Radon induced hyperplasia: effective adaptation reducing the local doses in the bronchial epithelium

Balázs G Madas

Radiation Biophysics Group, Environmental Physics Department, Centre for Energy Research, Hungarian Academy of Sciences, 1121 Budapest, Konkoly-Thege Miklós út 29-33., Hungary

E-mail: balazs.madas@energia.mta.hu

Received 7 March 2016, revised 15 June 2016
Accepted for publication 18 July 2016
Published 12 August 2016

Abstract

There is experimental and histological evidence that chronic irritation and cell death may cause hyperplasia in the exposed tissue. As the heterogeneous deposition of inhaled radon progeny results in high local doses at the peak of the bronchial bifurcations, it was proposed earlier that hyperplasia occurs in these deposition hot spots upon chronic radon exposure. The objective of the present study is to quantify how the induction of basal cell hyperplasia modulates the microdosimetric consequences of a given radon exposure. For this purpose, computational epithelium models were constructed with spherical cell nuclei of six different cell types based on histological data. Basal cell hyperplasia was modelled by epithelium models with additional basal cells and increased epithelium thickness. Microdosimetry for alpha-particles was performed by an own-developed Monte-Carlo code. Results show that the average tissue dose, and the average hit number and dose of basal cells decrease by the increase of the measure of hyperplasia. Hit and dose distribution reveal that the induction of hyperplasia may result in a basal cell pool which is shielded from alpha-radiation. It highlights that the exposure history affects the microdosimetric consequences of a present exposure, while the biological and health effects may also depend on previous exposures. The induction of hyperplasia can be considered as a radioadaptive response at the tissue level. Such an adaptation of the tissue challenges the validity of the application of the dose and dose rate effectiveness factor from a mechanistic point of view. As the location of radiosensitive target cells may change due to previous exposures, dosimetry models considering the tissue geometry characteristic of normal conditions may be inappropriate for dose estimation in case of protracted exposures. As internal exposures are frequently chronic, such changes in tissue geometry may be highly relevant for other incorporated radionuclides.
Keywords: adaptive response, alpha-particles, computational epithelium model, hyperplasia, microdosimetry, radon exposure

Online supplementary data available from stacks.iop.org/JRP/36/653/mmedia

(Some figures may appear in colour only in the online journal)

Introduction

The health effects of radon exposure are of significant importance both to public health and in radiological protection. Radon is considered as the second most important cause of lung cancer after smoking [1]. Its contribution to the effective dose originating from the natural background radiation is approximately 50%, and its contribution to the effective dose from all background radiation exposure is about 42% [2]. However, the mechanisms leading from radon exposure to lung cancer are quite unclear.

The heterogeneous aerosol deposition results in heterogeneous spatial activity distribution of inhaled radon progeny in the bronchial airways [3]. Due to the short range of emitted alpha-particles and the relatively short half life of radon progeny, the heterogeneity is reflected in the dose distributions too [4]. Whereas it remains an open question whether the measure of dose heterogeneity increases or decreases the risk, the understanding of the mechanisms leading from radon exposure to lung cancer is not expected if the effects of locally high doses are not studied [5].

Alpha-particles effectively kill cells [6, 7] resulting in high cell death rate in the deposition hot spots [8]. In order to maintain tissue homeostasis and function, the replacement of lost cells is necessary, i.e. the total number of cell divisions has to be increased in case of increased cell death rate. In general, there are two ways for enhancing the total number of cell divisions: the increase of the division rate of progenitor cells and the increase in the number of progenitor cells, i.e. hyperplasia [9, 10]. Theoretical considerations show that increasing the number of progenitor cells is a more effective way for tissue regeneration than increasing the cell division rate, although the simultaneous increase of both is the most effective [9, 10]. With regard to the effects of ionizing radiation, changes in tissue architecture were modelled in case of the haematopoietic system and small intestine [11].

Besides the theoretical considerations, the potential induction of hyperplasia in the lungs is also supported by experimental [12] and histological data [13]. The cell type of origin may be different even within the lungs. Chronic irritation and stimulation results in hyperplasia of progenitor basal cells residing in the respiratory epithelium [14]. Goblet cells also increase in number in response to a wide variety of drugs and irritants [15, 16], while cigarette smoke and nicotine cause neuroendocrine cell hyperplasia in hamsters [17]. It is important to note that exposures just over periods of a few days to weeks to different irritants markedly increases goblet cell number in the more proximal airways and induces the appearance of goblet cells in the more distal airways [16].

