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Progress in the mechanism of radiation-induced lung injury

Hang-Jie Ying[1,2,3], Min Fang[1,2,3], Ming Chen[1,2,3]

[1]Department of Radiation Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, Zhejiang 310022, China;
[2]Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China;
[3]Zhejiang Key Laboratory of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang 310022, China.

Radiation therapy is widely used to treat various thoracic tumors. However, X-rays inevitably cause damage to normal lung tissues while killing tumor cells, leading to the occurrence of radiation-induced lung injury (RILI). Recent data showed that lung cancer has the highest incidence of RILI (5–25%), followed by mediastinal lymphoma (5–10%), and breast cancer (1–5%).[1] With the progress in research, our understanding of the mechanism of RILI has changed from the traditional hypothesis of "target cell death" to "a continuous process involving multiple cells," which is dynamic and evolving [Figure 1]. In the present review, we summarize the current knowledge of RILI, and discuss the potential limitations of combined radio-immunotherapy.

Single-nucleotide polymorphisms (SNPs) are the most common human heritable variations, accounting for more than 90% of all known polymorphisms.[2] Studies have found that SNPs are associated with susceptibility to RILI. It was reported that lung cancer patients with the CT+TT genotype of interleukin (IL)-4 SNP rs2243250 had a lower risk of developing radiation pneumonia ≥ grade 3 after radiotherapy.[3] However, patients with autophagy related 16 like 2 (ATG16L2) rs10898880 CC variant genotype had a higher risk.[4]

Inherited illness caused by gene mutations will also lead to an increase in sensitivity to radiotherapy, such as ataxia telangiectasia and Nijmegen breakage syndrome, which are caused by the mutation of ataxia telangiectasia mutated (*ATM*) and Nijmegen breakage syndrome 1, respectively. These patients will have severe reactions even if they are exposed to a small dose of radiation.[5,6]

Large amounts of reactive oxygen species (ROS) are produced rapidly in lung tissue after irradiation, which is mainly caused by ionization of water molecules. ROS produced by X-ray irradiation disappear in a very short time. However, Hao *et al*[7] found that a significant decrease of blood oxygen partial pressure could be detected 180 days after lung irradiation with 15 Gy in dogs. Similarly, Yin *et al*[8] found that ROS showed dynamic changes after a single dose of 18 Gy irradiation on the right lung of dogs, which reached a peak after 4 weeks of irradiation. Those results support the theory that radiation-induced chronic oxidative stress occurs in the lungs. This process involves a variety of cytokines, cell types, and gene products. These secondary productions of large amounts of ROS deplete the body's antioxidant capacity rapidly, further aggravating tissue damage and allowing lung lesions to persist over time.

The alveolar capillary barrier, which comprises vascular endothelial cells (VECs) and alveolar epithelial cells (AECs), is very sensitive to ionizing radiation. Ionizing radiation can cause the increase of vascular permeability and inflammatory infiltration of VECs in of the early stage. With extended irradiation time and increased irradiation dose, VECs will rupture and fall off, accompanied by platelet attachment, resulting in capillary embolism. Type I AECs lack proliferative ability, and undergo necrosis or apoptosis directly after irradiation. Type II AECs (AEC IIs) activate fibroblasts through epithelial-mesenchymal transition, and then differentiate into myofibroblasts, which then form characteristic fibroblast foci and secrete the extracellular matrix, ultimately leading to fibrosis. The abnormal proliferation of AEC IIs also reduces the secretion of alveolar surfactant, which decreases the alveolar surface tension, resulting in pulmonary edema and atelectasis.[9]

The essence of RILI is lymphocytic alveolitis, which is closely related to the immune response mediated by lymphocytes. According to the different cytokines secreted, $CD4^+$ T cells can be divided into T_h1 and T_h2 cells. T_h1 cells mainly mediate cellular immune response by secreting T_h1 cytokines, such as interferon gamma (IFN-γ), tumor

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Correspondence to: Dr. Ming Chen, No. 1 East Banshan Road, Gongshu District, Hangzhou, Zhejiang 310022, China
E-Mail: chenming@zjcc.org.cn

