DOI: 10.1259/bjr/34124307

Radiation effects on the respiratory system

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Abstract. This paper discusses the lung response to irradiation in the context of accidental radiation exposure. The lung is a relatively radiation sensitive organ with a response to irradiation that is complex, involving killing of lung cells, death of endothelial cells, influx of inflammatory cells, and waves of inflammatory cytokines and reactive oxygen species (ROS) production. Two major functional outcomes are observed, radiation pneumonitis and radiation fibrosis. Elevated levels of the cytokine, transforming growth factor-β (TGF-β), appear to play an important role in the development of radiation-induced lung injury, particularly fibrosis. There is limited evidence from animal studies that irradiation of the bone marrow and bone marrow transplantation may affect the lung response, but information regarding irradiation of other organs is lacking. Protection against functional and histopathological damage has been demonstrated for a number of different agents when given before (and after) irradiation (*e.g.* amifostine, captopril, manganese superoxide dismutase (MnSOD), superoxide dismutase (SOD) mimetic). To what extent protection can be provided by agents given only after irradiation is uncertain and although steroids can relieve the symptoms of pneumonitis, it remains unclear whether they can protect against the development of late fibrosis.

Radiation response of the lung

The radiation response of the lung has been studied extensively in animals and humans because of the use of whole body irradiation for conditioning regimens for bone marrow transplantation and because lung is inevitably irradiated during treatments for malignancies in the upper body, *e.g.* lung and breast cancer and lymphomas such as Hodgkin's disease [1]. The lung is relatively sensitive to irradiation. In humans, the lethal dose (LD_{50}) for a single, whole thoracic, high dose rate exposure to X-rays or γ-rays is estimated to be approximately 10 Gy based on therapeutic studies of upper half body and whole lung exposures [2]. In rats and mice this dose is in the range 11–15 Gy, depending on the strain of animals studied [3–7]. The lung has been found to have considerable repair capacity so that it can tolerate substantially higher doses of fractionated or low dose rate X- or γ-irradiation [4, 7–14]. As a result, conditioning treatments for bone marrow transplantation that use radiation as part of the treatment for leukaemias are now given as fractionated radiation. This is advantageous since bone marrow-derived cells have a much lower repair capacity. For high-LET (linear energy transfer) radiation, in particular fast neutrons, the LD_{50} in mice was reported to be 8 Gy (compared with 13 Gy for X-rays) [15]. Fractionation or reduced dose rate for high-LET radiation has only a small effect owing to reduced repair, with the result that the relative biological effectiveness for high-LET radiation increases for smaller doses [15, 16]. Studies with inhaled radioisotopes have also demonstrated both early and late effects (including carcinogenesis) in a number of animal species, although this will not be discussed further here [17, 18].

The effects of irradiation on the lung are normally separated into two phases. Radiation-induced pneumonitis usually becomes apparent approximately 2–4 months after irradiation, whilst radiation-induced fibrosis develops 6 months or more after irradiation. These effects reduce the functional capacity of the lung and depending on their severity and extent (if the whole lung has not been irradiated), can be lethal. Many different end-points have been used to assess the development of radiation-induced lung injury, in the context of lung function, imaging or histopathological analysis (see Table 1). Functional end-points measure the response of the whole lung, whereas imaging or histopathological studies can assess regional effects. Because of the reserve capacity of the lung, substantial volumes can be rendered non-functional without affecting survival. Studies with mice have demonstrated that different strains can have significantly different susceptibility for developing pneumonitis or fibrosis following lung irradiation [5, 6, 19]. These differences have been demonstrated to be heritable, indicating that there are genetic components to the development of such damage. However, the underlying radiosensitivity of lung cells was found to be similar in the strains studied [20]. Work is currently underway to identify candidate genes involved in these genetic susceptibilities [21]. One gene of interest is the M6P/IGF2R locus, since it has been demonstrated that loss of heterozygosity at this locus correlates with increased lung fibrosis and increased transforming growth factor-β (TGF-β) levels [22].

