Advances in drug prevention and treatment of radiation-induced lung injury (Review)

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Abstract. Radiation-induced lung injury (RILI), including radiation pneumonitis and radiation-induced pulmonary fibrosis, is a common complication during or after radiotherapy for thoracic tumors. This complication severely restricts dose escalation in radiotherapy and delays subsequent antitumor treatment, thereby compromising patient prognosis. Therefore, it is crucial to develop safe and effective drug prevention and treatment strategies to ensure successful implementation of radiotherapy and improve patient prognosis. The present review systematically assesses recent advances in drug prevention and treatment-based approaches for RILI, focusing on the underlying molecular mechanisms and key therapeutic targets at different developmental phases of RILI (oxidative stress, inflammatory response and fibrosis formation). Progress from classical radioprotective agents and anti-inflammatory drugs to novel antifibrotic drugs and cutting-edge exploratory therapies are also comprehensively summarized, with an aim to inform clinical practice and guide future research directions.

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1. Introduction

Radiation-induced lung injury (RILI) is a general term for any pulmonary toxicity caused by radiotherapy and represents a continuous pathophysiological process. The acute phase manifests as radiation pneumonitis (RP), whereas the chronic phase manifests as radiation-induced pulmonary fibrosis (RIPF). RP typically develops within several weeks to several months after radiotherapy, whereas RIPF typically occurs several months to several years later (1). RILI causes symptoms such as fever, cough and dyspnea; moreover, in severe cases, it can lead to respiratory failure, substantially affecting the quality of life and prognosis of patients (2). Despite continuous advances in radiotherapy techniques, RILI remains an important clinical concern in patients receiving thoracic radiotherapy. Currently, glucocorticoids remain the first-line drugs for treating acute RP. However, their efficacy is limited due to the lack of specificity and minimal effects on the chronic fibrotic stage. Furthermore, long-term use of glucocorticoids may also be associated with adverse effects such as infections, osteoporosis and elevated blood sugar levels (3). As RILI is not a single pathological process and involves dynamic pathological changes over time, the development of effective pharmacological interventions remains challenging. The major research gaps in pharmacological treatment of RILI are the lack of effective stage-specific treatment strategies and drugs supported by sufficient clinical evidence. Advances in understanding the molecular mechanisms of RILI have revealed that the injury process progresses through three sequential phases: i) Immediate/early oxidative stress injury; ii) intermediate acute inflammatory response; and iii) late pro-fibrotic remodeling (4,5). The present review primarily follows this temporal pattern of RILI, systematically outlining the core mechanisms of each phase and the corresponding drugs (including those already available in the market, those currently in clinical trials and those undergoing preclinical research), with an aim to provide guidance for clinical practice and future research directions.

2. Review methodology

Literature searches were conducted for different topics covered in the present review, including drug prevention of RILI, corticosteroid therapy, antifibrotic drug therapy, targeted and immune-related therapy, and novel drug delivery systems. PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and Web of Science (https://www.webofscience.com/) databases were searched from inception to May 2026. The search terms included 'radiation-induced lung injury', 'radiation pneumonitis', 'radiation-induced pulmonary fibrosis', 'drug prevention', 'treatment' and their synonyms, supplemented with representative drug names [such as amifostine, N-acetylcysteine, pirfenidone (PFD) and nintedanib].

The inclusion criteria were as follows: i) Studies investigating pharmacological prevention or treatment of RP and pulmonary fibrosis; ii) full-text availability; and iii) publication in English. The exclusion criteria were as follows: i) Duplicate publications; ii) conference abstracts, comments, letters, news, editorials and case reports; iii) studies not relevant to the topic or with incomplete data; and iv) studies with substantial methodological limitations or insufficient reporting of relevant data. Although no temporal restriction was applied, recent literature (published within the last 3 years) was prioritized to ensure currency and clinical relevance. Following systematic deduplication, title/abstract screening and full-text assessment, a total of 68 eligible articles were included.

3. Phase of oxidative stress

Core mechanism of oxidative stress induced by ionizing radiation. When ionizing radiation acts on lung tissues, it directly excites and ionizes water molecules, leading to their decomposition and the generation of abundant reactive oxygen species (ROS)/nitrogen species. This early burst of oxidative stress represents the initiating step of RILI, which directly causes DNA double-strand breaks, lipid peroxidation and cell membrane damage in alveolar epithelial cells and vascular endothelial cells (6). Persistent oxidative stress further aggravates DNA damage and activates inflammatory signaling pathways, particularly NF-κB, while the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is activated as an endogenous antioxidant response to counteract excessive ROS accumulation. When oxidative stress persists, insufficient Nrf2-mediated antioxidant protection may allow NF-κB-dependent inflammatory signaling to become sustained. The resulting inflammatory mediators, including IL-6 and other cytokines, can further activate JAK/STAT signaling and amplify the inflammatory response. Persistent inflammation subsequently promotes TGF-β production and activation of the TGF-β/Smad pathway, thereby linking the early oxidative stress phase to the later fibrotic phase (7). Consequently, this early phase constitutes a critical window for therapeutic intervention. The core mechanism of this phase is shown in Fig. 1.

