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Some Advances on Non-Collagenous Extracellular Matrix in Radiation Pulmonary Injury

Xiaolin Wang[1], Rong Wang[2], Zaitian Zhang[1], Yongtai Tang[1], Jianqing Zhang[3], Jin Wang[4], Ziyue Ma[5], Dongdong Peng[6*], Junming Luo[7*]

[1]The First Affiliated Hospital of Hunan Medical University, Changsha, China
[2]The Second Department of Radiotherapy, The Fifth People's Hospital of Qinghai Province, Xining, China
[3]Department of Gynecology, Qinghai Tibetan Hospital, Xining, China
[4]Qinghai Health Vocational and Technical College, Xining, China
[5]School of Medicine and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, China
[6]Kangyi Outpatient Department of Chengbei District Hospital, Xining, China
[7]Department of Pathology, Xiangya Changde Hospital, Changde, China
Email: *jluo099@163.com, *372013747@qq.com

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Abstract

Introduction: Radiation pulmonary injury (RPI) is a prevalent complication in scenarios such as nuclear radiation disaster accidents, nuclear terror events, chest tumor treatment, and bone marrow transplantation preconditioning. Alongside the swift advancement of molecular biology and cell detection technology, research on cell radiation damage and its adaptive mechanism is becoming increasingly profound. It disrupts normal tissue structure and function. Understanding and addressing this issue is crucial for maintaining health. Research on extracellular matrix disorders of RPI is ongoing to find better treatments. **Methods:** A systemic search was conducted in major databases, including Pubmed, Web of Science and Scopus on non-collegenous extracellular matrix in RPI. **Results:** The adverse effects of radiation exposure can potentially lead to severe and irreversible injuries. Radiation pulmonary injury, as a potential lethal factor for cell growth, influences the cell cycle, morphology, metabolism, signaling pathways, proliferation, differentiation, and apoptosis. At present, there are only limited data available about the cellular and molecular mechanism of non-collegenous extracellular matrix in RPI. Herein, we summarize the current accomplishments and discuss the future outlooks regarding the cellular and molecular events in radiation pulmonary injuries. **Conclusion:** Elucidating the cellular injury and its adaptive mechanism re-

*Corresponding author.

sulting from radiation exposure holds great significance and can also offer novel concepts for the treatment of related diseases.

Keywords

Radiation Pulmonary Injury, Fibrosis, Extracellular Matrix

1. Introduction

Radiation therapy for cancers not only eradicates tumor cells but also inflicts damage upon healthy cells and, at times, induces side effects that can prove fatal and impact a wide array of tissues and organs, such as the skin, intestine, brain, lung, liver, and heart etc. The lung is among the moderately radiosensitive organs. Environmental nuclear radiation disasters [1], nuclear terror incidents, chest tumor treatment [2] [3], and bone marrow transplantation preconditioning [4] can all give rise to radiation pulmonary injury. At least approximately 50% of all cancer patients undergo this form of treatment during their course of therapy. The lung is a susceptible target organ [5] during radiation therapy, particularly in the case of radiotherapy for thoracic malignancies. RPI has emerged as a major clinical issue due to its high incidence, inevitability, and sometimes even fatal side effects [6]. Up to the present, there is a dearth of effective treatment. RPI encompasses acute radiation pneumonitis and chronic radiation-induced pulmonary fibrosis, which most frequently occurs in the radiotherapy of lung cancer [2], esophageal cancer [7], and other thoracic cancers. The clinical manifestations of RPI comprise dry cough, shortness of breath, chest pain, fever, and even severe respiratory failure and death. The pathogenesis of radiation pulmonary injury is a complex process involving diverse cellular and molecular interactions, ultimately leading to acute radiation pneumonitis and chronic large fibroblast accumulation, proliferation, and differentiation, resulting in excessive extracellular matrix deposition and causing pulmonary fibrosis [8]. The cellular and molecular events have been extensively explored, and considerable progress has been made in recent years. In this article, we delineate the current comprehension of the clinical presentation, pathogenesis, and future directions. The emphasis is primarily on the homeostasis of non-collagenous filamentous networks in this condition.

2. Radiation-Induced Pulmonary Injury

Pulmonary injury is a common complication resulting from radiation therapy and is even more widespread than clinical symptoms [5] [6] [8]. According to statistics, the incidence of clinical radiation pneumonia ranges from 1% to 34%, while that of radiological changes can be as high as 13% to 100% [9]. These disparities might be associated with the variations in diagnostic criteria, follow-up duration, radiation techniques, exposure dosage, and exposure field among different diseases.

