CELLULAR RESPONSES AT LOW DOSES OF IONIZING RADIATION

Dietrich Averbeck
Institut Curie-Section de Recherche,
UMR2027 IC/CNRS, CEA LRC n°28V,
Centre Universitaire d'Orsay, 91405 ORSAY Cedex, France

With the exception of radiation accidents, human beings are exposed during their life time only to low dose ionizing radiation (IR). The evaluation of risks for human health at low dose and low dose-rates remains an important matter in radiation protection. Epidemiological studies do not have sufficient statistical power to determine such risks from low dose exposure. Therefore, mechanistic studies are essential to understand and to estimate the risk involved at those dose levels. Recent research developments have changed previous radiobiological paradigms and concepts. Cells are now recognized as very dynamic entities able to sense even very low radiation impacts. In comparison to other genotoxic agents, ionizing radiation interacts with living matter rather distinctly, by direct energy deposition or indirectly via the formation of highly damaging radical species. Radiation damage to membranes, proteins and the nucleus can activate different signaling pathways, and, depending on dose, dose-rate and radiation quality, this leads to distinct responses on cellular and tissue levels including mutation induction and carcinogenesis. Furthermore, irradiation of the cytoplasm can initiate damage to the nucleus, and irradiated single cells can promote damage in untargeted neighbouring cells (bystander effects) which questions established microdosimetric concepts of target size and DNA as the unique relevant radiation target.

Radiation damage to genomic DNA is generally more complex than that produced by normal cellular metabolism which usually can be efficiently repaired. Radiation-induced lesions include double-strand breaks (DSB) and clustered lesions such as locally multiply damaged sites (LMDS). The latter lesions as well as complex DSB detected by pulsed-field gel electrophoresis analysis are in most cases refractory to DNA repair, and lethal to the cell.

A main discovery with direct implications on cellular responses to low dose and low dose-rate IR has been the recent finding that the processing of radiation-induced lesions highly depends on cellular signaling. Radiation damage has first to be recognized by specific sensor proteins that activate corresponding signaling pathways and effector proteins involved in the activation of cell cycle checkpoints (cell cycle arrest), DNA repair or cell death programs including apoptosis and/or necrosis and delayed mitotic death. In this way, proper cellular signaling conditions cellular responsiveness, especially at low doses and low dose rates. Thus, at very low doses (around 1 mGy) or at very low dose rates, cellular signaling does not necessarily imply activation of DNA repair. However, DNA repair occurs at slightly higher doses (5 mGy) (see Rothkamm and Löbrich, *Proc. Natl. Acad. Sci. USA 2003;100(9):5057-5062*). This dose-dependent response is probably related to the phenomenon of low dose radiation hypersensitivity and may also have some bearing on radioadaptive responses. At radiation doses above 200 mGy, there is apparently competition between DNA repair and apoptosis. Activation of error-prone DNA repair at the higher doses is likely to produce mutations, genetic instability, cell transformation and cancer. In

addition, recent studies of radiation-induced transcriptional changes in mammalian cells have identified clear differences in the activation of genes and gene families at different dose levels and dose rates. Taking together, these findings suggest that cellular radiation responses, at least at low doses and low dose rates, are non linear and cannot simply be extrapolated from high dose responses. In fact, they result from a fine-tuned dose- and dose-rate- dependent interplay of cellular re-activeness with the activation of essential cellular defense and genomic maintenance mechanisms. Radiation risk evaluations have to take into account these new facts.

Email: dietrich.averbeck@curie.u-sud.fr