On the basis of these observations and theoretical considerations, it was put forward earlier that progenitor cell hyperplasia occurs in the deposition hot spots upon chronic cell death caused by inhaled radon progeny [8]. However, the increase in the number of cells implies an increase in the epithelial thickness [16] along with other changes in the tissue geometry. As the tissue geometry and in particular the location of radiosensitive target cells are major determinant of effective dose of inhaled radionuclides [18], the consequences of such changes in tissue geometry are of interest to radiological protection.
The objective of the present study is to quantify the microdosimetric consequences of hyperplasia induced by radon exposure. Cellular burdens like hits received and dose absorbed by progenitor cells are determined as the function of alpha-decays per unit surface. While the induction of hyperplasia was proposed only above a threshold dose [8], theoretical considerations [9, 10] suggest that hyperplasia may occur even at lower dose rates. Nevertheless, it is expected that higher dose rates from alpha-particles results in higher measure of hyperplasia, and therefore, the focus of the study is on the deposition hot spots.

Methods

Construction of computational epithelium models

In order to determine hits received and doses absorbed by cell nuclei, computational models of the epithelium of the large bronchi were developed. As only cell nuclei are considered, the model is much simpler than our earlier ones [4, 8, 19]. In fact, the computational models are equivalent to configurations of spheres representing cell nuclei located in a rectangular cuboid corresponding to a small part of the epithelium in the large bronchi.

Volumes of cell nuclei are presented in Mercer et al [20] in case of basal (201 µm³), ciliated (310 µm³), goblet (243 µm³), and other secretory cells (230 µm³). The volume of preciliated cell nuclei (310 µm³) is supposed to be equal to the volume of ciliated cell nuclei. Cell nucleus volume of intermediate cells (156 µm³) is computed by supposing that the nucleus/cytoplasm volume ratio of intermediate and basal cells are uniform. Cell volume of intermediate cells is quantified in the same way as in case of our earlier study [8]. The number of cell nuclei within a rectangular cuboid representing a small part of the epithelium is the product of the area of base of the cuboid (400 × 400 µm²) and the cell numbers per unit basement membrane surface in the large bronchi derived from experimental data [20].

Mercer et al [21] have determined the total cross section of nuclei of a given cell type relative to the cross section of the tissue sample at six different depths in the epithelium of the large bronchi. Linear interpolation of these depth distributions provided continuous probability density functions for the depth of the centre of the cell nuclei. Position of the cell nuclei were determined by algorithm presented in the next paragraph and in the flow chart in supplementary figure 1 (stacks.iop.org/JRP/36/653/mmedia).

First, the depth (i.e. the third coordinate) of the nucleus centre is selected randomly from the continuous depth distribution. If the distance between the nucleus centre and either the top or the bottom face of the cuboid is smaller than the radius of the nucleus, then the random selection will be repeated using the same depth distribution function. After the depth of the nucleus centre is determined, the first two coordinates are selected randomly from a uniform distribution over the area of base of the cuboid (400 × 400 µm²). If the distance between the nucleus centre and one of the faces of the cuboid is smaller than the radius of the nucleus, then the selection of the first two coordinates, but not the depth will be repeated.

If the distance between the centre of the new nucleus and the centre of one of the previously located nuclei is smaller than the sum of the radii of the nuclei, the selection of the first two coordinates but not the depth will be repeated. The number of unsuccessful repetitions due to other nuclei is counted for a given nucleus (it is \(j\) in the flow chart presented in supplementary figure 1 (stacks.iop.org/JRP/36/653/mmedia)), and if it reaches an arbitrary threshold\(^1\), a new algorithm is applied which is called the shifting method.

\(^1\)This threshold is the ratio of the diameter of basal cell nucleus and the thickness of the epithelium multiplied by the total number of nuclei in the epithelium model (already located + to be located).
The motivation of the shifting method is to make the simulations faster. During the simulations, the number of nuclei increases. Thus it becomes more and more probable that the randomly selected position of the new nucleus intersects another nucleus. However, the probability that there is another nuclei within a given distance \( d \) from a nuclei increases with \( d \) if it is smaller than the radius of the other nuclei. Therefore, if the random selection of the first two coordinates is not effective, position of the new nucleus will be searched for in the neighbourhood of the lastly intersected nucleus. However, the depth will be not changed.

In case of the shifting method, the centre of the new nucleus is shifted by applying the following equation:

\[
C_{\text{new}}(i) = C_{\text{old}}(i) + r_{\text{old}} + (1 + (10 - k)/10) \times r_{\text{new}} \times u(i),
\]

where \( C_{\text{new}}(i) \) and \( C_{\text{old}}(i) \) are the \( i \)th coordinates of the centre, while \( r_{\text{new}} \) and \( r_{\text{old}} \) are the radii of the new and the previously selected nucleus intersected by the new nucleus, respectively. \( k \) is an integer variable running from 0 to 10. \( u(i) \) is the \( i \)th coordinate of the vertical projection of a unit vector with a direction towards the centre of the new nucleus from the centre of the previously selected nucleus. If the shift is unsuccessful due to another nucleus, the value of \( k \) is increased by 1, and equation (1) is applied with the parameters characterizing the nucleus lastly intersected by the new nucleus.

