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A Nontarget Mechanism to Explain Carcinogenesis Following α-Irradiation

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Abstract

This commentary highlights the published data on the metabolic processes that lead to the development of cancer following intakes of asbestos and chemical agents. Following exposure to both, the key initiating event is cell injury leading to cell death that may further lead to inflammation, fibrosis, and cancer. Since α-particle transits also kill cells, it is suggested that cell death and inflammation will also trigger carcinogenesis within tissues irradiated by these particles. Such an explanation would be consistent with the inflammation and fibrosis seen in tumor-bearing tissues irradiated by radon-222, radium-226, thorium-232, plutonium-239, and other α-emitting radionuclides. It would also provide an explanation for dose-related changes in latency and in the similar dose–responses for the same tissue in differently sized species.

Keywords

α-radiation, carcinogenesis, cell injury and death, inflammation, fibrosis

Commentary

It is commonly claimed that the effects of radiation, including cancer, result from direct random damage to DNA, produced by radiation-induced ions and free radicals, within individual, sensitive cells—the target theory of cancer induction by radiation.[1] It is also widely believed that at low γ-radiation dose rates, and following low cumulative doses, damage in cells could be repaired. In this case, the shape of the resulting induced disease response versus dose could be curvilinear, with the effect per unit dose failing to increase as expected until DNA repair processes in the cell are overwhelmed. Additional effects would then become a linear function of dose up to the point where radiation doses become sufficiently high to result in significant levels of cell death. In this way, many dose–response deviations from linearity, such as those that are found in the extensive radiation toxicity database, could be explained for low-LET radiations (X- and γ-) and target theory would not have to be rejected because of nonlinearity.

However, for high-LET radiations, including α-particles, the situation is different. α-Particles that are produced during the radioactive decay of isotopes, such as the medical isotope radium-223 (^{223}Ra) and industrially important isotopes including plutonium-239 (^{239}Pu), and uranium-235 (^{235}U), have high energy, a short range in tissues and deposit potentially lethal ionizations and free radicals along a linear track that may extend only few tens of μm away from the source radionuclide atom that decayed. Because of the high energy of α-particles, at very low-tissue doses only a small proportion of the cells within a tissue will be irradiated, and most of these cells will be impacted by a single track—giving a high dose to the cell.[2] Under these conditions, the range of doses received by various irradiated cells will be independent of tissue dose. All will have the same potential for genomic repair (or cell death). For α-radiation, cellular DNA repair processes cannot, therefore, be used to explain deviations from linearity at low-tissue doses and linearity would be expected. Indeed, some cell assays (eg, transformation assays and assays of cell survival/viability) show dose–responses that are consistent with a linear, no-threshold shape. Deviation away from a linear, no-threshold dose–response for cancer would, therefore, indicate that mechanisms other than damage to DNA caused by the radiation either cause or modify the dose–response. Such

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deviations have been long suggested—particularly for osteosarcoma in radium dial painters (the radium girls).[3,4]

In addition to the above, it is not clear how target theory can be used to explain the decreases in time between irradiation and overt tumor identification or death (the latency period) that occur as radiation doses/dose rates increase. While Guess and Hoel[5] felt able to attribute observed decreases to a simple mathematical consequence of the decrease in cancer incidence rate with increasing dose, it is not clear such an explanation is convincing when changes in latency are very large. For example, the latency period for osteosarcoma in dogs following plutonium administration can vary from 1000 to 3500 days depending upon dose rate.[6] Next (consistent with the Peto paradox, where it was observed that cancer does not increase in large animals despite their larger number of cells),[7] considerations of the number of cells within a tissue (approximately proportional to the mass of the tissue) suggest, for example, that the similar responses per unit tissue dose seen for lung irradiations in rats and man by plutonium (excess tumor frequency equals 6.4 times dose in rats[8] and 9.5 times dose in Mayak workers)[9] can only be explained if either rat lung cells are orders of magnitude more sensitive to cancer-inducing DNA damage than those of man or that the DNA repair mechanisms in man are orders of magnitude more efficient than those in the rat. Neither would seem likely. Similarly, the mortality rate ratios for lung cancer in beagle dogs that inhaled plutonium oxide and Mayak plutonium workers are similar over a wide range of average lung doses, spanning 0.1 to >10 Gy.[10] Such observations would suggest that it is average tissue dose, resulting in tissue damage, not damage within individual cells in the tissue, that is important for cancer induction and that the probability of random, transforming DNA damage produced directly by α-radiation traversing the cell nucleus in individual cells is unimportant.