The effect of irradiating different volumes of the lung is complex and in functional studies using rodent models it has been reported to depend both on the volume and the region of the lung irradiated. In particular, irradiation of a volume in the apex of the lung caused less functional deficit than irradiation of a similar volume in the base of the lung [3, 23]. Similar volume effects in rats have also been reported by Khan et al [24, 25] using an end-point involving the examination of micronucleus formation in cells (fibroblasts) derived from different irradiated regions of the lung (see Table 2). Reasons for these regional differences in response remain unclear but they have been

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The work of the author is supported by a grant from the Ontario Cancer Research Network.

Table 1. Major end-points used in studies of radiation effects on lung

	Functional[a]	Imaging	Histopathological/biochemical
Animals (A)	Lethality Increased breathing rate CO uptake Loss of surfactant Perfusion	CT MRI	Histological structure Inflammatory cell infiltrate Loss of Type I or II pneumocytes Endothelial cell apoptosis Area of fibrosis (collagen deposition)
Humans (H)	Volumetric parameters CO uptake Perfusion	Chest radiography CT (density)	Hydroxyproline context DNA damage (micronucleus formation) (A only) Levels of ACE, PLA, PGI2, TXA2

[a]Functional end-points assess whole lung function, whilst imaging or histopathological end-points can assess individual irradiated regions. ACE, angiotensin converting enzyme; PLA, plasminogen activator; PGI2, prostacyclin I2; TXA2, thromboxane A2.

postulated to be due either to different numbers of functional subunits in the base and apex of the lung [26] or to the induction of indirect effects associated with cytokine production induced by the irradiation [25]. Studies in pig lung using both imaging and functional (breathing rate) end-points also observed greater functional effects after irradiating a greater volume of lung but did not report regional differences [27, 28].

A further aspect of interest in relation to regional effects is the observation by Khan et al [25] that DNA damage is found in cells from regions of the lung that are out of the irradiation field. This effect is seen to a much greater extent in the apical region of the lung following irradiation of the base than in the base of the lung following irradiation of a similar volume of the apical region (see Table 2). Furthermore, some of this damage can be prevented by treating animals with superoxide dismutase (SOD) or the nitric oxide synthase inhibitor L-nitro arginine methyl ester (L-NAME). These findings suggest the possibility that inflammatory cells both inside and outside the field can be activated to produce reactive oxygen species (ROS) or reactive nitroxyl species that can cause such DNA damage. It has been reported that activated macrophages can be observed within 1 h of irradiation in lung tissue [29]. Our preliminary results suggest that such activated macrophages can be observed both in-field and out-of-field (data not shown).

Table 2. Number of micronuclei (per 1000 binucleate cells) detected in fibroblasts removed from different regions of the rat lung at 18 h following irradiation with a dose of 10 Gy. (a) Different volumes of lung (70% or 30%) were irradiated, and both irradiated and shielded regions of the lung were analysed. (b) Rats were given the protectors superoxide dismutase (SOD) before irradiation, or L-nitro arginine methyl ester (L-NAME) before and after irradiation (10 Gy) of the base of the lung

(a) Volume effect

Region of lung	Volume irradiated (70%)	Volume irradiated (30%)
Lung base (irradiated)	911 (±14)	439 (±23)
Lung apex (shielded)	433 (±38)	97 (±4)
Lung base (shielded)	80 (±3)	51 (±5)
Lung apex (irradiated)	663 (±15)	427 (±57)

(b) Protection

Region of lung	Volume irradiated (70%)	Treatment
Lung base (irradiated)	928 (±12)	Radiation only
Lung apex (shielded)	384 (±25)	
Lung base (irradiated)	832 (±38)	Radiation+SOD
Lung apex (shielded)	157 (±21)	
Lung base (irradiated)	650 (±35)	Radiation+L-NAME
Lung apex (shielded)	169 (±16)	

Data from [25].

