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特发性肺纤维化动物模型的研究进展

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【摘要】 作为一种预后不良的慢性进行性肺病,特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)的发病机制至今尚未明确,其治疗方法仍在不断探索。动物模型是研究疾病的发病机制与治疗作用的重要工具。本文将基于 IPF 动物模型与人 IPF 在疾病表型等方面的相似度,从药物和环境因素所诱导的纤维化机制、组织病理学改变、纤维化阶段、造模时间等方面梳理 IPF 动物模型的研究进展,阐述不同动物模型的优缺点、特征及应用概况。

【关键词】 特发性肺纤维化;动物模型;表型
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Research progress in animal models of idiopathic pulmonary fibrosis

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【Abstract】 As a chronic progressive lung disease with poor prognosis, the pathogenesis of idiopathic pulmonary fibrosis (IPF) has not yet been clarified, and its treatment is still being explored. Animal models are important tools for studying the pathogenesis and therapeutic effects of diseases. Based on the similarity between animal models and human of IPF in terms of disease phenotype, this paper will review the research progress of IPF animal models in terms of the fibrosis mechanism induced by drugs and environmental factors, histopathological alterations, fibrosis stage, modelling time, etc., and describe the advantages and disadvantages of different animal models, their characteristics and application profiles.

【Keywords】 idiopathic pulmonary fibrosis; animal models; phenotype
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特发性肺纤维化（idiopathic pulmonary fibrosis, IPF）是一种病因不明的慢性进行性的特发性间质性肺炎（idiopathic interstitical pneumonia, IIP）[1-2]。2018 年，中国将 IPF 纳入《第一批罕见病目录》[3]，可影响全球约 300 万人[4]。其特征为肺泡上皮重复性异常瘢痕形成，以及间质、远端呼吸道和肺泡腔的重塑，这些病理改变会导致细胞外基质（extracellular matrix, ECM）积聚和病理性肺重塑[5]。IPF 占所有间质性肺疾病（interstitial lung disease, ILD）的 20%，是 ILD 中最常见的类型[6]。患者主要为中老年人，其中男性患者居多[4]。尽管 IPF 的发病率较低，但肺泡上皮的损伤使气体交换障碍、肺容量减少、呼吸困难，最终易导致死亡[5]。

肺组织病理学检测被认为是评估 IPF 的黄金标准，其组织病理学表型包括：（1）肺泡和肺泡壁结构破坏呈蜂窝状，导致气体交换效率降低，是患者出现呼吸困难的主要原因；（2）中性粒细胞和巨噬细胞的炎症浸润，它们释放的炎症介质对肺泡上皮细胞造成损伤，促进成纤维细胞的活化，并参与 ECM 的降解和合成，从而加剧肺组织的炎症和纤维化过程；（3）伴有Ⅱ型肺泡上皮细胞（type Ⅱ elveolar epithelial cell, AT2）和支气管上皮细胞的增生，异常增生的 AT2 会分泌肺泡表面活性物质，使肺泡稳定性丧失；（4）IPF 中活化的成纤维细胞和肌成纤维细胞会组成成纤维细胞灶，肺中胶原沉积增加，这些是肺组织硬化和功能丧失的重要原因；（5）ECM 的过度沉积会改变肺组织的微环境，增加组织硬度，影响细胞行为，促进纤维化的持续发展[4,7-9]。这些组织病理学变化通常对胸膜下和膈膜旁实质的影响最为严重[4]，其中代表活动性病变区域的成纤维细胞灶是 IPF 常见的组织病理学特征[4,7]。

目前 IPF 发病机制尚未明确、无确切的治疗方法，因此进一步探索 IPF 的发病机制和治疗方法十分重要。动物模型在疾病的发病机制、病理学表型等方面的研究设计中发挥了重要作用，但 IPF 动物模型的建立方法多样，尚无明确的统一标准。目前已有文献对 IPF 动物模型进行综述，但缺少对其模型诱导时间、维持时间及不同纤维化阶段模型表型差异的总结。因此，本文从药物和环境因素所诱导的纤维化机制、组织病理学改变、纤维化阶段、造模时间等方面梳理 IPF 动物模型的研究进展，旨在完善 IPF 动物模型与人 IPF 疾病表型等方面的相似度，同时为 IPF 动物模型的选择和评价指标的优化提供理论依据。

