SELENIUM BASED AGENTS AS MODIFIERS OF RADIATION-INDUCED LUNG INJURY

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Abstract:

Radiation-induced lung injury (RILI) is the major side effect of thoracic radiotherapy. It encompasses radiation-induced pneumonitis and fibrosis. Clinically, it is managed with corticosteroids with its antecedent complications. Therefore, there is a need to develop specific radiotherapy adjuvant drugs which can prevent/mitigate RILI. Extensive research has been done in past few years in this regard, and several of candidate drug molecules have shown promising results in the preclinical studies. However, their clinical translation remains elusive. Selenium, a micronutrient has received a lot attention as a general radioprotector because of its antioxidant functions as well as physicochemical property favourable for free radical scavenging activity. Several of selenium compounds have been evaluated for radioprotective activity in general and shown considerable improvement in the survival from lethal dose of whole-body irradiation in the preclinical models. However, efficacy of selenium compounds against RILI is scarcely investigated. In this context, chemistry group of BARC has extensively studied a series of organo-selenium compounds to understand their redox biology and the efficacy against RILI. The growing evidences from these studies have established that selenium compounds hold a great promise for the development as specific drug molecules for treating RILI. The present book chapter briefly summarises the pathogenesis of RILI, various strategies currently under investigation for drug development against it, introduction of selenium as a micronutrient and its physiological functions and finally the status of selenium compounds against RILI.

Key words: Radiation-induced lung injury, pathogenesis, radioprotection, selenium

1. Radiation-induced lung injury (RILI):

Radiotherapy is the major treatment regime either as a single modality or in combination with other treatments for thoracic (lung and breast) cancers.[1] The aim of radiotherapy is to deposit higher doses of radiation to tumor tissue and a minimum dose to surrounding normal tissue to achieve desired tumor reduction with minimum side effects.[2] However, even with the availability of improved treatment protocols (such as image-guided intensity-modulated radiotherapy, stereotactic radiotherapy and particle beam therapy), there is the risk of unwanted exposure to normal lung parenchyma. This leads to normal lung tissue toxicity in the form of severe inflammatory response known as radiation-induced pneumonitis or alveolitis which further progresses to fibrosis.[3-12] The development of pneumonitis or fibrosis can result in weakened lung function and, ultimately, respiratory crisis. Radiation-induced pneumonitis and fibrosis are collectively known as RILI.[3-12] Around ~30% of lung/breast cancer patients receiving thoracic radiotherapy show RILI. These side effects typically develop during or within a few months (pneumonitis) after therapy, or late (fibrosis) occurring months to years after therapy.[3-12] Several factors such as genetic pre-disposition, age, pre-existing lung disease, smoking status, concomitant chemotherapy, total absorbed dose, dose rate and irradiation volume have been linked to the susceptibility and severity of RILI.[3-12] A host of quantitative trail loci (QTL) and single nucleotide poly-morphism (SNP) linked to susceptibility of RILI have been identified and mapped using murine models and in patients with lung cancer.[9] Further, smoking and certain chemotherapeutic drug like bleomycin may enhance the susceptibility for RILI.[5,6,9] The irradiation parameters like higher absorbed dose (>20 Gy) and greater volumes (>20%) of lung parenchyma irradiation have also been associated with the incidence and severity of RILI.[5,6,9] Further, researchers have also established that the pathologic changes of RILI may develop not only within the zone of irradiation but also outside the zone of irradiation.[3-12] Taken together, the development of RILI exerts a considerable impact on patient morbidity and mortality and therefore is a major hinderance or limitation for treating oncologist to plan radical radiotherapy. Apart from thoracic radiotherapy, the whole-body exposure in the event of nuclear accidents and warfare may also led to development of RILI.