Radiation exposure can give rise to radiation-induced pulmonary injury, which can be categorized into three phases: the early, middle, and late stages. In the early stage (within 0 - 2 months after radiotherapy), the typical damage emerges in small vessels and capillaries, accompanied by hyperemia and enhanced permeability. During the middle stage (2 - 9 months after radiotherapy), pulmonary capillaries are obstructed by platelets, and fibroblasts infiltrate the alveolar walls, leading to interstitial fibrosis. At this stage, the illness is not severe and can still be resolved. However, if it keeps progressing, it will evolve into the advanced stage, mainly characterized by the progressive thickening of the alveolar septum, interstitial fibrosis, and sclerosis of blood vessels [10].

The pathological mechanism of radiation-induced pulmonary injury is aseptic and specific inflammation of the normal lung tissue within the irradiated area. The sustained damage to alveolar epithelial cells and the repeated damage (destruction), repair, and reconstruction of the extracellular matrix at the alveolar septum balance the synthesis and degradation of the extracellular matrix, ultimately leading to an excessive accumulation of the extracellular matrix in this area [11] (**Figure 1**).

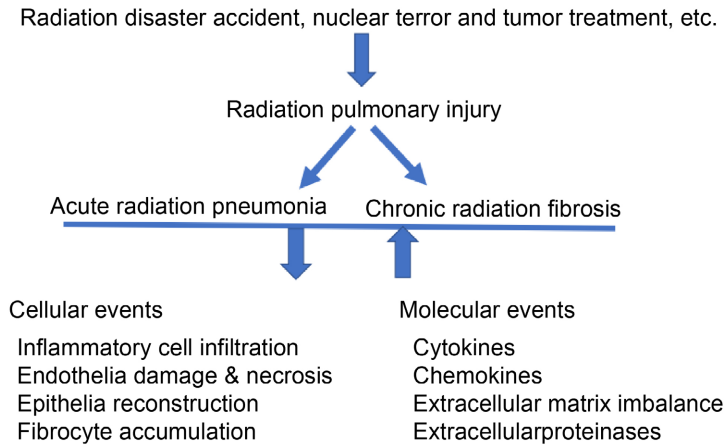

Figure 1. The framework of cellular and molecular events of radiation pulmonary injury.

3. Radiation-Induced Pulmonary Fibrosis

Interstitial lung disease is a group of diffuse pulmonary disorders, mainly involving the interstitial, alveolar, and bronchiolar sections of the lung, and is often termed as diffuse parenchymal lung diseases [11].

Radiation fibrosis typically occurs 6 to 24 months after radiotherapy and is a clinical syndrome resulting from the chest receiving radiation. Chronic lung injury and pulmonary fibrosis might be asymptomatic or merely characterized by breathing difficulties, and could occur in patients without a history of acute pneumonia. Irradiation can give rise to chronic lung dysfunction in patients and eventually lead to chronic cor pulmonale and pulmonary hypertension. Once radioactive pulmonary fibrosis emerges, it is hard to reverse, thus it is more crucial to

prevent the occurrence of this disease [12].

During the treatment of cancer patients, upon their receipt of radiotherapy, fibrosis emerges as a long-term and fatal side effect, giving rise to a variety of symptoms that markedly affect their quality of life [13]. This fatal side effect also has an impact on the effective strategies for preventing long-term disability and discomfort subsequent to radiotherapy [11]-[13].

An increasing number of factors have contributed to the risk of radiation-induced fibrosis. Crucial factors encompass the total dose of radiotherapy, the dose per fraction, the volume of exposed tissue, and the time course of treatment delivery, and so on [14]. Patients with connective tissue diseases [15], such as systemic scleroderma, systemic lupus erythematosus (SLE), or Marfan syndrome [16] [17], are regarded as a vulnerable factor for radiation-induced fibrosis. These patients are more inclined to develop severe radiation-induced fibrosis.