1　IPF 的发病机制与表型

IPF 的发生涉及多种因素，不良生活习惯[10]、环境影响[11]、职业危害[12]、遗传因素[13]等均可能导致 IPF 的发生。但其发病机制尚未完全阐明，目前，关于 IPF 发病机制的研究主要集中在慢性炎症、氧化应激和肺泡上皮-间质转化（epithelial-mesenchymal transition, EMT）等方面[14-16]（图 1）。

长期暴露于含有多种危险因素的环境中，会导致肺损伤，诱发异常的炎症反应和氧化应激，两者可相互促进[17]。炎症反应中的巨噬细胞分化为 M1 型和 M2 型两种不同的状态[18]，M1 型巨噬细胞诱导产生的促炎细胞因子，如白介素（interleukin, IL）-1β、IL-6、肿瘤坏死因子-α（tumor necrosis factor-α, TNF-α）会加快炎症产物对肺组织的浸润[19-20]。氧化应激通过氧化还原激活核转录因子-κB（nuclear transcription factor, NF-κB）信号通路释放 TNF-α、IL-1 和 IL-6 等炎症因子激活 EMT[21-23]，并导致 M2 巨噬细胞极化[21-25]。M2 型巨噬细胞及其亚型产生的转化生长因子-β1（transforming growth factor-β1, TGF-β1）、血小板衍生生长因子（platelet-derived growth factor, PDGF）、血管内皮生长因子（vascular endothelial growth factor, VEGF）等促肺纤维化因子来介导胶原蛋白沉积和 EMT[19-20]。EMT 与成纤维细胞相互作用，诱导肌成纤维细胞大量形成、肺上皮细胞中胶原蛋白、ECM 等物质产生，最终导致肺纤维化[26]。

2　实验动物

目前，用于 IPF 动物模型的实验动物种类众多，包括小鼠、大鼠、仓鼠、树鼩、美利奴羊、恒河猴、叙利亚仓鼠等[27]。由于给药剂量及给药途径的不同，这些动物模型具有高度的不均一性。大鼠和小鼠模型是应用最为广泛的 IPF 动物模型[28]，小鼠与人类基因相似性高、繁殖能力高、品系多样，以 C57BL/6J、C57BL/6、C6BL/8J、KM 小

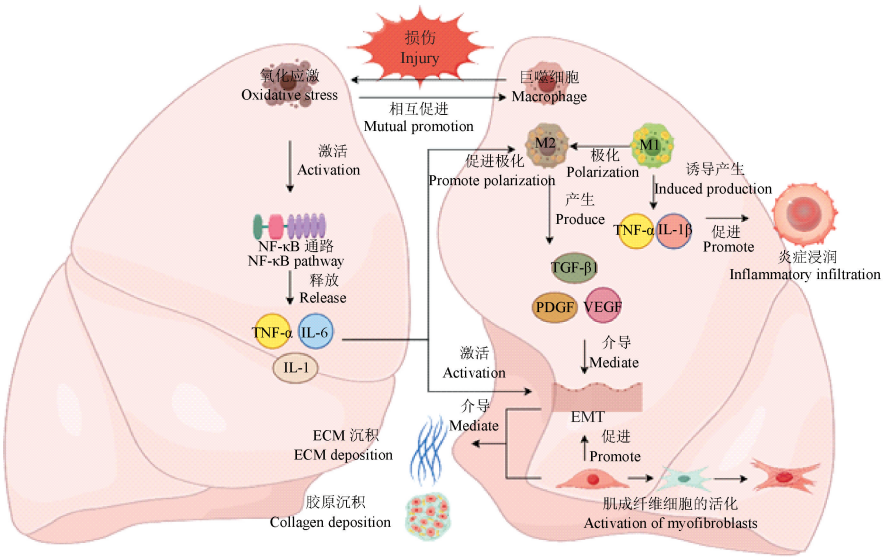

图 1 IPF 发病机制(由 Figdraw 绘制)

Figure 1 IPF pathogenesis(By Figdraw)

鼠为代表;大鼠的呼吸系统在解剖学和生理学上与人类有许多相似之处,且易于饲养和操作,以 Wister 和 SD 为主。树鼩、美利奴羊、恒河猴、叙利亚仓鼠等动物在基因、解剖学和代谢上更接近于人类[29-30],但因其价格昂贵,较少应用于实验研究。

