

Research Progress on Animal Models of Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a long-term respiratory condition with high rates of morbidity and mortality. Its pathophysiology is complex, and currently, there are no effective clinical treatments that can fully reverse or halt the disease's progression. Animal models play a significant role in elucidating the pathogenesis of COPD, dynamic pathological processes, and evaluating potential therapeutic strategies, serving as a key to advancing in-depth research on this disease. However, existing modeling methods still face many limitations in accurately simulating the clinical symptoms, pathophysiological features, and progression of human disease, and there is a lack of standardized guidelines and industry consensus. This paper systematically reviews methods for constructing COPD animal models reported in the literature by reviewing 5,071 relevant articles from CNKI, PubMed, and Wanfang Database published in the past decade. The main models include cigarette smoke exposure, protease-induced, genetically modified, harmful substance exposure, and various combined factor models. A comprehensive review and comparison of their construction principles, procedures, pathological features, advantages, and limitations are provided. This review aims to serve as a valuable reference for COPD researchers and clinicians in the construction of animal models of COPD.

Keywords: chronic obstructive pulmonary disease, animal models, pathological mechanisms, model reference

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a complex condition characterized by persistent, progressively worsening airflow limitation. According to the latest data from The Lancet's 2024 Global Burden of Disease study, although the age-standardized mortality rate from COPD has decreased slightly, it remains a major global public health issue due to its high prevalence and significant disability rate. It is estimated that, by 2060, more than 5.4 million people will die annually from COPD and related diseases. The disease burden of COPD is particularly severe in Asia, accounting for over 56% of global COPD-related deaths.¹ Its pathological features include chronic bronchitis and emphysema, with clinical signs such as cough, sputum production, and increasing dyspnea.²

Air pollution, including fine particulate matter (PM_{2.5}), along with cigarette smoking, may account for 50% of the risk factors for COPD. The pathogenesis of COPD is complex and not yet fully understood. It involves chronic airway inflammation characterized by infiltration of neutrophils, macrophages, and lymphocytes, an imbalance between oxidative stress and antioxidant defenses, dysregulation of the protease-antiprotease system, genetic factors such as α_1 -antitrypsin deficiency, apoptosis, and abnormal repair processes.³ This complexity makes it difficult for animal models to fully recapitulate the entire characteristics of human COPD. Therefore, developing animal models that can accurately reproduce key disease features, align with the pathogenesis, with good reproducibility and clinical relevance has become a core aspect in advancing in-depth research on COPD.⁴ Animal models not only offer a controlled platform for understanding molecular and cellular mechanisms of COPD, but also serve as essential tools for evaluating therapeutic approaches. We have observed that the animal models used in COPD-related research literature include full-disease

models, phenotype-specific models, exacerbation models, and mechanism-focused models. This paper systematically reviews the various animal models currently widely used in COPD research, focusing on their modeling methods, specific operational procedures, and applicability scope, aiming to provide a useful reference for researchers and clinical practitioners working on COPD.

Methods for Establishing Animal Models of Chronic Obstructive Pulmonary Disease

Cigarette Smoke Exposure

Cigarette smoke exposure modeling methods simulate core pathogenesis by repeatedly exposing animals to cigarette smoke over extended periods, triggering a series of pathophysiological changes similar to human COPD. The main mechanism of modeling relies on the combined effects of thousands of chemicals in the smoke—such as reactive oxygen species, aldehydes, nicotine, and tar—which cause oxidative stress damage to airways and alveoli, persistent inflammatory responses, and increased protease activity.⁵ Key variables in modeling operations include:

Animal Selection: Involving Mice,^{6–8} guinea pig,^{9–11} Snow Weasel,^{12,13} dog,^{14,15} fruit flies,¹⁶ etc. The sex was biased toward males, with no justification provided for this choice. It is also noteworthy that in a Chinese database analysis by Li L et al of 176 COPD animal model studies, 79.55% used male animals.¹⁷ Martinez FJ et al also noted that male animals are typically selected for COPD animal models to circumvent the interference of the female estrous cycle.¹⁸

Cigarette type: Commercial cigarettes used in the studies.^{6,7} (such as the Red Flag Canal and Red Tower Hill) or standard research cigarettes.^{9,11} (such as the 3R4F from the University of Kentucky). The 3R4F is preferred in international research because of its standardized composition (about 9.4 mg of tar and 0.73 mg of nicotine per cigarette), which makes it easier to compare results across different laboratories.

Exposure system: Usually uses a full-body exposure chamber or a nasal inhalation system or nasal inhalation system.^{8,12} Exposing the entire body simplifies manipulation but may cause fur to absorb contaminants; nasal inhalation (eg, modeling ferrets) more directly mimics human inhalation patterns.

Exposure parameter: smoke concentration determined by smoking chamber volume and number of cigarettes burned per session⁸ or total particulate matter concentration or CO concentration.¹² Along with daily exposure frequency, weekly exposure days, and total exposure duration, these factors collectively influence the severity and phenotypic traits of the model. For example, the mouse model cycle lasts 56 days, and it can extend up to 420 days.^{14,15} The longer the interval, the more evident the emphysema and decline in lung function typically become.

The choice of model evaluation metrics also varies. Liu et al,⁶ documented observation records of general mouse conditions such as body weight and coat luster. Lung tissue underwent hematoxylin and eosin (H&E) staining to examine pathological changes, and alveolar lavage fluid was analyzed to assess the expression of inflammatory factors. Studies by Jiang Yuhang et al,⁷ and Li et al,⁸ indicate that, although the overall condition of the mice after modeling was not included among the evaluation criteria, “lung function”—the gold standard for diagnosing COPD clinically—was among the assessment metrics. Raju S V and others.¹² In addition to selecting ferrets as experimental animals, expanded the evaluation criteria to include body volume scanning and audio/video synchronized recording for cough monitoring, which better confirmed the presence of symptoms related to chronic bronchitis. Chapman et al,¹⁵ while choosing Beagles as the model animals, also measured the heart weight-to-body weight ratio in the evaluation criteria to further assess the incidence of COPD complications. Due to their small size and other features fruit flies have been used by Prange et al,¹⁶ When employed as a model organism, evaluation metrics such as lifespan and body fat percentage were used to assess the model (Table 1).

