, respectively	[37]
尾静脉注射 BLM Tail vein injection of BLM	雄性, C57BL/6J 小鼠, 8 周龄, 18 ~ 22 g Male, C57BL/6J mice, 8 weeks, 18 ~ 22 g	适应性喂养后分为单次组和多次组, 单次组经尾静脉注入 BLM 溶液 (200 mg/kg); 多次组每周经尾静脉注射 BLM 溶液 (50 mg/kg), 连续 6 周 After adaptive feeding, they were divided into single group and multiple group, and the single group was injected with BLM solution (200 mg/kg) through the tail vein. The multiple groups were injected with BLM solution (50 mg/kg) through the tail vein every week for 6 consecutive weeks	[38]
腹腔注射百草枯 Intraperitoneal injection glyphosate	雌性, C57BL/6J 小鼠, 7 ~ 8 周龄, 14 ~ 16 g Female, C57BL/6J mice, 7 ~ 8 weeks, 14 ~ 16 g	麻醉小鼠后, 一次性腹腔注射百草枯 (20 mg/kg) After anesthetizing the mice, a one-time intraperitoneal injection of paraquat (20 mg/kg)	[39]
X 射线诱导 X-ray induction	雄性, Wistar 大鼠, 5 周龄, (200 ± 20) g Male, Wistar rat, 5 weeks, (200 ± 20) g	前 1 d 禁食水, 麻醉后大鼠取仰卧位, 用铅板挡住除胸部外 皮肤, 辐射区域严格限制在胸部, 使用 48 cm 的源表面距 离照射场进行 X 射线 40 Gy 单次局部照射 Fast the rats for 1 d prior to the experiment, place rats in a supine position after anesthesia, shield the entire body with lead plates except for the chest skin to strictly restrict the radiation field to the chest area, and perform a single local X-ray irradiation at a dose of 40 Gy using a source-to- surface distance of 48 cm	[40]
滴鼻吸入 SiO ₂ 混悬液 Nasal inhalation of SiO ₂ suspension	雄性, C57BL/6 小鼠, 6 ~ 8 周 龄, 20 ~ 25 g Male, C57BL/6 mice, 6 ~ 8 weeks, 20 ~ 25 g	连续 4 d 经小鼠鼻腔滴注 0.05 mL 的 SiO ₂ 混悬液 (1.664 mol/L) 0.05 mL of SiO ₂ suspension (1.664 mol/L) was instilled through the mice nasal cavity for 4 consecutive days	[41]

限情况、肺组织是否处于病理状态。IPF 模型动物在进行肺功能检测时, 肺活量 (vital capacity, VC)、吸气气流高峰流速 (peak inspiratory flow, PIF)、吸气容积 (tidal volume, TV)、每分钟通气量 (minute ventilation, MV)、呼出 50% 气量时流速 (50% tidal volume expiratory flow, EF50) 等指标显著下降, 提示动物出现气流受限情况^[44-45]。

3.3 肺组织病理评估

模型动物的肺组织病理可以直观显示肺组织的改变情况, 肺组织病理检测是 IPF 确诊的重要指标之一。麻醉动物后取出肺, 经甲醛固定、脱水、石蜡包埋、切片、苏木素-伊红 (HE) 和 (或) Masson 染色等操作后, 在显微镜下观察肺组织病理学变化。在 IPF 模型动物肺组织中, 可见模型组动物肺组织破坏严重, 肺泡间隔变宽, 肺泡壁断裂, 肺泡代偿性萎缩或增大, 肺泡腔内大量炎症细胞浸润, 肺间质出现大量条索状瘢痕及胶原纤维^[46-47]。

3.4 肺组织 HYP 含量评估

IPF 的一个主要病理特征是胶原蛋白的沉积, HYP 是胶原蛋白特有的氨基酸之一, 因此, 测定肺组织中 HYP 含量能够评估动物肺组织纤维化程度。测定 HYP 含量的方法有比色法和酶联免疫吸附测定法等。在应用比色法时, 烘干的肺组织所测得的 HYP 含量更高, 结果更稳定可靠^[48]。

3.5 其他指标评估

其他指标如肺组织中各种炎症因子含量、肺泡灌洗液炎性细胞计数、血氧饱和度、细胞内活性氧 (reactive oxygen species, ROS) 水平、氧化应激指标和 CT 等影像学的检测均对模型评估有重要辅助作用。