3 IPF 动物模型评价指标

评价指标是判断动物模型建立成功与否的重要依据。在 IPF 临床前模型中,模型动物需具有人类 IPF 类似的病理学特征,并且常使用 ASHCROFT 等[31]建立的评分系统(表 1)[32-33]作为模型评估的终点[7,10]。

4 造模方法

现有的造模方法包括药物诱导模型、环境诱导模型以及基因工程技术诱导模型。药物诱导包括博来霉素(bleomycin, BLM)、百草枯(paraquat, PQ)、异硫氰酸荧光素(fluorescein isothiocyanate, FITC)、胺碘酮(amiodarone, AMD)、油酸(oleic acid)等(表 2),其中最常用的为 BLM。环境诱导包括游离结晶二氧化硅(crystalline silica, CS)、石棉(asbestosis)、辐射、高浓度氧等(表 3),其中最常用的为 CS。基因工程技术通过敲除特定的基因使小鼠自发的发生肺纤维化或加快特定 IPF 模型的诱导进程。由于药物的化学

表 1 肺纤维化分级标准

Table 1 Grading criteria for pulmonary fibrosis

纤维化分级 Fibrosis classification	组织学特征 Histological characteristics
0	正常肺,肺组织结构正常 Normal lungs with normal lung tissue structure
1	肺泡或细支气管壁轻度纤维性增厚 Mild fibrous thickening of alveolar or bronchial walls
2 ~ 3	中度纤维性增厚对肺组织结构无明显损害 Moderate fibrous thickening without significant damage to lung tissue structure
4 ~ 5	纤维化增加,并对肺组织结构造成一定的损害,形成纤维带或小纤维团 Increased fibrosis and some damage to the lung tissue structure, forming fibrous bands or small fibrous masses
6 ~ 7	肺组织结构严重扭曲,纤维区域较大,即出现“蜂窝状肺” Severe distortion of the lung tissue structure with large fibrous areas, i.e. “honeycomb lung”
8	视野完全纤维性闭塞 Complete fibrous occlusion of the visual field

注:肺组织染色后镜下观察评分。

Note. Score for microscopic observation after staining of lung tissue.

性质和物理因素对肺损伤的诱导效果不同,因此它们在实验动物中诱导的纤维化机制、组织病理学变化、纤维化阶段以及造模时间等方面也存在差异。

表 2　药物诱导的 IPF 模型

Table 2　Models of drug-induced IPF

药物种类 Drug type	动物品系 Strain of animal	造模时间/周 Moulding time/week	表型 Phenotype						参考文献 References
			肺泡结构的改变与破坏 Alteration and destruction of alveolar structure	炎症细胞浸润 Inflammatory cell infiltrate	肺上皮细胞增生 Lung epithelial cell hyperplasia	胶原沉积 Collagen deposition	成纤维细胞灶 Fibroblastic focus	ECM 沉积 Extracellular matrix deposition	
BLM	C57BL/6、C57BL/6J 小鼠 C57BL/6、C57BL/6J mice	2 ~ 4	√	√	√	√	√	–	[34-35]
	瑞士白化小鼠 Swiss albino mice		√	√	√	√	√	–	[36]
	SD、Wistar 大鼠 SD、Wistar rat		√	√	–	√	–	–	[37-38]
	树鼩 Tree shrew		–	√	–	√	–	√	[29,39]
	美利奴羊 Merino		√	–	–	√	√	–	[40-42]
PQ	C57BL/6J 小鼠 C57BL/6J mice	2 ~ 4	√	√	√	√	–	–	[43-44]
	SD、Wistar 大鼠 SD、Wistar rat		√	√	–	√	–	–	[45-46]
	恒河猴 Rhesus monkey		√	√	–	√	–	–	[47]
FITCF	BALB/c、C57BL/6 小鼠 BALB/c、C57BL/6J mice	2 ~ 4	–	√	–	√	–	√	[48]
	KM 小鼠 KM mice		√	√	√	√	–	–	[49]
AMD	SD、Wistar 大鼠 SD、Wistar rat	2 ~ 4	√	√	–	√	√	–	[31,50]
	叙利亚仓鼠 Syrian hamster		√	√	√	√	–	–	[51]
油酸 Oleic acid	SD 大鼠 SD rat	1 ~ 4	√	√	√	√	–	–	[52]