Amifostine: A classical radioprotective agent. Given that ROS-mediated oxidative stress is the primary trigger of RILI, strategically enhancing the antioxidant capacity of normal tissues immediately before and after irradiation is a reasonable therapeutic approach. Among the numerous agents studied, amifostine is currently the only broad-spectrum cytoprotective agent approved by the U.S. Food and Drug Administration. Its mechanism of action involves hydrolysis by alkaline phosphatase to the active metabolite WR-1065, which directly scavenges radiation-induced ROS through its free thiol group and acts as a hydrogen donor to repair DNA damage, thereby providing radioprotection at the cellular level (8). A phase III randomized controlled trial by Antonadou *et al* (9) (146 patients with advanced lung cancer receiving thoracic radiotherapy) demonstrated that the amifostine group (340 mg/m^2, intravenous injection 15 min before radiotherapy) exhibited a significantly lower incidence of grade ≥2 RP than the control group (16 vs. 49%; $P<0.001$) and a lower incidence of RIPF at 6 months (28 vs. 53%; $P<0.05$), with comparable antitumor efficacy between the two groups. A further study explored the possibility of individualized protection; the results showed that patients with high mutagenic sensitivity were more susceptible to developing grade ≥3 RIPF, and amifostine markedly reduced its incidence (10). However, the clinical application of amifostine is limited by adverse effects such as hypotension, nausea and vomiting. Consequently, alternative administration routes have been investigated. A previous study indicated that subcutaneous injection shows improved toleration compared with intravenous administration during concurrent chemoradiotherapy, with comparable efficacy (11). Additionally, rat experiments have demonstrated that inhalation administration provides superior protection against RILI compared with intraperitoneal administration (12). With further advances in research, the clinical application of amifostine is expected to reach a broader platform.

Other antioxidants. Apart from amifostine, various other antioxidants have also demonstrated the potential to prevent and treat RILI. Among these, N-acetylcysteine, a precursor of glutathione, enhances intracellular antioxidant defense capacity and effectively alleviates endothelial dysfunction, inflammation and fibrosis (13). A further study showed that it mitigates radiation-induced oxidative stress and preserves lung function (14). Unlike conventional antioxidants, omeprazole alleviates RILI through a dual mechanism, whereby it reduces protein carbonylation to counteract oxidative stress and downregulates caspase-3 to inhibit apoptosis. Notably, short-term administration of a low dose (10 mg/kg) of omeprazole markedly improves pathological damage and shows a favorable safety profile (15). More promisingly, pretreatment with thrombopoietin mimetics 24 h before irradiation provides long-term protection against RILI, whereby it reduces tissue pathological damage and inflammation in the short term (2 weeks), while long-term follow-up (7 months) shows that it can reduce collagen deposition, improve lung function and increase survival rates (16).

Natural antioxidants have also received considerable attention due to their safety advantages. Among dietary polyphenols, curcumin and resveratrol effectively mitigate RILI through the Nrf2/GSH pathway (17,18), whereas dihydroartemisinin regulates the Nrf2/HO-1 pathway to prevent ferroptosis and thereby reduce the incidence of RILI (19). Regarding the complexity of the mechanism of action, PM014 is a notable

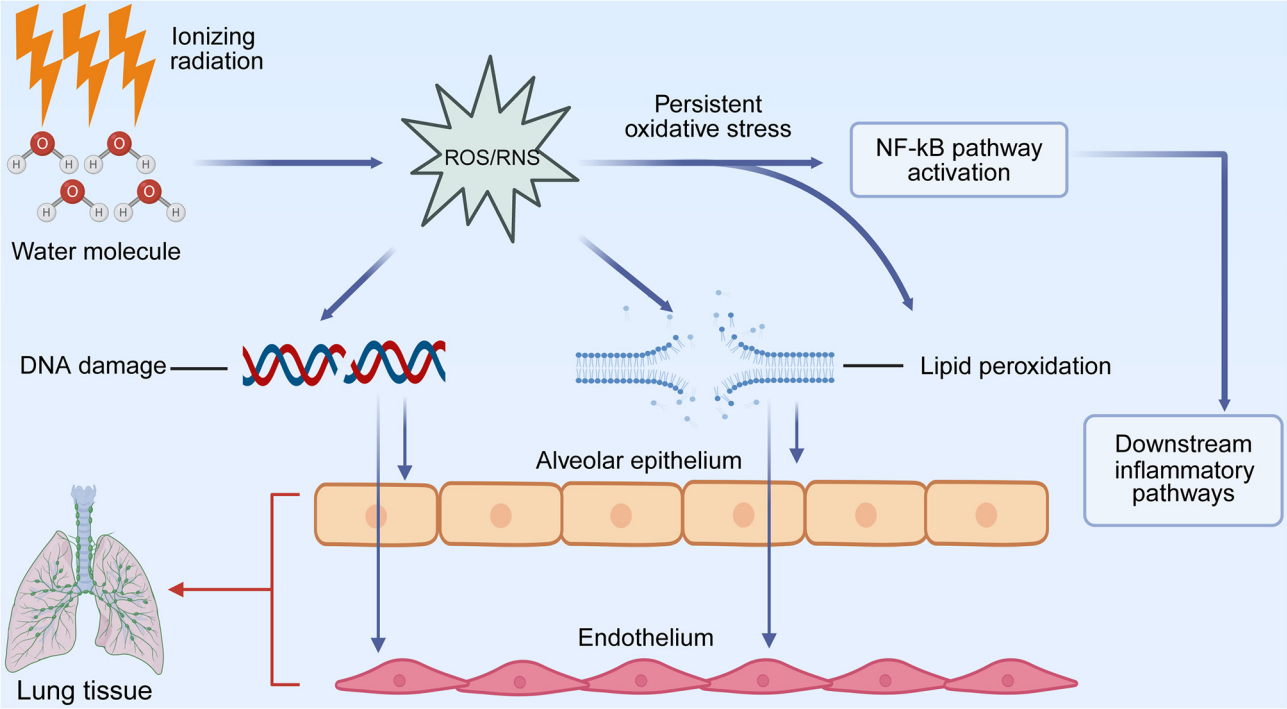

Figure 1. Core mechanism of oxidative stress induced by ionizing radiation. Ionizing radiation triggers water radiolysis, generating ROS/RNS that damage DNA, lipids and membranes in alveolar epithelial and vascular endothelial cells. Persisting oxidative stress overwhelms the Nrf2 antioxidant response, activating NF-κB and downstream cytokines, which stimulate JAK/STAT signaling and amplify inflammation. ROS, reactive oxygen species; RNS, reactive nitrogen species; Nrf2, nuclear factor erythroid 2-related factor 2.