If all the shifts are unsuccessful, i.e. there is an intersection with one of the previously selected nuclei for all values of \( k \) between 0 and 10, a new horizontal position is selected uniformly over the area of base of the epithelium model, and \( k \) is set to zero. Then position is searched for around this new position by applying the shifting method. Finally, if an
appropriate position is found without intersections with the previously selected nuclei and the faces of the epithelium model, the search for the position of the next nucleus is started until all the nuclei are located in the epithelium model.

In order to study the microdosimetric consequences of hyperplasia, epithelium models with different number of progenitor cells were constructed (table 1). For the sake of simplicity, only the number of basal cells was different in these models, which are the main progenitor cells of the central airways [22]. The number of secretory cells (including neuroendocrine cells) was the same in all epithelium models, although they are considered by ICRP as progenitor cells, as well [18, 22]. Despite the evidence for the induction of goblet cell hyperplasia upon exposure to different drugs and irritants [15, 16], the number of goblet cells was not changed either.

We supposed that the additional basal cells have the same volume as the original ones (622.8 µm³) [8, 20]. Thus the thickness of the tissue was increased linearly according to equation (2) from 57.8 µm characterizing the epithelium of the large bronchi in normal conditions [21]:

\[ h = \sum_{i=1}^{6} n_i \times v_i = 57.8 \mu\text{m} + n_{\text{basal}+} \times 622.8 \mu\text{m}^3, \]  

(2)

Here, \( h \) denotes the thickness of the epithelium, \( v_i \) is the cell volume, while \( n_i \) is the cell number per unit surface of the \( i \)th cell type, and \( n_{\text{basal}+} \) is the additional number of basal cells per unit surface. The relative number of additional basal cells, the absolute number of basal cells per unit basement membrane surface, and the epithelium thickness for models with different measures of hyperplasia are summarized in table 1.

The positions of the centres of cell nuclei were determined in the same way as for the epithelium model with normal thickness. The only difference was that the probability density functions for basal cells were obtained by multiplying the depths where experimental data were available with the thickness ratio of the epithelium models. In this way, basal cells were placed deeper in the hyperplasia models than in the normal one. The depth distributions of other cell nuclei changed only due to the lack of reselection of those nuclei whose centres were placed too close to the bottom face of the cuboid representing the normal epithelium. Figure 1 shows epithelium models with different measures of basal cell hyperplasia.

In case of some cell types, the number of cell nuclei in a surface area of 400 × 400 µm² is not high enough to provide a representative sample of the experimental depth distribution. Thus the microdosimetric quantities depend on the randomness of the position of the nuclei. Therefore 500 independent computational epithelium models were constructed by the same

Table 1. Properties of the constructed epithelium models characterizing the measure of basal cell hyperplasia: increase in number of basal cells relative to their normal number, absolute number of basal cells per unit basement membrane surface, and the thickness of the epithelium.

| Relative increase in basal cell number (%) | Total basal cell number per unit surface (mm²) | Thickness of the epithelium (µm) |
|------------------------------------------|-----------------------------------------------|---------------------------------|
| 0%                                       | 17 100                                        | 57.80                           |
| 5%                                       | 17 956                                        | 58.33                           |
| 10%                                      | 18 813                                        | 58.86                           |
| 50%                                      | 25 650                                        | 63.12                           |
| 100%                                     | 34 200                                        | 68.45                           |
| 150%                                     | 42 750                                        | 73.77                           |
| 200%                                     | 51 300                                        | 79.10                           |
code for each given measure of hyperplasia in order to estimate empirical standard deviations. Then 500 independent simulations were performed for each value of alpha-decays per unit surface using these 500 different configurations of cell nuclei.

**Microdosimetry model**

It is supposed that an 11-micron-thick layer consisting of an upper mucus and a bottom cilia layer covers the epithelium [18], and that the distribution of alpha-decays within the layer decreases exponentially by depth with a half-value thickness of 6 µm [23, 24]. Only alpha-particles were taken into account which are emitted isotropically and travel in straight lines. Since we focus on the deposition hot spots in the peak of the bifurcations, decays taking place on the surface of other parts of the bronchi can be neglected besides decays taking place on the modelled part of the epithelium.