Genetic factors have also been discovered to exert an influence on the predisposition to radiation-induced fibrosis. For instance, genetic variants, single-nucleotide polymorphisms (SNPs), and several distinct loci such as CADM1(Cell Adhesion Molecule 1), SLAMF6 (Signaling Lymphocytic Activation Molecule Family Member 6), and CDKN1A (Cyclin-Dependent Kinase Inhibitor 1A) have been implicated [18]. More recently, a quantitative trait locus on chromosome 17 has been identified in the pulmonary fibrotic response [19]. The degradation of post-radiation extracellular matrix (ECM) genes like CAP1 (Cyclase Associated Protein 1), IL18 (Interleukine 16), MMP12 (Metaloproteinase 12), PER3 (Period Circadian Regulator 3), LTF (Lactotransferrin), and RAD51AP1 (RAD51 Associated Protein 1), etc. [20], as well as mitochondrial DNA, epigenetic modifications to DNA and histones have also been associated with radiation-induced fibrosis [21], as demonstrated by the suppression of the cutaneous radiation syndrome through histone deacetylase inhibitors [22].

The mechanism of radiation-induced fibrosis bears resemblance to that of any chronic wound healing process. In the early phase of radiation exposure, the acute inflammatory response leads to the recruitment and activation of fibroblasts, resulting in the excessive secretion of extracellular matrix. There are two main mechanisms of radiation injury: the first is direct DNA damage [23]; the second is the formation of free radicals through the ionization of radiation with water molecules [24]. Free radicals constitute a detrimental factor that can inflict damage on all cellular components, such as proteins, nucleic acids, and lipids [25] [26]. On the contrary, radiotherapy can give rise to various local cell impairments, including pulmonary epithelial cells and capillary endothelial cells, leading to thrombosis and aggravated hypoxia. Concurrently, injured cells can release a considerable number of chemokines and cytokines [23] [27] [28], thereby inducing non-specific inflammation. Additionally, thrombosis and ischemia intensify local damage, causing the further release of inflammatory chemokines and cytokines [29] [30].

The alveoli are an exquisitely designed structure. The various cells and extra-

cellular matrix of the alveolar septum are precisely regulated by numerous factors. The synthesis and degradation of extracellular matrix (ECM) in the alveolar septum is also a complex process that is controlled. Radiotherapy leads to the subsequent deposition of extracellular matrix in the alveolar septum of fibrous tissue and fibrosis. Connective tissue growth factor (CTGF) plays a crucial role in the remodeling of alveolar septa in radiation-induced fibrogenesis and promotes the development of fibrosis in multiple scenarios, including pulmonary radiation injury [31]-[33]. Blocking CTGF alleviates radiation-induced pulmonary remodeling and can reverse the process after its initiation. FG-3019, one of the CTGF inhibitors, might be beneficial for patients with radiation-induced pulmonary fibrosis or those with other forms or origins of chronic fibrotic diseases. Radiotherapy is a main treatment modality for lung cancer, which can induce pneumonitis or pulmonary fibrosis. The matricellular protein CTGF is a central mediator of tissue remodeling [31]-[33].

Non-collagenous filamentous network in radiation-induced pulmonary injury

Multicellular organisms comprise not merely cells but also a considerable number of extracellular matrix proteins. The extracellular matrix is most prevalent in connective tissues, occupying the majority of the space of connective tissues, and is mainly secreted by fibroblasts, endothelia, and epithelia [34]-[36]. The molecule of extracellular matrix protein is not only a crucial component in maintaining the morphology of cells from damage but also an important participant in intercellular communication [34]-[36].

It is mainly composed of a collagen network protein, proteoglycans, and non-collagen filamentous network protein. The first one is a network of structural proteins, encompassing collagen and elastin, which respectively bestow strength and toughness upon the extracellular matrix. The second one is a covalent composition of protein and polysaccharide, highly hydrophilic in nature, and distributed in the extracellular space—the extracellular matrix (ECM), conferring stress resistance to the extracellular matrix. The third is non-collagenous filamentous network proteins, such as fibronectin, Cartilage Oligometic Matrix Protein (COMP), laminin, and matrilins, etc., which assist cells in attaching to the extracellular matrix. In recent years, greater attention has been directed towards the role of non-collagenous microfilamentous network proteins in maintaining the biological functions of tissues and cells and the homeostasis of the extracellular matrix. More recent findings indicate that non-collagenous microfilamentous network proteins can be regarded as intracellular information transducers. They form an extracellular filamentous network and play a significant role in connecting the extracellular collagen fiber network with membrane surface receptors. It assumes an important role in various physiological functions such as intracellular information transmission and exchange [34]-[36].