molecule as it inhibits inflammation by blocking NF-κB nuclear translocation and downregulates the TGF-β1/NADPH oxidase 4 pathway to prevent epithelial-mesenchymal transition (EMT) and collagen deposition, with therapeutic effects exceeding those of amifostine (20). Tanshinone IIA also maintains mitochondrial function and inhibits M1 polarization of alveolar macrophages through the PARP-1/NF-κB pathway, thereby reducing the release of pro-inflammatory mediators (21). However, the widespread application of natural products is limited by their low bioavailability and challenges associated with their clinical translation. In this context, nanomaterials, possessing lung-targeting accumulation properties, offer a promising solution. For instance, inhalable chitosan-modified poly(lactic-co-glycolic acid) nanoparticles (ASX@P@CS) effectively overcome the poor water solubility issue of astaxanthin and significantly inhibit the progression of RILI in mice (22). Selenium nanoparticles also exert substantial protective effects during the early and intermediate post-irradiation phases by scavenging ROS (23). Therefore, the development of intelligent nanotargeted drug delivery systems currently represents a key strategy to achieve efficient, low-toxicity and early intervention of RILI.

4. Phase of inflammation response and immune regulation

Core mechanisms of the inflammatory cascade reaction. Although antioxidant therapy can alleviate the initial damage, it cannot completely halt disease progression. This limitation is partly attributable to the release of damage-associated molecular patterns (DAMPs), which activate innate immune responses following radiation-induced tissue injury. DAMPs activate macrophages and inflammatory pathways, including NF-κB and JAK/STAT, promoting the release of TNF-α, IL-1β and IL-6 (24). These mediators further recruit neutrophils, disrupt the alveolar-capillary barrier, and increase vascular permeability, leading to pulmonary edema and inflammatory exudation (24). Persistent inflammation and oxidative stress may promote fibrotic remodeling (25). The core mechanisms of this inflammatory and immune-regulatory phase are illustrated in Fig. 2. Therefore, suppressing this excessive inflammatory cascade constitutes a core strategy to prevent the transformation to fibrosis.

Cornerstone drugs: Glucocorticoids. Glucocorticoids are an important treatment option for acute RILI (26,27). A retrospective study of 385 patients with lung cancer demonstrated that initiating treatment with prednisone at 30-40 mg/day stabilized the condition of most patients; those exhibiting fever, dyspnea or rapid radiological progression after radiotherapy required more aggressive hormonal therapy and had a poor prognosis (26). Another study revealed that the median overall survival period was notably longer in patients who successfully tapered off glucocorticoids compared with those who failed to taper (43.4 vs. 22.2 months), suggesting that the tapering regimen influences survival outcomes (27).

Although glucocorticoids are the first choice for treating moderate-to-severe RP, the dosing and treatment duration remain empirical, with no standardized guidelines (28). The 2025 French Association for Supportive Care in Oncology-French Society of Radiation Oncology guidelines recommend the following symptom severity-based management approach: i) Grade 1 (asymptomatic), whereby