4 中药对 IPF 动物模型的干预作用

4.1 抗氧化应激

氧化应激是指机体内氧化与抗氧化作用失

衡,导致 ROS 和活性氮(reactive nitrogen species, RNS)等氧化产物过度积累。ROS 和 RNS 的大量堆积可直接损伤肺上皮细胞,促使肺上皮细胞凋亡而导致间质纤维化倾向,同时 ROS 和 RNS 还可通过改变与 IPF 发病机制有关的介质,如促纤维化生长因子、转化生长因子 β (transforming growth factor- β , TGF- β) 的表达来促进肺纤维化的发展^[49]。在 IPF 的发生发展过程中,氧化应激可诱导炎症细胞活化并释放炎症介质,如白细胞介素-1(interleukin-1, IL-1)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 等,引发炎症反应,这些介质又可进一步促进 ROS 和 RNS 的产生,加重氧化应激,二者相互作用,共同推动 IPF 的病情进展,这是包括 IPF 在内多种疾病的病理过程^[50-51]。

中药防己提取所得的汉防己甲素具有抗炎、抗纤维化及免疫调节的作用^[52],严业超等^[53]对重复多次气管内滴注 BLM 建立的 IPF 小鼠模型连续灌胃,发现汉防己甲素能够抑制 TGF- β /Smad3 通路诱导的成纤维细胞活化相关蛋白纤连蛋白(fibronectin)、I 型胶原(collagen type I, collagen I)、波形蛋白(vimentin)和 α -平滑肌激动蛋白(α -smooth muscle actin, α -SMA)的表达水平,且细胞实验结果表明汉防己甲素可能通过表达 *AGTRAP* 及 *MPP6* 基因进而降低 ROS 水平,抑制成纤维细胞活化,从而达到治疗效果。梁梓琛等^[54]研究证实桔梗素 D 除了可以介导 P2X7r-NLRP3 信号通路或抑制 TLR4 信号通路调控肺纤维化外,还可下调瞬时受体电位阳离子通道蛋白 6(transient receptor potential cation channel 6, TRPC6)表达进而减少 ROS 产生,减弱肺纤维化程度。

4.2 抑制上皮间质转化(epithelial-mesenchymal transition, EMT)

EMT 指上皮细胞向间质细胞转化,进而赋予细胞迁移、侵袭和分泌细胞外基质(extracellular matrix, ECM)能力的过程。在 IPF 患者的肺组织中, TGF- β 的表达通常上调,它可通过与细胞表面受体结合,激活下游 Smad 蛋白等信号分子,诱导上皮细胞发生 EMT,转化后的上皮细胞会改变其 ECM 的分泌模式,分泌大量的胶原蛋白、纤维连接蛋白等,加快纤维组织的沉积,同时发生 EMT 的上皮细胞可分泌多种炎症因子和趋化因子,如

白细胞介素-6(interleukin-6, IL-6)、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)等,引发炎症反应,形成炎症与 EMT 的恶性循环,推动 IPF 的进展^[55-56]。

虫草素可通过激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路发挥抗纤维化作用,王小叶等^[57]发现虫草素可作用于组蛋白去乙酰化酶 7(histone deacetylase 7, HDAC7)的活性位点,使 vimentin 乙酰化降解,抑制 collagen I 蛋白表达与 EMT,从而明显改善 IPF 小鼠的病理状态与肺组织结构。黄芪总黄酮可下调 BLM 诱导的 IPF 小鼠体内 miRNA-21 及 TGF- β 1 表达,加强 Smad7 表达及 Smad7 对 Smad3 磷酸化水平的抑制,显著减少 α -SMA 蛋白表达,阻滞 EMT,发挥对 IPF 的治疗效果^[58]。

4.3 调控巨噬细胞极化

巨噬细胞是维持组织稳态的关键参与者^[59],在不同的微环境信号刺激下,巨噬细胞会被诱导极化成 M1 型和 M2 型两种表型, M1 型巨噬细胞会释放大量的炎症介质(如 IL-1、TNF- α 等)和 ROS,引发炎症反应和氧化应激水平升高,导致肺组织损伤;而 M2 型巨噬细胞分泌的 TGF- β 会激活肺成纤维细胞,并使其增殖并转化为肌成纤维细胞,促进细胞外基质如胶原蛋白、纤维连接蛋白等的合成和沉积,导致肺组织纤维化,在 IPF 患者的肺组织中,二者动态平衡被打破, M2 型巨噬细胞极化占优势且功能异常增强,持续分泌促纤维化因子,导致 IPF 不断进展^[60-61]。