A search for alternative mechanisms, that do not require direct DNA damage to produce the cancer seen, has revealed several possibilities that link carcinogenesis variously to cell death, inflammation, tissue repair with fibrosis, and the generation of reactive oxygen species (ROS). One such mechanism is that proposed to produce lung tumors following the inhalation of asbestos fibers. In a 2010 publication,[11] the following mechanism was proposed for asbestos-induced lung cancer:

> Asbestos causes mesothelial necrotic cell death and the release of HMGB1 (high-mobility group box 1 protein—a factor that starts and promotes inflammation), thereby promoting an inflammatory response. Macrophages and mesothelial cells release ROS, such as H_2O_2, and secrete TNF-α;-both amplify the inflammatory process. Moreover, ROS cause DNA damage and aneuploidy. TNF-α activates NF-κB, a survival pathway that allows some mesothelial cells that have undergone asbestos-induced DNA damage to survive rather than die, thereby creating a pool of aneuploid mesothelial cells with the potential to develop into cancer cells. The chronic release of HMGB1 around areas of asbestos deposits sustains the inflammatory process. At the same time, TNF-α and other cytokines released by inflammatory cells may further promote the division of mutation-bearing HM (human mesothelial cells), ultimately leading to the emergence of malignant cell clones.

Necrotic cell death and inflammatory processes also occur in lungs following the inhalation of α-emitting radionuclides. Cell necrosis is an inevitable consequence of extensive and unrepairable cellular damage, including that caused by clustered DNA damage[2,12] resulting from the transit of an α-particle through the cell. It follows that similar responses are likely to be induced by both α-particles and asbestos in the lung. Indeed, if "α-particles" is substituted for "asbestos" in the above description then the text provides a plausible mechanism for α-induced carcinoma in the lung. It is reasonable to assume, therefore, that both α-radiation induced- and asbestos induced-carcinogenesis share common pathways that involve chronic inflammation. In addition to the above, asbestos intake initiates an inflammation-induced chronic wound healing process that results in fibroblast recruitment and activation with extracellular matrix deposition. This results in fibrosis, which is a characteristic of asbestosis.

Similar pathways to fibrosis following exposure to radiotherapy doses of external radiation were described by Straub et al.[13] More recently, these have been reviewed by Kim and Jung.[14] The pathway to chemical-induced fibrosis has been described by Landesmann.[15] Her adverse outcome pathway (AOP), published in Aopwiki by the Organization for Economic Co-operation and Development, describes the linkage between hepatic injury and cell death leading to the formation of liver fibrosis. Following exposure to protein alkylating chemicals, hepatocytes may become apoptotic and undergo genomic DNA fragmentation and form apoptotic bodies. When these are phagocytosed by Kupffer cells (liver macrophages), the Kupffer cells are activated. The activated cells are the main source of TGF-β1, which is the most potent profibrogenic cytokine. In the AOP, TGF-β1 expression, therefore, is considered a key event that causes hepatic stellate cell activation, meaning the transdifferentiation from a quiescent vitamin A-storing cell to a proliferative and contractile myofibroblast, the central effector in hepatic fibrosis. The excessive accumulation of extracellular matrix proteins progressively affects the whole organ and alters its normal functioning, resulting in liver fibrosis—the adverse outcome. However, the AOP also lists 2 further events that play an important role in driving fibrogenesis, namely oxidative stress and chronic inflammation. Both are described as on-going processes that are present throughout the pathway. The inflammatory response is described as playing an important role in driving fibrogenesis, since persistent inflammation precedes fibrosis. Inflammatory signaling stems from injured hepatocytes, activated Kupffer cells, and hepatic stellate cells. Inflammatory and fibrogenic cells stimulate each other in amplifying fibrosis. Oxidative stress is also described as playing a crucial role in liver fibrogenesis by inducing hepatocyte apoptosis, activation of Kupffer cells and hepatic stellate cells, and fueling inflammation; ROS, contributing to oxidative stress, are generated by hepatocytes, Kupffer cells, hepatic

stellate cells, and inflammatory cells. In addition, the author (Landesmann, personal communication, JRC-ISPRA, 2019) has confirmed that she regards cancer as a consecutive outcome. She plans to expand the AOP such that chronic inflammation and fibrosis leading to a distortion of the hepatic architecture, cirrhosis,[16] and cancer. That is a nonmutagenic route to carcinogenesis.[17] In addition, she is considering α-particles as an alternative stressor to chemical agents that could also drive fibrosis and carcinogenesis.