2. Pathophysiology and diagnosis of RILI:

RILI is characterised by influx of inflammatory cell types, fibroblast and myofibroblast in the lung parenchyma followed by deposition of extracellular matrix protein (ECM) such as collagen in the lung interstitium and the formation of scar ultimately leading to impaired lung functions.[3,4,6,8,10,12] The pathogenesis of RILI is very complex and remains to be fully understood. Briefly, the lung parenchyma consists of type I (~ 90%) and type II (~10%) alveolar epithelial cells. RILI starts with the production of reactive oxygen species (ROS) through the radiolysis of cellular water molecules which in turn causes oxidative damages to the critical bio-molecules like DNA, protein and lipid in the alveolar cells. This is followed by apoptosis of type I alveolar epithelial cells and loss of barrier function in the lung parenchyma. The disruption of epithelial barrier function facilitates the influx of inflammatory cell types like lymphocytes, macrophages, neutrophiles and monocytes in the lung parenchyma. This phase is also marked by the increase in systemic as well as pulmonary

levels of proinflammatory cytokines (like IL-1β, TNFα and IL6), chemoattractant (like selectin and ICAM1) and immunogenic growth factors (like G-CSF). Simultaneously, type II alveolar epithelial cells undergo proliferation to compensate the loss of type I alveolar epithelial cells and also secrete growth factors. Under normal circumstances, inflammatory response subsides with the healing of injury. However, in case of RILI, evidences have suggested that although radiation-induced initial cytokines levels return to basal level, their production is mainly dysregulated. Additionally, loss of alveolar cells also induces hypoxic environment in the lung. Together, these factors mount second wave of cytokine storm weeks or months after irradiation. The manifestation of this phase is clinically known as pneumonitis or alveolitis. The resolution of this phase is marked by Th2 polarisation. The Th2 cytokines (such as IL4, IL13, IL17) facilitate the differentiation of resident pro-inflammatory or the classically activated M1 macrophages in to alternatively activated or anti-inflammatory M2 macrophages. These macrophages secrete anti-inflammatory and profibrogenic growth factor like TGFβ. The abundance of TGFβ in the lung parenchyma stimulates type I alveolar cells to differentiate in to fibroblast by the process known as epithelial mesenchymal transition (EMT). Additionally, circulating fibrocytes also contribute to the recruitment of fibroblast in the lung. These fibroblasts differentiate into myofibroblast with the help of growth factor like PDGF. The myofibroblasts secrete ECM proteins such as collagen and fibronectin. The deposition of ECM in the lung parenchyma leads to permanent scarring which is clinically diagnosed as radiation-induced fibrosis. The clinical diagnosis of RILI primarily relies on imaging techniques such as X-ray, CT scan, Micro CT scan, MRI and PET.[3,6,8,9,11] However, MRI is the most preferred technique as it doesn't give additional radiation dose to the lung parenchyma. Apart from imaging techniques, pulmonary function test is also widely used to corroborate the diagnosis. Till date there is no specific drug available for the management of RILI. [3,4,6,7,8,11,12] Clinically, RILI is manged through corticosteroids. However, this class of drug is associated with several side effects. Therefore, there is a need for the development of radiotherapy adjuvant drugs which can prevent/mitigate RILI without compromising the radiosensitivity of tumor cells and thus can improve the overall quality of life of cancer patients.
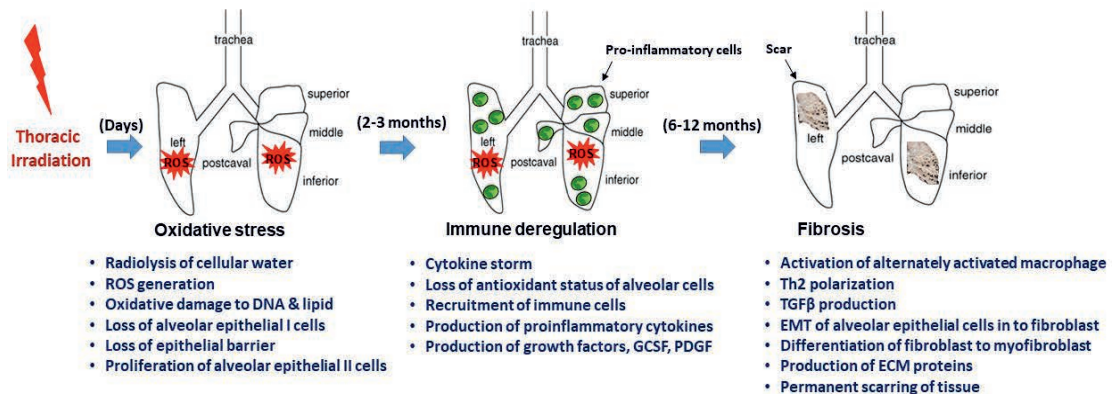

