Promising Biomarkers of RILI

Subjects: Oncology

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Radiation-induced lung injury (RILI) is one of the main dose-limiting side effects in patients with thoracic cancer during radiotherapy. No reliable predictors or accurate risk models are currently available in clinical practice. Severe radiation pneumonitis (RP) or pulmonary fibrosis (PF) will reduce the quality of life, even when the anti-tumor treatment is effective for patients. Since the clinical symptoms or imaging changes identifying toxicity do not appear in the early stage, ideal biomarkers are crucial for early diagnosis and intervention in order to prevent lung complications.

Keywords: radiation-induced lung injury ; signaling pathways ; biomarkers

1. Key Immune Cells

An increasing number of studies have suggested that inflammatory responses are closely associated with RILI. Especially in RP, the variation in the number of immune cells is a potential indicator (**Table 1**). It was found that $CD4^+$ T lymphocyte levels were obviously lower in the early period of RP, and decreased lymphocyte count was associated with the severity of RP in lung cancer patients after thoracic radiotherapy, which was consistent with animal experiments [1]. Moreover, as T cells determine the specificity of immune responses in tissue inflammation, the quantity of $CD4^+$ T cells and $CD4^+$:$CD8^+$ T cell ratio decreased significantly at the onset of RP compared with the no-RP group, and increased $CD4^+$ T-cell quantity and reduced C-reactive protein (CRP) level were observed after effective steroid therapy [2][3]. Clinically, higher neutrophil-lymphocyte ratio (NLR) has been used as a biomarker of systemic inflammation, and it is relevant to the poor prognosis of cancer patients [4]. For stage III non-small-cell lung cancer (NSCLC) patients with radiological RP, NLR was used to predict subsequent progression to symptomatic RP, although their lymphocyte counts were not significantly different initially [5][4].

In addition to RP, a study revealed that the frequency of Th17 cells increased after irradiation, which was associated with PF in mice. The activation of the IL-6/TGF-β/IL-17 signaling pathway is involved in radiation-induced severe fibrosis [6][7]. These results suggest that T-cell differentiation and proliferation are altered dynamically during the development of RILI. With the development of single-cell RNA sequencing (scRNA-seq) technology, comprehensive human single-cell landscapes have been constructed, especially for lung immune and collagen-producing lung cells [8][9]. scRNA-seq, a central genome-wide sequencing method to portray cellular identities, is capable of exploring the differentiation procedure of key immune cells and distinguishing the source of important cytokines or proteins in RILI [10].

2. Cytokines and Proteins

As described in **Table 1**, cytokines and proteins play essential roles in the process of lung damage. Owing to the convenience of blood sample collection, blood testing has become the most promising method to identify RILI risk [11][12]. In this review, relevant molecular factors of lung toxicities were divided into four categories according to their functions, including inflammation-related factors, fibrosis-related factors, chemokines, and other proteins (**Table 1**).

Table 1. Potential biomarkers for monitoring radiation-induced lung injury.

Categories	Biomarkers	Function	Correlation Research	Ref.
Immune cells	T-cell subsets	T cells determine the specificity of immune responses in tissue inflammation, autoimmunity and host defense	Decreased lymphocytes predicted the severity of RP in LC patients	[2][3] [6][7]
	NLR	NLR is an important biomarker of inflammatory status and disease exacerbation	Higher NLR in NSCLC patients with radiological RP predicted the development of symptomatic RP	[5][4]

