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RADIATION–INDUCED LUNG INJURY. LITERATURE REVIEW

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Abstract

Introduction. Despite the numerous data about results of morphological studies of lungs at the cellular and tissue levels in different radiation situations, and also regarding connection assessment of increasing bronchopulmonary diseases with the values of external and internal doses exposure during acute and long–term periods, hitherto not fully explored the association revealed pulmonary disorders with exposure to γ– and neutron radiation effects, it is not fully proven the value of radiation dose and duration of radiation influence on the nature of detectable pathology, there are no systemic data about morphogenesis of their damaging effect on the lungs.

The review purpose was to analysis of the literature regarding the nature of morphofunctional disorders in the lungs during exposed to radiation of different levels and types.

Materials and methods. To achieve this purpose we have searched and analysis of scientific publications. All received working to the review formation has been indexed in the databases PubMed, Medline, E–library, Cyberleninka using «Google Scholar» scientific search engine. The following search filters have been delivered before the start of the search: experimental studies carried out on mice and rats, for the past 10 years, published in English, Japanese and Russian languages, as well as full versions of papers with legibly formulated and statistically proven conclusions. Exclusion criteria included a review of publications became summary reports, newspaper articles and personal notifications.

Results. Analysis of published data showed that radiation–induced lung injury defined by the defeat by bronchial lesion, causing the development of atelectasis with subsequent connective tissue organization, serous–fibrinous alveolitis with epithelial desquamation, vascular damage and endothelial proliferation, increased vascular permeability with excretion of plasmatic proteins. It should be noted that the secondary immunodeficiency condition, developing under the influence of radiation factor are realization of pathogenetic mechanisms that contributes to formation of inflammatory and fibrotic processes in the lungs, inducing development of acute inflammatory infiltrative pneumonitis and chronic fibrosing pneumonitis.

Conclusion. The findings data support a role of ionizing radiation in the formation of morphological signs of the radiation–induced pneumonitis and pulmonary fibrosis which are form of lung damage depending on both the dose and type of radiation. According to result of majority of leading research in the field of radiology regarding the assessment of neutron radiation effect on the lungs, there is no consensus. Thus, radiobiologists and morphologists have opportunity to continue studies concerning neutron radiation effects, moreover to evaluate and compare the degree of pulmonary structural changes, which will develop diagnostic criteria for the study of persons' lungs exposed to different types of ionizing radiation.

Keywords: *ionizing radiation, pulmonary pathology, morphofunctional changes, pro–inflammatory mediators, lung fibrosis.*

Резюме

РАДИАЦИОННО–ИНДУЦИРОВАННЫЕ ПОВРЕЖДЕНИЯ ЛЕГКИХ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Несмотря на существующие многочисленные данные по результатам морфологических исследований легких на клеточном и тканевом уровнях в различных радиационных ситуациях, по оценке связи увеличения бронхолегочных заболеваний с величинами доз внешнего и внутреннего облучения в остром и отдалённом периодах, до настоящего времени не до конца изучена связь выявленных легочных нарушений с воздействием γ– и нейтронного излучения, не полностью доказано значение дозовых нагрузок и длительности радиационного влияния на характер выявляемой патологии, отсутствуют системные данные о морфогенезе их повреждающего действия на легкие.

Целью обзора явился анализ литературы о характере морфофункциональных расстройств в легких при разных уровнях и типах радиационного воздействия.

Материалы и методы исследования. Для достижения поставленной цели нами проведен поиск и анализ научных публикаций. Все принятые к формированию обзора работы были индексированы в базах данных PubMed, Medline, E–library, Cyberleninka при помощи научной поисковой системы «Google Scholar». Перед началом поиска были выставлены следующие поисковые фильтры: экспериментальные исследования, выполненные на мышах и крысах, в течение последних 10 лет, опубликованные на английском, японском и русском языках, а также полные версии статей с чётко сформулированными и статистически доказанными выводами. Критериями исключения публикаций в обзор стали резюме докладов, газетные публикации и личные сообщения.