Cytokine production in lung following irradiation has been documented in many studies over the last 10 years. The early work of Rubin, Finkelstein and co-workers [30–33] demonstrated changes in mRNA levels for a number of inflammatory cytokines, in particular interleukin-1α (IL-1α) and IL-1β, tumour necrosis factor-α (TNF-α) and TGF-β. These workers demonstrated changes within 1 day of irradiation (5 Gy or 12.5 Gy) and found that the changes occurred in a cyclic pattern over the time period of development of the symptoms described above (see Figure 1). They postulated that these waves of cytokine expression preceded the development of the symptoms of radiation-induced pneumonitis and fibrosis. Other workers have confirmed that such changes in cytokine mRNA levels can occur at very early times (within 1 h) and after quite low doses (~1 Gy), but the patterns of expression have not necessarily agreed between these studies, suggesting different patterns of response in different experimental systems (see Figure 1).

Although the differences between the experimental systems have made it difficult to define exact temporal patterns of cytokine changes, the results have demonstrated that early changes in cytokine levels do occur in the lung and that these changes do not follow a clear dose–response relationship [29, 34–38]. More recent studies have implicated changes in a wide range of cytokines and chemokines following lung irradiation, although to what extent such changes are a direct result of the radiation as opposed to reactive changes associated with the upregulation of other cytokines and chemokines remains to be established [39]. Early changes (within 6–24 h) in the level of the adhesion molecules ICAM-1 and E-selectin in lung endothelial cells have also been reported to occur following lung irradiation (2 Gy and above), thereby increasing the arrest of inflammatory cells in the lung capillaries [40]. Mice knocked out for the ICAM-1 gene have been reported to be more resistant to the development of radiation-induced pneumonitis