Applicability

CS exposure is the primary method for modeling the main causes of human COPD. This model shows the strongest link to causes and can mimic the long-term, progressive nature of COPD. It is useful for studying the development of COPD over time, environmental factors, and testing interventions to slow or stop disease progression.

Table 1 Cigarette Smoke Exposure

Smoke Preparation		Model Animal	Molding Process and Cycle	Evaluation Criteria	Literature
Cigarette Information	Smoke Concentration				
Lanzhou (Gansu Tobacco Industry Co., Ltd.)	Smoking room (50cm×30cm×35cm);4cigarettes Cigarette flow rate:40L/hAir flow rate:5L/min Exhaust flow rate:9L/min 30±5% Total particulate matter concentration:200µg/L;CO concentration:1%-3%	BALB/c mice (Male;6–8weeks old)	45min/session,Rest 1h.4times/ day;90days	Pulmonary Function Assessment;HE-stained lung tissue	[8]
Hongta Mountain (Yunnan, China)		C57BL/6 mice (Male; 8 weeks)	60min/day,6 d/week;120days	General condition;HE-stained lung tissue; Inflammatory cytokine expression;	[6]
Red Flag Canal (Tar content:10mg Smoke nicotine content:0.8mg Smoke carbon monoxide content:12mg)		BALB/c Mice(Male; 6–7weeks old)	40min/day,2times/day;56days.	Pulmonary Function Assessment;HE-stained lung tissue;Inflammatory Cytokine Expression;Airway remodeling status	[7]
3R4F Cigarettes (University of Kentucky;Tar: approximately 9.4 mg per stick Nicotine: approximatel0.73mg per stick Carbon monoxide: approximately11.9mg per stick)		Dunkin-Hartley Guinea pig (Male, 350g-400g)	6cigarettes/d,5d/week;90days	HE-stained lung tissue	[9,11]
Commercial cigarettes		Hartley guinea Guinea pig (Male)	7cigarettes/d,5d/week;90days	Weight;Lung tissue HE and Absolute Position Dyeing	[10]
Commercial cigarettes		Hartley guinea Guinea pig (Female)	5d/week;180days	Pulmonary Function Assessment;Lung Tissue Lavage Fluid Analysis	[19]
3R4F Cigarettes		C57BL/6 Mouse (8–10weeks of age)	12 cigarettes/session,2 times/ day,5d/week;84days	Body weight, lung function, bronchoalveolar lavage fluid, paraffin-embedded lung tissue sections	[20]
Marlboro Cigarettes (1.0 mg nicotine, 11 mg tar)		cGAS–/–Mouse and TLR9–/–Mouse (8 weeks old)	75min/2times/day,30 cigarettes/ day,5d/week;84days	Pulmonary function, NETs infiltration, immunofluorescence co-staining of lung tissue	[21]
3R4F Cigarettes		Wild-type ferret (Female,0.6–0.8kg; Male,1.2–2.0kg)	For nasal inhalation only:60min/ session,2times/day;180days	Full-body volume scanning+synchronized audio/video recording; Pulmonary Function Assessment;Organize PAS and AB-PAS staining;BALF Cell Counting Lung tissue AB-PAS staining and HE staining; µCT Assess airway structure;Airway Mucus Kinetics Testing	[12] [13]
Beginning with one low-tar cigarette per day, gradually increase to12standard cigarettes per day over 227 days.		Dog (purebred Beagle,Female 1; Male 9)	Tracheostomy"voluntarily" inhalng cigarette smoke,2times/ day,7d/wk;420days	General condition (Cough reflex, etc.); Pathological Analysis of Lung Tissue;Heart- to-body weight ratio;Hematological changes; Complication Monitoring	[14]
3R4F Cigarettes		Fruit fly (Larva,2days old;Adult stage:5–7days,predominantly female)	Larva:3times/day,30min/session; Adult stage:1times/day,30min/ session,7d/week. Period:2days,7–14days,Lifelong	Lifetime Curve Analysis;Body Fat Percentage Measurement;Basal Metabolic Rate Measurement;Physical Activity Monitoring; Bronchial tree analysis	[16]

Limitations

The simple cigarette smoke exposure model can simulate chronic disease progression, but it struggles to induce severe, stable inflammation and injury within a short timeframe. Some studies have also pointed out that the simple cigarette smoke model primarily manifests as excessive alveolar dilation, and the degree of inflammatory infiltration may not be as significant as that in the combined model. Additionally, the modeling cycle is lengthy (usually requiring several months), expensive, and individual animals show variable responses to smoke exposure.

Cigarette Smoke Exposure Combined with Lipopolysaccharide Infusion

The combined use of cigarette smoke and bacterial endotoxin lipopolysaccharide (LPS) quickly intensifies the inflammatory response, mimicking an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).²² LPS is a component of the cell wall of Gram-negative bacteria, acting as a pro-inflammatory factor that plays a key role in the development of the airway inflammation. CS-induced epithelial damage and compromised barrier function facilitate access and activation of innate immune cells within the airways and alveoli by subsequent infusion of LPS, producing a “second-hit” effect that rapidly triggers intense neutrophilic inflammation and tissue injury.²³ LPS is typically administered via endotracheal instillation or nasal drops. Single or multiple interventions are performed at specific time points during CS exposure (eg, Day 1 and Day 14),^{24,25} SD or Wistar rats are commonly used animals. Based on the evaluation results, the CS+LPS model shows a more pronounced decline in lung function and denser inflammatory cell infiltration (particularly neutrophils),²⁶ along with a more significant rise in inflammatory mediators in bronchoalveolar lavage fluid (BALF) and earlier signs of airway remodeling within shorter cycles (eg, 28–56 days) (Table 2).