Результаты. Анализ литературных данных показал, что радиационно–индуцированные повреждения легких определяются поражением бронхов, вызывающем развитие ателектазов с последующей соединительнотканной организацией, серозно–фибринозным альвеолитом с десквамацией эпителия, поражением сосудов, с пролиферацией эндотелия, повышенной проницаемостью сосудов с выхождением белков плазмы. Следует отметить, что вторичные иммунодефицитные состояния, развивающиеся под действием радиационного фактора являются патогенетическими механизмами, реализация которых способствует формированию воспалительных и фибротических процессов в легких, обуславливающих развитие острого воспалительно–инфильтративного пневмонита и хронического фиброзирующего пневмонита.

Выводы. Полученные данные подтверждают роль ионизирующего излучения в формировании морфологических признаков, характерных для радиационно–индуцированного пневмонита и фиброза легких, являющихся формой повреждения легких, зависящая не только от дозы, но и от вида излучения. По результатам большинства ведущих исследований в области радиологии по вопросу оценки действия нейтронного излучения на легкие нет единого мнения. Таким образом, для радиобиологов и морфологов представляется несомненной актуальность

продолжения исследований, посвященных изучению воздействия нейтронного излучения, оценить и сравнить степень структурных изменений в легких, что позволит разработать диагностические критерии при исследовании легких лиц, подвергавшихся воздействию различных видов ионизирующего излучения.

Ключевые слова: *ионизирующее излучение, легочная патология, морфофункциональные изменения, провоспалительные медиаторы, фиброз легких.*

Түйіндеме

РАДИАЦИЯ ӘСЕРІНЕН ТУЫНДАҒАН ӨКПЕ ЗАҚЫМДАНУЛАРЫ. ӘДЕБИЕТТЕРГЕ ШОЛУ

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Семей қаласының мемлекеттік медицина университеті, [1] Патологиялық анатомия және сот медицина кафедрасы, [3] Тағамтану және гигиеналық пәндер кафедрасы, Семей қ., Қазақстан;
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Кіріспе. Көптеген радиациялық жағдайлар кезінде туындайтын өкпенің жасуша мен тін деңгейіндегі морфологиялық зерттеулердің сан алуан нәтижелері бар екеніне және бронх–өкпелік аурулар саны жоғарылауының жедел мен кейінгі кезеңдердегі ішкі мен сыртқы сәулелеу дозаларының мөлшерімен байланысын бағалаудағы мәліметтің бар болуына қарамастан, қазірге дейін өкпелік бұзылыстардың γ– мен нейтрон сәулелері әсерімен байланысы аяғына шейін зерттелмеген, аңғарылған дерттің сипатына радиациялық ықпалдың ұзақтығы мен дозалық жүктеменің мәні де толықтай дәлелденбеген, сонымен қатар олардың өкпеге зақымдаушы әсерінің морфогенезі жайлы жүйелік ақпараттың жоқтығы да күмән тудырмайды.

Әдеби шолудың мақсаты – радиацияның түрлі деңгейі мен типтерінің әсері кезінде өкпедегі морфофункционалды бұзылыстардың сипаты туралы ғылыми әдебиеттерді талдау.

Материалдар мен әдістер. Алға қойылған мақсатты жүзеге асыру үшін ғылыми жарияланымдар табылып, талқыға салынған. Әдеби шолуды іске қосуға ұсынылған барлық жұмыстар «Google Scholar» ғылыми іздеу жүйесі арқылы PubMed, Medline, E–library, Cyberleninka базаларында индекстелген. Таңдау алдында келесі шарттар ескерілген: ағылшын, жапон және орыс тілдерінде жарияланған соңғы 10 жыл ішіндегі тышқандар мен егеуқұйрықтарға жасалған эксперименттік зерттеулер, сонымен қатар айқын мәлімделген және статистика тұрғысынан дәлелденген қорытындылары бар мақалалардың толық ақпараты қолданылған. Әдеби шолу кезінде баяндамалар тұжырымдары, газет мақалалары мен жеке іс ақпараттары қажет емес жарияланымдар ретінде қолданылмаған.