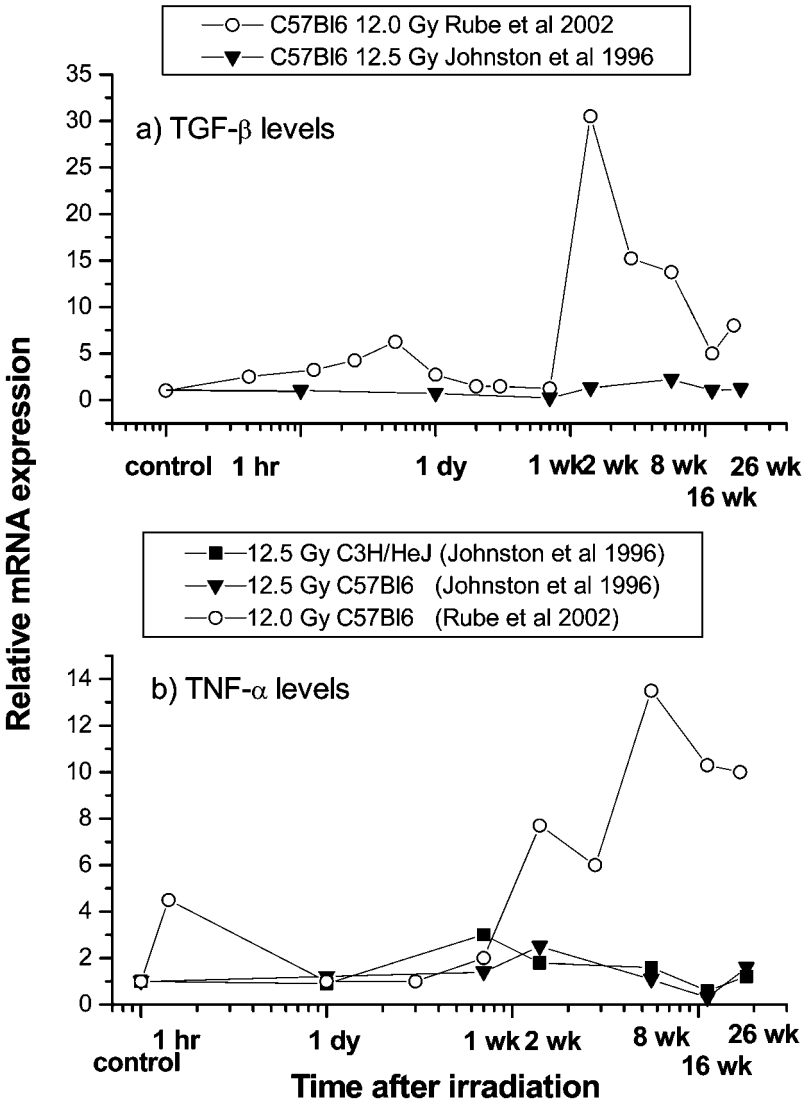

Figure 1. Cytokine mRNA levels after irradiation of lung of different strains of mice: (a) transforming growth factor-β (TGF-β); and (b) tumour necrosis factor-α (TNF-α). Redrawn from [31, 34].

[40, 41]. The cells responsible for these various changes are believed to be primarily activated macrophages/monocytes.

The cytokine TGF-β plays an important role in radiation-induced fibrosis in the lung, although the relative importance of the three isoforms is not known. The results in Figure 1a show elevated levels of the mRNA for this cytokine at times up to months after whole lung irradiation in rats and mice. Recent studies in rats have linked changes in active TGF-β levels to the development of functional symptoms such as changes in breathing rate [38, 42]. Studies in lung cancer patients have also implicated prolonged increases in plasma TGF-β levels in the development of radiation-induced lung damage [43]. In these studies it was demonstrated that patients whose plasma TGF-β levels remained elevated above the pre-treatment baseline after therapy (on average they maintained a 1.5–2.0-fold elevation over 24 months) had a significantly increased chance of developing symptomatic radiation-induced lung injury. Furthermore, it was demonstrated that patients who did not show elevated TGF-β levels after the end of conventional treatment (73.6 Gy) could receive increased doses of irradiation (up to 86.4 Gy) before the tolerance level was reached [44].

Since TGF-β also has anti-inflammatory properties, it has been proposed that the prolonged increased levels of TGF-β may result as a reaction to the waves of expression of the inflammatory cytokines that occur following irradiation, as discussed above. In this context, radiation-induced injury has been compared with injury induced by chronic wounds [45]. This may occur because the radiation causes damage in the cells that can essentially remain dormant until the cells are required to divide in order to restore or replace cells in the damaged tissue. In the context of the genetic differences discussed above, it has been reported that polymorphisms associated with higher circulating levels of TGF-β were found to be significantly associated with more severe radiation-induced fibrosis in breast cancer patients [46].

Does irradiation of other organs affect the radiation response of the lung?

In a radiation accident many different organs may be irradiated, thus there is the possibility that interactions may occur to exacerbate (or alleviate) the expression of damage in specific organs. Very little is known about such possible interactions. However, one organ that can influence the lung response is the bone marrow. Studies

in patients given bone marrow grafts following whole body irradiation have suggested an increased likelihood of pneumonitis in patients who develop graft-versus-host disease following an allogeneic graft [47, 48]. In mice, total body irradiation followed by autologous bone marrow transplantation has been reported to increase the development of pneumonitis following subsequent irradiation of the thoracic cavity, relative to the same total dose of irradiation given to the thoracic cavity only [49] (see Table 3). The mechanism for this effect is not clear, but when the mice were thymectomised at a young age prior to the start of the experiment, this was found to substantially reduce the difference in the level of pneumonitis between the two groups of mice, suggesting a role for T-cells in the development of pneumonitis.

However, this does not rule out the possibility that other effects of total body irradiation may impact on the lung response. One factor that might be important is that irradiation of other organs such as the liver can result in increased levels of TGF-β over prolonged time periods [50–52], and other tissues such as the skin have been reported to have increased local levels of TGF-β and other cytokines following irradiation [53]. In our own studies examining DNA damage in lung cells at 1 day after irradiation, we did not observe any increase in damage in the lung following irradiation of a strip of the abdomen immediately below the lung that would have involved a significant volume of the liver [25]. Equally, we did not observe any early increase in damage to skin fibroblasts outside the field following lung irradiation. However, it is unclear what role these early effects may play in the later development of symptoms due to pneumonitis or fibrosis.