升陷化纤方(黄芪、知母、桔梗等)及其拆方可降低 IPF 大鼠血清 IL-6、TGF- β 1 含量,上调 SOCS1、SOCS3 蛋白表达,阻抑 STAT6/PPAR- γ 通路活性,进而抑制巨噬细胞极化为 M2 型,并促进 M2 型向 M1 型转化,维持二者动态平衡,达到抑制 IPF 效果^[62]。中药桔梗分离得到的桔梗皂苷 E 能够降低血清中白细胞介素-10(interleukin-10, IL-10)、白细胞介素-4(interleukin-4, IL-4)、IL-6、TNF- α 等细胞因子浓度及 p-STAT6、p-JAK1 蛋白表达,抑制 JAK/STAT 信号通路阻抑巨噬细胞极化为 M2 型,减少胶原沉积从而有效改善 IPF 小鼠肺组织病理损伤^[63]。

4.4 抑制细胞凋亡

细胞凋亡是指细胞主动死亡从而维持细胞

内稳态的程序性死亡。细胞内促凋亡因子与抗凋亡因子平衡失调是 IPF 发生的重要原因,促凋亡因子 C/EBP 同源蛋白可诱导肺上皮细胞凋亡,激活成纤维细胞,使其增殖并转化为肌成纤维细胞并促进 ECM 沉积,导致肺组织的异常重塑及纤维化^[64]。同时 IPF 患者体内的成纤维细胞可通过分泌高水平的促凋亡分子(半胱天冬蛋白酶-3、肿瘤坏死因子受体 1 等)和下调 B 淋巴细胞瘤-2 (B-cell lymphoma-2, Bcl-2) 基因表达来诱导肺组织 T 细胞凋亡和功能障碍,无法有效控制炎症反应,使炎症持续存在,促进肺纤维化发展^[65]。

升陷汤可有效改善 IPF 患者的临床症状和生活质量,LIANG 等^[66]发现升陷汤可以降低血清中 TNF- α 、干扰素- γ (interferon- γ , IFN- γ)、IL-1 β 和 IL-18 等炎症因子水平,抑制肺组织中纤维蛋白的表达,具体机制为通过抑制泛凋亡体 (PANoptosis) 进而抑制细胞凋亡以延迟或逆转大鼠肺纤维化的病理变化。芪冬活血饮(黄芪、麦冬、虎杖等)在临床上治疗间质性肺疾病疗效较好,贺倩雯等^[67]进一步研究证实芪冬活血饮能降低 IPF 小鼠肺组织 PI3K/Akt/mTOR 信号通路蛋白磷酸化水平以及蛋白 PI3K、Akt、mTOR mRNA 的表达,抑制细胞凋亡,延缓 IPF 进程。

4.5 促进细胞自噬

自噬是细胞在应急状态下的一种自我保护方式,在机体组织修复和细胞凋亡等过程中发挥重要作用^[68]。正常情况下,自噬参与细胞外基质降解酶的合成和分泌调节,自噬缺陷时 ECM 的合成增加而降解减少,使得 ECM 在肺间质过度沉积,而且自噬缺陷时会使得细胞内的 TGF- β 信号增强,诱导肺泡上皮细胞发生 EMT,促进 ECM 的分泌和沉积,推动肺纤维化的发生发展^[69]。

TGF- β 1 能通过激活 PI3K/Akt-mTOR 通路使 p62 蛋白表达降低,诱导自噬的发生,而 Beclin-1 可参与自噬体膜形成并触发自噬,扶正通络方(生地黄、山萸肉、女贞子等)能够使 BLM 诱导的 IPF 大鼠体内自噬小体和 Beclin-1 蛋白表达增加但降低 p62 蛋白表达,从而促进自噬以改善肺纤维化^[70]。于竞泽等^[71]发现益肺散结方(黄芪、防风、白术等)可以降低 BLM 诱导的 COPD-IPF 模型大鼠的肺中炎症相关细胞因子白细胞介素-8 (interleukin-8, IL-8)、TNF- α 含量,增高自噬相关