The same author[18] is preparing a second AOP that describes an alternative route to hepatic cell death resulting from the disruption of macrophages following the phagocytosis of nanoparticles. This provides a second possibility for α-particle carcinogenicity as many radionuclides, including ^{239}Pu, concentrate within the lysosomes of these cells.[19]

That inflammation produced by cell necrosis, pathogens, and some chemicals can result in cancer is established.[20,21] Also, that intakes of nonsteroidal anti-inflammatory drugs, such as aspirin, may reduce both inflammatory responses and the probability of cancer.[22,23] Inflammation has been demonstrated to initiate tumors by blocking the base-excision repair of damage produced by reactive oxygen and nitrogen species.[24] It has been shown to promote cancer by enhancing tumor cell survival via gene modulation produced by the activation of NF-κB by inflammatory cytokines such as tumor necrosis factor α.[25] Finally, it may facilitate cancer progression because of the recruitment of tumor-associated macrophages within the primary tumor.[26] Inflammation also results in the activation of fibroblasts, and possibly the recruitment of additional cells by epithelial mesenchymal transition, to "repair" damaged tissues by the production of a fibrotic scar.[27] This recruitment may stimulate the division of either damaged or otherwise compromised stem cells.[28] As suggested by Landesmann, tissue fibrotic processes parallel and interact with those that may result in cancer such that they commonly occur together.[8,29] Moreover, lysyl oxidase-mediated collagen cross-linking within fibrotic tissues is reported to be responsible for fibrosis-enhanced tumor metastasis.[30]

Finally, α-irradiation, leading to cancer in the presence of tissue fibrosis, is indicated in humans and animals for the irradiated lung (pulmonary fibrosis) following the inhalation of α-emitters,[31-34] liver (cirrhosis) following thorium-232 (^{232}Th) colloid administration[35,36] and in the skeleton (peritrabecular fibrosis/osteonecrosis) following intakes of bone-seeking radionuclides—including americium-241 (^{241}Am)[37] and radium-226 (^{226}Ra; first described for ^{226}Ra in man by Lloyd and Henning[38]). In dogs injected with ^{239}Pu, the percentage of animals with both osteosarcoma and peritrabecular fibrosis was the same over a wide range of administered doses and the prevalence of adenocarcinomas and squamous lung tumors closely matched pulmonary fibrosis.[8] Similarly, the frequency of cirrhosis, as a function of time and administered dose, in Thorotrast patient populations closely tracks the frequency of liver cancer.[39] These observations are consistent with a common, inflammation-induced causation/trigger for both fibrosis and cancer.

Although this commentary has focused on the pathway to carcinogenesis following α-irradiation of tissues, it is recognized that a similar case can be made for some β-induced cancer—particularly when the β-emitting radionuclide is focalized within a tissue resulting in high local doses. Examples might include bone cancer following the administration of strontium-90 (^{90}Sr)[39] and lung cancer following intakes of a variety of β-emitting radionuclides.[40]

In conclusion, a plausible mechanism for carcinogenesis, resulting from chronic inflammation and tissue damage following α-particle irradiation, is provided. Moreover, if chronic inflammation is an obligate step in α-induced carcinogenesis, then it is reasonable to speculate that, following very low levels of tissue irradiation there might be insufficient tissue damage to sustain a chronic inflammatory response and no cancer will be produced. This would provide an explanation for the absence of bone cancer and nasal sinus tumors in the radium-dial workers who received the lowest occupational doses of ^{226}Ra and/or ^{228}Ra[41-43] and bone tumors in the ankylosing spondylitis who received the lowest doses of ^{224}Ra.[44] Alternatively, the length of time required to accumulate significant tissue damage will be too long for the observation of overt cancer during the lifespan of the individual. These would result in an effective threshold for cancer in the dose–response relationship and, in the case of the latter, a decrease in latency with increasing tissue dose.

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