Figure 1: Schematic shows the molecular events during the pathogenesis of RILI.[3-12]

3. International research status on developing drugs for RILI:

The development of therapeutics against RILI relies on the use of radio-modifiers, agents which can modulate the radio-response of normal tissues to favour protection from radiation toxicity, if administered either prior or along or after the radiotherapy.[13] In general, radio-modifiers can be classified into three categories viz., "radioprotectors", "radiomitigators" and "therapeutic agents" depending on the timing of their administration in relation to the radiation exposure. The agents, whose presence during or prior to radiation exposure can reduce the radiation toxicity in normal tissues are termed as "radioprotectors". On the other hand, agents which are given after radiation exposure but prior to the onset of radiation sickness to reduce radiation toxicity are called as "radiomitigators". Lastly, the agents which are administered to treat after the appearance of radiation sickness/toxicity symptoms are called as "therapeutic agents". Ideally, radio-modifiers for clinical usage should possess a number of qualities such as minimal toxicity, favourable biodistribution and pharmacokinetics, cost effectiveness and easily administrable.[13] However, the most important criterion is the ability of a radio-modifying agent to differentiate normal versus cancerous cells. The radio-modifying agent should selectively protect the normal tissue from radiation-induced toxicities without protecting tumor tissue (or improve therapeutic ratio).[13] Thus, in the quest of ideal radio-modifier for treating RILI, a lot of research has been done across the world. Table 1 briefly highlights several classes of agents that have been evaluated as radio-modifiers for preventing RILI in the laboratory studies.[3,4,6,7,8,11,12]

Table 1. The table presents various molecular interventions investigated through preclinical models against RILI

Intervention Strategy	Agents investigated	Molecular mechanism
ROS scavenging	Amifostine, ACE inhibitor like captopril, Isoflavin, Genestein, Flex seed, Mn-porphyrin-based superoxide dismutase mimic like Eukarion -189, Hydrogen molecule	Reduction of radiation-induced oxidative stress
Immunomodulation	Sivelestat (Neutrophile elastase inhibitor), Imatinib/Gleevec (Mast cell inhibitor), MyD88 (Recombinant protein involved in TLR signalling), Statin (anti-inflammatory drug)	Inhibition of the recruitment of inflammatory cell types and suppression of the production of proinflammatory cytokines
Antifibrogenic	TGFβ/Smad inhibitors: SM16 (Anti-TGF-β antibody), LY2109761 (quinoline-derived compound) and SB203580 (pyridinylimidazole compound)	Inhibition of TGF-β/Smad signal transduction pathway
Targeting growth factor signalling	Fluorofenidone	Inhibition of connective tissue growth factor expression by blocking PI3K/Akt signalling pathway

Although a number of compounds as mentioned above were found to be successful in preclinical studies or in early clinical trials, none of them have been clinically approved till date.