基因 Beclin-1 与 LC3B 的表达,促进细胞自噬明显改善大鼠肺组织损伤,减弱肺纤维化程度。

4.6 调控凝血系统

当肺组织损伤后,凝血系统会激活进而导致纤维蛋白原转化为纤维蛋白沉积于肺泡和间质中,沉积的纤维蛋白还会进一步诱导成纤维细胞增殖和迁移,同时凝血酶可通过激活蛋白酶激活受体-1 (protease activated receptors-1, PAR-1),刺激肺泡上皮细胞和成纤维细胞释放 TGF- β ,促进胶原合成和肌成纤维细胞分化,致使肺组织发生纤维化^[72-73]。此外,血小板中所含有大量的 TGF- β 是诱导各种组织发生纤维化的主要促纤维化细胞因子,且血小板活化后引发的高凝状态和持续纤维蛋白沉积亦可导致 IPF 发生发展^[74]。

血栓通注射液是以三七总皂苷为主要有效成分的注射液,常用于临床瘀血证的治疗,高云航等^[75]证实血栓通注射液可通过调控 PAR-1 mRNA 水平与可溶性血纤蛋白单体复合体 (soluble fibrinmonomer complex, SFMC)、纤维蛋白降解产物 (fibrinogen degradation products, FDP) 蛋白水平,抑制凝血酶激活进而改善凝血途径,达到治疗 IPF 的作用。刘勇明等^[76]发现益气养阴活血通络方(黄芪、北沙参、熟地黄等)可抑制血小板活化和 CD40-CD40L 系统,显著降低 IPF 大鼠体内血小板 CD41、CD62P 表达水平及 PAI-1、FIX、FVII 表达水平,改善凝血功能障碍并延缓 IPF 进展。

传统中医在治疗疾病的过程中更多强调辨证论治、三因制宜、同病异治,根据不同患者患病时自身的体质、身体机能情况以及证型,采取不同措施进行干预治疗。随着现代医学对中药成分的不断探索挖掘,中药治疗多靶点、多途径的优势越来越明显,因此,IPF 患者可在口服西药干预纤维化进程时,同时服用中药汤剂,通过辨证论治、因证组方、随证加减,进而达到既缓解临床症状(标),又恢复身体整体机能(本)的效果,最终延缓纤维化进展甚至治愈纤维化。中药干预作用机制总结,见表 3。

5 小结

综上,在 IPF 动物模型中,大鼠和小鼠因其饲养简单、价格低廉、个体差异性小等优点被大多

数研究者所选择,树鼯因自身种属优势及 BLM 诱导后肺部出现的病理特征较符合人 IPF,可能会成为新的 IPF 实验模型动物。在 IPF 动物模型的建立方法中,BLM 诱导模型造模简单、造模周期短、与人类 IPF 病理表现最为相似,应用最为普遍,但同样缺少人类 IPF 进行性和不可逆性特征。在 IPF 动物模型的评估方法中,肺组织病理改变和肺组织 HYP 含量是最稳定且直观的评估方法,此外,还可以借助动物的一般体征、肺系数、肺功能、血氧饱和度、ROS 水平及 CT 影像学等指标共同评价模型建立情况。

当前各种 IPF 诱导模型的病理表现都与人类存在一定的差异,无法完全复制人类间质性肺炎进行性和不可逆性特征,而且在建模过程中并无明确的操作流程及药物剂量规定,造模结束后的具体评估方法也未标准化、规范化,所以还需要不断完善并探索新的规范化的 IPF 动物模型建立方法。目前研究者对 IPF 动物模型的建立上主要

以西医“病”的建立为主,对于中医“肺痿”“肺痹”具体的“证”的诱导建立较少。IPF 动物模型建立后,在未进行中医“证”的诱导的情况下,研究者给予动物中药干预以验证中药的治疗效果,并未将中医“辨证论治”的核心理论应用其中,缺乏中医治疗疾病的独特思维。未来应将中医思维与现代研究相结合,建立中医病证结合的 IPF 动物模型,根据不同证型因证施治,进一步探索中医药治疗 IPF 的有效药物及具体作用靶点。IPF 的常见中医证型主要有肺气虚证、肺肾气虚证、阴虚肺燥证、痰湿证及血瘀证 5 种证型^[77]。传统中医的“辨证论治”强调整体和个体差异,现代研究方法更注重客观和可重复性,二者结合,关键在于将证候标准转化为可以监测到的量化指标。如肺气虚证不仅涉及呼吸系统,同时也涉及免疫、消化和神经等多个系统的变化。因此,在构建动物模型时,可通过基因编辑或药物诱导等技术模拟出具体疾病,再结合中医病因如饮食