The following decay ratio characterises the most exposed parts of the large bronchi of a worker in the former New Mexico uranium mine: 10.4% of the alpha-particles are emitted by ²¹⁸Po (6.00 MeV) and 89.6% by ²¹⁴Po (7.69 MeV) [8]. The ranges of alpha-particles was obtained with the freely available ‘SRIM’ software [25]. It provides the range of alpha-particles as the function of their energy in different targets. The compound dictionary of the software contains also the trachea which was chosen as target representing both the bronchial epithelium and the layers covering the epithelium.

Cell nucleus hits and cell nucleus doses were quantified by an own-developed Monte-Carlo code. Its flow chart is presented in supplementary figure 2 (stacks.iop.org/JRP/36/653/mmedia). As alpha-particles were considered as straight lines, and cell nuclei were represented by spheres, hit numbers can be quantified by determining the number of intersections of these spheres with these straight lines. Applying the relationship between the energy and range of alpha-particles, the energy deposited along the track between the intersections can be quantified. If it is divided by the mass of the nucleus, dose absorbed in the cell nucleus is obtained.

Based on our earlier study, 0.047 WLM (working level month)² equivalent to 8h of work in a mine environment characterised by an exposure rate of 1 WL (working level) results in approximately 0.125 µm⁻² alpha-decay per unit surface corresponding to 0.93 Gy tissue dose in the most exposed hot spot of 0.14 mm² [8, 27] if mucociliary clearance is neglected and alpha-decays take place on the top of a 5-micron-thick mucus layer. While there may be at least as many hot spots in the central airways as the number of bifurcations, we focus on the most exposed part of an airway geometry composed of five bifurcation units [8, 27]. The tissue dose in the hottest spot is about two orders of magnitude higher than the average in the central airways [3, 27], and about four orders of magnitude higher than the average absorbed dose in the lungs if the detriment-adjusted nominal risk coefficient for radon exposure [26] and the value of total radiation detriment per unit effective dose for workers [28] are considered. Mucociliary clearance would decrease the number of alpha-decays and tissue dose in the hot spot by approximately one order of magnitude [5, 29].

The tissue dose of 0.93 Gy (for 0.047 WLM exposure) in the hot spot applies only to normal conditions without hyperplasia, when the tissue thickness is 57.8 µm. For hyperplastic conditions, the tissue thickness is higher, and the tissue dose can be different. For this reason, the independent variable in our simulations is the number of alpha-decays per unit surface.

²Working level month is the historical unit of exposure to radon progeny applied to the uranium mining environment. One WLM (equivalent to 3.54 × 10⁻³ Jh m⁻³) is defined as the cumulative exposure from breathing an atmosphere at a concentration of one working level (WL) for a working month of 170h. A concentration of 1 WL is any combination of short-lived radon progeny in one litre of air that will result in the emission of 1.3 × 10⁸ MeV of alpha-energy [26].
Since it is proportional to exposure in WLM independently on the tissue thickness, the exposure in WLM is also depicted in figures 2–4 as an upper x-axis.

Results

Figure 2 shows that the induction of hyperplasia results in changes in the average tissue dose. Due to the additional number of basal cells, tissue thickness increases, and the dose absorbed by the epithelium with the same surface area decreases. The left panel shows the average tissue dose as the function of alpha-decays per unit surface for different number of additional basal cells relative to their normal number. In the right panel, different curves refer to different exposure rates. In case of exposure in WLM and exposure rate in WL, mucociliary clearance is neglected, and data refer to the deposition hot spots in the large bronchi.
basal cells. Tissue dose increases linearly by the number of alpha-decays. The slope of the curve decreases in the sequence of 7.03 Gy µm² (0%), 6.99 Gy µm² (5%, not shown), 6.95 Gy µm² (10%, not shown), 6.58 Gy µm² (50%), 6.09 Gy µm² (100%), 5.65 Gy µm² (150%), and 5.27 Gy µm² (200%). It means that doubling the number of basal cells from their normal number reduces tissue dose by 13.4%, while tripling it results in a decrease in tissue dose of about 25.0%.

The reduction in tissue dose can also be seen in the right panel, where tissue dose is plotted for 8 h of work in a mine environment as the function of the measure of hyperplasia, i.e. the relative increase in basal cells number. The different curves refer to different exposure rates.

In the deposition hot spots, even relatively small exposure rates result in high local doses. One working level month results in 12 mSv effective dose if the detriment-adjusted nominal risk coefficient for radon exposure of $5 \times 10^{-4}$ WLM$^{-1}$ [26] and the value of total radiation detriment per unit effective dose of $4.2 \times 10^{-5}$ mSv$^{-1}$ for workers [28] are considered. An exposure rate of 0.518 WL results in 6.22 WLM yr$^{-1}$ equivalent to 74 mSv yr$^{-1}$ effective dose rate, but causes a local tissue dose rate of about 0.45 Gy d$^{-1}$ which is reduced to less than 0.35 Gy d$^{-1}$ if basal cell number is tripled.