Applicability

This model exhibits more severe inflammation and more pronounced pathological changes. It is suitable for investigating the pathological mechanisms of acute exacerbations in COPD, such as infection-triggered inflammatory cascades and

Table 2 Cigarette Smoke Exposure Along with Lipopolysaccharide Infusion

Smoke Preparation		Model Animal	Molding Process and Cycle	Evaluation Standard	Literature
Cigarette Information	Smoke Concentration				
Front Gate	5%	Wistar rats (Male;270±20g)	Smoke exposure 30min/session, 1time/day;On days 1and 14,LPS was administered via intubation for a total of 2 times.200µg/200µl;28days	Pulmonary function; Pulmonary histological changes;Inflammatory Cytokine Expression;	[25]
Red Flag Canal (Henan Tobacco Industry Co., Ltd.)	(3000±500)×10 ⁻⁶	SD rats (Half male,half female;200±20g)	Smoke exposure2times/day,30min/session; nasal instillation LPS((1mg/kg)),2times/ week;56days	General condition; Pulmonary histological changes;Airway remodeling status	[24]
Hongta Tobacco (Yuxi,China)	Smoking Room (45×30×30cm);6cigarettes	ICR Mouse (male;8weeks old)	Smoke exposure2times/day,30min/session; On 1, 15day,20µL LPS (1µg/µL) nasal instillation,Do not smoke on the day of application;56days	Pulmonary Function Test;Pulmonary histological changes; Inflammatory factors	[26]
Red Flag Canal	Smoking Room	C57BL/6J Mouse (male;20–22 g)	Smoke exposure2times/day (with 6-hour intervals),10 cigarettes/30min/session;On 1, 14day, Instill into the nostrils LPS (7.5 µg/piece, Dissolve in 50 µL of saline solution);112days	Weight;Pulmonary Function Assessment; HE-stained lung tissue;	[27]
Front Gate (Nicotine content: 15mg per cigarette)	Smoking Room (50cm×70cm×70cm,The wall features multiple 1.5cm×1.5cm ventilation holes)	SDrat (270±20g)	Smoke exposure 2times/day,30min/session (with 4-hour intervals),12 cigarettes/day;On the 1, 15th day, tracheal instillation of a 1g/L LPS solution,The dosage is2mg·kg ⁻¹ ; 30days	HE-stained lung tissue	[28]
The source of the smoke has not been clearly identified		C57BL/6Mouse (Male,6–8weeks of age)	Smoke exposure 2times/day,120min/ session,7d/week;On 1, 14daynasal instillation LPS (75 µg per mouse);	Weight;Pulmonary Function Assessment; Pulmonary Function Assessment;HE-stained lung tissue	[29]

hypermucus secretion, as well as for evaluating drugs designed to control acute inflammation, such as novel anti-inflammatory agents and Mucus Modifier.^{28,29}

Limitations

It is challenging to identify the specific contributions of individual factors in disease development. Animals show poor tolerance, with some individuals prone to severe stress or even death under multiple stimuli.

Cigarette Smoke Exposure Combined with Bacterial/Viral Infections

COPD patients show increased airway colonization by bacteria, and bacterial and/or viral infections are the most common triggers for acute exacerbations.³⁰ The CS co-pathogen infection model, which emphasizes infection-induced complexity, more accurately represents the complex interactions between infection and chronic airway disease seen in clinical settings. Common pathogens include *Klebsiella pneumoniae* (Kp)³¹ and influenza viruses (such as H3N2).³² Kp, as a common respiratory pathogen, Liu Shujuan team fields,³¹ Wang Weiyi team fields.³³ Both approaches involve repeated intranasal instillation of Kp bacteria on a CS-pretrauma basis to induce persistent bacterial colonization and chronic infection, leading to more intractable airway inflammation, hypermucus secretion, and airway wall structural changes remodeling; Similarly, Fan Zhengyuan et al,³⁴ selected the CS+Kp method, which only differed in the concentration of the Kp solution compared to the former. Li suyun and others,³⁵ When employing the same modeling method, Wistar rats were selected with progressively increasing smoke exposure frequency. With all other conditions unchanged, the modeling period was 84 days, 28 days longer than in the previous modeling method of the same type. Viral models can show how viral infections worsen COPD by disrupting innate immunity and causing immunopathological effects damage. For example, Jang J H et al,³² Based on CS exposure, a single intranasal instillation of H3N2 influenza virus was used to establish macaque and C57BL/6 mouse models, both with a 42-day cycle. Xie Yuan et al,³⁶ polyinosinic:polycytidylic acid(Poly I:C) was used to simulate viral infection signals.

Repeated intranasal instillations of Poly I:C were given alongside smoke exposure over a 56-day period, successfully establishing a BALB/c mouse model. The cigarette smoke-bacterial/viral co-infection model offers a unique platform for studying the mechanisms behind persistent post-infection chronic inflammation, abnormal lung tissue repair, and increased susceptibility to secondary bacterial infections (Table 3).

Applicability

This model not only captures the features of AECOPD but also accurately reflects the clinical reality where COPD patients frequently experience acute exacerbations caused by infections. It also simulates the clinical progression of incomplete lung function recovery after infection and the “stepwise” decline in disease baseline levels. This makes it a valuable tool for studying the interaction between COPD and infection, as well as for developing combined therapies that target infections or modulate host responses.

Limitations

It needs biosafety facilities for operation and requires strict control over infection dose and timing.