The homeostasis of the extracellular non-collagenous matrix network depends on the dynamic balance between the synthesis and degradation of this protein, which directly affects the communication relationships between the extracellular

matrix and cells, as well as between cells and matrices. For example, matrilin-2 is an adapter molecule that can form collagen-dependent and collagen-independent extracellular matrix networks. Current research has shown that matrilin-2 is closely related to other extracellular matrix proteins, such as collagen fibers and cell membrane protein molecules, especially integrin and BMP [37]. There are seven Smad binding sites in its promoter region and may also be regulated by certain transcription factors [11] [37]. Its participation in a series of cell functions has positive biological significance for maintaining the homeostasis of the extracellular matrix [11] [36] [37]. Our studies on mouse mesangial cell lines treated with high glucose indicated that high glucose induced a high level of matrilin-2 expression in this cell line, and its activity was inhibited by TGF-β1 and Smad [11] [36] [37]. Furthermore, we discovered high levels of matrilin-2 protein and mRNA expression in the lung tissues of irradiated mice, as well as in the irradiated HPAEpiC cell line. These discoveries suggest that matrilin-2 plays a vital role in the structural disorder and fibrosis of the extracellular matrix [38].

4. A Comparative Summary of Major Non-Collagenous ECM Proteins in RPI

A concise subsection or table should synthesize key non-collagenous extracellular matrix (ECM) proteins linked to radiation-induced pulmonary injury (RPI) and their evidence levels.

Key proteins include:

Fibronectin: Stronger causal support exists—preclinical studies demonstrate that blocking fibronectin's integrin-binding domain reduces myofibroblast activation and collagen deposition. Yet, human translational data (e.g., serum fibronectin levels correlating with clinical fibrosis severity) lack interventional trials to validate it as a therapeutic target.

Tenascin-C: Evidence is largely correlative. Elevated tenascin-C in fibrotic lungs correlates with disease stage, but functional studies (e.g., tenascin-C neutralizing antibodies) show inconsistent anti-fibrotic effects across models, suggesting context-dependent roles that require further clarification.

Overall, most evidence relies on association rather than causation; more mechanistic studies (e.g., genetic manipulation, targeted inhibition) and well-powered human cohort analyses are needed to establish these proteins as key drivers of lung fibrosis.

Current evidence linking matrilin-2 to lung fibrosis is preclinically focused but mechanistically incomplete. Rodent models (e.g., bleomycin-induced fibrosis) show matrilin-2 upregulation in fibrotic foci, colocalizing with activated fibroblasts; however, causal links remain unproven—knockout/overexpression studies to confirm its direct role in fibrosis progression are scarce, limiting evidence strength.

5. The Extracellular Proteinases

Extracellular proteases are of vital significance for numerous developmental and

homeostatic processes. The malfunction of extracellular protease or its substrate may give rise to excessive degradation or accumulation of macromolecules within the extracellular matrix, thereby causing various human diseases. For example, the degeneration and loss of macromolecules in the extracellular matrix of the lungs can lead to severe impairment of lung function. Extracellular proteases encompass the well-defined matrix metalloproteinases (MMPs) and members of the ADAMTS (A Disintegrin and Metalloproteinase and Thrombospondin Motifs) family. Here, we place greater emphasis on ADAMTS. The molecular structure of ADAMTS protease is composed of the Adam-like protease domain and the matrix-binding extracellular matrix protein of thromboreactive protein 1-repeat. [39] [40]. There exist two types of aggrecanase in the lungs, namely aggrecanase-1 (ADAMTS-4) and aggrecanase-2 (ADAMTS-5), which are upregulated in human fibrosis. They are accountable for the degradation of aggrecan in the absence of other matrix metalloproteinases [41]. ADAMTS-4 is a glutamyl endopeptidase that has a preference for the Glu-Xaa bonds of the core proteins of proteoglycans such as aggrecan, brevican, and versican [42] [43]. This proteolytic process is believed to rely on the presence of glycosaminoglycans in the substrate [44]-[46].

Potential biomarker for predicting the risk of Radiation-Induced Fibrosis

Biomarkers can exert a crucial role in radiological events [47]. A growing number of biomarkers have furnished valuable information regarding the subsequent developing consequences, which might encompass the treatment strategy. Surfactant protein D (SP-D) is an essential host defense molecule secreted by type II pneumocytes and is utilized to evaluate lung epithelial injury in several lung injury models [48] [49]. The serum SP-D level is highly sensitive to variations in individual radiation sensitivity and is associated with the development of fibrosis. It can be detected at an early stage after exposure and possesses specificity for radiation damage. This indicates that the level of serum SP-D might be a valuable biomarker for radiation-induced pulmonary fibrosis [50].