表 3 中药干预作用机制

Table 3 Mechanism of intervention of traditional Chinese medicine

作用机制 Mechanism of action	中药 Traditional Chinese medicine	相关信号通路 及分子 Related signaling pathways and molecules	动物选择 Animal selection	造模方法 Modeling methods	模型组动物指标 Model group animal indicators	参考文献 References
抗氧化应激 Anti-oxidative stress	汉防己甲素 Tetrandrine	TGF-β/Smad3 通路, fibronectin、collagen I、vimentin 和 α-SMA, <i>AGTRAP</i> 和 <i>MPP6</i> 基因 TGF-β/Smad3 pathway, fibronectin、collagen I、vimentin、α-SMA, <i>AGTRAP</i> and <i>MPP6</i> genes	雄性, C57BL/6J 小鼠, 6 ~ 8 周龄, 22 g Male, C57BL/6J mice, 6 ~ 8 weeks, 22 g	气管内滴 注 BLM Intratracheal instillation of BLM	(1) 肺功能检测: 小鼠深吸气量及 呼吸系统顺应性降低; 肺重指数和 HYP 含量增加 (2) 肺组织 HE 及 Masson 染色; 小鼠肺组织结构混乱, 肺泡壁变厚, 肺 泡及间质腔内有大量炎症细胞浸润 及纤维化改变 (1) Lung function test: deep inhalation volume and respiratory system decreased; lung weight index and HYP content increased (2) HE and Masson staining of lung tissue: structure of the lung tissues of mice were chaotic, the alveolar wall were thickened, and abundant inflammatory cells infiltrated and fibrosed in the alveoli and interstitial cavity	[53]
	桔梗素 D Platycodonin D	TRP 通道, P2X7r-NLRP3 通 路, TRPC6 TRP channel, P2X7r-NLRP3 pathway, TRPC6	雄性, C57BL/6J 小鼠, 6 ~ 8 周龄, 20 ~ 24 g Male, C57BL/6J mice, 6 ~ 8 weeks, 20 ~ 24 g	气管内滴 注 BLM Intratracheal instillation of BLM	肺组织 HE 染色; 小鼠肺组织肺泡间 隔增宽, 肺泡腔内纤维化渗出和血管 周围炎细胞浸润较明显 HE staining of lung tissue: alveolar septum widened, fibrotic exudation in the alveolar cavity and perivascular cell infiltration were obvious in the lung tissues of mice	[54]

