



Biodosimetry in Skin and Mitigation in Lung following Radiation Exposure

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Following accidental exposure of humans to irradiation, the dose to different parts of the body is likely to be heterogeneous. We have been developing a biological approach that can be used to assess dose to the skin with a particular emphasis on DNA damage in cells of the dermis and epidermis. Our work has demonstrated that it is possible to detect micronuclei (MN) in skin fibroblasts from both mice, rats and humans and that it should be possible to estimate skin dose (in the range 0–10 Gy) using a small punch (3 mm) biopsy that could be taken within a week after radiation exposure. A potential practical problem with this assay is that it requires the early processing of the fresh tissue sample. Consequently we are also investigating the potential for predicting the dose received by the skin using sections obtained from fixed skin biopsies by measurements of radiation-induced foci (RIF) of proteins in the cell nuclei. Preliminary data indicate that this may also be possible in the same dose range, using specimens obtained up to 1 week after irradiation. This result indicates the possibility of using DNA damage in skin as a biodosimeter that could potentially be used in many parts of the body.

Analysis of micronuclei is also possible in fibroblasts obtained from the lung following irradiation. However, we have found that such DNA damage can be observed in both irradiated and shielded areas of rat lung, whereas such damage is not observed in shielded regions of rat skin. We have been using this endpoint (among others) to examine approaches to mitigating lung damage following irradiation. 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 ROS production. These latter two processes are believed to be major factors driving the development of the two major functional outcomes that are observed, radiation pneumonitis (at 2–3 months) and radiation fibrosis (at 4+ months). Protection against functional and histopathological damage has been demonstrated for a number of different agents when given before irradiation but the extent to which radiation-induced lung damage can be mitigated by agents given only after irradiation is uncertain. Our studies have demonstrated that treating Spague-Dawley rats with a genistein diet (0.75g genistein per Kg of food) post irradiation can mitigate the formation of micronuclei completely and can partially prevent an increased breathing rate at 2–3 months after the irradiation suggesting a reduced level of pneumonitis. However, the genistein diet was unable to prevent an increase in breathing rate and death of the animals at later times when fibrosis had developed. This was despite the fact that the genistein treatment reduced the number of activated macrophages and the amount of collagen (as assessed by Masson Trichrome staining) in the lung at the 28 week endpoint of the study. Radiation caused increased levels of inflammatory cytokines (TNF- α , IL-1 α , IL-1 β , IL-6, TGF- β) in the tissue at this late time but genistein prevented most of this increase only for three of the cytokines (TNF- α , IL-1 β , TGF- β). Further studies demonstrated that



fluctuating levels of cytokines occurred at earlier times in the lung tissue despite the genistein diet. These studies indicate that complete mitigation of micronucleus formation (thought to be due to ROS production in the lung post irradiation) by genistein does not translate into complete mitigation of radiation-induced functional damage in the lung. This may suggest that there are different sources of ROS within the irradiated lung and some may be more effective in causing DNA damage and others more effective in inducing changes which lead to functional deficits. Since genistein is well tolerated and has low toxicity, it may be appropriate to examine the efficacy of larger doses of this agent in mitigating radiation-induced functional damage in the lung.