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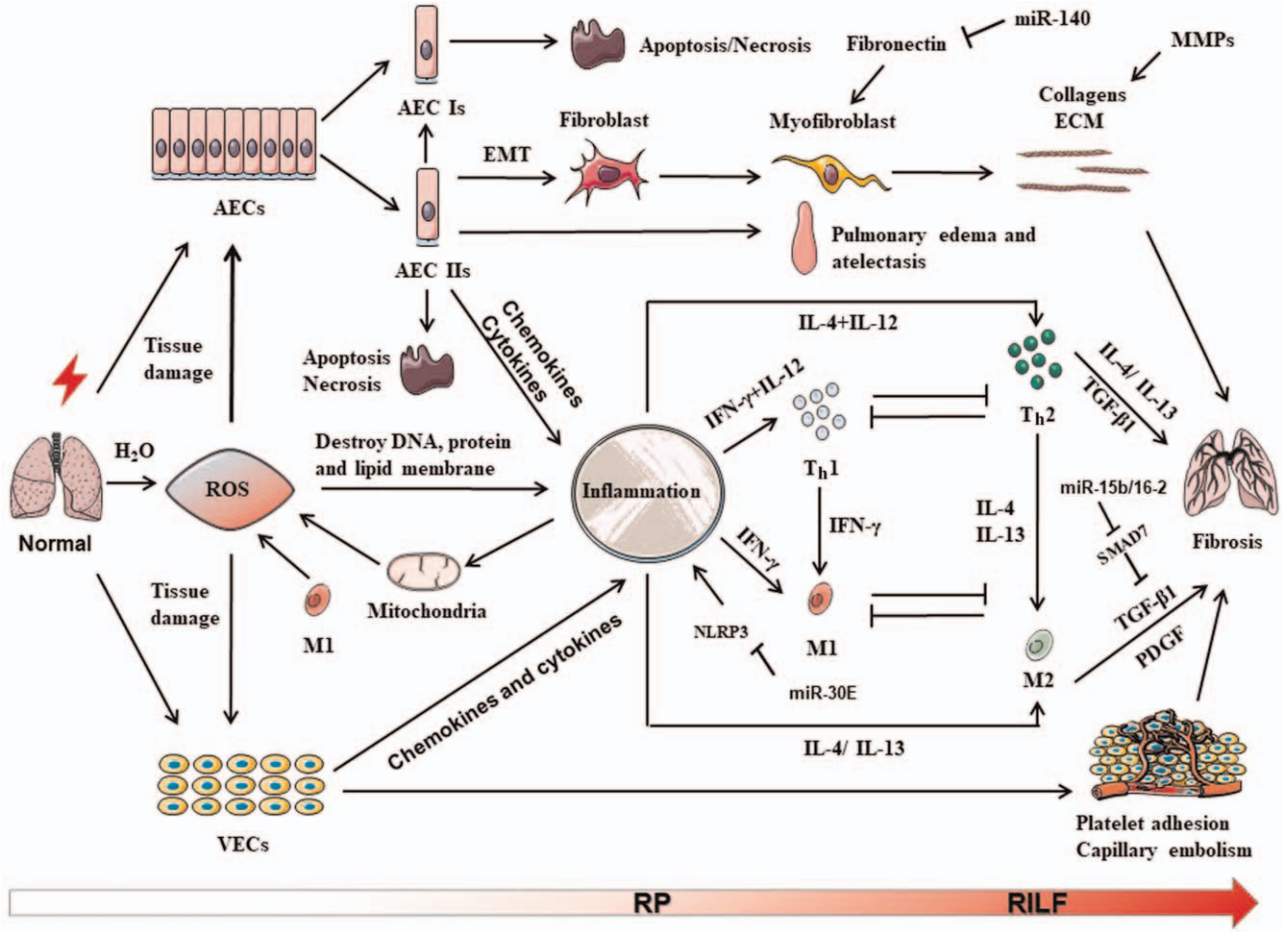

Figure 1: Pathogenesis of RILI. RILI is frequently caused by oxidative stress injury, lung effector cell injury, and a cascade effect caused by the release of a large number of cytokines and chemokines (Figure 1 was produced using Servier Medical ART: http://smart.servier.com). AEC: Alveolar epithelial cells; MiR-140: MicroRNA-140; EMT: Epithelial-mesenchymal transition; ECM: Extracellular matrix; MMP: Matrix metalloproteinase; IL: Interleukin; ROS: Reactive oxygen species; IFN-γ: Interferon-γ; TGF-β1: Transforming growth factor-β1; T_h1: T-helper type 1; T_h2: T-helper type 2; VEC: Vascular endothelial cell; NLRP3: Nod-like receptor family pyrin domain containing 3; MiR-15b/16-2: MicroRNA-15b/16-2; SMAD7: Mothers against decapentaplegic homolog 7; MiR-30E: MicroRNA-30E; PDGF: Platelet-derived growth factor; RP: Radiation pneumonia; RILF: Radiation-induced lung fibrosis; RILI: Radiation-induced lung injury.