Categories	Biomarkers	Function	Correlation Research	Ref.
Inflammation-related factors	IL-1β	IL-1β promotes the recruitment of inflammatory cells and the release of chemokines	IL-1β level was a significant initiator of RILI both in vivo and in vitro studies	[13] [14]
	IL-6	IL-6 regulates cells proliferation and differentiation, hematopoiesis, angiogenesis and immune reactions	IL-6 level was a potential monitor for RILI development clinically	[15] [16] [17]
	IL-10	IL-10 is an anti-inflammatory cytokine by blocking the production of pro-inflammatory cytokines and inhibiting the capabilities of antigen-presenting cells	IL-10 level was low throughout the irradiation period in RP patients, various IL-10 levels monitored different RP scales	[18]
	CRP	CRP is an acute phase inflammatory protein and elevated after injury, infection or inflammation	CRP level in plasma was a potential predictor for RILI development in LC patients	[2]
	IL-8	IL-8 has an anti-inflammatory effect and mediates pulmonary fibrosis	Lower pre-IL-8 level predicted higher risk of grade 2 RILI in LC patients	[19] [20] [21]
Fibrosis-related factors	TGF-β	TGF-β promotes the differentiation of fibroblasts into myofibroblasts and synthesis of ECM proteins, and reduces collagen degradation, leading to lung fibrosis	Higher TGF-β1 in plasma monitored symptomatic RILI both in vivo and in vitro studies	[22] [21]
	ET-1	ET-1 inhibits the proliferation and migration of endothelial cells and promotes ECM production	ET-1 monitored the dynamic changes of PF in mice	[23] [24]
	KL-6	KL-6 has chemotactic and anti-apoptotic effects on fibroblasts, leading to lung fibrosis	Increased KL-6 level monitored PF activity and predicted RP severity in patients	[25] [26] [27]
	PAI-1	PAI-1 inhibits the plasmin system through blocking fibrinolysis and degradation of the ECM	PAI-1 level predicted PF development in patients	[28] [29] [30]
Chemokines	CCL2/MCP-1	CCL2, also called MCP-1, is a potent chemokine for monocytes	Lower CCL2 level monitored patients with grade 2 RP	[16] [21] [31]
Other proteins	IFN-γ	IFN-γ is a pleiotropic cytokine with antitumor, antiviral, antibacterial, pro-inflammatory and antifibrotic properties	IFN-γ level indicated the ability to attenuate fibrosis formation in patients	[29] [32]
	SP-D	SP-D works in host defense and regulates immune responses and lung phospholipid levels	Elevated SP-D is a sensitive biomarker for early RILI prediction both in patients and murine models	[33] [34] [35]
miRNAs	miR-21	BMSCs inhibit the pro-inflammatory pathway of macrophage 1 in a miR-21 dependent manner	miR-21 over-expressed in BMSCs significantly alleviated alveolitis in RILI rats	[36]
	miR-140	miR-140 protects lung tissue from fibrosis through blocking TGF-β1 signaling and inhibiting myofibroblast differentiation	Loss of miR-140 in the lung tissue is a key risk factor for PF murine	[37]

Abbreviations: RILI: Radiation-induced lung injury; RP: Radiation pneumonitis; LC: Lung cancer; NSCLC: Non-small-cell lung cancer; NLR: Neutrophil-lymphocyte ratio; TGF: Transforming growth factors; IL: Interleukins; CRP: C-reactive protein; PTX3: Pentraxins 3; ET-1: Endothelin-1; KL-6: Krebs von den Lungen-6; IFN: Interferons; ECM: Extracellular matrix; CCL2: Chemokine C-C motif ligand 2; MCP-1: Monocyte chemoattractant protein-1; PAI-1: Plasminogen activator inhibitor-1; EMT: Epithelial-mesenchymal transition; SP-D: surfactant protein D; PF: Pulmonary fibrosis; BMSCs: Bone marrow mesenchymal stem cells.

Inflammation-related factors are involved in acute or chronic inflammatory responses. TNF-α is the main initiator of the pro-inflammatory cascade by activating the expression of transcription factors, intercellular adhesion molecules, and numerous acute phase proteins. TNF-α also promotes fibroblast growth and collagen deposition [38][39]. Overproduction of TNF-α after irradiation has been well documented to be correlated with early cell apoptosis and latent lung function damage [40]. Augmented levels of TNF-α in the plasma were observed after radiotherapy. Although TNF-α level is related to RP, it failed to be used as a predictor in a previous study [41]. As another vital pro-inflammatory cytokine in human

diseases, IL-1β can promote the recruitment of inflammatory cells by inducing the expression of adhesion molecules on endothelial cells and enhancing chemokine release [13]. The level of IL-1β was significantly elevated after thoracic irradiation both in vivo and in vitro; this could trigger the production of TGF-β and IL-6, which are involved in fibroblast proliferation and interstitial cell infiltration [14].