续表 3

作用机制 Mechanism of action	中药 Traditional Chinese medicine	相关信号通路 及分子 Related signaling pathways and molecules	动物选择 Animal selection	造模方法 Modeling methods	模型组动物指标 Model group animal indicators	参考文献 References
抑制 EMT Inhibit EMT	虫草素 Cordycepin	HDAC7 活性位 点, collagen I HDAC7 active site, collagen I	雄性, C57BL/6J 小 鼠, 6 ~ 8 周龄 Male, C57BL/6J mice, 6 ~ 8 weeks	气管内滴 注 BLM Intratracheal instillation of BLM	肺组织 HE 染色: 小鼠肺泡壁增厚, 肺 泡结构紊乱, 肺泡间隔增宽, 出现大 量炎性细胞渗出, 有纤维灶形成 HE staining of lung tissue: thickening of alveolar walls, disruption of alveolar structure, widening of alveolar septa, and the presence of abundant inflammatory cell infiltration with fibrous foci formation (1) 造模后小鼠毛发枯黄蓬乱, 精神 萎靡, 活动度减少, 体质量减轻 (2) 肺组织 HE 染色: 肺组织炎性细 胞浸润, 肺泡塌陷, 肺间隔增厚 (3) 肺组织 Masson 染色: 肺实变区胶 原增生明显, 胶原纤维聚集成块状 (4) 肺组织 HYP 含量明显增高 (1) After modeling, mice's fur had become dry, disheveled, their spirit were low, their activity decreased, and their body mass decreased (2) HE staining of lung tissue: inflammatory cell infiltration in lung tissue, collapse of alveoli, and thickening of lung interstitium (3) Masson staining of lung tissue: collagen proliferation in the area of pulmonary consolidation was evident, with collagen fibers forming clumps (4) Lung tissue HYP content was significantly increased	[57]
	黄芪总黄酮 Astragalus total flavonoids	miRNA-21, let-7d 及 TGF- β /Smad 通路, α -SMA miRNA-21, let- 7d, and TGF- β / Smad pathway, α -SMA	雄性, C57BL/6 小 鼠, 8 周龄, 19 ~ 21 g Male, C57BL/6 mice, 8 weeks, 19 ~ 21 g	气管内滴 注 BLM Intratracheal instillation of BLM	(1) 造模后小鼠毛发枯黄蓬乱, 精神 萎靡, 活动度减少, 体质量减轻 (2) 肺组织 HE 染色: 肺组织炎性细 胞浸润, 肺泡塌陷, 肺间隔增厚 (3) 肺组织 Masson 染色: 肺实变区胶 原增生明显, 胶原纤维聚集成块状 (4) 肺组织 HYP 含量明显增高 (1) After modeling, mice's fur had become dry, disheveled, their spirit were low, their activity decreased, and their body mass decreased (2) HE staining of lung tissue: inflammatory cell infiltration in lung tissue, collapse of alveoli, and thickening of lung interstitium (3) Masson staining of lung tissue: collagen proliferation in the area of pulmonary consolidation was evident, with collagen fibers forming clumps (4) Lung tissue HYP content was significantly increased	[58]
	升陷化纤方 及其拆方 Shengxian Huaxian Fang and Its Deconstructed Formula	STAT6/PPAR- γ 通路, IL-6、TGF- β 1, SOCS1、 SOCS3 STAT6/PPAR- γ pathway, IL-6、 TGF- β 1, SOCS1、 SOCS3	雄性, SD 大鼠, 6 ~ 8 周龄, (200 $\pm$ 20) g Male, SD rat, 6 ~ 8 weeks, (200 $\pm$ 20) g	气管内滴 注 BLM Intratracheal instillation of BLM	(1) 肺功能检测: 大鼠 PEF、PIF、 EF50 均降低 (2) 肺组织 Masson 染色: 大鼠肺间 质出现大量条索状或片状蓝色胶原 纤维沉积 (1) Lung function test: PEF, PIF, and EF50 were all decreased in rats (2) Masson staining of lung tissue: abundant cord-like or flaky blue collagen fibrillary deposits were found in the interstitium of rats lungs	[62]
调控巨噬细 胞极化 Regulating macrophage polarization	桔梗皂苷 E Platycodon saponin E	JAK/STAT 通路, IL-10、IL-4、IL-6、 TNF- α , p- STAT6, p-JAK1 JAK/STAT pathway, IL-10、 IL-4、IL-6、TNF- α , p-STAT6、 p-JAK1	雌性, BALB/c 小鼠, 17 ~ 22 g Female, BALB/c mice, 17 ~ 22 g	滴鼻吸 入 BLM Nasal inhalation BLM	(1) 肺组织 HE 染色: 小鼠肺组织 结构呈扭曲状态, 肺泡壁增厚且肺间 质有很多胶原沉积 (2) 肺组织 Masson 染色: 小鼠肺泡 壁增厚, 肺泡隔塌陷, 有炎性细胞浸 润, 大量沉积胶原蛋白 (1) HE staining of lung tissue: structure of mice lung tissues appeared twisted, with thickened alveolar walls and abundant collagen deposition in the interstitium (2) Masson staining of lung tissue: alveolar walls of the mice lung were thickened, alveolar septa have collapsed, and there were infiltration of inflammatory cells with abundant deposition of collagen protein	[63]

