A New Understanding of Radiation Damage at the Molecular & Cellular Level

[1]Melvyn Folkard and [2]Kevin M Prise

[1]Gray Cancer Institute, University of Oxford, PO Box 100, Mount Vernon Hospital, Northwood, HA6 2JR, UK
[2]Centre for Cancer Research and Cell Biology, Queen's University Belfast, Lisburn Road, Belfast, BT9 7AB, UK

folkard@gci.ac.uk

Soon after the discovery of DNA, its importance as a critical target for biological radiation damage was recognised. Since then, the mechanisms by which ionising radiations interact with DNA have been widely investigated. By the 1990s, a picture was emerging that placed the formation of DNA double-strand breaks (DSB) through ionisation as central to all critical biological radiation damage and that it was the complexity of the DSB that determined the probability of a break repairing, not-repairing (leading to cell death) or mis-repairing (leading to possible mutation and carcinogenesis). However, the past decade has seen the emergence of a new paradigm, where critical radiation damage can be induced by processes other than ionisation and where cell killing and potentially carcinogenic damage can arise through processes other than direct damage to the DNA helix.

In the 1990s, we initiated a series of studies to quantify the energetics of DNA damage. The approach we used was to expose plasmid DNA to low-energy ionizing radiation at a range of energies (7 eV to 150 eV) and look for thresholds below which single-strand and double-strand breaks are not produced. Much to our surprise, we found that both SSB and DSB are readily induced with energies as low as 7 eV. Later studies have involved the use of a novel ‘wet cell’ that permits the exposure of DNA in solution to energies below 10eV. We found that SSB and DSB are readily induced in DNA and that indirect damage through the formation of radicals in the water is important. These studies pointed to the possibility that mechanisms other than direct or indirect ionisation may be important in producing observable biological effects.

Another key finding that challenged the classical model of radiation damage was the observation that unirradiated cells can be critically damaged simply through proximity to an irradiated cell. First reported in the early 1990s, the bystander effect has since been widely studied because of its potential impact on our understanding on radiation effects at low doses. The bystander response shows us that direct damage to the DNA helix is not the only trigger for radiation-induced effects, but that unirradiated cells can also respond to signals from irradiated neighbours. Furthermore, through the use of micro-irradiation methods, we have shown that the bystander response can be initiated even when no energy is deposited in the genomic DNA of the irradiated cell (i.e. by targeting just the cytoplasm). It is becoming evident therefore that other sub-cellular organelles, such as mitochondria, may be initiating targets for radiobiolical effects.