IL-6 plays a critical role in regulating lymphocyte proliferation and differentiation and participates in acute phase responses and immune hematopoiesis. Overexpression of IL-6 was detected clinically in the earlier phase of lung toxicity, which is closely related to the development of RP [15][16]. Nonetheless, it is still controversial whether IL-6 is a predictor of RILI because of its non-specific effects on inflammation [17]. IL-10 functions as an anti-inflammatory cytokine by suppressing the production of pro-inflammatory cytokines, including IL-6, and inhibiting the capabilities of antigen-presenting cells. Persistent low levels of IL-10 were found in RP patients throughout the radiotherapy period, and varied IL-10 concentrations were detected among different RP scales [18]. Moreover, the level of another inflammatory factor, CRP, was found to be higher at the onset of RP than in the no-RP group in lung cancer patients [2]. CRP has a prognostic value in disease severity and is associated with adverse outcomes in patients with lung infections. CRP, combined with other relevant factors, is a potential predictor of radiation toxicity [42][43].

As the most important pro-fibrotic factor, TGF-β1 promotes the differentiation of fibroblasts into myofibroblasts and the synthesis of ECM proteins [22]. Its central role in fibrosis progression is summarized in Section 2. Numerous studies have confirmed that plasma TGF-β1 levels are significantly correlated with both pulmonary and non-pulmonary radiation toxicity in patients after radiotherapy [44][45][46]. It was validated that higher levels of TGF-β1 and lower baseline levels of IL-8 were significantly associated with an increased grade ≥ 2 risk of RILI in NSCLC patients treated with definitive radiotherapy [21]. IL-8, an anti-inflammatory cytokine that is associated with symptomatic inflammatory responses, induces lung fibrosis by augmenting the mesenchymal cell population and recruiting more activated macrophages [19]. In addition, IL-4 and IL-13 play key roles in the adaptive immune response, and are both Th2-derived pro-fibrotic cytokines. In rat models, IL-4 levels increased with time after irradiation, leading to type I and III collagen formation in fibroblasts [47]. Both IL-4 and IL-13 can promote fibrosis by upregulating the expression of cell surface β1 integrin and VCAM-1 and simulating M2 macrophage polarization [48][49].

Although excessive ECM deposition is crucial in lung fibrosis, ECM initially contributes to wound healing of damaged lung parenchyma by binding cytokines and growth factors, such as platelet-derived growth factors (PDGFs) [50]. PDGFs are released from the endothelium, macrophages, or platelets, which can accelerate tissue repair by stimulating cell proliferation and ECM synthesis [51]. PDGF receptor α (PDGFR-α) is transactivated by TGF-β1 and is involved in tissue fibrosis. High levels of PDGF/PDGFR have been observed in lung, liver, kidney, and heart fibrosis [52]. Moreover, endothelin-1 (ET-1) is present downstream of TGF-β1. On the one hand, ET-1 can inhibit the proliferation and migration of endothelial cells, while on the other hand it promotes the expression of fibrosis-associated genes, such as plasminogen activator inhibitor-1 (*PAI-1*) [23]. ET-1 inhibition prolonged the survival of patients with idiopathic pulmonary fibrosis (IPF) [24]. In irradiated mice, serum ET-1 levels were obviously increased in the early stage, potentially indicating dynamic changes in lung injury.