The imbalance of extracellular matrix metabolism is considered as the most crucial pathological basis of radiation lung injury [51]. Our previous study revealed that non-collagen filament network proteins, such as matrilin 2, play a vital role in the imbalance of the extracellular matrix during radiation exposure [11]. From the animal model and HPAEpiC (Human Pulmonary Alveolar Epithelial Cell) cell culture, the results suggested that the mRNA and protein levels of matrilin 2 were increased after irradiation treatment in both lung tissue and HPAEpiC cells. Furthermore, overexpression of matrilin 2 suppresses the proliferation and promotes the apoptosis of HPAEpiC cells, while downregulation of matrilin 2 inhibits irradiation-induced apoptosis of HPAEpiC cells. Matrilin 2 promotes G1 phase arrest via the p53/p21 pathway. Collectively, these data suggest that matrilin 2 might be a potential target for regulating the pathogenesis of radiation-induced pulmonary injury [11].

6. Confounders in Interpreting Post-Irradiation ECM Changes

Concurrent therapies and infections complicate linking ECM changes to irradia-

tion. Chemotherapeutics (e.g., bleomycin) directly damage lung tissue, accelerating collagen deposition independently of radiation. Immunotherapy (e.g., PD-1 inhibitors) triggers immune-related pneumonitis, altering ECM remodeling via inflammatory cascades. COVID-19 infection induces acute lung injury, with viral-induced fibrosis and inflammation overlapping radiation's ECM effects. These confounders may amplify or mimic radiation-driven ECM alterations, requiring stratification in analyses to isolate radiation's specific impact.

In the "Biomarker" section, integrate recent pre-clinical and early-phase clinical data. For instance, a 2023 pre-clinical study by FibroGen found that FG-3019, a CTGF blocker, reversed radiation-induced lung fibrosis in mice, improving lung function and survival (FibroGen, 2023). Aileron Therapeutics' phase 1b trial in 2024 on LTI-03, an anti-fibrotic drug, showed positive trends in reducing profibrotic proteins in idiopathic pulmonary fibrosis patients (Aileron Therapeutics, 2024).

In "Future directions", GRI Bio presented pre-clinical data in 2024 that GRI-0621 reduced inflammatory and fibrotic drivers in a mouse model of IPF (GRI Bio, 2024). These findings suggest potential future research directions for treating fibrosis.

7. Future Directions

Radiation-induced pulmonary injury is a potentially fatal clinical complication resulting from radiation exposure. It has not been recognized as a treatment option for patients with radiation-induced pulmonary fibrosis, partly because of the absence of effective targets. Current research advancements in the cellular and molecular events of radiation-induced pulmonary injury offer an in-depth comprehension of acute radiation pneumonitis and chronic radiation pulmonary fibrosis. The insights gained from this study have heightened interest in disease progression and prognosis, triggered the development of novel anti-fibrosis drugs, and provided a more targeted approach to the treatment of radioactive pulmonary fibrosis. Particularly, in-depth investigations into the pathogenesis and industrialization of biomarkers will possess potential application prospects for the early diagnosis, prognosis, and identification of candidate drugs for prevention and treatment.

8. Conclusions

Research on the cellular and molecular mechanisms of radiation-induced lung injury has made certain progress; however, there has been strikingly limited advancement in the development of safe and effective therapeutic strategies. Therefore, further research on the prevention and treatment of radiation pulmonary injury is requisite.

In this article, we underscore the significance of cellular and molecular events in maintaining the homeostasis of non-collagenous extracellular matrix proteins during radiation therapy. Consequently, more cell lines, animal models, and clin-

ical trials are indispensable for such research. In conclusion, recent advancements in molecular knowledge have given rise to more sustainable developments, facilitating studies targeting epithelial damage, fibroblast-specific changes, and the regulation of inflammatory cells during fibrosis, as well as epithelial-mesenchymal crosstalk.

The emergence of multisystem involvement in COVID-19 can lead to a similar etiology between SARS-CoV-2 infection and radiation damage. Moreover, this intersection between radiation pulmonary injury and COVID-19 might suggest approaches that could expedite the discovery of treatments for both.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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