Protecting against radiation-induced lung damage

An important issue for radiation accidents is the possibility of protection against radiation-induced lung injury either physically or biologically. Here I will consider only the possibility of protection against the biological effects of radiation. For victims of the accident itself, such protective agents need to be effective when administered after the exposure, whilst for rescue workers a possibility exists to provide protection pre exposure. One of the best known protectors for administration before irradiation is amifostine (WR2721), which is a thiophosphate compound that is converted to an aminothiol *in vivo* by alkaline phosphatase. It has been reported to protect rats given hemithoracic irradiation (35 Gy in 5 fractions) against both pneumonitis (changes in breathing rate) and fibrosis as well as reducing plasma TGF-β levels [54–56]. This agent has also been reported to protect humans against lung injury during radiotherapy [1, 57].

In patients, the symptoms of pneumonitis can often be alleviated by administration of steroids at the time of symptom development, but it is unclear whether such treatment can provide long-term protection [1]. In animals, treatment with dexamethasone was found to reduce the early increases in inflammatory cytokines but a rebound was observed on withdrawal of the treatment [36]. Furthermore, this agent was not found to affect the dose at which radiation-induced pneumonitis became lethal for the animals. Pentoxifylline, given 1 week before and continuously after irradiation, has been reported to reduce TNF-α levels in mouse lung following irradiation as well as in the inflammatory infiltrate [34], whilst in rats it was reported to have little effect on early pneumonitis or fibrosis but it did modulate reduced lung perfusion at late times after irradiation [58, 59]. In humans, pentoxifylline has recently been reported to reduce pneumonitis when given during radiation therapy [60]. Other pharmacological agents that have been found to be effective for lung protection in rats are the angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, including captopril (see Table 4). These agents, given before and after irradiation or immediately after irradiation have been reported to protect against both the inflammatory response and fibrosis [62]. The agents are believed to act by reducing the effects of irradiation on pulmonary endothelial cell dysfunction, particularly expression of ACE and plasminogen activator, although they also modify the effects of irradiation on levels of prostacyclin (PGI2) and thromboxane (TXA2).

Table 3. Effect of thymectomy on the per cent lethality of C3H mice during the "pneumonitic phase" (80–180 days) following total body irradiation (TBI), bone marrow transplantation (BMT) and local thoracic irradiation (LTI). Thymectomy only affected per cent lethality in mice given TBI and BMT

Treatment	Total dose to lung (Gy)			
	0–11.5	11.6–13.0	13.1–14.5	15
TBI+LTI (thymectomised)	0	19	39	
TBI+LTI (sham thymectomised)	7	61	65	
LTI only	0	6	33	
LTI (thymectomised)	—	13	47	100
LTI (sham thymectomised)	—	13	40	100

Mice were thymectomised or sham thymectomised at 4–6 weeks of age. At 12 weeks of age the mice received 10 Gy TBI followed immediately by doses of LTI, to give the indicated total dose levels to the lung, and then BMT. Another group of age-related mice received LTI only to the indicated doses either with or without thymectomy.
Data from [49].

Table 4. Effect of ACE inhibitors on endothelial cell function and hydroxyproline content in rat lung

	ACE	PLA	PGI2	TXA2	HP
Radiation only	↓	↓	↑	↑	↑
Radiation+captopril				DRF=1.4–1.8	
Radiation+CL242817	DRF=1.3–2.1				
Radiation+CGS13945				DRF=1.0	
Radiation+pentoxifylline			DRF=1.0		

ACE, angiotensin converting enzyme; PLA, plasminogen activator; PGI2, prostacyclin I2; TXA2, thromboxane A2; HP, hydroxyproline content; DRF, dose reduction factor.
Captopril, CL242817 and CGS13945 are ACE inhibitors; captopril and CL242817 contain thiol gps; pentoxifylline is a vasodilator and blocks tumour necrosis factor-α activity.
The irradiated lung tissue was analysed 2 months after irradiation of the right hemithorax with single doses of 0–30 Gy.
Data from [61].