Нәтижелер. Әдеби мәліметтерді талдау радиация әсерінен туындаған өкпе зақымдануларының ателектаздар мен дәнекер тіндік организациясы дамуын тудыратын бронх бүліністерін, эпителий десквамациясымен көрінетін серозды–фибринозды альвеолитпен, эндотелий пролиферациясымен және плазма нәруыздары шығуына алып келетін қантамыр қабырғасы өткізгіштігі жоғарылауымен анықталатын қантамыр бұзылыстарымен сипатталатынын көрсетті. Жедел қабынулық–инфильтрациялық пневмонитті және созылмалы фиброздаушы пневмонитті тудыратын өкпедегі қабынулық пен фиброздық үрдістердің

қалыптасуын жүзеге асыратын патогенездік механизмдер ретінде радиациялық фактор әсерінен дамитын екіншілік иммундық тапшылықты жағдайлардың болып табылатынын айта кеткен жөн.

Қорытынды. Алынған нәтижелер иондаушы сәулелердің өкпе зақымдануларының бір түрі болып табылатын радиациялық–индукцияланған пневмонит пен өкпе фиброзына тән морфологиялық белгілердің дамуындағы рөлін дәлелдейді. Бұл белгілер сәуленің дозасы мен түріне байланысты туындайды. Радиология саласындағы көптеген зерттеулердің нәтижелеріне сай нейтронды сәулелердің өкпеге әсерін бағалаудағы ортақ көзқарастардың қалыптаспағаны анықталды. Демек, радиобиологтар мен морфологтарға нейтронды сәулелердің әсерінен туындайтын өкпедегі құрылымдық өзгерістер деңгейін бағалау мен салыстыру ықпалын қарастыруға арналған зерттеулерді жалғастырудың өзектілігі еш күмән тудырмайды. Бұл әр түрлі иондаушы сәулелер әсеріне ұшырағандардың өкпесін зерттеу кезіндегі диагностикалық нышандарды құрастыру мүмкіндігін туғызады.

Негізгі сөздер: *иондаушы сәулелер, өкпе патологиясы, морфофункционалды бұзылыстар, қабыну медиаторлары, өкпе фиброзы.*

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Introduction

It is known that in 2012, a technical meeting and symposium were held to discuss the problem of residual radiation exposures to the A–bomb survivors of Hiroshima and Nagasaki [50]. It was allowed for participants to evaluate the use of data from many different research programs in clarifying the potential residual radiation doses to survivors of Japanese cities bombing. Factors for the evaluation of exposure to γ– and neutron radiation at both cities are discussed in the external and internal doses from residual radiation exposure. Questions were asked about the conclusion that manganese–56 (^{56}Mn) is the most important radionuclide, and offering were made to consider not only half–lives but the number and energies of γ–rays emanated by each radionuclide and time–dependent survivor actions. Radiobiologists concluded that the methodological guides on external and internal dose estimation developed for the public living near Semipalatinsk Nuclear Test Site can be applied with modifications to the conditions of residual radiation exposure to Japanese A–bomb survivors. A view, based on an analysis using a multi–step pathologic process model, suggests that residual radiation doses in Hiroshima were approached to 2 Gy to match the modeled incidence. This analysis suggests a residual γ–dose that could dominate over the initial radiation dose for most survivors [49]. Therefore, the radiation dose of critical organs affected by the A–bombing should be particularly taken into account [39]. Scientists have long been proven that exposure to ionizing radiation can cause long–term effects, such as chronic inflammation and diffuse fibrosis of the affected organ and tissue [14, 98]. Nevertheless, despite decades of research the pathophysiological mechanisms of fatal radiation–induced lung injury in organ level warranted further investigations [51]. Moreover, the presence of numerous data on the results of morphological study of the lung at the cellular and tissue levels in different radiation situations, according to the connection of increasing bronchopulmonary diseases with the values of external and internal doses exposure during acute and long–term periods. Did not fully demonstrated the link identified pulmonary disorders with exposure to γ– and neutron

radiation, it is not fully proved the value of radiation dose and duration of radiation effect on the nature of detectable pathology, there are no system data on the morphogenesis of their damaging effect on the lungs.