4. Selenium and physiological importance:

Selenium is the chalcogen element which belongs to the group sixteen in the periodic table.[14] It was discovered by the Swedish chemistry Jöns Jacob Berzelius in the year 1817.[14] The biological importance of selenium came into realization in the year 1957, when Schwarz and co-workers performed a series of experiment to establish that selenium is an essential micronutrient which can prevent the starvation induced liver necrosis.[15] It was soon followed by the discovery of a selenium containing antioxidant enzyme, glutathione peroxidase (GPx).[16,17] Tappel and co-workers in the year 1978 established that GPx enzyme possess selenium in its active site as an amino acid called selenocysteine (SeCys).[18] SeCys is considered as the 21st naturally occurring amino acid. The discovery of GPx as selenoenzyme created a lot of interest among researchers to understand the molecular functions of selenium. Accordingly, the following decades and so witnessed tremendous research in the field of selenium biology. The evidences gathered over the years have conclusively established that SeCys is inserted in to a class of proteins through a complex biological process involving termination codons, UGA and such proteins are called as selenoproteins.[19-21] Till date, selenoproteins have been identified in all domain of life like virus, bacteria, alga, mice, zebrafish and human except plants and fungus. In human, around 25 selenoproteins have been discovered till date.[19-21] The majority of selenoproteins from human have been characterised for their functionally, and are reported to play roles in the antioxidant, thyroid, immune, fertility, redox homeostasis, anti-aging and anti-viral functions. The examples of important selenoproteins in human are GPx1, GPx2, GPx3, GPx4, GPx6, thioredoxin reductase 1-3 (TrxR1-3), iodothyronine deiodinase 1-3 (DIO1-3) and selenoprotein P among others.[19-21] The source of selenium for human is through dietary intake in the form of selenite, selenate, and selenoaminoacids. The daily recommended dose of elemental selenium for human is 50-60 µg/day.[19-22] The selenium intake below this range has been linked with onset of several chronic diseases like cardiomyopathy (Keshan disease), disorders of skeleton muscle and bones (Kashin Beck disease), cancer and neurodegeneration.[19-22] Further, long term epidemiological studies, have indicated that selenium intake up to 200 µg/day may exert health benefits whereas higher doses may be associated with severe toxicity symptoms like garlic breath, brittle nails and hair and selenosis.[19-22] The toxicity of selenium is mainly attributed to its high redox activity leading to oxidation of intracellular thiols. In the late nineties, realising the importance of selenium in cellular physiology, medicinal chemist started exploring selenium-based compounds for therapeutic benefits. The initial interest was to design selenium compounds which can mimic the functions of selenoproteins like those of GPx and DIO.[22,23] A lot of research was carried out in this direction and this led to the understanding of the redox chemistry of selenium compounds. Briefly, it was established that selenium compounds depending on their dosage and chemical form can take part in redox reactions leading to several kinds of perturbations such as formation of selenotrisulfide (S-Se-S), formation of selenenyl sulfide (S-Se), formation of diselenide (Se-Se), formation of

disulfide (S-S), oxidation/reduction, and formation of selenoproteins within the cells.[22-25] Each of these modifications can be exploited to achieve desired biological effects in the form of enzyme mimicking activity, disturbance in redox homeostasis, inhibition of enzymes, inhibition of cell signalling proteins and so on.[22,26-28] This has prompted the current researchers to explore selenium compounds as anticancer, anti-inflammatory, neuroprotective and chemo preventive agents.[22,26-28]. Indeed, several selenium compounds are currently at different stages of clinical trial for various indications. Ebselen is one such compound which has been clinically approved as a drug for treatment of bipolar disorder.[29] Its mechanism of action is through mimicking GPx like activity and reducing oxidative stress. Recently, this compound also received a lot of attention for its antiviral activity against COVID19.[29]

