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THE COMPETITION BETWEEN OXIDANTS AND REDUCTANTS IN MODIFYING RADIATION DAMAGE TO DNA

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Alexander and Charlesby proposed in 1955 the basis for the competition model of cellular radiosensitivity which was formalised in the Alper/Howard-Flanders equation describing the dependence of radiosensitivity on oxygen concentration. Whilst this application of competition kinetics is obviously a gross oversimplification, the concept of net radiation damage reflecting, at least in part, competition between damage-enhancing reactions of oxygen and damage-reducing reactions of cellular thiols is generally accepted. Also accepted is the view that this competition takes place mainly at the free-radical level of cell damage to DNA rather than the enzymic repair stage, and the extension of this basic competitive scenario to oxidants other than oxygen (such as nitroaromatic and other 'electron-affinic' radiosensitizers). There is less certainty concerning the substitution of reductants other than thiols, except possibly for the potential role of ascorbate in 'repairing' radicals.

Although these basic concepts seem well-established, little is known with certainty concerning the detailed molecular mechanism of this free-radical competition of fundamental importance in radiotherapy. Several individual types of reactions of DNA-derived radicals are rather well characterized, reactions with both oxidants and reductants, but no single pair of reactions of a DNA-derived radical seems to satisfy all the experimental constraints. Thus the 'target' radical in the Alper/Howard-Flanders formalism, for example, can not be confidently assigned to a single radical species. The major questions in molecular mechanisms of radiosensitivity[1,2] are; (i) Do oxygen and other oxidants sensitize by a common mechanism? (ii) Is sugar or base damage (or both) of major importance? (iii) Does radiosensitization involve radical-addition or electron transfer? Do radioprotectors act competitively at sugar or base sites? (v) Does this protective role involve hydrogen or electron donation?

The redox relationships established for radiosensitization by oxidants[1,2] place obvious constraints on the identity of molecular lesions which lead to cell death. With nitroimidazoles, for example, an order of magnitude increase in radiosensitizing efficiency accompanies an increase in reduction potential of ~ 0.1 V. A number of model systems have been studied which demonstrate redox relationships with nitroaryl compounds, including the sensitized release of phosphate from irradiated 5'-guanosine monophosphate,[3] sensitization of thymine glycol production in irradiated thymine solutions[4] (but not in cells), and the diminished yield of R-8,5'-cycloadenosine in irradiated polyadenylic acid solutions.[5] The rates of adduct formation of nitroimidazoles with ether or hydroxymethyl radicals, models for sugar damage, show rather a weak redox relationship,[6] whilst the heterolysis reaction of the radical-adducts of ethanol radicals with nitrobenzenes/nitropyridine showed a redox dependence similar to that of radiosensitization.[7] Pyrimidin-6-yl radicals add to nitroaryl compounds,[8] (also with a redox-dependent heterolysis fo the adduct) so that there are

considerable similarities in the radical reactions of oxygen and nitro compounds.[9] Although radical-adduct formation is documented for oxygen, nitro compounds, and quinones, sensitization by viologens seems likely to involve electron-transfer oxidation, recent work providing redox relationships for the rate constants for oxidation of such compounds with pyrimidine and purine radicals.[10]

Simple competition between oxidants and reductants for the same species is not, of course, a requirement for a plausible model. Reaction of thiols with oxidizing base radicals,[11] or base peroxyl radicals (which could be precursors to sugar damage)[12] is known. Radiobiologists have largely ignored known reactivity of thiyl radicals produced in 'repair' reactions,[13] which will inevitably frequently involve 'misrepair' or epimerization. Ascorbate is a superior electron donor compared to thiols, but an inferior hydrogen donor: demonstrated competition between ascorbate and misonidazole in thiol-depleted cells[14] must also be considered if we are to progress from plausible to probable reaction schemes.

For reliable comparison between the results of model experiments in dilute aqueous solution and radiosensitivity in vitro, a knowledge of relative concentrations of radiation modifiers in the vicinity of the target site(s) in cellular systems is essential. Recent work has shown that positively charged radioprotectors[15] or radiosensitizers[16] bind to DNA, and a novel fluorescence quenching method[17] can be used to demonstrate subcellular concentration gradients in intact cells.

Our knowledge of many of the molecular mechanisms discussed above has arisen largely as result of studies at the Max-Planck-Institut für Strahlenchemie, summarized in a recent book.[18]

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