The research purpose: identification of differences between the nature of the structural changes in the lungs at different levels and types of radiation exposure.

Materials and methods

To achieve this purpose we have searched and analysis of scientific publications. All received working to the review formation has been indexed in the databases PubMed, Medline, E–library, Cyberleninka using «Google Scholar» scientific search engine. The following search filters has been presented before the start of the search: experimental studies carried out on mice and rats, for the past 10 years (from 2006 to 2016), published in English, Japanese and Russian languages, as well as full versions of papers with legibly formulated and statistically proven conclusions. The key points of search requests were submitted to the following elements: «ionizing radiation», «pulmonary pathology», «morphofunctional changes», «pro–inflammatory mediators», «pulmonary fibrosis».

Exclusion criteria included a review of publications became summary reports, newspaper articles and personal notifications. There were found 1210 literary sources of which were for analysis selected 100 papers. After fulfillment the stage of automatically search we had conducted the search of publications by «simple method», which made it possible further to identify the scientific sources included in this review.

Results and discussion

It was proved that lung exhibits the abrupt dose–related response to ionizing radiation [99]. At estimate the internal doses in rat organs exposed to neutron–activated ^{56}Mn using nuclear reactor (Experimental facility «Baikal–1», Kurchatov, Kazakhstan) with neutron flux 4×10^{14} n/cm² [7], the highest doses were recorded in the lung. Consequently, the cumulative absorbed dose of internal radiation exposure for the first version (without forced ventilation) was equal to 0.1 Gy, and for the second variant of radiation (with forced ventilation box with animals) cumulative absorbed dose of internal radiation was 0.03 Gy for the lung, respectively [8]. Therefore, currently, particular interest is a comparative characteristic of morphofunctional changes in the persons' lung exposed to ^{60}Co and ^{56}Mn, allowing to identify the informative criteria for assessing the effect of the radiation factor on the respiratory organs, depending on the acumulative dose [89].

Radiation–induced lung injury (RILI) produces an eligible pre–metastatic microenvironment for cancer cells [34]. According to many scientists, one of the common neoplastic diseases ascribable to ionizing radiation in A–bomb survivors and nuclear reactor workers are lung cancers [1, 2, 74], which accounts for almost a quarter of radiotherapy–induced secondary malignant tumors [5, 6, 56]. Some researchers argue that radiation–induced pulmonary injury of varying severity still significantly affects the quality of patients life, and may even lead to death [81, 92]. According to the results of foreign authors, about 10–15% of non–small cell lung cancer patients develop severe lung toxicity after chest irradiation, and a significant percentage of patients die due to irreversible pulmonary inflammation [13, 27, 78, 79].

It is known that development of lung damage after radiotherapy is a continuous process that can be attributed to radiation damage in parenchymal cells, specifically the inflammatory, fibroblastic, and epithelial cells, that appear to play the most critical roles in radiation–induced pulmonary pathogenesis [85]. However, available data on histological alterations after radiotherapy human lung is limited, since patients are unlikely to give consent for diagnostic thoracotomy and autopsy. The existing histological data have mostly come from animal models [96]. For this reason, animal models that reproduce radiation injuries in humans are mandatory. Rodents are the animal models of selection, because they are well characterized, easy to work with, and have genetically altered strains accessible for advanced research [28, 95]. It was experimentally confirmed that the lungs are damaged when exposed to a single lethal dose of γ–radiation. Several radiation dose– and time–dependent tissue outcome develop following acute high–dose radiation exposure. One of the recognized delayed effects of such exposures is pulmonary injury, characterized by respiratory failure as a

result of pneumonitis that may subsequently develop into lung fibrosis. Since this pulmonary subsyndrome associated with high morbidity and mortality [29]. It should be noted that clinically, radiation induced lung toxicity also manifested by cough, fever, shortness of breath and other signs of respiratory failure [15, 21].