Elastase (ELA) Induction

Proteinase/anti-proteinase imbalance is one of the key theories in the pathogenesis of emphysema.³⁸ Direct instillation of exogenous proteases (such as porcine pancreatic elastase, PPE, or human leukocyte elastase, HLE) into the airways rapidly disrupts the elastic fiber network of the alveolar walls, inducing significant pulmonary emphysema, consistent with the typical clinical manifestations of COPD.³⁹ This model bypasses the chronic inflammatory process and directly targets the pulmonary parenchymal structures. Chan et al,^{40,41} A single intratracheal instillation of HLE induced marked alveolar space enlargement and pulmonary function alterations (such as increased static compliance) in New Zealand white rabbits within 28 days. Tonon J et al.⁴² Then select Syrian golden hamsters for a single intravenous infusion of papain (PAP), with significant alterations in alveolar structure detected as early as 40 days post-infusion. In large animals such as sheep, HNE aerosol inhalation has been used to study physiological changes, including mucociliary clearance function, such as by the teams led by Sabater and Abraham.^{43,44} All chose sheep as their modeling subjects. Typical

Table 3 Cigarette Smoke Exposure Combined with Bacterial/Viral Infections

Smoke Preparation		Bacteria/Viruses	Model Animals	Molding Process and Cycle	Evaluation Criteria	Literature
Cigarette Information	Smoke Concentration					
Red Flag Canal (Henan Tobacco Industry Co. Ltd.)	(1000±10) mg/m ³	<i>Klebsiella pneumoniae</i> (Kp)	SD rat (Half male,half female;200±20g)	Smoke exposure2times/day,30min/ session;1time/5days,Instill drops into both nostrils. Kp solution 0.1mL(6×10 ⁸ CFU/ mL);56days	General condition;Pulmonary function; Pulmonary histological changes; Inflammatory Cytokine Expression; Respiratory mucus secretion;Airway remodeling status	[31]
Red Flag Canal (Henan Tobacco Industry Co., Ltd.)	(30,000±500) mL/m ³	<i>Klebsiella pneumoniae</i> (Kp)	SD rat (male;8 weeks old)		Pulmonary function;Pulmonary histological changes;Inflammatory Cytokine Expression;Respiratory mucus secretion; Airway remodeling status	[33]
Red Flag Canal (Henan China Tobacco Industrial Co., Ltd.)	(3000±500)ppm	<i>Klebsiella pneumoniae</i> (Kp)	SD rat (180±20g)	Smoke exposure2times/day,30min/ session;1time/5days,Instill drops into both nostrils.Kp0.1mL(6×10 ¹¹ CFU/mL);56days	Pulmonary function; Pulmonary histological changes; Inflammatory Cytokine Expression;	[34]
Red Flag Canal (Henan China Tobacco Industrial Co., Ltd.)	(3000±500)×10 ⁻⁶	<i>Klebsiella pneumoniae</i> (Kp)	SD rat (male; 6–8 weeks old)	Smoke exposure2 times/day,30min/session; 1time/5days, Instill drops into both nostrils Kp (6×10 ¹¹ CFU/L, 100 µL/mouse); 56days	Pulmonary function;Pulmonary histological changes;Inflammatory Cytokine Expression;	[37]
	300LSmoke Box; 14 animals per group	<i>Klebsiella pneumoniae</i> (Kp)	Wistar rat, (Half male, half female; 300±50g)	Smoke exposure30min/session (8cigarettes/ session, 2times/day, 1–2wk; 15cigarettes/ session, 3times/day, 3–12wk); 1time/5days, Intranasal injection Kp 6×10 ⁸ CFU/mL0.1mL; 84days	General condition; Pulmonary function assessment; Light Microscopy-Based Pathological Examination of Lung Tissue	[35]
3R4F Cigarettes	Total particulate matter concentration: 100 mg/m ³ (the first week); 200 mg/m ³ (2–4 weeks)	H3N2 Influenza A Virus	Crab-eating macaque (female; 2–5years old; 2.2–3.8 kg) C57BL/6Mouse (8–10weeks old)	Smoke exposure6h/day,5days/week, 28days; Post-28dinstilled10 ⁶ pfu virus into the right lung's diaphragmatic lobe/caudal lobe, with sampling observed at 14days.; 42dsys Smoke exposure6h/day, 5days/week, 28days; Post-28dIntranasal instillation5× 10 ³ pfu, with sampling observed at 14days; 42days	Immunofluorescence staining of lung tissue	[32]
Red Flag Canal (Henan Tobacco Industry Co., Ltd.)	(30±5) %	Poly I:C	BALB/c Mouse (male; 6–7weeks old)	Smoke exposure2times/day, 20min/session; 1time/7days Intranasal instillation Poly I:C 25µg; 56days	Pulmonary Function Test; Pulmonary histological changes; Inflammatory factors; Airway remodeling status	[36]

Table 4 Elastase (ELA) Induction

Protease	Model Animal	Molding Process and Cycle	Evaluation Criteria	Literature
Porcine Pancreatic Elastase (PPE)	C57BL/6 Mouse (female, 6–8 weeks old)	1.2 Unit PPE Nasal Drip; 10 days	HE-stained lung tissue section	[39]
Human Leukocyte Elastase (HLE)	New Zealand White Rabbit (male; 2.5–3.5 kg)	Tracheal instillation of HLE. The dose is 0.3 U/kg dissolved in 2 mL of saline solution; 28 days	Pulmonary Function Assessment; HE-stained lung tissue; Blood Gas Analysis	[40]
Papain (PAP) + Trypsin (TRY)	Miniature pig (male 10, female 5, 25±5 kg)	1 time/week, Bronchial instillation PAP 6U/kg, Reinject after 3 days TRY 300U/kg; 140 days	HE-stained lung tissue; Blood Gas Analysis	[41]
Human Neutrophil Elastase (HNE)	Sheep	Single-dose nebulized inhalation of HNE 2.55 units; 14h	General condition; Pulmonary Function Assessment; Pathological Examination of Lung Tissue	[45]
Papain (PAP)	Syrian Golden Hamster (male, 130–150 g)	Intratracheal instillation of 40 mg/mL PAP solution observation; 40 days	Whole-lung MCC measurement; Tracheal Mucus Velocity Measurement	[43,44]
			Lung tissue HE staining; Number of times crossing the alveolar septa	[42]