5. Selenium compounds as radio-modifiers for RILI:

The rationale of exploring selenium as a radio-modifier was conceptualized soon after the discovery of its role in antioxidant functions of the body as discussed in the previous section. Since radiation toxicity is primarily mediated through ROS, it was believed that selenium by virtue of controlling the expressions of antioxidant selenoproteins like GPx and TrxR could contribute to radioprotection.[30] Further, by the time antioxidant action of selenium was recognised, the Armed Force Radiobiology Institute (AFRI), USA had already developed Amifostine a sulfhydryl (-SH) based synthetic compound as a radioprotective agent.[30] The extensive studies by researchers at AFRI had also proposed that sulphur containing compounds could be potential radio modifying agents through the free radical scavenging mechanism. Since selenium and sulphur belong to the same group in the periodic table and selenium can undergo oxidation easily as compared to sulphur, it was assumed that selenium-based compound could be superior free radical scavenger.[31] All these considerations prompted researcher to explore selenium-based compounds as radio-modifiers. Over the years, a number of selenium compounds both in inorganic and organic forms have been evaluated for radioprotection using cellular as well as *in vivo* model systems. Most of these studies were focused on testing the efficacy of selenium compounds as radioprotectors against sublethal to lethal doses (5-10 Gy) of whole-body irradiation (WBI). The results of these studies indicated that selenium in different chemical forms could protect from WBI-induced mortality. Sodium selenite (Na_2SeO_3), sodium selenate (Na_2SeO_4), selenomethionine (SeM), selenocystine (CysSeSeCys), methylselenocysteine (MSeCys), ebselen and dihydroxyselenolane (DHS) are few of the selenium compounds which are reported in literature for improving the survival from lethal dose of WBI.[32-39] Notably, none of the selenium compounds studied till date could show dose modification factor (DMF) anywhere close to that of amifostine, the clinically approved radioprotector.[30] This fact dampened the enthusiasm among researchers to position the selenium-based compounds as the next generation radioprotector for the nuclear emergency condition. However, it was soon realized that selenium compounds could play a very important role in preventing inflammatory response by reducing the extent of lipid peroxidation and affecting the differentiation of haematopoietic stem cells.[32,40] Since most of the organ specific radiation toxicity are associated with the inflammatory response, it was anticipated that selenium compounds could also be explored as radio modifying agent to reduce organ specific toxicity. Accordingly,

clinical trials have been conducted using the commonly available selenium supplements such as Na_2SeO_3 and SeM for improving the side effects of mucositis/xerostominia mainly associated with radiotherapy of head and neck cancer.[41-44] The results of these trials have indicated the possible role of selenium in general for improving the quality of life of cancer patients.

With regard to RILI, there are not many studies done with selenium compounds. Peyman et al has recently reported that SeM exhibits protective effect against RILI in rat model and it was attributed to the modulation of immune responses (specifically lowering of IL4 and IL13 expressions) and of redox modulations (lowering of oxidative stress).[45] The chemistry group of BARC has also been working on related research topic. Over the years, our group has evaluated a series of organoselnium compounds of different classes like selone, seleno-aminoacid, monoselenide (R-Se-R) and diselenide (R-Se-Se-R) for radioprotection using *in vitro*, cellular and *in vivo* model systems.[34,46] The systematic investigations have led to the identification of a lead compound called 3-3'-diselenopropionic acid (DSePA) for radioprotection.[46] It is a water-soluble structural analogue of CysSeSeCys. Initially this compound was tested for its ability to improve the survival against sub lethal and lethal doses (5-10 Gy) of γ-irradiation using cellular and murine models. The results of these investigations have established that pre-administration of DSePA at a dosage of 2.5 mg/kg body weight through intraperitoneal (IP) route for five consecutive days prior to WBI (10 Gy) enhances the survival by 35% in swiss albino mice.[47] Further, the compound at a treatment concentration of 25 µM also enhances the survival of Chinese Hamster Ovary (CHO) cells against γ-irradiation with the DMF of 1.26.[48] The detailed mechanistic studies involving both cellular and murine models have established that the radioprotective activity of DSePA is through induction of antioxidant selenoprotein like GPx, followed by scavenging of ROS and reduction of DNA damage, lipid peroxidation and apoptosis in the radiosensitive organs like haematopoietic system and small intestine.[47-49] Notably, DSePA also shows reduction of inflammatory responses and the restoration of villi length in mice subjected to lethal dose (7 Gy) of WBI.[49] The potential of DSePA to upregulate the levels of antioxidant selenoproteins has been attributed to its oxidative/reductive metabolism in to hydrogen selenide (H_2Se) followed by incorporation into selenoproteins.[47-50] Additionally, DSePA has also been reported for mimicking the activity of GPx. However, the efficiency of DSePA as a GPx mimic within biological system is limited due to its poor metabolic stability.[46] As discussed previously, one of the major issues linked with the therapeutic usage of selenium compounds is their toxicity. Accordingly, DSePA has also been evaluated in detail for its toxicology and pharmacokinetics using murine models. The acute toxicity studies have established that DSePA has significantly higher median lethal dose (LD_{50} = 88 and 200 mg/kg body weight through IP and oral routes respectively in mice model) or tolerability as compared to commonly used supplemental forms (selenite and SeM) of selenium.[50] Further pharmacokinetic and bio-distribution studies have indicated that DSePA has the plasma elimination life of about four hours and is absorbed maximum in the lung tissue.[51] Another important feature of DSePA is that it shows similar bioavailability in the lung of murine model irrespective of the mode of administration.[46,51] This observation prompted us to examine DSePA as a radio modifying against RILI. Briefly, the studies have been carried out in C3H/HeJ strain of mice which is known to be highly susceptible for developing radiation-