One of acute or subacute form of the lung damage related to radiation dose is radiation pneumonitis (RP) [45]. RP always associated with fibrosis and never relapses, while organizing pneumonia (OP) usually resolves without fibrosis but commonly relapse [24, 66]. OP is identified inside and outside of the tangential irradiated field and occurs independent of the radiation dose. Also, OP lesions are characterized by lung infiltrates out side the radiation field and frequently migrate. This type of pneumonia is a form of lung toxicity that arises due to some interaction between radiotherapy and the immune system, which may also explain the occurrence of OP lesions outside the irradiated field. It is an important question why OP occurs after radiotherapy for breast cancer more frequently than after radiotherapy for other malignancies. Lungs are often exposed to radiation for the treatment for malignant tumor. Late damage to the lung, which usually manifests as fibrosis, is a radiation dose–dependent occurrence in patients undergoing radiotherapy for lung cancer. The incidence of OP after radiotherapy in patients with breast cancer significantly higher than another one. In contrast, RP occurs much more commonly after radiotherapy in patients with lung cancer [67].

As is known that underlying molecular and cellular mechanisms of RP are very complex [10, 59, 75, 77]. Although the molecular mechanism for RP is complex and obscure, involvement of cytokines, chemokines, and cell adhesion molecules has been implicated [15, 21]. Many investigators have shown that in the pathogenesis of RP or alveolitis essential roles play interleukins (IL) [42, 82, 93] produced through epithelial cells [46]. Clinical as well as experimental findings have suggested the participation of IL–6 as a pro–inflammatory cytokine in RP [18]. RILI includes various types of radiation damage of target cells and the release of multiple inflammatory mediators [30, 44]. A number of authors have described the mechanisms of interaction of the pulmonary and cardiac pathology that associated with development of RILI [31, 90]. It was noted that in rats exposed to letal dose of γ–radiation is observed loss of pulmonary vessels, right ventricular hypertrophy, increased pulmonary vascular resistance, an increase in the dry weight of the lungs and reduce the overall activity of pulmonary angiotensin–converting enzyme (ACE), and extensibility of the pulmonary artery. In contrast, subletal dose alone resulted in a moderate increase in weight of the right ventricle and the decrease in the activity of ACE in lungs [32]. This data confirm the clinically significant lesions that appear in time and on the dose–exposure after a relatively low radiation doses [60]. Irradiation with 10 Gy resulted in increased breathing rate, a reduction in oxygen saturation, an increase in bronchoalveolar lavage fluid protein and attenuation of vascular reactivity between 2–3 months after irradiation. These changes were not observed with the lower dose of 5 Gy. Histological examination revealed perivascular edema at 4–8 weeks after exposure to both doses, and mild fibrosis beyond some month after fatal dose of γ–radiation [62, 100]. Some authors believe that pulmonary vascular resistance associated with hypoxia of the lung tissue and decreased cardiac output [73, 87]. Thus, lethal RP may happen if a large volume of normal lung tissue is irradiated, even at dose lower than 5 Gy [43].

In a setting of chronic inflammation, the persistent lung tissue damage and cellular proliferation are associated with superfluous of reactive oxygen species (ROS) [11, 72]. It has been suggested that the generation of ROS instantly after irradiation, together with a cyclic up–regulation of cytokines and the recruitment of inflammatory cells are responsible for the injury observed in the lung [23, 25]. Thereby, accumulation of lipoperoxidation (LPO) products in the lung tissue homogenates caused by free radicals effects after γ–radiation exposure was noticed by several authors. Free radical–mediated LPO is harmful not only because damaged lipids disrupt the structure of pulmonary cell membrane, but also because the process produces potentially mutagenic and carcinogenic byproducts. One such product is the highly reactive carbonyl compound, malondialdehyde (MDA), which can react with deoxyadenosine and

deoxyguanosine in deoxyribonucleic acid (DNA) to form DNA adducts. LPO reactions can occur at the both the cellular membrane and mitochondria membranes, and either can subsequently trigger cell death through apoptosis [3, 4].