necrosis factor alpha, IL-2, and IL-12. T_h2 cells mainly mediate the humoral immune response by secreting T_h2 cytokines, such as IL-4, IL-5, IL-13, and monocyte chemoattractant protein-1. The imbalance of immune function of T_h1/T_h2 cells is one of the important pathogeneses of RILI. For example, compared with C57BL/6J mice, the fibrotic response of IFN-γ−/− mice, deficient in T_h1 cells, was significantly enhanced.[10] IL-4 levels increased in the lungs of mice within 3 weeks after irradiation, and inhibiting the expression of IL-4 could effectively inhibit the progress of radiation-induced lung fibrosis (RILF).[11]

Macrophages play a key role in the development of RILI because they are the first line of defense against external invasion. Macrophages can be divided into two types: T_h1-derived cytokine IFN-γ can promote the expression of inducible nitric oxide synthase, which is a marker for classically activated macrophages (CAMs or M1). T_h2-derived cytokines IL-4 and IL-13 can active the activity of arginase-1 (Arg-1), which is a marker for alternatively activated macrophages (AAMs or M2). M1 macrophages have been shown to prevent the development of pulmonary fibrosis, and M2 macrophages are the most prominent type of macrophages in pulmonary fibrosis. Therefore, the balance transition from M1 macrophages that promote inflammation to M2 macrophages that promote fibrosis and wound healing is one of the important reasons for the formation of pulmonary fibrosis after radiation.

Macrophages can also be divided into alveolar macrophages (AMs) and interstitial macrophages (IMs), according to their different anatomical sites. Chen *et al*[12] found that AMs are the primary inflammatory cells that infiltrate irradiated lung tissues, and a single high dose of chest irradiation led to the depletion of AMs, but not IMs. Moreover, AMs possibly reflect a more pro-inflammatory phenotype. IMs are mainly distributed in the alveolar septum, bronchus, and blood vessels, and play an important role in the regulation of immune responses. At steady state, IMs expressed 10-fold more Arg-1 than AMs, and a 40-fold up-regulation of Arg-1 was found in IMs isolated from lung tissue of RILF mice. IMs, but not AMs, were able to induce myofibroblast activation *in vitro*.[13]

Radiotherapy can induce immunogenic death of tumor cells, expose tumor antigens, produce damage-associated molecular patterns, and promote the maturation of dendritic cells (DCs). The phenotype of mature DCs changed and migrated to local draining lymph nodes. Tumor antigens are delivered to $CD8^+$ T cells through major histocompatibility complex I (MHC I), and $CD8^+$ T cells are activated to differentiate into cytotoxic T lymphocytes (CTLs). These tumor-specific CTLs enter the blood circulation and home to the tumor, specifically identifying all cells expressing similar antigens, mediating target cell death through perforin, granzyme, and other pathways, then removing tumors inside and outside the radiotherapy field.[14] Radiotherapy combined with immunotherapy can regulate and magnify this process. In the model of spontaneous lung metastasis and double leg transplanted tumor in mice, Vanpouille-Box *et al*[15] found that radiotherapy combined with transforming growth factor-β (TGF-β) inhibitor could produce abscopal effect, which may be related to the promotion of DCs activation and enhancement of T-cell immune response to tumor-specific antigen after the inhibition of TGF-β. However, uncontrolled pro-inflammatory signals induced by immunotherapy alone can cause toxic effects in normal tissues, such as immune-related adverse effects, which often occur in liver, heart, lung, and so on. Radiotherapy combined with immunotherapy increases the risk of radiation-induced side effects, including RILI.[16] Therefore, radiotherapy combined with immunotherapy must be regarded as a "double-edged sword" that needs to be handled carefully. How to choose the treatment time, treatment sequence and dose to achieve the best effect of combined therapy needs further research.

Clinically, corticosteroids are mainly used to treat radiation pneumonitis, and early intervention is expected to lead to recovery. Antioxidant drugs have also proven to prevent and treat radiation pneumonitis. For example, amifostine, which scavenges tissue-free radicals and has antioxidation effects, shows a good protective effect on radiation damage in the human body, and was the first broad-spectrum cell protector recognized by international authorities.[17] Although the risk of RILF can be predicted by detecting many blood biochemical indexes, such as TGF-β, IL-6, krebs von den lungen-6 (KL-6), surfactant protein, and interleukin-1 receptor antagonist (IL-1ra),[18] most drugs for RILF are still undergoing preclinical research. Thus, it could be said that there are no effective treatments for RILF. Pirfenidone and nintedanib have been approved by FDA for the treatment of idiopathic pulmonary fibrosis. The pathological features of idiopathic pulmonary fibrosis and RILF are very similar, and both go through the process of early inflammation, lung parenchyma injury, damaged alveolar repair, and fibrosis.[19] At present, clinical trials on the effects of pirfenidone (NCT03902509) and nintedanib (NCT02496585) on RILI are ongoing. We expect that these drugs will have promising clinical prospects in the management of RILI.

Conflicts of interest

None.

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