induced pneumonitis against single high dose (15-18 Gy) thoracic irradiation.[52,53] The results have shown that DSePA therapy (2.5 and 5 mg/kg body weight thrice a week) during post irradiation period significantly prevents/delays and in some mice reverses the manifestation of pneumonitis.[52-53] Notably, the therapeutic effect of DSePA against RILI is independent of the mode of administration (IP versus oral).[52-53] Mechanistically, DSePA significantly reduces the radiation-mediated infiltration of polymorphonuclear (PMN) leukocytes and levels of pro-inflammatory cytokines such as TGF-β, IL1-β, IL-17, ICAM-1 and E-selectin in the lung. Furthermore, DSePA lowers neutrophil-mediated oxidants, maintains GPx activity and suppresses NF-kB/IL-17/G-CSF/neutrophil maturation following thoracic irradiation in mice.[53] Since lung radioprotectors/mitigators are expected to be used along with radiotherapy, it is important to understand their tumour response. Therefore, recently, DSePA has also been evaluated for its effect alone as well as in combination of γ-irradiation on the growth of lung cancer (A549) cells. The results have shown that DSePA *per se* induces cell death in A549 cells by disturbing the redox homeostasis towards reduction rather than oxidation followed by unfolded protein response, cell cycle arrest and apoptosis.[54] On the other hand, DSePA treatment post radiation exposure sensitizes lung cancer cells by supressing cell migration (Akt/G-CSF/EMT) and DNA repair (ATM/RAD51/DNAPKs/p53) pathways.[55] Briefly, DSePA blocks the radiation-induced above signalling cascades by lowering their phosphorylation status. The anticancer and the radio-sensitizing effect of DSePA have also been corroborated through *in vivo* studies.[54,55] For instance, DSePA treatment in the dosage range of 1-2.5 mg/kg body weight through oral route significantly suppresses the growth of A549 derived xenograft tumor. Indeed, the efficacy of DSePA is comparable to fluorouracil, a known anticancer drug.[54] Similarly, the sequential treatment of γ-radiation (2 Gy) and DSePA (0.1 - 0.25 mg/kg body weight orally) shows better efficacy than the individual treatment for supressing A549 derived xenograft tumor.[55] Taken together, DSePA is the first selenium-based compound which has been shown act as an oral radiomitigator against RILI. Currently, the efforts are on to delineate the mechanism responsible for the differential action of DSePA in normal versus lung cancer cells. Additionally, clinical studies aimed at collecting data on safety (Phase I) and efficacy (Phase II) of DSePA as a radiotherapy/chemotherapy adjuvant drug is under progress at ACTREC/TMC with financial support from Biotechnology Industry Research Assistance Council (BIRAC), under its "Early Translation Accelerators Funding Scheme".
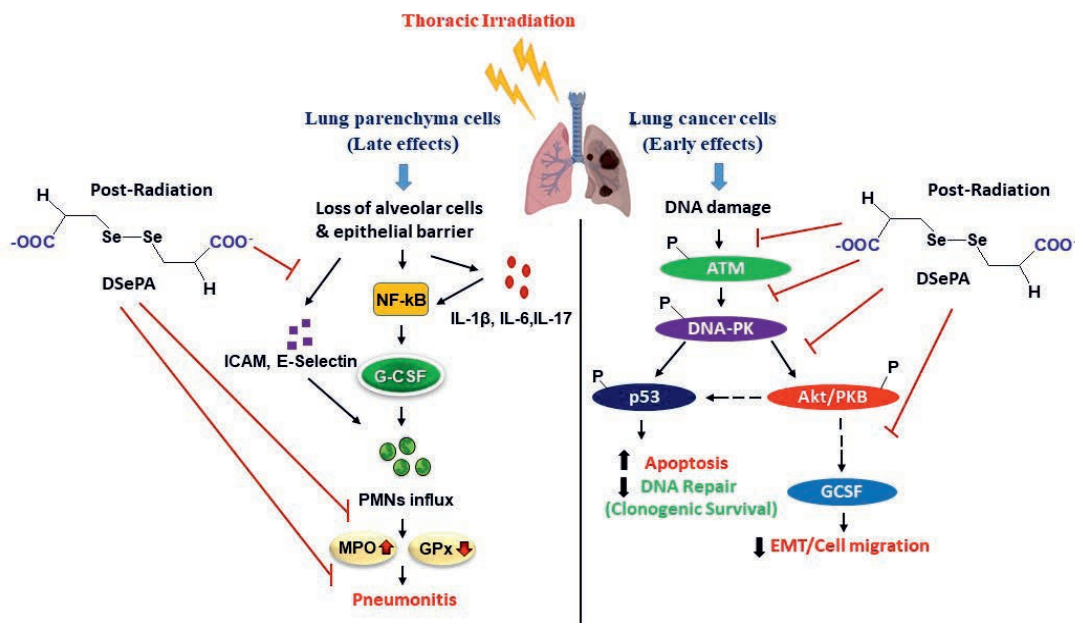
Figure 2: Schematic shows the molecular effects of the post-irradiation treatment of DSePA in lung cancer and normal lung parenchyma cells.[53-55]

