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DNA radiation damage in the nucleosome: the molecular dynamics perspective

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Despite a vast accumulated basic knowledge in irradiating single cells and tissues, medical radiotherapy of cancer is still based on the application of simple empirical models, with little or no reference to the microscopic complexity of DNA damage and molecular repair pathways. In cell irradiation experiments, the amount of radiation-induced DNA damage is found to be systematically proportional to the dose. Conversely, clonogenic survival (at least in traditional x-ray beam external irradiation) appears to obey a linear-quadratic (L-Q) function of the dose. Empirical models fitting the L-Q behavior are derived from target theory, generally based on the following principles: (i) "hits"obey a Poisson distribution, and (ii) cell survival is due to the absence of (lethal) hits in sensitive areas of irradiated cells. However, cells survive because DNA damage is systematically repaired, not just because escaping radiation hits by chance.

Double strand breaks (DSB) are generated in much smaller proportion, and are removed with extremely fast kinetics from the damaged DNA, compared to other "simpler"lesions. Why then DSBs are so lethal for the cell? In fact, DSB repair is associated with a high error rate, much higher than for any other DNA lesion: their lethality derives by the errors in processing just a few of them. DSBs are usually associated with generating chromosome disruption. However, the ratio of translocations/DSB is of the order of 0.01 per cell/Gy. Then, do all DSBs evolve into lethal defects? Does the molecular structure of DSBs influence the repair likelihood, and the choice of repair pathway? Is there a threshold number of DSBs leading to cell arrest and subsequent death, or is it one particular type of "unrepairable"DSB that kills the cell? These are but a few key questions at the molecular scale, among many others, which can shape the actual radiation response of each cell.

In the past decade, we started a combined theoretical-experimental effort aimed at elucidating some aspects of the microscopic response of DNA to radiation, notably by focussing on the molecular dynamics of individual lesions, and statistical mechanics of damage population evolution. DSBs have been the initial focus of our work, however more recently we shifted also to including SSBs and base-damage, by connecting molecular theory with such diverse experimental techniques ranging from microsystems and microfluidics, to single-molecule force spectroscopy, to biochemical assay and cryo-microscopy. Our most recent interest is in coupling DNA molecular damage with single- and multi-nucleosome dynamics, to unravel the action of repair proteins in the early stages of their interaction with chromatin.

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