注：√：具有此表型；–：不具有此表型。（下表同）

Note. √. Has this phenotype. –. Does not have this phenotype. (The same in the following tables)

4.1　药物诱导的 IPF 动物模型

4.1.1　BLM 诱导的 IPF 模型

BLM 是从垂直链霉菌中分离得到的 1 组糖肽类抗生素，由 5 种氨基酸组成，通过产生自由基与体内的铁结合形成络合物，诱导 DNA 的断裂，导致细胞凋亡或坏死，引起炎症反应和纤维化[65-67]。自 1970 年以来，BLM 被用于诱导动物纤维化[68]，是诱导纤维化的典型药物。

BLM 诱导纤维化的给药方式较多，大多通过单剂量气管内滴注[34]、尾静脉注射[34]、腹腔注射[34]、鼻腔雾化[35]等。模型的建立通常为 2 ~ 4 周，6 ~ 8 周后肺纤维化会消失[69-71]。重复 BLM 滴注诱导的 IPF 模型中纤维化可持续 3 ~ 6 个月[72-73]，产生此差异的机制尚不清楚，可能与研究中使用 BLM 的不同剂量或小鼠品系有关。其中 C57BL/6 小鼠对 BLM 具有更好的反应性[34-35,74]。

BLM 诱导 IPF 的过程可分为 3 个阶段，第 1 阶段为给药后的第 1 周主要以炎症为主，炎症细胞大量涌入，并激活和分泌多种炎症介质，原因

表 3 环境诱导的 IPF 模型

Table 3 Environmentally induced IPF models

药物种类 Drug type	动物品系 Strain of animal	造模时间/周 Moulding time/weeks	表型 Phenotype						参考文献 References
			肺泡结构的改变与破坏 Alteration and destruction of alveolar structure	炎症细胞浸润 Inflammatory cell infiltrate	肺上皮细胞增生 Lung epithelial cell hyperplasia	胶原沉积 Collagen deposition	成纤维细胞灶 Fibroblastic focus	ECM 沉积 Extracellular matrix deposition	
BLM	C57BL/6、C57BL/6J 小鼠 C57BL/6、C57BL/6J mice	4 ~ 12	√	√	√	√	–	–	[53-56]
	KM 小鼠 KM mice		√	√	–	–	–	–	[57]
	SD、Wistar 大鼠 SD、Wistar rat		√	√	√	√	–	–	[57-59]
石棉 Asbestosis	C57BL/6J 小鼠 C57BL/6J mice	1 ~ 2	√	–	–	√	–	–	[41-42]
X 射线 X-ray	C57BL/6 小鼠 C57BL/6J mice	24 ~ 28	√	√	√	√	√	–	[60-61]
高浓度氧 High oxygen concentration	SD、Wistar 大鼠 SD、Wistar rat	2	√	–	–	√	–	–	[62-64]

是上皮损伤,并有血管渗透,促炎细胞因子、趋化因子的上调[72]。第 2 阶段为给药后的第 2 周从炎症发展为纤维化的过渡期,此阶段可见炎症反应减弱、纤维增生增加、肌成纤维细胞出现[75]。第 3 阶段为给药后的第 3 ~ 4 周为慢性纤维化阶段,可见肺泡结构破坏、肺泡内及肺间隔纤维化明显、肺泡壁和肺泡间隔增厚、炎症细胞浸润(如巨噬细胞)、成纤维细胞灶、胶原沉积增加、基底膜增厚、Ⅰ型肺泡上皮细胞变形、崩解脱落、肿胀、Ⅱ型肺泡上皮细胞增殖、畸形层状体、层状小体液泡样转化,EMT 水平升高,ECM 的更新和重塑,Ashcroft 肺纤维化评分升高[34-36,65,76-78],出现明显的牵引性支气管扩张和胸膜下纤维化[73];可见 IPF 模型中的炎症因子 TGF-β1、TNF-α、IL-1β 和 IL-6 表达水平升高[34-35,78-79]。BLM 诱导 IPF 具有价格实惠、易于处理、重复性高的优点,并出现了多种人 IPF 疾病表型,是实验室最常用的造模方式之一。但此模型并不能保证所有动物都能完全发展成肺纤维化,疾病发展的时间间隔较长[65,76]。不同给药方式产生的肺纤维化会有差异,如 BLM 鼻腔雾化给药,药物在体内分布较均匀,肺纤维化病变更均匀、范围更广、可达胸膜下区域,形成胸膜下纤维化,更符合人肺纤维化的临床特点,但需要特殊的设备,使用较少[35];腹腔注射和尾静脉注射 BLM 纤维化主要位于胸膜下,胶原分布在肺间质间隙,但给药次数和剂量较大,造模时间长,成本高[34];单剂量气管内给 BLM 为目前最常用的造模方式,胶原主要分布在支气管附近,对操作者技术要求较高[34,71]。

