Department of Oncology-Pathology

Modelling and Calculation of DNA Damage and Repair in Mammalian Cells Induced by Ionizing Radiation of Different Quality

AKADEMISK AVHANDLING
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av

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ABSTRACT

Recent experimental data have revealed a wealth of information that provides an exceptional opportunity to construct a mechanistic model of DNA repair. The cellular response to radiation exposure starts with repair of DNA damage and cell signalling that may lead to mutation, or cell death. The purpose of this work was to construct a mechanistic mathematical model of DNA repair in mammalian cells. The repair model is based on biochemical action of repair proteins to examine the hypotheses regarding two or more components of double strand break (DSB) repair kinetics.

The mechanistic mathematical model of repair proposed in this thesis is part of a bottom-up approach that assumes the cell is a complex system. In this approach radiation induces DNA damage, and the cellular response to radiation perturbation was modelled in terms of activating repair processes. A biochemical kinetic method based on law of mass action was employed to model the repair pathways. The repair model consists of a set of nonlinear differential equations that calculates and explains protein activity on the damage step by step. The model takes into account complexity of the DSB, topology of damage in the cell nucleus, and cell cycle.

The solution of the model in terms of overall kinetics of DSB repair was compared with pulsed-field gel electrophoresis measurements. The repair model was integrated with the track structure model to calculate the damage spectrum and repair kinetics for every individual DSB induced by monoenergetic electrons, and ultrasoft X-rays. For this purpose we proposed a method to sample the protein repair actions for every individual DSB, and finally calculate the total repair time for that specific DSB. The DSB-repair kinetics for the number of DSB induced by 500 tracks of monoenergetic electrons and ultrasoft X-rays were calculated and compared with experimental results for cells irradiated with Al_K, C_K, and Ti_K ultrasoft X-rays.

The results presented here form the first example of mechanistic modelling and calculations for NHEJ, HR and MMEJ repair pathways. The results, for the first time, quantitatively confirm the hypothesis that the complex type double strand breaks play a major role in the slow kinetics of DSB repair. The results also confirm that simple DSB located in the heterocromatin delay the repair process due to a series of processes that are required for the relaxation of the heterochromatin. The repair model established in this work provides a unique opportunity to continue this study of cellular responses to radiation further downstream that may have important implications for human risk estimation and radiotherapy.

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