In addition, the TGF-β-related protein Krebs von den Lungen-6 (KL-6/MUC1) has chemotactic and anti-apoptotic effects on fibroblasts. The serum level of KL-6/MUC1 reflects the severity of interstitial lung disease associated with connective tissue disease [26][27]. KL-6 is produced by epithelial cells, especially AEC II, and is released from these damaged cells following irradiation. It was reported that serum KL-6 levels increased almost in line with the occurrence of grade ≥2 RP and decreased after steroid administration in NSCLC patients [25]. Moreover, surfactants secreted by type II pneumocytes are vital for maintaining alveolar structure and function. The increased club cell secretory protein/surfactant protein D (CCSP/SP-D) ratio in plasma was positively correlated with fibrosis development and was detected early after radiation exposure in a murine model [33][34]. SP-D functions in host defense and regulates immune responses and lung phospholipid levels [53]. Previous studies have suggested that circulating SP-D levels were elevated in RP patients, which may be a sensitive and useful biomarker for early RP prediction [35].

Chemokines are associated with the migration of immune cells in response to infection or inflammation [54]. Chemokine C-C motif ligand 2 (CCL2), also known as monocyte chemoattractant protein-1 (MCP-1), is a potent chemokine for monocytes and contributes to lung pneumonitis and fibrosis [31]. The CCL2 level in the plasma was significantly lower in patients with grade 2 RP [16][21]. Furthermore, using high-throughput detection methods, the bronchoalveolar lavage fluid (BALF) of NSCLC patients was analyzed. The results showed that several cytokines, including C-X-C motif chemokine ligand 1 (CXCL-1), PAI-1, and IFN-γ, were upregulated in grade ≥ 3 RP patients [29]. Among them, CXCL-1 is a remarkable neutrophil chemoattractant and is involved in angiogenesis and inflammation. PAI-1 inhibits the plasmin system by blocking fibrinolysis and degradation of the ECM, and plays an important role in the development of PF [28][30].

IFN-γ is a pleiotropic cytokine with antitumor, antiviral, antibacterial, pro-inflammatory, and antifibrotic properties [32]. IFN-γ secreted by Th1 cells can inhibit Th2 cell differentiation and Th2-derived cytokine expression (IL-4 and IL-13), which further attenuates fibrosis formation by restricting fibroblast proliferation and reducing excessive collagen production [55].

3. MicroRNAs

MicroRNAs (miRNAs) are single-stranded, highly conservative small noncoding RNAs [56] involved in the regulation of gene expression, transcription, translation, and epigenetic modification; miRNAs have been studied in various fields, including disease diagnostics and cancer therapeutics [57][58][59]. The relationship between miRNAs and radiosensitivity or radiotoxicity has been reported in recent years. MiR-18-5p was reported to be a potential target for improving radiosensitivity in lung cancer by regulating the ataxia telangiectasia mutated (*ATM*) gene and hypoxia-inducible factor 1 alpha (*HIF-1α*) gene [60]. Additionally, overexpression of miR-26b-5p inhibited the expression of activating transcription factor 2 (*ATF2*) gene, which resulted in enhanced radiosensitivity of A549 lung adenocarcinoma cells [61].

During the acute phase after irradiation, the lower levels of miR-21 were related to a higher incidence and grade of RILI in patients by increasing the expression of IL-6 and TNF-α [36]. Similarly, another key protective molecule, miR-140, protected normal lung tissue from fibrosis by blocking TGF-β1 signaling and inhibiting myofibroblast differentiation [37]. Decreased levels of circulating miR-29a-3p and miR-150-5p in secreted exosomes were correlated with the delivered RT dose, and miR-29a might be useful biomarkers for lung fibrosis after irradiation [62]. Prominent changes in systemic miRNA profiles were observed within the early period after radiation exposure; miR-34b-3p, -96-5p, and -802-5p were identified to be associated with the TGF-β/SMAD signaling in C57BL/6 mice [63]. MiRNAs are stable in tissues or plasma and can be easily detected. Therefore, it is worthwhile to explore the value of circulating miRNA signatures for monitoring RILI.