airway hyperresponsiveness and marked mucociliary dysfunction were detected 14 hours after a single nebulized HNE inhalation. Yang Zhi et al,⁴⁵ To observe cardiac lesions induced by COPD, miniature pigs were used as experimental subjects. Through alternating multiple instillations of papain (PAP) and trypsin (TRY), typical early COPD symptoms emerged by the fifth week of modeling (Table 4).

Applicability

Featuring a short cycle, simple operation, stable phenotype, and good consistency, this model efficiently generates significant pulmonary emphysema lesions. Consequently, it is suitable for investigating the cellular and molecular mechanisms underlying the onset and progression of pulmonary emphysema, and is particularly useful for studying elastic fiber degradation and repair. Furthermore, the model is effective for screening and evaluating anti-protease therapies or those that promote alveolar regeneration.

Limitations

This model is essentially an “emphysema model” rather than a complete “COPD model”, lacking the chronic inflammatory processes and airway lesions typical of COPD (such as chronic bronchitis and small airway fibrosis). This model often incorporated as part of a composite model (such as the LPS+PPE model discussed later) and combined with other methods to simulate more comprehensive pathologies.

Genetic Knockout and Transgenic Models

Alpha-1 antitrypsin (AAT) deficiency is the most clearly established genetic risk factor for COPD.³⁸ Genetic models generated using gene-editing technology provide a powerful tool for investigating the role of genetic background in COPD. Borel et al,⁴⁶ Using CRISPR/Cas9 technology, all five functional *Serpina1* genes (encoding AAT) in mice were knocked out in a single step, successfully generating homozygous mice with complete absence of AAT in serum. This model spontaneously develops pulmonary emphysema with increasing age even in the absence of exogenous stimuli (such as smoking), perfectly mimicking hereditary alpha-1 antitrypsin deficiency. Another type of model, such as *pIgR*^{−/−} mice, their airways lack secretory IgA (SIgA), resulting in a defective mucosal immune barrier.⁴⁷ These mice do not readily develop disease under conventional conditions, but when exposed to cigarette smoke or specific bacteria, they exhibit exacerbated inflammation and emphysema, revealing the importance of the interaction between genetic susceptibility and environmental exposure (Table 5).

Applicability

Genetic models can elucidate the causal role of specific genes or pathways in disease development and allow for the study of disease natural history without environmental interference. They are crucial for discovering new susceptibility genes, validating drug targets, and developing gene therapies.

Table 5 Knockout and Transgenic Models

Model Animal	Molding Mechanism	Molding Process and Cycle	Evaluation Indicators	Literature
C57BL/6J Mice (male; 10 weeks old)	Using CRISPR/Cas9 gene editing technology, all five functional Serpina1 gene paralogs were knocked out in mice in a single step., Ultimately, offspring lacking AAT protein in serum were bred, resulting in protease/anti-protease imbalance mice.	1 Identify the gene to be knocked out 2 Cas9 mRNA and all four gRNAs were co-injected into fertilized eggs of the C57BL/6J mouse strain. 3 Obtain serum from young mice lacking AAT protein 4 Perform multiple backcrosses between the mice obtained in step 3 and wild-type C57BL/6J mice to eliminate potential CRISPR off-target effects. 5 Establish the final strain;	RNA Sequencing Once the loss of gene function is confirmed; Pathological Phenotype Determination: Pulmonary function measurement Pulmonary tissue morphology measurement; Detection of BALF	[46]
plgR ^{-/-} mice	plgR ^{-/-} mice lack SIgA in their airway surfaces, thereby creating immunodeficient barrier mice.	1 Select lines that have been backcrossed to the C57BL/6 background for at least eight generations plgR ^{-/-} mice. 2 Placed in a sterile environment, completely prevented the COPD phenotype. 3 Anti-inflammatory drugs can partially reverse emphysema. 4 Smoke exposure increases susceptibility to developing emphysema and COPD symptoms.	Perform histometric analysis on tissue sections; BALF Cell Count; Western Blot analysis of protease levels in lung tissue homogenates	[47]

Limitations

The breeding and maintenance of gene-edited animals are costly, and certain gene knockouts may cause developmental abnormalities or other complications, necessitating meticulously designed controls; single-gene knockouts may fail to fully replicate the complexity of human COPD; the process is time-consuming, requiring multiple backcrosses to eliminate genetic background interference.

Sulfur Dioxide (SO₂) Exposure

SO₂ is an irritant gas. High-concentration inhalation can directly damage airway mucosal epithelial cells, triggering acute inflammatory responses, increased mucus secretion, and goblet cell hyperplasia. Long-term exposure may lead to airway wall thickening, fibrosis, and chronic bronchitis-like changes, mimicking the airway pathology characteristics of COPD such as Wagner et al.⁴⁸ Using SD rats exposed to 20 ppm SO₂ throughout the day for 25 days, an early model of COPD was successfully established. In addition to observing pulmonary histopathological changes during evaluation, BrdU assays and AgNOR analysis were employed to assess the proliferative activity and functional status of airway epithelial cells (Table 6).

Applicability

Suitable for studying COPD phenotypes characterized by chronic bronchitis, hypersecretion of mucus, and airway inflammation. The model establishment period is relatively short (eg, 25 days), and the procedure is relatively straightforward.