近年来,BLM 诱导的 IPF 模型在 IPF 的研究中被广泛应用。例如,在此模型基础上开展的与 IPF 发病相关的机制研究,包括炎症[80-81]和氧化应激[80,82]、EMT[83-85]等。此外,该模型还用于筛选治疗 IPF 的潜在药物,如川芎嗪[86]、黄芪[87]、白芍[87]、生陷汤[88]、橘皮素[83]、罗红霉素[89]等。同时,也被用于评估新治疗方法的疗效,如 IL-11 的 siRNA 纳米颗粒的吸入法[90]、超分子纳米纤维法[91]、高压氧疗法[92-93]等。

4.1.2 PQ 诱导的 IPF 模型

PQ 是一种被广泛使用的高效非选择性接触性除草剂。PQ 中毒会导致肺、胃肠道、胰腺、肾、肝、心脏、脑等多器官功能衰竭,其中主要的靶器官为肺和肾,肺纤维化是 PQ 中毒最典型的特征[94]。PQ 导致肺纤维化主要是引起肺泡损伤和

肺泡上皮细胞的重构;因此产生氧化应激反应、炎症反应和基因表达异常[95]。PQ 动物模型的建立常用的实验动物为 C57BL/6J 小鼠[43-44]、Wistar 大鼠[45]、SD 大鼠[46]、恒河猴[47]等,常通过一次性灌胃[45-47]和腹腔注射给药[43-44],造模时间为 2 ~ 4 周[43-47]。PQ 给药 3 d 后,可见支气管和肺泡壁充血、水肿和炎症细胞浸润;给药 14 d 后,可见肺泡间隔增厚伴肺泡管腔变窄、弥漫性肺出血及有透明膜形成;给药 28 d 后,可见肺泡壁增厚,纤维细胞增生,胶原纤维增加,TGF-β1、IL-4 表达水平升高;给药 28 d 后肺纤维化水平明显下降[43,45-47]。PQ 诱导的 IPF 模型具有死亡率高,操作困难,给药剂量难控制等缺点[96]

PQ 诱导的 IPF 模型适用于研究 IPF 发病机制,包括非免疫机制[97]、氧化应激[97-99]、炎症反应[97-99]以及 EMT[100]等途径。此外,该模型还可用于筛选潜在的 IPF 治疗药物,例如雷帕霉素[101]、雷公藤内酯[102]、阿米替林[103]等。同时,RASOOLI 等[104]应用该模型评估了吡非尼酮加泼尼松龙的联合疗法治疗 PQ 诱导 IPF 的疗效,为联合治疗策略提供了实验依据。

4.1.3　FITC 诱导的 IPF 模型

FITC 是一种可用于诱导肺纤维化的化学荧光分子,能与呼吸道蛋白结合,附着在肺蛋白上,持续定位于最初的损伤区域,可通过荧光识别受损区域和周围的纤维化[48,105]。常用的实验动物为 BALB/c、C57BL/6 小鼠[48]。单次气管内滴注 FITC,纤维化的出现需要 2 ~ 4 周,并一直持续至 24 周[48,105]。首先,给药 1 d 后,出现肺泡壁水肿和肺泡渗出物,表现为急性肺损伤,给药 7 d 后,可见急性和慢性炎症细胞浸润,如单核细胞;给药 21 d 后,可见斑片状肺纤维化、ECM 增加、单核细胞持续存在、胶原沉积增加[48]。但实际上很少使用该药物诱导肺纤维化模型,因为该模型明显缺乏 UIP 表现和主要的炎性浸润物,某些组织病理学特征观察不到,如成纤维病灶,而且不同批次的 FITC 所产生的纤维化反应有较大的差异[48,105-106]。