As ICRP [18] identifies radiosensitive target cells in the human respiratory tract, the radiation burden of these cells is of higher interest than the average tissue dose. ICRP [18] considers basal cells and columnar secretory cells as progenitors of the bronchial epithelium. As in vitro experiments show that cell survival probability depends on cell nucleus hits [6, 7], figure 3 shows the average number of hits of basal (left panel) and secretory cells (right panel) identified with ‘other secretory cells’ of the large bronchi in Mercer et al [20, 21].

The average number of hits increases linearly by the number of alpha-decays per unit surface. The additional number of basal cells decrease the slope of the curves for basal cells in the sequence of 6.79 µm² (0%), 6.63 µm² (5%, not shown), 6.49 µm² (10%), 5.29 µm² (50%), 3.93 µm² (100%), 2.80 µm² (150%), and 1.95 µm² (200%). The relative difference in the number of hits is higher than it is in tissue dose: doubling the number of basal cells from their normal number reduces the average number of hits by 42.1%, while tripling the number of basal cells results in a decrease of average hit number of about 71.3%.

This decrease in the average number of basal cell nucleus hits is the consequence of the different depth distribution of basal cells due to the increased epithelial thickness. In the same time, the average number of secretory cell nucleus hits does not change by the measure of basal cell hyperplasia, because their depth distribution is not affected by the additional basal cells and increased tissue thickness. The slope of the curves in the right panel varies minimally between 19.27 and 19.13 µm² (0% and 200%, respectively).

The average total dose of progenitor cell nuclei was also computed. Results for basal and secretory cell nuclei are plotted in figure 4 (left and right panel, respectively). Similarly to the average tissue dose and the average number of nucleus hits, the average cell nucleus dose also increases linearly by the number of alpha-decays per unit surface. For secretory cells, the slope of curve is almost independent on the number of basal cells: it varies between 7.36 and 7.31 Gy µm² (0% and 200%, respectively).

For basal cells, the slope decreases by tissue thickness in the sequence of 3.38 Gy µm² (0%), 3.31 Gy µm² (5%, not shown), 3.24 Gy µm² (10%), 2.64 Gy µm² (50%), 1.94 Gy µm² (100%), 1.36 Gy µm² (150%), and 0.944 Gy µm² (200%). The relative reduction in average dose of basal cell nuclei is similar to the average hit number, but much higher than the average tissue dose. Doubling the number of basal cells from their normal number reduces the average dose of nuclei by 42.6%, while tripling the number of basal cells results in a decrease of about 72.1% of average basal cell nucleus dose.
Figure 4. Average cell nucleus dose for basal (left panel) and secretory cells (right panel). The different curves refer to different number of basal cells relative to their normal number. In case of exposure in WLM, deposition hot spots are considered, and mucociliary clearance is neglected.

Figure 5. Hit distribution of basal (left panel) and secretory cell nuclei (right panel) in a deposition hot spot of \(400 \times 400 \mu m^2\) if a uranium miner works eight hours in an exposure rate of 1.01 WL. Bars with different colours and patterns refer to different number of basal cells relative to their normal number. Mucociliary clearance is neglected.

Figure 5 shows the hit distribution of basal and secretory cells in a deposition hot spot if a uranium miner works eight hours in an exposure rate of 1.01 WL resulting in approximately 0.125 \(\mu m^{-2}\) alpha-decay per unit surface if mucociliary clearance is neglected. It reveals that the changes in average hit number and average dose of basal cell nuclei do not show the essential microdosimetric consequences of the induction of hyperplasia. Although the number of basal cells receiving 2–4 hits are significantly lower for the epithelium with tripled basal cell number (green bars with horizontal pattern) than for the epithelium having doubled or less number of basal cells (left panel), it cannot explain the decrease in the average hit number of basal cells. Instead, the number of non-hit basal cells increases dramatically due to the induction of hyperplasia, which results in the strong reduction of average hit number of basal cell nuclei. The hit distribution of secretory cell nuclei (right panel) is not affected by the higher basal cell number and the increased epithelium thickness.
Figure 6 shows the dose distribution of basal and secretory cell nuclei in a deposition hot spot of $400 \times 400 \mu m^2$ if a uranium miner works eight hours in an exposure rate of 1.01 WL resulting in approximately $0.125 \mu m^{-2}$ alpha-decay per unit surface if mucociliary clearance is neglected. While the dose distribution of secretory cells (right panel) does not change due to the additional number of basal cells, the dose distribution of basal cells (left panel) shows the same increase in the non-hit fraction as figure 5.