4. Genetic Characteristics

Clinically, there is great variability among cancer patients in response to radiotherapy. Therefore, it is possible that the genetic characteristics of individuals are significantly associated with RILI occurrence [64][65]. Single-nucleotide polymorphisms (SNPs) have been considered hotspots in the development of RILI. A previous review summarized several SNPs in DNA repair-, inflammation-, angiogenesis-, and stress response-related genes that were involved in the underlying mechanisms of RP [66]. New discoveries continue to enrich the contents of SNPs related to RILI, and the latest findings are reviewed in this paper in **Table 2**.

Table 2. SNPs in genes associated with radiation-induced lung injury.

SNPs	Year of Publication	Gene Function	Correlation Research	Ref.
***TOPBP1*: rs1051772**	**2016**	**DNA repair**	**decreased risk of RP in NSCLC patients**	[67]
***MTHFR*: rs1801131**	**2017**	**DNA repair**	**decreased risk of grade ≥ 2 RP in esophageal squamous cell carcinoma patients**	[68]
***NEIL1:* rs4462560**	**2021**	**DNA repair**	**decreased risk of grade ≥ 2 RP in LC patients**	[69]
***NEIL1:* rs7402844**	**2021**	**DNA repair**	**higher risk of grade ≥ 2 RP in LC patients**	[69]
***PI3CA*: rs9838117 *AKT2*: rs33933140, rs11880261**	**2016**	**Inflammation**	**higher risk of grade ≥ 3 RP in LC patients**	[70]
***IL4*: rs2243250**	**2019**	**Inflammation**	**higher risk of grade ≥ 3 RP in LC patients**	[71]
***ATG16L2*: rs10898880**	**2018**	**Autophagy**	**higher risk of RP in NSCLC patients**	[72]
***PAI-1:* rs7242**	**2017**	**Plasmin system inhibition**	**higher risk of grade ≥ 3 RP in LC patients**	[28]
***ITGB6*: rs4665162**	**2016**	**Cell surface adhesion**	**higher risk of grade ≥ 2 RP in LC patients**	[73]
***MMP-1*: rs1144393**	**2018**	**Protein degradation**	**higher risk of grade ≥ 2 RILI in LC patients**	[74]
***HIPK2*: rs2030712**	**2020**	**Cell apoptosis, proliferation and DNA repair**	**higher risk of grade ≥ 2 RP in LC patients**	[75]

Abbreviations: SNPs: Single-nucleotide polymorphisms; RILI: Radiation-induced lung injury; RP: Radiation pneumonitis; LC: Lung cancer; NSCLC: Non-small-cell lung cancer; TOPBP1: Topoisomerase DNA binding II binding protein 1; MTHFR: Methylenetetrahydrofolate reductase; NEIL1: Nei endonuclease VIII-like 1; PI3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AKT2: AKT serine/threonine kinase 2; IL4: Interleukins 4; ATG16L2: Autophagy related 16 Like 2; PAI-1: Plasminogen activator inhibitor-1; ITGB6: integrin beta6 subunit; MMP-1: Matrix metalloproteinase-1; HIPK2: Homeodomain interacting protein kinase 2.

Among the DNA repair-related genes, the SNP rs1051772 of topoisomerase DNA binding II binding protein 1 (*TOPBP1*) gene was found to be associated with a decreased risk of RP in NSCLC patients through DNA replication checkpoint control and genomic stability maintenance [67][76], and SNP rs1801131 of the methylenetetrahydrofolate reductase (*MTHFR*) gene was reported to be statistically correlated with grade ≥2 RP among esophageal squamous cell carcinoma patients in the Chinese Han population [68]. Nei endonuclease VIII-like 1 (NEIL1) is a bifunctional enzyme in the base excision repair (BER) pathway. Genetic variants (rs4462560 and rs7402844) of *NEIL1* gene can serve as independent biomarkers for predicting RP in patients treated with thoracic radiotherapy through regulation of NEIL1 expression [69]. Moreover, the inflammation-related gene *IL4*: rs2243250 was validated as a potential predictor of severe injury due to its high correlation with grade ≥ 3 RP in lung cancer patients [71]. The variant of autophagy-related gene autophagy related 16 Like 2 (*ATG16L2*) could predict the RP risk and better prognosis in NSCLC patients treated with radiotherapy, either with or without chemotherapy [72].