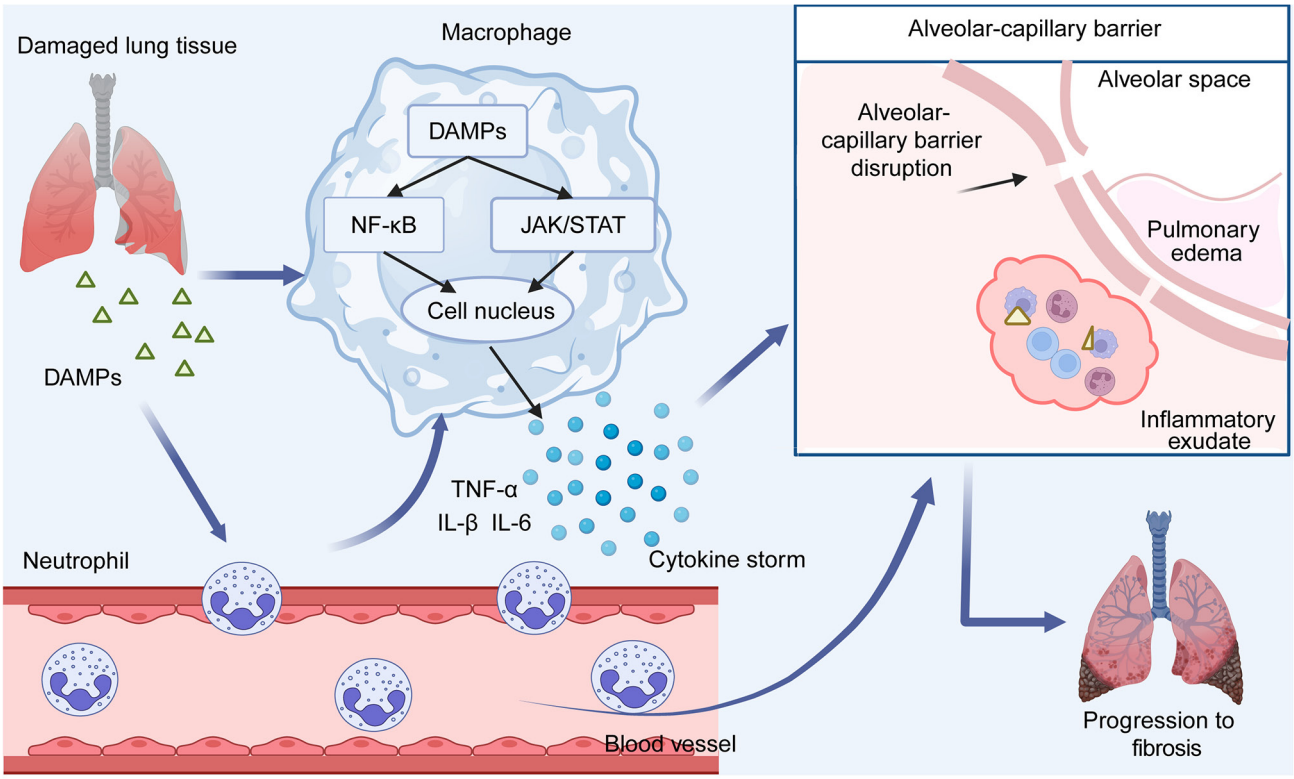

Figure 2. Core mechanisms of the inflammatory cascade reaction. DAMPs activate the innate immune system and macrophages, triggering inflammatory signaling through NF-κB and JAK/STAT pathways. These signals promote pro-inflammatory cytokine release, recruit neutrophils and disrupt the alveolar-capillary barrier, leading to pulmonary edema and inflammatory exudation and ultimately contributing to progression toward pulmonary fibrosis. DAMP, damage-associated molecular pattern.

only follow-up is required; ii) grade 2 (cough, dyspnea and chest pain), whereby treatment with oral prednisone at 0.5-1 mg/kg/day for 2 weeks, followed by a stepwise taper over 4 weeks (immunotherapy can be continued) is recommended; and iii) grade ≥3 (hypoxia, acute respiratory distress syndrome and other life-threatening manifestations), whereby initial treatment with intravenous methylprednisolone at 2-4 mg/kg/day for 1 week and subsequent transition to oral administration based on the condition of the patient is recommended (29). However, glucocorticoid treatment is associated with a high recurrence rate after discontinuation, and long-term use of glucocorticoids may increase the risk of infection, hyperglycemia, osteoporosis and muscle atrophy, with limited efficacy against RIPF (30). These limitations have prompted the development of more targeted and safer alternative or combination strategies.

Other anti-inflammatory and immunomodulatory strategies. With progression of the understanding of the immune microenvironment in RILI, novel regulatory strategies continue to emerge. Basic research has confirmed that dihydroartemisinin, in addition to its antioxidant effects, can also alleviate lung inflammation by downregulating TNF-α and TGF-β expression (19). Further exploration of the underlying mechanism revealed that two TNF-related apoptosis-inducing ligand pathway agonists not only ameliorate acute RP by inhibiting macrophage-derived C-C motif chemokine ligand 22, but also significantly suppress fibrotic progression within 22 weeks (31). At the clinical translation level, a prospective randomized study demonstrated that combining glucocorticoids with recombinant human endostatin can reduce the recurrence rate of RP from 45 to 15%, with median overall survival of 16.0 months compared with 7.7 months in the control group, and show a favorable safety profile (32). At the cellular level, regulatory dendritic cells, by interacting with regulatory B and T cells, and inducing the production of immunosuppressive molecules, constitute a key hub for controlling inflammation (33). These advancements signify a paradigm shift in RILI treatment from empirical anti-inflammatory approaches to precise immune mechanism-based interventions.

5. Phase of fibrogenesis

Core mechanism: TGF-β/Smad signaling axis and myofibroblast activation. RIPF represents the chronic and irreversible stage of RILI, in which activation of the TGF-β/Smad2/3 pathway plays a central role. TGF-β signaling promotes fibroblast-to-myofibroblast transformation, excessive extracellular matrix (ECM) production and impaired matrix degradation, thereby driving progressive fibrotic remodeling (34). Persistent activation of NF-κB and JAK/STAT during the preceding inflammatory phase may promote TGF-β activity, thereby facilitating the transition from inflammation to fibrosis. Thus, the progression from inflammation to fibrosis reflects the interaction between persistent profibrotic signaling and endogenous protective mechanisms. The core mechanism of this fibrotic phase is shown in Fig. 3. Consequently, targeting this axis to delay, block or potentially