Discussion

Previous exposures modulate the microscopic effects of a present exposure

Earlier, the induction of progenitor cell hyperplasia in the deposition hot spots was put forward as a consequence of high cell death rate upon chronic exposure to radon progeny [8]. This study highlights that the induction of hyperplasia during previous exposures modulates the effects of a present exposure. In this work, we focussed on the modulation of microscopic doses, i.e. on the changes in hits received and doses absorbed by progenitor cell nuclei. We found that the increase in basal cell number and the resultant increase in tissue thickness decreases significantly the average dose and hit number of basal cell nuclei by strongly enhancing the non-hit fraction of basal cells. While the modulation of biological effects due to the induction of hyperplasia was not studied here, the fraction of basal cells shielded from radiation may have significant impacts on such biological effects of radiation as the changes in cell division rate of progenitors [8] or the rate of clonal growth of preneoplastic cells [19, 30].

Aiming the support of the system of radiological protection, significant efforts have made to develop biokinetic and dosimetric models taking into account the location of incorporated radionuclides and radiosensitive target cells in order to determine effective doses [18, 31]. However, even if these models are fully appropriate for acute exposures, the present study shows that the location of radiosensitive target cells may change due to radiation exposure. Thus dosimetry models considering the irradiation geometry characteristic of normal conditions may be inappropriate for dose estimation in case of chronic exposures. As internal exposures are frequently chronic exposures, such changes in tissue geometry may be highly relevant for other incorporated radionuclides emitting short-range particles.
Hyperplasia induced by radon exposure as a radioadaptive response at the tissue level

Radioadaptive responses belonging to the group of non-targeted effects are described as the reduced damaging effect of a challenging radiation dose when induced by a previous low priming dose [32]. The induction of hyperplasia has a similar effect reducing the local radiation burden of progenitor cells because of the increased tissue thickness and the increased depth of basal cell nuclei. From this point of view, basal cell hyperplasia induced by radon exposure can be reckoned as a radioadaptive response at the tissue level. Indeed, the induction of hyperplasia is considered as an adaptation, however, it is not mentioned among the radioadaptive responses.

Besides the similarities, however, there are important differences between classic adaptive responses and hyperplasia induced by radon exposure. While most forms of adaptive responses manifest themselves at the cellular level, hyperplasia is an adaptation of the tissue. Another difference is that in case of hyperplasia, the reduction in biological damage is the result of the decreased local dose consequences of a given macroscopic exposure, while in case of classic adaptive responses, the damage caused by the same cellular dose is reduced. As opposed to classic adaptive responses, the priming dose for the induction of hyperplasia is not necessarily low, moreover high dose rates may be even more effective. Nevertheless, intercellular communication is a prerequisite for the induction of hyperplasia which is also part of the process of classic radioadaptive responses [32].

While the induction of hyperplasia diminishes the local tissue damage by alpha-particles, on one hand, it may increase the risk of stochastic effects, on the other hand. Some analyses of epidemiological data suggests that radon exposure is primarily a promoting agent for lung carcinogenesis [33, 34]. It is expected that the induction of progenitor cell hyperplasia is accompanied by an increase in the number of preneoplastic progenitor cells, and so it may contribute to promotion. It means that the induction of hyperplasia as an adaptation of the tissue does not necessarily result a decrease in cancer risk.

Acute and chronic exposures, the dose and dose rate effectiveness factor

The role of dose rate as a modifier of radiation effects is reflected in the present system of radiological protection by the dose and dose rate effectiveness factor [28]. It implies the assumption that the risk of the same dose is lower if the exposure is protracted. Challenging this assumption, however, a comparison of data from epidemiological studies involving low and high dose rates of low-LET radiation does not suggest any dose rate effect [35]. In addition, epidemiology of lung cancer among uranium miners suggests directly the opposite, i.e. an inverse exposure rate effect [36–38]. Among others, these studies feed the on-going debate about the role of dose rate as a modifier of radiation effects [39].

The induction of hyperplasia provides an example for the basic differences between the effects of acute and chronic exposures. As progenitor cell hyperplasia increases the local maintenance capacity of the tissue, it is expected that its measure (i.e. the additional number of progenitors) increases by cell death rate and so by dose rate. It means that the induction of hyperplasia is not a binary response of the tissue as we earlier proposed [8], which challenges the application of dose and dose rate effectiveness factor from a mechanistic point of view because the effects of chronic exposures seem too complex to be described by a single value.