4.1.4　AMD 诱导的 IPF 模型

AMD 是一种广泛用于治疗心律失常的Ⅲ类抗心律失常药,但因其会诱导严重的肺毒性,临床上很少用于疾病的治疗[107-108]。AMD 诱导肺纤维化的发病机制与多种细胞、线粒体破坏、免疫调节机制和血管紧张素酶系统的综合作用有关,但目前并没有明确的定论[109-110]。其诱导的 IPF 模型常用的实验动物为 KM 小鼠[49]、叙利亚仓鼠[51]、Wistar 大鼠[31]和 SD 大鼠[50]等,可通过单次气管内注入 AMD 或者连续灌胃给药,在 4 周内发展为肺纤维化,4 周后肺纤维化水平下降[51]。AMD 给药 1 d 后,可见肺泡腔内急性炎症细胞浸润,并伴有出血;给药 5 d 后,可见间质增厚、单核细胞进入肺间隔、肺泡上皮细胞增生、纤维蛋白渗出明显并且急性炎症细胞消失;在给药 14 d 后,肺泡间隔明显增厚,充斥炎症细胞、纤维蛋白渗出物和Ⅱ型肺泡上皮细胞明显增加、急性炎症细胞再次出现;给药 21 d 后,可见间质和肺泡腔中含有大量中性粒细胞、嗜酸性粒细胞和单核细胞、胶原沉积增加、肺泡间隔增厚、含有大量巨噬细胞;给药 28 d 后,肺纤维化改变有所恢复[32,49,51,107]。临床上对胺碘酮所致纤维化的认识和治疗有限,该药不良反应众多,在引起肺毒性的同时也会造成其他损伤,其诱导产生肺毒性的发病机制,至今没有确切结论,因此对其进一步研究尤为重要。目前该模型可用于肺纤维治疗药物的筛选,包括川陈皮素[111]、硫辛酸[107]、左旋肉碱[112]等潜在药物。

4.1.5　油酸诱导的 IPF 模型

油酸是动植物体内的一种不饱和脂肪酸,是健康人体内常见的一种营养素,但油酸可通过触发不同的细胞途径,改变细胞功能,刺激组织发生纤维化[113]。通过尾静脉注射油酸,诱导 IPF 模型,7 d 可见肺泡壁明显增厚、肺泡和肺间质水肿,大量中性粒细胞浸润,肺泡腔缩小,肺泡塌陷等,以急性肺泡炎为主;14 d 可见肺泡炎症减轻,病灶内出现肺泡萎缩和肺泡上皮细胞增生,局部出现胶原沉积及斑片状纤维,部分肺泡结构消失;28 d 可见肺泡结构萎陷、破坏,炎症细胞减少,病变部位扩大,胶原沉积在新生毛细血管周围,肺泡间隔及部分肺泡腔中充满胶原和纤维蛋白,肺泡壁增厚[52]。油酸诱导的肺纤维化模型虽然不能完全模拟人类疾病的全过程,但该模型重复性好,更接近人类肺纤维化病变的分布特点,缺点是需要掌握尾静脉注射的技术,且成功率不高[113-114]。