It was considered that tissue reactions in cases where the threshold dose has been exceeded may be of the inflammatory type resulting due to the cellular factors release, or can be reactions resulting from cell lesion [84]. The time at which an effect may be discovered depends on the temporal course of the injury and progresses with time after irradiation [36]. It is known that radiation activates immunity via initiation of T–cells recruitment [16, 54]. More relevant than the availability of lymphocytes in the irradiated lung is their profile of secreted mediators. In particular, the pro–inflammatory T–helper cells oppose the pro–fibrotic T–lymphocytes [37]. As evidenced by a number of authors, the T–helper response to thoracic irradiation of different lines of mice has not been reported, but mouse strains have been shown to differ in their cytokine response post radiation and in gene expression profiles suggestive of differing adaptive immune responses [38, 47, 52, 83]. Thoracic irradiation causes also activation of various immune cells into the lung, including monocytes, neutrophils and basophils, that are responsible for local and systemic expression of mediators after radiation exposure [22, 48, 57], which are important in the pathogenesis of lung injury [97]. It should be noted that inflammatory infiltrates appear as secondary effects in the setting of high–single or fractionated radiation doses [51]. Basically, irradiation induces tissue injury across sensitization of autoreactive lymphocytes, reacting with lung tissue [64]. Endogenous and migrating leukocytes together with lung epithelial and endothelial cells create a feedback loop where stimuli from damage responses can activate alveolar and interstitial macrophages [19]. Various inflammatory mediators released from injured alveolar and interstitial cells produce inflammation, which also increase of vascular permeability. Moreover, the alveolar space is filled with exudates because of direct radiation damage and inflammatory process [69].

It was experimentally confirmed that in the rats, morphologically, mild interstitial inflammatory cell infiltration was observed at third day and intra–alveolar hyaline material was found at second week after γ–irradiation. Concerning focal irradiation, numerous foamy macrophages aggregated in a distal part of the irradiated area, while hemosiderin–laden macrophages were observed in the center of the irradiated zone. Two month after irradiation, the hyaline materials fragmented and disappeared to a definite extent, and fibrous exudates were present in the air spaces along with inflammatory cellular infiltration. The alveolar inflammation score at 2 weeks post–irradiation characterised by a small amounts of collagen which were detected in the intra–alveolar and interstitial areas. At 1 month after irradiation, extensive collagen was observed, correlating with late–stage fibrosis [41]. It is important to note that pathological final stage which characterised by excessive deposition of this fibrillar component in the pulmonary interstitium leads to disorder of normal gaseous exchange [65, 80]. Pathologists' results showed minimal edema and minimal to mild increase of cellularity in alveolar walls, interstitial inflammation, enlargement and atypical pneumocytes by 3 month post irradiation [58]. Histologically, lung tissue of irradiated rats include also highly thickened, corrugated and distorted arterial walls with different granulomatous masses, and also congested alveolar septae, highly elongated and branched bronchioles, their lumen contained debris of degenerated epithelial cells with ruptured epithelial lining of these bronchioles and dense fibrous layers nearby them [9]. After radiation effect the majority of pneumocytes are lost at which point alveolocytes begin to proliferate and produce important biopolimers to repair the surrounding injury changes [68].

Depending on both radiation dose and volume, lung injury is characterized by formation of pulmonary fibrosis [35, 94] that is integral to development and progression inflammatory airway diseases, including asthma, chronic bronchitis and bronchiectasis, where histological development of airway remodeling correlates with irreversible lesion of lung function. Diffuse parenchymal pulmonary diseases are a heterogeneous group of illnesses characterized by various degrees of lung inflammation and fibrosis [61]. Pathohistologists showed that

fibrogenesis phase was characterized by development of typical fibroblast foci in lungs irradiated animals. Furthermore, the later fibrogenesis phase was accompanied by a strong second onset of leukocyte infiltration that began some month after irradiation. At later time points the fibrotic foci evolved and combined into widespread fibrosis with remodelling of the lung architecture [53].