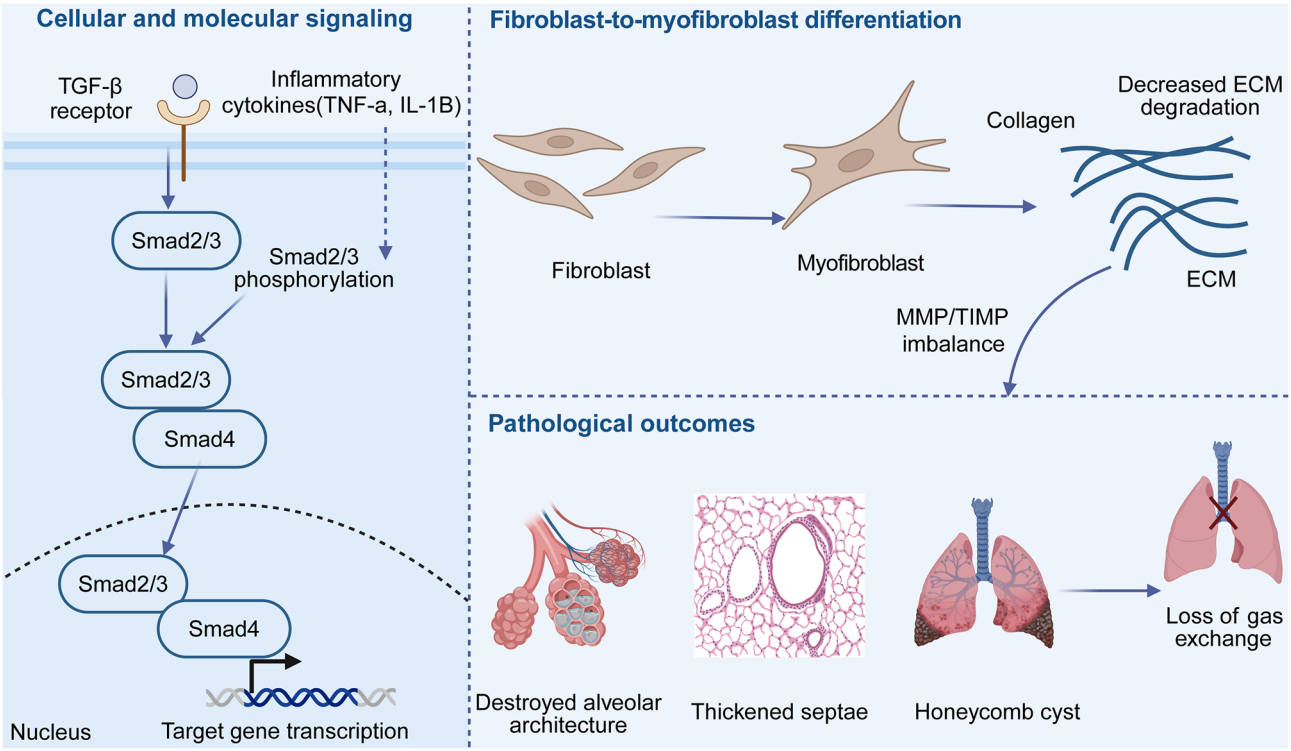

Figure 3. TGF-β/Smad signaling axis and myofibroblast activation. Radiation-induced pulmonary fibrosis is the chronic irreversible stage of radiation-induced lung injury, driven by TGF-β-mediated Smad2/3 activation, which induces fibroblast-to-myofibroblast transition and excessive ECM deposition, leading to loss of lung architecture and gas exchange. ECM, extracellular matrix; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

reverse fibrosis has become a pivotal strategy in drug development. Notably, these fibrotic mechanisms are not unique to RIPF, but overlap with those observed in other progressive fibrotic lung diseases, particularly idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated interstitial lung disease. As summarized in Table I, TGF-β signaling, inflammatory and immune dysregulation and ECM remodeling represent shared pathological mechanisms across these diseases (24,34,35-37). These common pathways provide a mechanistic rationale for exploring whether established antifibrotic therapies used in other fibrotic lung diseases may also be applicable to RIPF.

Application of anti-pulmonary fibrosis drugs in RILI. Nintedanib is a multitarget tyrosine kinase inhibitor that suppresses pathways regulating fibroblast proliferation, migration and activation, for example, platelet-derived growth factor receptor, fibroblast growth factor receptor and vascular endothelial growth factor receptor. A preclinical study has shown that nintedanib can regulate the TGF-β/Smad and PI3K/AKT/mTOR pathways in a mouse model of RIPF, thereby suppressing epithelial inflammation and preventing fibroblast-to-myofibroblast transformation (34). A phase II clinical trial (trial no. NCT02517861) confirmed that combining nintedanib with a reduced dose of prednisone markedly lowers the risk of acute pulmonary exacerbation in patients with grade ≥2 RP (38). This dual action (simultaneously suppressing acute inflammation and blocking the progression of fibrosis) renders nintedanib a highly promising therapeutic agent for treating RILI. However, it delays rather than reverses the established fibrosis. As it targets the downstream fibroblast pathways, the optimal intervention window may be restricted to the fibrosis progression phase rather than the acute inflammation phase. Therefore, further studies are urgently required to define the optimal treatment timing.

PFD is an oral drug approved for treating IPF; this drug reduces M2 macrophage infiltration and inhibits TGF-β1/Smad3 pathway activation (39). Given the shared core mechanism of aberrant TGF-β signaling pathway activation between RIPF and IPF, PFD has been repurposed for treating RILI (40). A prospective phase II clinical trial by Hou *et al* (40) demonstrated that PFD combined with corticosteroid therapy improved the carbon monoxide diffusion capacity and forced vital capacity percentages. This study addressed the gap in antifibrotic treatment during the 'post-hormone era' of RILI. Another study also confirmed that patients with non-small cell lung cancer (NSCLC) complicated with RILI derived clinical benefits and exhibited good tolerance when treated with PFD combined with standard therapy (41). Based on the positive results of the aforementioned phase II trials, larger phase III clinical trials are anticipated to further validate its therapeutic value. A summary of relevant research on the treatment of RIPF with antifibrotic agents is presented in Table II (34,38-44).

Drugs targeting other targets or mechanisms. Regarding the TGF-β pathway, anlotinib showed marked improvement in lung fibrosis in mice, representing a novel promising therapeutic strategy for clinical application (45). Beyond the TGF-β pathway, cellular senescence and the senescence-associated secretory phenotype are key mechanisms in RIPF (46,47). Senolytic drugs, such as dasatinib +

Table I. Overlapping mechanisms between RIPF and other fibrotic lung diseases.

Shared mechanism	Mechanism of RIPF	Mechanism of IPF	Mechanism of CTD-ILD
TGF-β signaling and fibroblast activation	TGF-β activation promotes fibroblast activation and ECM deposition (34).	TGF-β signaling promotes fibroblast activation and myofibroblast differentiation (35).	TGF-β-related signaling contributes to fibroblast activation and fibrotic remodeling (36).
Inflammation and immune dysregulation	Persistent inflammation and immune-cell activation promote fibrotic progression (24).	Abnormal epithelial injury and inflammatory responses contribute to fibrosis (37).	Autoimmune abnormalities and chronic inflammation contribute to pulmonary fibrosis (37).
ECM remodeling	Increased ECM production and impaired degradation lead to collagen accumulation (34).	Abnormal ECM production and degradation promote progressive fibrosis (37).	Inflammatory responses and fibroblast activation promote ECM deposition (37).