4.2 环境诱导的 IPF 动物模型

4.2.1 CS 诱导的 IPF 模型

矽肺病是由于人体吸入大量 CS 或二氧化硅(SiO_2)引起的[115],CS 会导致肺部炎症,纤维化和肺功能障碍,但其导致机体疾病的机制尚不清楚,实验研究中用 SiO_2 粉末诱导 IPF 模型的建立有利于了解其致病机制,为疾病的治疗,药物的研究提供理论依据[116-117]。SiO_2 诱导的 IPF 是一种弥漫性间质性纤维化疾病,其特征是肺组织中 ECM 的大量沉积[118]。模型中常用动物为 C57BL/6 小鼠[53-54]、C57BL/6J 小鼠[55-56]、KM 小鼠[119]和 Wistar 大鼠[57-58]、SD 大鼠[59],给药途径多为气管内滴注 SiO_2[53-59],少部分使用鼻腔吸入[119];造模时间最短为 28 d[57-58],最长可达 5 个月[55-56]。SiO_2 给药后 28 d 可见肺部出现纤维化;给药 2 个月后,可见细胞性结节(肉芽肿)并伴有明显的上皮增生;给药 4 个月后,可见肺泡结构破坏、肺泡壁增厚、肺上皮细胞增生、细胞性结节(肉芽肿)、炎性细胞浸润、肺泡腔内有渗出液、肺间质充血、胶原沉积增加、ECM 沉积增加[56-59],还可见 IL-1β、IL-6、IL-4、TNF-α、IL-18 等炎症因子的表达水平升高,Ashcroft 肺纤维化评分升高[56-59]。CS 诱导的 IPF 操作简单,成果率高、诱导的肺纤维化组织病理变化与人类更相似,但 SiO_2 动物模型所需的造模时间较长难以广泛应用[54-56]。该模型被用于 IPF 治疗药物的筛选和潜在疗效的评估[120-121]。

4.2.2 石棉诱导的 IPF 模型

石棉纤维为天然存在的矿物硅酸盐(角闪石和温石棉),在环境中暴露时会导致肺和胸腔纤维化、肺癌等,但其诱导疾病的机制尚未完全确定。石棉纤维进入人体后会被血管内皮细胞内化,导致产生铁衍生的活性氧物种,DNA 损伤和细胞凋亡,诱导的肺泡上皮细胞(alveolar epithelial cells,AECs)的凋亡是石棉纤维引起肺纤维化的早期事件[122]。常用的实验动物为 C57BL/6 小鼠[123]、C57BL/6J 小鼠[124],闪石纤维通过气管内滴注给药,第 7 天可见肺部出现纤维化,第 14 天肺纤维化达到成熟,并可持续 60 d,不会自发消退[123],可见肺结构破坏,支气管周围纤维化,并延伸至邻近的肺泡实质,胶原沉积增加[123-124]。该模型也存在一定的局限性,诱导的纤维化病变在肺组织中分布不均匀,大多位于肺组织的中间而非胸膜下[125]。吸入法诱导的 IPF 的病变更接近胸膜,但所需的时间较长,常使用温石棉[126]。

目前,该模型主要用于预测 IPF 的潜在治疗靶点,包括腺嘌呤核苷酸转位酶 1[127]、去乙酰化酶 3[128-129]、NADPH 氧化酶 4[130]等。

4.2.3 辐射诱导的 IPF 模型

放射性肺损伤(radiation-induced lung injury,RILI)是放射治疗中最常见的副作用,其中包括急性放射性肺炎和慢性放射性肺纤维化[131]。辐射是通过导致成纤维细胞和肌成纤维细胞的积累、增殖、分化,最终增加胶原蛋白的产生、炎症细胞的浸润和 ECM 的重塑从而诱导肺的纤维化[132]。辐射诱导的 IPF 模型常用 C57BL/6 小鼠,对其最为敏感[132];采用 12 ~ 20 Gy X 射线照射,4 ~ 8 周后,可见肺泡间隔增宽、肺泡完整性降低、肺纹理轻度增厚、胶原沉积出现;16 ~ 24 周后可见肺间质细胞增多、肺泡壁增厚、胶原沉积增加,肺纤维化面积增大、炎症细胞浸润、肌成纤维细胞分化增加、IL-6、TGF-β 表达升高[60-61]。辐射造模所采用的技术较为复杂,因为其无法避免照射到其他器官,但造模时应只辐射于肺部;而且辐射造模所需的时间较长,多为 24 ~ 28 周,限制了其在临床前环境中的有效应用[60-61,106,132]。

该模型可用于 IPF 发病机制的研究,通过靶向寡肽/组氨酸转运体来调节巨噬细胞中的氧化应激[133];TU 等[134]应用该模型尼探究了尼达尼布对辐射诱导肺纤维化的抗纤维化影响,并揭示其基本机制。DADRICH 等[135]应用该模型评估了血小板衍生生长因子和 TGF-β 信号传导的小分子抑制剂的联合使用是一种安全有效的治疗辐射诱导 IPF 的方法。