Kazakhstan morphologists featuring Japanese researchers revealed that in majority of experimental animals exposed to neutron–activated ^{56}Mn on the 3rd and 14th days after irradiation observed thickening of intra–alveolar septa in virtue of leucocytes, erythrocytes, lymphocytes, histiocytes, alveolocytes, and on the 60th day was found fibrosis phenomenon, whereas like rats exposed to γ–radiation except signs of inflammation were noted foci of emphysematous expanded alveoli [89]. Pathologists reported that, especially, the combination of pulmonary fibrosis and emphysema, which are defined by the presence of emphysematous foci and overgrowth of connective tissue in the same patients lung, has a poor prognosis, similar to that of idiopathic pulmonary fibrosis [76]. Although according to some scientists, none of the currently accepted animal models of radiation–induced lung fibrosis accurately mimic human idiopathic pulmonary fibrosis [63, 71, 86].

Scientists have proved that susceptibility to fibrosis can be a strain–specific or organ–specific. A systematic review was conducted to obtain the results of the feasibility of using a particular mouse strain to simulate the human body specific fibrotic pathology. Such information is useful in determining which genetic signatures are associated with susceptibility to fibrosis and also important to identify individuals susceptible to the development of a fibrotic phenotype in the organ following injury [91]. Regulation mechanism of lung fibroblast proliferation remains not fully understood. To elucidate the key molecules in it, the authors established mortal and immortal nontransformed lung fibroblast cell line or strains with elongated life span by telomerase reverse transcriptase gene transfection. Comparing the expression profiles of them, genes were explored to be the candidates responsible for regulation of cellular proliferation of lung fibroblasts. This set of fibrobrast strains of same origin with different proliferative capacities may become useful model cells for research on lung fibroblast growth regulation and the candidate genes explored that may provide biomarkers or therapeutic targets of pulmonary fibrosis [40]. Combining genomic approaches identified variation within specific genes which function in the tissue response to injury as associated with fibrosis following thoracic irradiation in mice [70]. Thus, whole–genome studies have provides a useful conception into that gene patterns may influence the development of fibrotic process to various injurious agents [12].

Equally important is the fact that, microvascular injury is a prominent feature of normal tissue radiation injury and plays a decisive role in both inflammatory and fibrotic radiation responses. Injury of the vascular endothelium is presumed to play a principal role in the response of most normal tissues to ionizing radiation and to the progressive character of chronic radiation fibrosis. This is particularly true for chronic radiation toxicity, in which microvascular injury seems to be a key to the unique self–perpetuating nature of radiation injury [17]. Others authors have demonstrated that the recovery after vascular injury and reendotelization enhanced by circulating endothelial progenitor cells [55]. Studies of microcirculation, inflammation and leukocyte–endothelium interactions at radiation influence could enhance understanding of the underlying pathophysiological mechanisms that result in histological changes [33].

Conclusion

Summing up, presented by us the information by virtue of foreign and domestic literature indicates assess the effect of different types of ionizing radiation on the lung. The findings data support a role of ionizing radiation in the formation of structural disorders of the radiation–induced pneumonitis and pulmonary fibrosis which are form of acute or chronic lung damage depending on both the dose and type of radiation [20, 26].

Thus, at present according to result of majority of leading research in the field of radiobiology and radiation medicine regarding evaluation the effects of different types of ionizing radiation on the bronchopulmonary system, there is no consensus. In this regard, for scientists of

Kazakhstan and Japan are undoubted relevance of continuing research concerning radiation effects on the lungs, to evaluate and compare the degree of pathological processes in them under the influence of γ– and neutron radiation, which will develop diagnostic criteria of morphofunctional changes in the lungs exposed individuals [88].

Interest conflict

All authors declare that they have no conflict of interest.

Authors contributions:

Uzbekov D. – literature collection, writing the paper;

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Chaizhunusova N. – scientific guidance on the literature collection;

Shabdarbaeva D. – literature collection, scientific guidance in writing the paper;

Sayakenov N. – literature collection.

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