RIPF, radiation-induced pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis; CTD-ILD, connective tissue disease-associated interstitial lung disease; ECM, extracellular matrix.

quercetin, can selectively eliminate senescent cells and have shown potential to reverse fibrosis in various fibrosis models, including RILI, thereby emerging as a novel therapeutic direction (48). Opaganib reduces radiation-induced lung inflammation and fibrosis by regulating sphingolipid metabolism. As shown previously, opaganib notably increased the long-term (180-day) survival rate of irradiated mice from 10 to 60% (49). A 2024 study identified spleen tyrosine kinase as a key driver target of RILI. Its inhibitor, fostamatinib, attenuates RP and RIPF in mice by downregulating fibrotic factors, providing preclinical evidence for spleen tyrosine kinase-targeted therapies (50).

In recent years, bifunctional immune fusion proteins targeting both PD-L1 and TGF-β have emerged as a potential strategy for simultaneously modulating immune suppression and fibrotic signaling. M7824 (bintrafusp alfa) combines programmed death-ligand 1 (PD-L1) blockade with a TGF-β trap, thereby targeting two pathways that contribute to immune evasion and tissue fibrosis. One preclinical study suggested that this dual blockade may enhance the antitumor effects of radiotherapy while reducing radiation-induced tissue injury (51). Although its development for tumor therapy was discontinued, this approach validated the feasibility of co-blocking PD-L1 and TGF-β for the management of RILI (52). SHR-1701 is another bifunctional fusion protein targeting PD-L1 and TGF-β signaling. An early study evaluated the efficacy and safety of SHR-1701 combined with XELOX + bevacizumab as a first-line regimen for the treatment of unresectable metastatic colorectal cancer. The results showed that the objective response rate was 59.7%, the disease control rate was 83.9%, the median progression-free survival was 10.3 months and the safety was controllable (53). However, this study focused on cancer treatment rather than RILI-specific outcomes. Nevertheless, these agents provide a rationale for simultaneously targeting inflammatory/immune and pro-fibrotic pathways, suggesting that multi-target strategies may represent a promising direction for future RILI treatment.

6. Exploration of frontier and innovative therapeutic strategies

Targeted drug delivery systems based on nanotechnology. Owing to the complex pathology of RILI, nanomedicine-based delivery systems have become a research hotspot due to their advantages in targeted delivery and controlled release (5). Specifically, by engineering modification of carriers, these systems have successfully overcome the instability of conventional anti-inflammatory and antifibrotic drugs in circulation, enabling effective drug accumulation in the injured lung tissue (54). At the application level, inhalable nano-curcumin formulations have markedly enhanced the pharmaceutical properties of the drug (55), while the novel X-ray-responsive nanocomposite $Au@mSiO_2@Mn(CO)_5$5Br, consisting of gold nanorods coated with mesoporous silica and functionalized with $Mn(CO)_5Br$, enables X-ray-triggered local release of carbon monoxide and manganese ions, thereby modulating the ROS microenvironment and alleviating RILI (56). Therefore, the development of intelligent nanoplatforms that integrate multiple therapeutic mechanisms represents a critical trend toward achieving precise interventions for RILI.

Cell therapy: Mesenchymal stem cells (MSCs) and their derivatives. MSCs exert therapeutic effects primarily through paracrine mechanisms. Upon homing to the injured lung tissue, MSCs release exosomes, microvesicles and trophic factors that collectively mediate immunomodulatory, anti-inflammatory, antifibrotic and tissue repair effects (57). A comparative study of MSC sources indicated that umbilical cord-derived MSCs exhibit superior therapeutic efficacy (58). Furthermore, innovative constructs such as the MSC-Lipo-OPC complex, in which MSCs are combined with liposomes and oligomeric procyanidin, have been developed to enhance cellular antioxidant capacity and improve enrichment efficiency at pulmonary lesions, markedly ameliorating RILI in murine models (59).

Table II. Summary of studies on nintedanib and PFD for treating RIPF.

First author, year	Research design	Sample	Grouping and experimental scheme	Research indicators	Results	(Refs.)
De Ruysscher *et al*, 2017	Animal experiments (mouse models)	266	Grouping: 0, 4, 8, 12, 16 and 20 Gy local right lung irradiation. Starting 1 week after irradiation, oral nintedanib (0, 30 and 60 mg/kg) or placebo was administered daily for 39 weeks.	Monthly CT scan for lung density. Pathological score after 39 weeks.	Lung density on CT increased with the dose, but nintedanib did not affect the CT value; pathological examination showed that nintedanib alleviated microscopic fibrosis and inflammation.	(42)
Rimner *et al*, 2023	Phase II double-blind, placebo-controlled, randomized clinical trial	30	Group A: 18 individuals [nintedanib (150 mg twice per day) + prednisone tapering]; group B: 12 individuals (placebo + prednisone tapering); total duration of 8 weeks.	The primary endpoint was the rate of no acute exacerbation of the lung within 1 year; the secondary endpoints included PFTs, PROs and AEs.	1-Year rate of no acute exacerbation: 72% in the nintedanib group vs. 40% in the placebo group (P=0.037). PFTs and PROs: No marked differences were observed between the two groups. Grade ≥2 AEs: 16 in the nintedanib group and 5 in the placebo group. The most common were diarrhea and dyspnea.	(38)
Tu *et al*, 2024	Preclinical research (mouse + cell experiments)	120	Grouping: Control group, single drug group, radiotherapy group (16 Gy), prevention group (drug administration 2 days before radiotherapy), early treatment group (drug administration 4 weeks after radiotherapy) and late treatment group (drug administration 12 weeks after radiotherapy). Nintedanib dose: 30 mg/kg/day. Cell experiments: To detect the effect of nintedanib on the signaling pathways of irradiated epithelial cells and fibroblasts.	Survival rate, body weight, CT, histo-pathological analysis and *in vitro* mechanism exploration.	Prevention and early treatment can alleviate lung pathological damage and collagen deposition in mice and improve survival. Mechanism: Inhibiting the epithelial PI3K/AKT/MAPK, fibroblast TGF-β/Smad and PI3K/AKT/mTOR pathways.	(34)
Zhang *et al*, 2025	Animal experiments (mouse models)	80	Grouping: Control group, radiotherapy group (18 Gy), low-dose nintedanib + radiotherapy group (40 mg/kg) and high-dose nintedanib + radiotherapy group (80 mg/kg). 18 Gy whole lung irradiation. Protocol: Daily intragastric adminis-tration. Animals were sacrificed and	General condition, pathology, serum inflammatory factors and TGF-β1/Smad2 pathway proteins.	i) Nintedanib improved the general condition of mice and alleviated the pathological damage of lung tissues; ii) it reduced the levels of serum IL-6, TNF-α and TGF-β1; and iii) it dose-dependently inhibited the expression of Smad2 and α-SMA in lung tissues.	(43)