For stress response-related genes, the association between the glutathione S-transferase-P1 (*GSTP1)* Ile105Val polymorphism and the risk of RP was observed in lung cancer patients of the Chinese population [77]. The *GSTP1* gene abundantly expresses glutathione S-transferase (GST), a detoxification enzyme that protects against radiation-induced oxidative damage [78]. In addition, homeodomain-interacting protein kinase 2 (HIPK2) is a member of the serine/threonine kinase family, and there is a clearly increased risk of RP in lung cancer patients with the CC genotype of *HIPK2*: rs2030712 after radiotherapy [75]. A team has systematically investigated a series of genes relevant to RP in lung cancer patients, and found that the SNP rs4665162 of integrin beta6 subunit (*ITGB6*) gene, rs1144393 in matrix metalloproteinase-1 (*MMP-1*) gene, and three SNPs in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway (*PI3CA*: rs9838117, *AKT2*: rs33933140 and rs11880261) were associated with higher RP risk [70][73][74]. Among them, the PI3K/AKT pathway is an important downstream pathway of TGF-β involved in the pathogenesis of inflammation and fibrosis diseases [79][80]. Although the clinical application of the above potential markers of SNPs in genes requires further prospective studies, SNPs are still a potential strategy for selecting high-risk patients for radiotherapy toxicity.

5. Imaging Based Biomarkers and Others

As there is a latency between radiotherapy and symptomatic lung toxicity, changes in the lung can be detected by advanced imaging technologies. Some non-invasive biomarkers are under investigation for early diagnosis of RILI. For thoracic tumor patients after radiotherapy, studies showed that vascular damage led to the reduction of regional lung perfusion. By using two functional single-photon emission computed tomography (SPECT) probes, regional pulmonary perfusion and pulmonary cell death were measured in the same irradiated rat model. The results demonstrated that the decrease of perfused volume of the lung was closely associated with lung tissue damage [81][82]. Especially in patients with RP, perfusion reduction was found more serious in high dose regions than those without RP with the performance of SPECT/CT [83]. Besides lung perfusion, alterations in pulmonary vascular resistance and permeability are also potential indicators of lung injury. A whole body contrast enhanced dynamic near-infrared fluorescence imaging was recently carried out in a rat model to track lung vascular permeability after acute RILI [84].

In addition, pre-treatment [18F]-2-fluoro-2-deoxyglucose positron emission tomography (FDG PET) imaging has also been investigated to predict RILI in several studies. Petit et al. firstly evaluated the correlation between symptomatic RP and pre-treatment FDG PET evidence of pulmonary inflammation. This retrospective study found that the 95th percentile of the standard uptake value (SUV95) within the lungs was potentially a predictor of RP on multivariate analysis [85]. The value of SUV95 for assessing lung toxicity was similarly validated by the treatment modality of the SBRT technique [86]. Through quantitative assessment of FDG PET/CT imaging before and after radiation therapy in stage III NSCLC patients, a pilot study suggested that global lung parenchymal glycolysis and lung parenchymal SUVmean may serve as potentially useful biomarkers to lung inflammation after thoracic radiation therapy [87]. Moreover, based on pretreatment planning CT in patients after SBRT delivery, the radiomic predictive model of lung volume irradiated with more than 5 Gy (LV5) was considered the best for RP estimation than the DVH model [88]. By the combination use of cone-beam CT radiomics features (NGTDM25: Contras and others) and two pretreatment CT radiomics features (SHAPE: Mass and SHAPE:

Orientation), the prediction specificity of lung toxicity was further improved from 80.77% to 84.62% after SBRT in stage I NSCLC patients [89]. Therefore, it may contribute to the discovery of more convenient methods to predict RILI for patients with the development of noninvasive molecular imaging.

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