Limitations

SO₂ exposure primarily simulates pathological changes induced by chemical irritants, exhibiting weak correlation with major human COPD causative factors (eg, smoking); may induce significant acute injury, which does not fully align with the chronic progressive nature of human COPD; model reproducibility is susceptible to variations in SO₂ concentration, exposure duration, and individual animal differences.

Table 6 Sulfur Dioxide (SO₂) Exposure

SO ₂ Concentration	Model Animal	Molding Process and Cycle	Evaluation Indicators	Literature
20ppm	SD rats (male; 350–400 g)	24-hour exposure to SO ₂ air mixture; 25days	HE staining and PAS reaction of lung tissue; Airway Secretion Testing; BrdU Assay and AgNOR Analysis	[49]

Particulate Matter (PM_{2.5}) Induction

Fine particulate matter (PM_{2.5}) can deposit in the alveoli and bronchioles via the respiratory tract, triggering oxidative stress and persistent inflammatory responses. This activates various inflammatory cells and cytokines, leading to lung tissue damage, fibrosis, and airway remodeling.⁵⁰ Exposure to PM_{2.5} from different sources can simulate exposure to environmental pollutants, leading to COPD.⁵¹ As He et al,⁵² Expose SD rats to pollution caused by burning cedar sawdust and motorcycle exhaust emissions, respectively, over a period of 7 months. Assessing abnormal lung function and the occurrence of pulmonary fibrosis, Structural remodeling, and elevated expression of inflammatory mediators indicate successful modeling (Table 7).

Applicability

This is of significant importance for studying COPD unrelated to smoking and for investigating the pathogenesis of COPD associated with environmental air pollution. It is particularly suitable for exploring oxidative stress, immune responses, the inflammatory cascade, and the process of pulmonary fibrosis.

Limitations

The modeling cycle is lengthy, typically requiring several months to establish stable pathology, and is relatively costly. PM_{2.5} exhibits complex composition, with varying toxic effects among particles from different sources, making model standardization challenging.

Lipopolysaccharide (LPS) Infusion

Intratracheal or intranasal instillation of LPS directly induces a robust neutrophilic inflammatory response, leading to airway mucosal injury, goblet cell hyperplasia, increased mucus secretion, and partial emphysematous changes.⁵³ The mechanism lies in simulating and amplifying the acute exacerbation and chronic inflammatory state of COPD.⁵⁴ Wang Shanshan and others⁵⁵ using Wistar rats, a successful model was established by administering two intravascular injections of LPS over a period of 28 days; Liu Junbo and others,⁵⁶ SD rats were selected, and repeatedly administered LPS via tracheal instillation at a frequency of once per week, successfully establishing the model over 56 days; Similarly, Pera T et al,⁵⁷ Guinea pigs were selected as experimental subjects and administered LPS via nasal instillation twice weekly for 84 days. In addition to conventional pulmonary function assessments and histopathological observations of lung tissue, Wang Shanshan et al,⁵⁵ assessed the level of oxidative stress in lung tissue by detecting the function of the MRP1 transporter in pulmonary epithelial cells; Pera T et al,⁵⁷ By measuring mean alveolar spacing to assess the severity of emphysema, and by measuring pulmonary artery/arteriolar wall thickness to assess the severity of COPD-associated pulmonary vascular remodeling and pulmonary hypertension (Table 8).

Table 7 Particulate Matter (PM_{2.5}) Induced

Pollution Source	PM Concentration	Model Animal	Molding Process and Cycle	Evaluation Indicators	Literature
Burning cedar sawdust (40g each time)	20.4 mg/m ³	SD rats (female; 180–200 g)	Smoke Injection: 1h/session, 4times/day, 5days/week; 7 months	Pulmonary Function Assessment; Lung tissue H&E staining, Masson's trichrome staining, α-SMA Immunohistochemistry; Bronchoalveolar Lavage Fluid Analysis	[52]
125cc four-stroke gasoline motorcycle exhaust (using low-sulfur gasoline)	1.46 mg/m ³		2h/session, 2times/day, 5d/week; 7 months		

Table 8 Lipopolysaccharide (LPS) Infusion

Model Animal	Molding Process and Cycle	Evaluation Indicators	Literature
Wistar rats (Male; 200±20g)	On day 1, 14, 200 µg of LPS was administered via tracheal injection.; 28days	Pulmonary Function Assessment; Functional Assessment of the MRPI Transporter in Pulmonary Epithelial Cells; Immunohistochemical Analysis of Lung Tissue	[55]
SD rats (half male, half female); 200±20g)	1time/week, Intratracheal injection of 200 µg LPS; 56days	Measurement of Airway Resistance and Lung Dynamic Compliance; BALF White Blood Cell Count; HE staining and AB-PAS staining of lung tissue	[56]
Dunkin Hartley guinea pig (Male; 350–400g)	2times/week, Intranasal instillation of 200 µL LPS solution (5 mg/mL); 84days	HE-stained lung tissue section, Morphometric Analysis; Neutrophil infiltration; Goblet cell hyperplasia/metaplasia; Mean alveolar space; Pulmonary Artery/Arteriolar Wall Thickness	[57]

Applicability

Suitable for simulating bacterial infections or endotoxin-triggered acute exacerbations of COPD, studying airway inflammatory cell infiltration, excessive mucus secretion, and immune response mechanisms. The procedure is straightforward and highly reproducible.

Limitations

The pathology mainly involves acute inflammation, unlike the chronic persistent nature of COPD. Single or multiple LPS stimulations have difficulty fully reproducing pulmonary emphysema and progressive airflow limitation, so they are usually combined with other methods, such as the CS+LPS model or the LPS+PPE model.