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作用机制 Mechanism of action	中药 Traditional Chinese medicine	相关信号通路 及分子 Related signaling pathways and molecules	动物选择 Animal selection	造模方法 Modeling methods	模型组动物指标 Model group animal indicators	参考文献 References
抑制细胞 凋亡 Inhibit cell apoptosis	升降汤 Shengxian Decoction	泛凋亡体, TNF- α 、IFN- γ 、IL-1 β 、IL-18 PANoptosis, TNF- α 、IFN- γ 、IL-1 β 、IL-18	雄性, SD 大鼠, 7 周龄, (200 $\pm$ 10) g Male, SD rat, 7 weeks, (200 $\pm$ 10) g	气管内滴注 BLM Intratracheal instillation of BLM	(1) 肺功能检测: 大鼠 PIF、PEF、MV、EF50 均较低 (2) 肺组织 HE 及 Masson 染色: 大鼠肺组织沉积大量胶原蛋白 (3) Micro-CT 示: 肺组织出现较大灰白色高密度阴影及毛玻璃样变化 (1) Lung function test: PIF, PEF, MV, and EF50 were lower (2) HE and Masson staining of lung tissue: large amounts of collagen were deposited in rat lung tissues (3) Micro-CT: lung tissues showed a large gray-white high-density shadow and ground-glass changed	[66]
	芪冬活血饮 Qidong Huoxue Decoction	PI3K/Akt/mTOR 通路 PI3K/Akt/mTOR pathway	雄性, C57BL/6 小鼠, (20 $\pm$ 2) g Male, C57BL/6 mice, (20 $\pm$ 2) g	气管内滴注 BLM Intratracheal instillation of BLM	(1) 造模后小鼠体质量显著降低, 毛发有脱落, 活动量及饮食减少 (2) 肺组织 HE 染色: 小鼠肺泡壁增厚, 肺泡腔狭窄塌陷, 大量炎性细胞浸润 (3) 肺组织 Masson 染色: 小鼠肺组织大量胶原纤维蓝染 (1) After modeling, body mass of mice was significantly reduced, hair was lost, and the amount of activity and diet decreased (2) HE staining of lung tissue: alveolar walls of the mice were thickened, alveolar cavities were narrow and collapsed, and there were extensive infiltration of inflammatory cells (3) Masson staining of lung tissue: abundant collagen fibers indigo staining in mice lung tissue	[67]
	扶正通络方 Fuzheng Tongluo Formula	自噬小体、p62 与 becline-1 蛋白 Autophagosome, p62 and becline-1 protein	雄性, SD 大鼠, 10 ~ 12 周龄, (200 $\pm$ 20) g Male, SD rat, 10 ~ 12 weeks, (200 $\pm$ 20) g	气管内滴注 BLM Intratracheal instillation of BLM	(1) 大鼠肺大体见散状出血, 黑色瘀斑, 肺重量及硬度增加, 表面呈结节样 (2) 肺组织 HE 染色: 支气管壁及血管壁外周出现炎细胞聚集, 外膜小血管扩张 (3) 肺组织 Masson 染色: 支气管周围及肺泡间隔出现大量蓝绿色胶原纤维 (4) 肺系数增加, 肺组织 HYP 增加 (1) Rat lungs showed scattered hemorrhage, black bruises, increased lung weight and hardness, and a nodular appearance on the surface (2) HE staining of lung tissue: inflammation cells gathered around bronchial and vascular walls, and outer layer of small blood vessels expanded (3) Masson staining of lung tissue: abundant blue-green collagen fibers appeared around bronchi and alveolar septa (4) Lung coefficient increased, and HYP of lung tissue increased	[70]
促进自噬 Promote autophagy						