Table 5. Protection of rat lung using a small molecule superoxide dismutase (SOD) mimetic (AEOL 10113). Various different end-points were assessed at different times after the irradiation

Treatment	Peak breathing rate (breaths min^{-1})	Fibrosis score	Hydroproline content (mg g^{-1} wet weight)	Relative peak plasma TGF-β
Irradiation only	185 ($\pm$13) @ 14 weeks	5.89 ($\pm$0.43)	6.76 ($\pm$0.38)	2.95 (@ 12 weeks)
Irradiation+SOD mimetic	162 ($\pm$11) @ 19 weeks	3.55 ($\pm$0.10)	5.2 ($\pm$0.55)	2.15 (@ 10 weeks)
No irradiation	107 (consistent over 23 weeks)	0.66 ($\pm$0.36)	2.19 ($\pm$0.22)	1
SOD mimetic only	107 (consistent over 23 weeks)	0.56 ($\pm$0.32)	1.91 ($\pm$0.13)	1

The right hemithorax of rats was irradiated with a dose of 28 Gy and AEOL 10113 was given 15 min before and for 4 days after irradiation. Fibrosis score (assessed histologically on a scale of 0–8) and hydroxyproline content were measured in the right lung at 6 months after irradiation. Breathing rate and plasma transforming growth factor-β (TGF-β) were measured biweekly.
Data from [38].

An adenovirus vector carrying the gene for manganese superoxide dismutase (MnSOD) has been found to protect against radiation pneumonitis and fibrosis in mice when administered as an inhalant 1 or 2 days before irradiation [63, 64]. This approach was also shown to reduce the early cytokine response [65]. Transgenic mice that carry the gene for extracellular SOD and express increased levels in their blood also have reduced radiation-induced fibrosis following thoracic irradiation and this is paralleled by reductions in plasma levels of active TGF-β1 and lipid peroxidation products [66]. A transient transfection of rats with a recombinant human adenoviral vector, which carried soluble TGF-β1 type II receptor (TβRII) gene, was also found to reduce functional and histological evidence of lung damage at 4 weeks after irradiation of the right hemithorax with a dose of 30 Gy. The macrophage content and TGF-β levels in the plasma were also reduced [42]. Recent studies with a small molecule SOD mimetic (a manganese–porphyrin compound), given immediately before and for 4 days after a dose of 28 Gy to the right hemithorax, reported significant protection both for early breathing rate changes (pneumonitis) and for late fibrosis, as well as reductions in the plasma TGF-β levels [38] (see Table 5).

Administration of keratinocyte growth factor (FGF-7) to mice prior to and immediately after thoracic irradiation has been reported to reduce the symptoms of pneumonitis and fibrosis [67]. This was suggested to be due to enhanced proliferation of the type I and II pneumocytes, but interestingly this did not translate into an increase in the lethal dose. Administration of basic fibroblast growth factor (FGF-2) prior to irradiation has also been reported to protect lung endothelial cells from early apoptosis after irradiation and in one report was found to increase the lethal dose following thoracic irradiation [68]. However, in another study, a change in the lethal dose following FGF-2 treatment was not observed [69].

To date, it is unclear to what extent these agents can be effective in providing protection when given only after irradiation, although some, including steroids, appear to be capable of delaying the onset of the symptomatic effect of radiation-induced lung injury. However, agents that can block the development of the underlying cytokine responses or the oxidative stress they produce may hold promise in this area. Longer term there is the possibility that stem cell transplantation into specific organs may be able to promote tissue recovery from radiation damage [70, 71].

Acknowledgment

The work of the author is supported by a grant from the Ontario Cancer Research Network. Many of the ideas presented in this paper have been development in discussion with my colleagues Drs Mohammed Khan, Jake Van Dyk and Ivan Yeung.

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