Cigarette Smoke Exposure (CS) Combined with Particulate Matter (PM_{2.5}) Induces

The CS+PM_{2.5} model combines the dual-damage effects of tobacco-related harmful substances and environmental particulate matter, synergistically causing more severe inflammation, oxidative stress, and tissue remodeling. This method more accurately reflects the multifactorial pathogenesis of COPD observed in real-world settings.⁵⁸ Hisata et al,⁵⁹ C57/BL6 mice were exposed to cigarette smoke and particulate matter at a concentration of 150 mg/m³ for 2 hours daily, 5 days a week, and lung function was evaluated at 8 months. Lung tissue sections stained with Giemsa revealed pathological changes consistent with COPD (Table 9).

Applicability

Ideal for studying the role of multifactorial interactions in the onset and progression of COPD, especially for assessing lung function decline and pathological changes under combined exposure.

Limitations

Model development is complex and demands strict control of two exposure conditions; the process is time-consuming and requires significant resources.

Forced Swimming + Cigarette Smoke Exposure (CS) + Hypoxia

Long-term hypoxia can worsen pulmonary vascular remodeling, pulmonary hypertension, and right ventricular hypertrophy.⁶⁰ Combining chronic hypoxia with cigarette smoke exposure effectively mimics the hypoxic conditions commonly seen in COPD patients. Forced swimming triggers a systemic stress response, significantly increasing the

Table 9 Cigarette Smoke Exposure (CS) Combined with Particulate Matter (PM_{2.5}) Induces

Smoke Preparation		Model Animal	Molding Process and Cycle	Evaluation Indicators	Literature
Source of Smoke	PM _{2.5} Concentration				
3R4F Cigarettes	150 mg/m ³	C57/BL6 mouse	CS exposure + PM _{2.5} exposure, 2h/day, 5d/week; 6–8 months	Pulmonary Function Assessment; Lung tissue biopsy; Gimsa Dyeing	[59]

Table 10 Forced Swimming + Cigarette Smoke Exposure (CS) + Hypoxia

Smoke Preparation		Modeling Animals	Molding Process and Cycle	Evaluation Indicators	Literature
Source of Smoke	Oxygen Concentration				
Lion Brand Cigarettes (Tar: 13mg, Nicotine: 0.9mg, Carbon Monoxide: 14mg)	O ₂ :(10 ± 0.5) %; CO ₂ :0.03%	SD rats (200±20 g)	Smoke exposure 20 cigarettes/60min/1 time/day, 6d/week; Hypoxic exposure 7h/day, 6d/week; 28days	Pulmonary Function Assessment; HE-stained lung tissue;	[61,62]

body's oxygen consumption, which closely aligns with the "hypoxia-inflammation" vicious cycle observed in COPD. This makes it suitable for studying COPD complicated by pulmonary heart disease or hypoxemia-related complications. Luan X and others,⁶¹ rats were subjected daily to forced swimming (30 minutes), exposure to Lion brand cigarette smoke (20 cigarettes/hour), and hypoxia exposure (10% O₂, 7 hours). These procedures were performed six days per week for four weeks. Results showed that model rats experienced a significant decline in lung function and chronic airway inflammation, among other characteristic indicators, indicating that this model can systematically simulate the pathophysiology and molecular features of COPD (Table 10).

Applicability

Suitable for studying the systemic effects of COPD, especially cardiovascular complications and hypoxia-induced inflammatory and remodeling processes.

Limitations

The model is difficult to operate and requires specialized equipment to sustain a stable hypoxic environment; it may indicate late-stage COPD complications rather than early-stage pathology.

Lipopolysaccharide (LPS) Combined with Porcine Pancreatic Elastase (PPE) Infusion

The combined infusion of lipopolysaccharide (LPS) and porcine pancreatic elastase (PPE) induces LPS-mediated airway inflammation, while PPE directly degrades pulmonary elastic fibers, collectively causing significant emphysematous changes, inflammatory cell infiltration, and fibrosis,⁶³ which can mimic the core mechanism of the protease-antiprotease imbalance in COPD. Collie DDS and others field,⁶⁴ using sheep as experimental animals, sequentially administered PPE and LPS via combined instillation into the same target lung lobe over 70 days to simulate the complex pathology of COPD. The results showed destruction of the alveolar structure, with the emergence of typical COPD emphysema features, whereas chronic LPS stimulation replicated persistent airway inflammation, hypermucous secretion, and fibrotic remodeling (Table 11).

Applicability

Especially suitable for simulating COPD phenotypes characterized by pulmonary emphysema, examining elastin breakdown, alveolar damage, and the interaction between inflammation and proteases. Sheep models, for example, better mimic human lung anatomy and physiology, making them ideal for testing intervention devices or surgical techniques.

Limitations

Demands high technical skill; PPE-related injuries may be too severe to match the slow progression typical of human COPD.

Table 11 Lipopolysaccharide (LPS) Combined with Porcine Pancreatic Elastase (PPE) Infusion

Model Animal	Molding Process and Cycle	Evaluation Indicators	Literature
Sheep	PPE (single dose of 50 mg) + chronic LPS (500 mg weekly for 8 weeks) combined with infusion into the target lung lobe.;70days	Pulmonary Function Assessment; Lung tissue HE and Masson trichrome staining; Alveolar Lavage Fluid Cell Count	[64]