6. Conclusions & future directions:

The most widely used chemical form for selenium supplementation is Na_2SeO_3. Indeed, selenium supplement is available in both inject-able and oral formulations under the brand name of Selenase® for all phases of the treatment and care of oncological patients. However, due to inherent toxicity, selenium in inorganic form cannot be administered at a therapeutic dose limiting its potential as a drug. On the other hand, organic form of selenium is considered to be much safer as compared to inorganic form. In this regard, DSePA an organoselenium compound has been identified as a much safer organo-selenium derivative with the potential chemotherapeutic and radio-modifying activities. A detailed preclinical evaluation has been carried on this compound to establish the proof of concept, its mechanism of action, acute toxicity, and preliminary pharmacokinetics in murine model. All these studies together have suggested that DSePA is a potent radio modifying agent for mitigation of radiation-induced pneumonitis without compromising the sensitivity of lung cancer cells towards radiotherapy. The fact that not many selenium compounds have been evaluated against RILI, the findings of DSePA gain a lot of significance for future clinical translation. Despite growing interest in the selenium based therapeutic agents, their clinical translation has been limited. The major challenge involved in the clinical translation of selenium compounds is their narrow therapeutic index (difference between the dosage showing therapeutic benefit and the toxicity). Therefore, future studies should be directed to envisage various strategy to control the toxicity of selenium compounds in order to utilize their potential as therapeutic agent.

7. Acknowledgements:

8. References:

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