4.2.4 高浓度氧诱导的 IPF 模型

高浓度氧可用于治疗缺氧性呼吸衰竭,但高浓度的氧也会影响肺的发育,导致肺泡损伤、肺间质纤维化和肺血管发育不良等,使早产儿患上支气管发育不良(bron-chopulmonary dysplasia,BPD)[136]。暴露于 95% ~ 100%的氧浓度环境中 72 ~ 96 h,会导致急性肺损伤,长时间暴露于 50% ~ 85%氧浓度环境中可导致渐进性肺纤维化[137]。高氧引起的肺纤维化的特征为

EMT[62,136]。其诱导的 IPF 模型常用的动物为新出生的大鼠,将新生大鼠与母鼠一同置于高氧环境中,持续高氧培养 14 d,新生大鼠在第 3 ~ 7 天肺部开始出现纤维化,在第 14 天纤维化达到最高峰,可见肺泡数量减少,肺泡扩张,间质增厚,肺间质纤维化增加,胶原沉积增加,肌成纤维细胞分化增加,TGF-β1 表达水平升高[62-64,136-137]。高浓度氧诱导的肺纤维模型所需的时间较短,但所需的条件比较高,要将氧的浓度控制在一定范围,才可导致肺纤维化。

4.3　其他

近年来随着研究的不断深入,一些转基因小鼠及基因敲除小鼠也成为了研究的热点。*Fra2*^{tg} 转基因小鼠(*Fra2* transgenic mice, *Fra2*^{tg})来源于转基因小鼠异位表达 *Fra2*,小鼠异位表达 *Fra2* 可导致多器官的纤维化,肺组织的纤维化最严重[138]。几种与人类肺纤维化有关的生长因子、趋化因子和细胞因子在 *Fra2*^{tg} 转基因小鼠的病变肺中高度表达,且在 IPF 的人肺纤维化标本中可见强烈的 *Fra2* 免疫反应,因此 *Fra2*^{tg} 转基因小鼠可成为 IPF 研究中一种有前途的动物模型[138-140]。

5-羟色胺(5-hydroxytryptamine,5-HT)为色氨酸中提取的单胺分子,可由色氨酸羟化酶 2(tryptophan hydroxylase 2, TPH2)和色氨酸羟化酶 1(tryptophan hydroxylase 1, TPH1)合成,中枢的 5-HT 由 TPH2 合成,外周的由 TPH1 合成。外周的 5-HT 可调节血小板凝集、骨骼发育、免疫反应和炎症反应等。研究发现 5-HT 可以通过促进肺胶原蛋白沉积、炎症和氧化应激加速博来霉素诱导的肺纤维化,因此在肺纤维小鼠血清、肺泡灌洗液(bronchoalveolar lavage fluid, BALF)、肺组织中可见 5-HT 水平显著升高[141]。

黏蛋白 1(mucin 1, MUC1)是一种Ⅰ型跨膜糖蛋白,其可通过抑制巨噬细胞中 TLR/NF-κB 通路的激活来干扰 NLRP3 炎性体的活性,MUC1 的缺乏就可能通过增加 IL-1β 的产生而加剧肺纤维化[142]。通过转基因技术使小鼠自发的发生肺纤维化或者通过敲除特定的基因加快肺纤维模型的建立有利于进一步研究 IPF,同时也有利于缩短实验的时间,也可增加造模的成果率,但该实验模型的建立有价格昂贵的局限性。

5　总结与展望

本文系统总结了 IPF 动物模型的研究进展,从药物诱导和环境诱导两个方面,梳理了不同模型的造模方法、表型特征、优缺点及应用概括。理想的 IPF 动物模型的发病机制、组织病理学改变、生化指标等应较全面的与人类 IPF 疾病相近,但目前尚无一个模型能够完全模拟人类身上检测到的 IPF 所有典型特征。未来研究应注重模型的标准化,规范造模流程,统一评价指标;开发多因素诱导模型,结合药物、环境因素和遗传背景,更真实地模拟人类 IPF 的发病过程;引入新技术,如单细胞测序和基因编辑,以构建更接近人类病理特征的模型;加强跨物种研究,寻找更适合的模型动物或开发人源化动物模型;同时,关注慢性纤维化阶段的研究,为 IPF 的长期治疗提供理论支持。通过这些优化和创新,推动 IPF 的发病机制研究和临床治疗策略的开发。

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