Table II. Continued.

First author, year	Research design	Sample	Grouping and experimental scheme	Research indicators	Results	(Refs.)
			evaluated at 14 days (acute phase) and 3 months (chronic phase) after radiotherapy, respectively.			
Qin *et al*, 2018	Animal experiments (mouse models)	120	Grouping: Normal control, PFD alone (300 mg/kg/day for 4 weeks), simple RT (single 16 Gy to the whole thorax), RT + PFD (same dose of PFD). Observation until 20 weeks.	Survival period, RT-induced lung density (micro-CT), collagen deposition, fibrosis Ashcroft score and mechanism.	i) The median survival period of the RT group was 73 days, while that of the RT + PFD group was extended to >140 days ($P<0.01$); ii) PFD reduced RT-induced lung density (micro-CT), collagen deposition and Ashcroft score of fibrosis; and iii) PFD inhibited TGF-β1 expression and Smad3 phosphorylation.	(44)
Ying *et al*, 2021	Animal experiments (mouse models + cell experiments)	40	Grouping: Normal control, PFD alone (300 mg/kg/day by gavage), simple RT (single whole thorax irradiation of 50 Gy) and RT + PFD. Observation was conducted until 150 days after irradiation.	Macrophage polarization (M1/M2), TGF-β1/Smad3 pathway and lung tissue pathology.	PFD alleviates fibrosis and inflammation, promotes the polarization of macrophages to the M2 type and inhibits the TGF-β1/Smad3 pathway.	(39)
Hou *et al*, 2025	A multicenter, open-label, randomized controlled phase II trial	134	Experimental group (combined treatment): Oral administration of PFD three times per day. A stepwise dose escalation was adopted: 200 mg in the first week, 300 mg in the second week and maintained at 400 mg from the third to the 24th week. Initiated glucocorticoid dose equivalent to 40 mg of prednisone/day, divided into two oral doses, and maintained for 2 weeks; then reduced by 10 mg every 2 weeks over 6 to 8 weeks. Control group (standard treatment): Received only the same glucocorticoid treatment course as aforementioned.	Primary endpoint: DLCO%; secondary endpoints: FVC%, FEV1% and APEFS; AEs.	i) DLCO%: The experimental group improved by 8.0%, while the control group decreased by 2.4%; ii) FVC%: The experimental group improved by 6.1%, while the control group decreased by 2.8%; iii) FEV1%: The experimental group improved by 2.4%, while the control group deteriorated by 4.3%; iv) APEFS: The experimental group reached as high as 81.7%, while the control group was only 61.9%; and v) incidence of grade ≥3 pneumonia: 6% in the experimental group and 12% in the control group.	(40)

Table II. Continued.

First author, year	Research design	Sample	Grouping and experimental scheme	Research indicators	Results	(Refs.)
Liu *et al*, 2025	A single-center retrospective preliminary study	33	All patients received PFD (gradually increased to 400 mg three times per day) combined with standard treatment (methylprednisolone 20-40 mg/day for 5 days, then gradually reduced and discontinued). There was no control group.	Symptom improvement, imaging changes and AEs.	i) In the PFD group, both symptoms and imaging showed improvement, with an overall imaging response rate of 78.8% (26/33), including 6 cases (18.2%) of complete response and 20 cases (60.6%) of partial response; and ii) no PFD-related adverse events of grade ≥3 were observed.	(41)

PFTs, pulmonary function tests; PROs, patient-reported outcomes; AEs, adverse events; DLCO%, diffusing capacity of the lungs for carbon monoxide (% predicted); FVC%, forced vital capacity (% predicted); FEV1%, forced expiratory volume in 1 second (% predicted); APEFS, acute pulmonary exacerbation-free survival; PFD, pirfenidone; α-SMA, α-smooth muscle actin; RT, radiotherapy; RIPF, radiation-induced pulmonary fibrosis; CT, computed tomography.

Given that the therapeutic efficacy of MSCs is predominantly mediated by their secreted extracellular vesicles, 'cell-free therapy' has emerged as a promising alternative. Specifically, MSC-derived exosomes attenuate inflammatory responses, suppress ECM accumulation and inhibit EMT by blocking the Akt/NF-κB signaling pathway, effectively reversing fibrotic progression in rat models of RIPF (60). This cell-free strategy mitigates risks associated with live cell transplantation, such as tumorigenicity and embolism, while preserving core therapeutic functionalities, positioning it as a novel strategy with high potential for clinical translation.