Quantitative studies on the effects of hyperplasia may help us to understand the biological effects of chronic exposures. Based on the equilibrium between cell death and cell proliferation, the measure of hyperplasia and division rate of progenitors can be estimated by...
quantifying cell death rate. These estimations can provide input for mathematical models analysing epidemiological data resulting in more accurate risk assessment for chronic exposures to radon progeny. While it is not clear whether the induction of hyperplasia increases or decreases cancer risk, it may highly modulate both the biological and health effects of radon exposure and other incorporated radionuclides.

Conclusions

In the present study, it was pointed out that recent exposure history of the tissue modulates its geometrical properties and thus the microscopic dose consequences of a given macroscopic exposure to radon progeny. As the local tissue dose and the radiation burden of basal cells decrease due to the induction of hyperplasia, it can be considered as a radioadaptive response which manifests itself at the tissue level. Such an adaptation of the tissue provides an example of the fundamental differences between acute and chronic exposures, and challenges the validity of the application of the dose and dose rate effectiveness factor from a mechanistic point of view. In addition, as the location of radiosensitive target cells may change due to radiation exposure, dosimetry models considering the irradiation geometry characteristic of normal conditions may be inappropriate for dose estimation in case of chronic exposures. As internal exposures are frequently chronic, such changes in tissue geometry may be highly relevant for other incorporated radionuclides emitting short-range particles.

Acknowledgments

The author thank Kornél Félf for his help in running simulations in Ubuntu Linux environment, and the anonymous referees whose constructive reports contributed to the improvement of the manuscript. This work was supported by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 ‘National Excellence Program’ (A2-EPFK-13-0160) and by the National Research, Development and Innovation Office under the contract VKSZ_14-1-2015-0021.