Summary and Discussion

Currently, the establishment of animal models of COPD has formed a technical system primarily based on single-factor induction and multi-factor combined stimulation. The main methods for constructing full-disease models include cigarette smoke (CS) exposure, CS + PM_{2.5} exposure, CS + lipopolysaccharide (LPS), and CS + bacterial/viral infection. These full-disease models aim to simulate the core manifestations of human COPD as closely as possible, including emphysema, chronic airway inflammation/mucus hypersecretion, accompanied by progressive airflow limitation. Phenotype-specific COPD models are established using various approaches: elastase induction for a dominant emphysema phenotype, SO₂ exposure or LPS instillation for notable airway injury, and PM_{2.5} induction for extensive respiratory system damage. These models aim to recapitulate either a distinct clinical phenotype or the pathological alterations driven by particular etiological triggers. Exacerbation models of COPD are primarily established using CS + LPS, CS + bacterial/viral infection, or LPS instillation. The routine operation of this model is to first establish a chronic disease background and then superimpose stimuli to induce an acute inflammatory response. LPS instillation alone, lacking a chronic background, represents only acute lung injury. The acute exacerbation model superimposes an acute severe inflammatory response on chronic underlying lesions. In addition, there are mechanism-focused models. The main methods for establishing these include gene knockout/transgenic approaches to investigate the genetic pathogenesis of COPD, single LPS instillation to explore the mechanism of acute inflammation, PM_{2.5} exposure alone to study the toxicological mechanism of particulate matter, and a more specialized combined method involving forced swimming, CS exposure, and hypoxia to simulate the neuro-immune-metabolic crosstalk mechanism. Furthermore, the construction parameters of animal models, such as animal strain selection, gender, cigarette type, exposure system, modeling cycle setting and intervention routes, have not yet formed unified standards, which also affects the comparability of research results and clinical translation potential to a certain extent. At the same time, there is still diversity in the model evaluation criteria. Research purposes are usually used as detection indicators to determine the success of the model, which does not fully comply with the diagnostic criteria for human COPD.

Different modeling methods are selected according to the specific aims of the study. To simulate the natural course of COPD, long-term interventions, or the reversal of emphysematous remodeling, CS exposure is the first choice and is currently regarded as the gold standard for animal models of COPD. On this basis, if a shorter modeling period is desired, alternative methods such as CS + LPS or CS + PM_{2.5} exposure can also be selected. To model acute exacerbation of COPD or to study anti-inflammatory drug mechanisms, CS + LPS or CS + bacterial/viral infection are appropriate methods. The underlying principle of which is to first establish a background of chronic disease, followed by the superimposition of additional stimuli to trigger an acute inflammatory response. To study a pure emphysema phenotype, the elastase-induced method is an appropriate choice. To study mucus hypersecretion or chronic bronchitis, SO₂ exposure or repeated LPS instillation are recommended. To study the pathogenic mechanisms underlying exposure to airborne particulate matter, PM_{2.5} exposure alone is an appropriate method. To investigate the impact of specific genes on this disease from a genetic perspective, gene knockout or transgenic models can be selected. To study COPD with comorbidities, special models are required. For instance, to study the mechanisms of comorbid conditions such as depression, anxiety, or sleep apnea in COPD, the combined method of forced swimming, CS exposure, and hypoxia can be selected. (Table 12).

Even when the same modeling method is selected (eg, the classic single cigarette smoke exposure protocol), differences still exist across studies in core parameters such as species, sex, cigarette type, exposure system, and modeling duration, with no further explanation provided. Currently, the sex of animals used for modeling is predominantly male. However, epidemiological studies on COPD have shown that the risk of developing the disease is significantly higher in women than in men. Should this finding be taken into consideration in future animal model preparation, using female animals as the primary choice? As a primary justification for selecting male animals, is the cyclic variation of female hormones precisely the factor that influences the pathogenesis of COPD? In the model evaluation system, it is also necessary to integrate multidimensional assessment methods, including pulmonary function testing, histomorphological analysis, imaging evaluation, and quantitative detection of inflammatory cells and related mediators, in order to systematically validate the reliability and reproducibility of the model at the functional, structural,

Table 12 Recommendations for Modeling Method Selection

Research Objective	Modeling Method	Supplemental Explanation
Natural History, Long-term Intervention, Reversal of Emphysema Remodeling	CS exposure	The gold standard animal model of COPD
Shorten the modeling period	CS+LPS; CS+PM _{2.5}	Combined stimulation accelerates the formation of pathological damage
Acute exacerbation phase of COPD, Anti-inflammatory drug efficacy	CS+LPS; CS combined with bacteria/viruses	First simulate the chronic course of CS exposure, then induce acute symptoms
Significant emphysema phenotype	Elastase-induced (eg, PPE)	PPE directly degrades pulmonary elastic fibers; Without significant airway mucus hyperplasia
Significant chronic bronchitis phenotype; Mucus hypersecretion	SO ₂ exposure; Repeated intratracheal instillation of LPS	Focusing on airway goblet cell hyperplasia and mucus hypersecretion
Pathogenic mechanism of PM _{2.5}	PM _{2.5} exposure	To exclude confounding factors of cigarette smoke
Gene-targeting study	Gene knockout/transgenic animals	Genetics; Validation of specific gene function
Mechanistic study of comorbidities in COPD	eg, Forced Swimming+CS Exposure + Hypoxia	This model is applicable to the study of COPD complicated with depression, anxiety, and sleep-disordered breathing.

and molecular levels. These issues will become the key directions for further in-depth research on animal models of COPD, aiming to promote the establishment of animal models that more closely reflect the natural history of the disease and integrate multisystem pathological features.

Although this article provides some reference for COPD researchers in selecting animal modeling methods, due to inherent differences among species in physiological structure, immune response, and repair mechanisms, constructing an animal model that highly simulates the entire pathological progression of human COPD remains a significant challenge.

Abbreviations

COPD, Chronic obstructive pulmonary disease; CS, Cigarette Smoke; LPS, Lipopolysaccharide; AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; BALF, Bronchoalveolar Lavage Fluid; Kp, *Klebsiella pneumoniae*; Poly I:C, Polyinosinic:polycytidylic acid; ELA, Elastase; HLE, Human Leukocyte Elastase; HNE, Human Neutrophil Elastase; PPE, Porcine Pancreatic Elastase; PAP, Papain; TRY, Trypsin; AAT, Alpha-1 Protease Inhibitor; PM_{2.5}, Particulate Matter 2.5.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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