续表 3

作用机制 Mechanism of action	中药 Traditional Chinese medicine	相关信号通路 及分子 Related signaling pathways and molecules	动物选择 Animal selection	造模方法 Modeling methods	模型组动物指标 Model group animal indicators	参考文献 References
	益肺散结方 Yifei Sanjie Formula	自噬相关基因 <i>Beclin1</i> 与 <i>LC3B</i> , IL-8、TNF- α Autophagy-related genes <i>Beclin-1</i> and <i>LC3B</i> , IL-8、 TNF- α	雄性,SD 大 鼠,4 周龄, (200 $\pm$ 20) g Male, SD rat, 4 weeks, (200 $\pm$ 20) g	气管内滴 注 BLM + 香烟烟雾 刺激 Intratracheal instillation of BLM + cigarette smoke irritation	(1)造模结束随机处死 3 只大鼠初步 观察病理情况 (2)取材后肺组织 HE 染色:大鼠 支气管纤毛上皮细胞变性、坏死、脱 落,支气管周围大量炎性细胞浸润, 肺泡结构紊乱,肺泡壁变薄、断裂,肺 泡腔扩大融合 (1)At the end of modeling, 3 rats were randomly sacrificed to observe the pathological conditions (2)HE staining of lung tissue after sampling: degeneration, necrosis, and shedding of ciliated epithelial cells in the bronchi of rats, accompanied by extensive inflammatory cell infiltration around the bronchi, disruption of alveolar structure, thinning and rupture of alveolar walls, and enlargement and fusion of alveolar spaces	[71]
	血栓通注 射液 Xueshuantong injection	凝血级联途 径,PAR-1, SFMC、FDP Coagulation cascade pathway, PAR-1, SFMC、FDP	雄性, Wistar 大鼠, 8 ~ 10 周龄, (200 $\pm$ 20) g Male, Wistar rat, 8 ~ 10 weeks, (200 $\pm$ 20) g	气管内滴 注 BLM Intratracheal instillation of BLM	(1)造模后大鼠食量及饮水量下降, 精神状态差,毛发黄粗糙,部分大 鼠拱背,口唇及爪甲暗紫,少数口鼻 出血,呼吸较困难 (2)肺 CT:大鼠肺纹理模糊,有致密 阴影及蜂窝样改变 (1)After modeling, food intake and water consumption of rats decreased, their spirit was low, their fur became yellow and rough, some rats hunched their backs, their lips and claws turned dark purple, and a few experienced nosebleeds and difficulty breathing (2)CT of lung: lung texture of rat was blurred, with dense shadows and honeycomb-like changed	[75]
调控凝血 途径 Regulating the blood clotting pathway	益气养阴活 血通络方 Yiqi Yangyin Huoxue Tongluo Formula	CD40-CD40L 系 统,PAI、FIX、FVII CD40-CD40L system, PAI、 FIX、FVII	雄性, Wistar 大鼠, 6 ~ 8 周龄, (180 $\pm$ 20) g Male, Wistar rat, 6 ~ 8 weeks, (180 $\pm$ 20) g	气管内滴 注 BLM Intratracheal instillation of BLM	(1)造模后大鼠精神萎靡,毛发黄 脱落,呼吸困难,进食减少 (2)病理学:第 7 天肺泡间隔增宽,有 炎症细胞聚集,肺间质见水肿;第 14 天肺泡腔缩小,腔内炎症细胞减少成 纤维细胞增多,间质内见胶原纤维增 生;第 28 天肺泡间隔塌陷,大量胶原 纤维沉积,见纤维瘢痕与蜂窝肺 (3)模型组大鼠第 7、14、28 天肺组织 HYP 含量均显著升高 (1)After modeling, rats appeared lethargic, with yellowing and shedding fur, difficulty breathing, and reduced appetite (2)Pathology demonstration: on the 7th day, alveolar septum was widened, inflammatory cells were accumulated, and edema was seen in the lung interstitium; on the 14th day, alveolar cavity shrank, inflammatory cells in the cavity decreased, fibroblasts increased, and collagen fibrils proliferated in the interstitium; on the 28th day, alveolar septum collapsed, and abundant collagen fibers were deposited, as seen in fibrous scars and honeycomb lungs. (3)Lung tissue hydroxyproline content of model group rats at 7, 14, and 28 days significantly increased	[76]

不节、情志内伤等内外因构建出完整的所需证候的动物模型,如肺气虚模型可在经 BLM 进行诱导后,对动物进行强制游泳和吸烟,使小鼠达到肺气虚的临床表现。在进行模型评价时,因传统“望闻问切”四诊在动物身上无法应用,这就需要根据生理生化指标、行为学测试等手段更为精确的评估模型是否符合中医的证候标准。

西药治疗 IPF 效果并不理想,中医药具有治疗靶点多、疗效较好、安全性高等优势。通过中药组方或单味药对 IPF 动物模型进行干预,确定中药治疗 IPF 的具体作用机制,是动物实验研究的重点与目的,同样是临床新药研发与推广的关键依据。综合分析中医药治疗 IPF 的研究现状,经典方和自拟方受到研究者的重点关注,此外经典方和自拟方中起主要治疗作用的单味药及其成分亦是研究的热点^[78]。研究者应关注方剂中君臣佐使的配伍关系,某些中药在组方中可能并未直接治疗 IPF,但是其佐助和引经作用亦不容忽视,中药方剂正是从多药物搭配、联合奏效的角度去治疗疾病,各味药物的作用都不可小觑。多个机制互相串扰、互为因果、共同作用是 IPF 的发病机制特点,因此从多药物联合作用、多机制串扰关系研究中医药治疗 IPF 前景可观。

动物实验研究的最终目的是应用于临床,改变患者的疾病状态,因此,应及时掌握目前研究现状,找出问题并尽力完善,模拟出最符合的人类 IPF 病理表现的动物模型,再加以中药干预,验证疗效,发挥出中医药治疗 IPF 的最大优势。

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[收稿日期] 2024-11-28