References

[1] National Research Council (NRC) 1999 Health Effects of Exposure to Radon: BEIR VI (Washington, DC: National Academy Press)
[2] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2000 Sources and Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes vol 1-Sources (New York: United Nations)
[3] Balásházy I, Farkas A, Madas B G and Hofmann W 2009 Non-linear relationship of cell hit and transformation probabilities in a low dose of inhaled radon progenies J. Radiol. Prot. 29 147–62
[4] Madas B G, Balásházy I, Farkas A and Szőke I 2011 Cellular burdens and biological effects on tissue level caused by inhaled radon progenies Radiat. Prot. Dosim. 143 253–7
[5] Madas B G 2016 Radon exposure and the definition of low doses—the problem of spatial dose distribution Health Phys. 111 47–51
[6] Hei T K, Wu L J, Liu S X, Vannais D, Waldren C A and Randers-Pehrson G 1997 Mutagenic effects of a single and an exact number of alpha particles in mammalian cells Proc. Natl Acad. Sci. USA 94 3765–70
[7] Soyland C and Hassfjell S P 2000 Survival of human lung epithelial cells following in vitro alpha-particle irradiation with absolute determination of the number of alpha-particle traversals of individual cells Int. J. Radiat. Biol. 76 1315–22
[8] Madas B G and Balásházy I 2011 Mutation induction by inhaled radon progeny modeled at the tissue level Radiat. Environ. Biophys. 50 553–70
Madas B G and Balashazy 2016 Erratum to: Mutation induction by inhaled radon progeny modeled at the tissue level Radiat. Environ. Biophys. 55 265–6 (erratum)
[9] Lander A D, Gokolfiški K K, Wan F Y M, Nie Q and Calof A L 2009 Cell lineages and the logic of proliferative control PLoS Biol. 7 e15
[10] Marciniak-Czochra A, Steihl T, Ho A D, Jäger W and Wagner W 2009 Modeling of asymmetric cell division in hematopoietic stem cells—regulation of self-renewal is essential for efficient repopulation Stem Cells Dev. 18 377–85
[11] Smirnova O A 2009 Blood and small intestine cell kinetics under radiation exposures: mathematical modeling Adv. Space Res. 44 1457–69
[12] McDowell E M, Becci P J, Schürch W and Trump B F 1979 The respiratory epithelium. VII. Epidermoid metaplasia of hamster tracheal epithelium during regeneration following mechanical injury J. Natl Cancer Inst. 62 995–1008
[13] Auerbach O, Stout A P, Hammond E C and Garfinkel L 1961 Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer New Engl. J. Med. 265 253–67
[14] Gordon I O, Sitterding S, Mackinnon A C and Husain A N 2009 Update in neoplastic lung diseases and mesothelioma Arch. Pathol. Lab. Med. 133 1106–15
[15] Rogers D F 2003 The airway goblet cell Int. J. Biochem. Cell Biol. 35 1–6
[16] Rogers D F 1994 Airway goblet cells—responsive and adaptable front-line defenders Eur. Respir. J. 7 1690–706
[17] Tabassian A R, Nylen E S, Linnoila R I, Snider R H, Cassidy M M and Becker K L 1989 Stimulation of hamster pulmonary neuroendocrine cells and associated peptides by repeated exposure to cigarette smoke Am. Rev. Respir. Dis. 140 436–40
[18] International Commission on Radiological Protection (ICRP) 1994 Human respiratory tract model for radiological protection ICRP Publication 66 Ann. ICRP 24 1–482 (PMID: 7726471)
[19] Madas B G and Varga K 2014 Biophysical modelling of the effects of inhaled radon progeny on the bronchial epithelium for the estimation of the relationships applied in the two-stage clonal expansion model of carcinogenesis Radiat. Prot. Dosim. 159 237–41
[20] Mercer R R, Russell M L, Roggli V L and Crapo J D 1994 Cell number and distribution in human and rat airways Am. J. Respir. Cell Mol. Biol. 10 613–24
[21] Mercer R R, Russell M L and Crapo J D 1991 Radon dosimetry based on the depth distribution of nuclei in human and rat lungs Health Phys. 61 117–30
[22] International Commission on Radiological Protection (ICRP) 2015 Stem cell biology with respect to carcinogenesis aspects of radiological protection ICRP Publication 131 Ann. ICRP 44 7–357
[23] Bremner D J, Miller R C, Huang Y and Hall E J 1995 The biological effectiveness of radon-progeny alpha particles. III. Quality factors Radiat. Res. 142 61–9
[24] Kirichenko V N, Khachirov D G, Dubrovin S A, Kliuch V E and Bykhovskii A V 1970 (Experimental study of the distribution of short-lived daughter products of radon in the respiratory tract) Gig. Sanit. 35 52–6
[25] Ziegler J F, Ziegler M D and Biersack J P 2010 SRIM – the stopping and range of ions in matter (2010) Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At. 268 1818–23
[26] International Commission on Radiological Protection (ICRP) 2010 Lung cancer risk from radon and progeny and statement on radon ICRP Publication 115 Ann. ICRP 40 1–64
[27] Szőke I, Farkas A, Balásházy I and Hofmann W 2008 Modelling of cell deaths and cell transformations of inhaled radon in homes and mines based on a biophysical and microdosimetric model Int. J. Radiat. Biol. 84 127–38
[28] International Commission on Radiological Protection (ICRP) 2007 The 2007 recommendations of the International Commission on Radiological Protection ICRP Publication 103 Ann. ICRP 37 1–332
[29] Farkas Á and Szőke I 2013 Simulation of bronchial mucociliary clearance of insoluble particles by computational fluid and particle dynamics methods Inhal. Toxicol. 25 593–605
[30] Heidenreich W E and Paretzke H G 2008 Promotion of initiated cells by radiation-induced cell inactivation Radiat. Res. 170 613–7
[31] International Commission on Radiological Protection (ICRP) 2006 Human alimentary tract model for radiological protection ICRP Publication 100 Ann. ICRP 36
[32] Tapio S and Jacob V 2007 Radioadaptive response revisited Radiat. Environ. Biophys. 46 1–12
[33] Eidemüller M, Jacob P, Lane R S D, Frost S E and Zablotska L B 2012 Lung cancer mortality (1950–1999) among Eldorado uranium workers: a comparison of models of carcinogenesis and empirical excess risk models PLoS One 7 e41431
[34] Luebeck E G, Heidenreich W F, Hazelton W D, Paretzke H G and Moolgavkar S H 1999 Biologically based analysis of the data for the Colorado uranium miners cohort: age, dose and dose-rate effects Radiat. Res. 152 339–51
[35] Jacob P, Rühm W, Walsh L, Blettner M, Hammer G and Zeeb H 2009 Is cancer risk of radiation workers larger than expected? Occup. Environ. Med. 66 789–96
[36] Lubin J H et al 1995 Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects Health Phys. 69 494–500
[37] Tomasek L, Rogel A, Tirmarche M, Mitton N and Laurier D 2008 Lung cancer in French and Czech uranium miners: radon-associated risk at low exposure rates and modifying effects of time since exposure and age at exposure Radiat. Res. 169 125–37
[38] Walsh L, Tschense A, Schnelzer M, Dufey F, Grosche B and Kreuzer M 2010 The influence of radon exposures on lung cancer mortality in German uranium miners, 1946–2003 Radiat. Res. 173 79–90
[39] Rühm W et al 2015 Dose and dose-rate effects of ionizing radiation: a discussion in the light of radiological protection Radiat. Environ. Biophys. 54 379–401