Application of organ chips and organoids in drug screening. Lung organ chips and organoids are revolutionizing the development of drugs for RILI. Traditional two-dimensional cultures fail to simulate the three-dimensional architecture and dynamic mechanical microenvironment of lung tissues. By contrast, alveolar chips can precisely reconstruct the alveolar-capillary interface by integrating the gas exchange barrier, fluid shear stress and respiratory-like mechanical strain. Dasgupta *et al* (61) developed a human alveolar chip that, following exposure to 16 Gy of γ-rays, reproduced the core features of acute RILI within 6 h, including DNA double-strand breaks, cellular hypertrophy, upregulation of inflammatory mediators and loss of barrier function. After 7 days, the TNF-α/NF-κB, IL-6/JAK-STAT3 and IFN-γ pathways were markedly activated, closely mirroring the clinical time window for RP onset (61). This model provides a highly physiologically relevant *in vitro* platform for elucidating the molecular mechanisms of acute RILI and evaluating novel radioprotective countermeasures.

Comparison of emerging therapeutic strategies. These emerging strategies have distinct advantages and limitations. Nanotechnology-based drug delivery systems improve drug stability and lung targeting but face challenges in safety, manufacturing and clinical validation (54-56). MSC-based therapies provide broad anti-inflammatory and antifibrotic effects, but their efficacy varies with cell source and preparation, and concerns regarding tumorigenicity and pulmonary embolism remain (57,58). MSC-derived extracellular vesicles may reduce these risks, although their optimal dosage, delivery route and long-term safety remain unclear (60). Organ chips and organoids provide physiologically relevant platforms for drug screening and mechanism-based evaluation, but cannot fully reproduce the systemic immune and vascular environment (61). Thus, nanomedicine and cell-based therapies may have greater potential for future therapeutic application, whereas organ chips and organoids are more suitable as translational platforms for drug development and optimization.

7. Identification and management of special types of RILI

Radiation recall pneumonitis (RRP). RRP is defined as acute pneumonia occurring months to years after thoracic radiotherapy, triggered by specific drugs and confined to the original irradiation field. Common triggers include chemotherapeutic agents such as paclitaxel and gemcitabine, as well as immune checkpoint inhibitors (ICIs) (62). Chest computed tomography is crucial for diagnosis, with typical findings of ground-glass

opacities or consolidation within the irradiation field. The differential diagnosis for RRP should include tumor recurrence, infectious pneumonia, typical RP and drug-induced pneumonitis (63). The underlying mechanism involves drug-induced immune activation. Therefore, the treatment is focused on immediate discontinuation of the suspected agent and initiation of glucocorticoid therapy. Most patients respond favorably to moderate-dose corticosteroids, with resolution of symptoms and radiographic abnormalities typically occurring within several weeks.

Radiation immunotherapy-related pneumonitis. The combination of ICIs and thoracic radiotherapy has emerged as standard care for locally advanced NSCLC. However, this synergy substantially increases the pneumonitis risk. Real-world data indicated a pneumonitis incidence of 26.9% in the combination group, which was markedly higher than that (6.7%) observed for ICI monotherapy (64). The timing of ICI administration profoundly influences pneumonitis risk, with the incidence of grade ≥2 RP increasing to 45.3% when ICIs preceded chemoradiotherapy, compared with 25.3% when administered afterward and 24.3% in concurrent regimens. Notably, shorter intervals between modalities correlate with a greater risk (65). Proposed mechanisms include disruption of self-tolerance, cross-reactive immunity between tumor and normal tissues, release of inflammatory mediators, the abscopal effect and microbiome alterations, potentially modulated by genetic and environmental factors (66). Management should follow the principles of graded, individualized intervention.

RP complicated by infection. Patients with RP face a substantially elevated risk of secondary infections, a phenomenon termed 'superimposed infection' involving bacterial, viral or fungal pathogens, which was first described as early as 1988 (67). A large-scale analysis of 1,746 patients with severe RP revealed a notably high secondary infection rate of 44.5%. The predominant pathogens were *Acinetobacter baumannii* (27%), *Klebsiella pneumoniae* (26.2%) and *Pseudomonas aeruginosa* (13.6%), which frequently exhibited multidrug resistance (68). Therapeutically, a careful balance must be maintained between RP management and effective antimicrobial therapy. Empirical treatment with cefoperazone-sulbactam is a rational initial choice, and initiating empirical antifungal therapy for a duration of ≥9 days may improve outcomes (68). Corticosteroid administration should be strictly contingent upon adequate antimicrobial coverage, and critically ill patients require prompt transfer to the Intensive Care Unit with consideration of mechanical ventilation support (29).

8. Conclusions and perspectives

To address the key limitation restricting the therapeutic efficacy of thoracic tumor radiotherapy, the drug prevention and treatment for RILI is evolving from single-modality symptomatic management toward a multimodal, full-cycle intervention model. The present review comprehensively summarized advances from classical radioprotectants and anti-inflammatory drugs to novel antifibrotic drugs and cutting-edge exploratory therapies based on the molecular mechanisms and key targets operative at distinct phases of RILI pathogenesis. However, most candidate drugs remain in the preclinical stage, and clinical evidence is currently limited to a small number of agents, such as amifostine, nintedanib and PFD. The translation of promising preclinical therapies is further challenged by differences between experimental models and clinical RILI, uncertainty regarding the optimal timing and duration of treatment, limited prospective clinical evidence, and the need to balance lung protection with antitumor efficacy. Future efforts should prioritize accelerating clinical translation, engineering intelligent drug delivery systems with high efficacy and low toxicity, and implementing an individualized patient stratification approach based on multi-omics profiling to enable precision prevention and treatment, ultimately establishing a safe and effective RILI management system that spans the entire disease course.

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Authors' contributions

SL, WB and ZZ conceived the present review, conducted the literature review and wrote the manuscript. MM, CZ and YZ assisted with the literature review and manuscript revision. YS and QA contributed to manuscript writing and interpretation. WB and ZZ provided critical feedback and helped with manuscript revision. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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