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Mechanism of non-DNA targeted mutagenesis: The role of intra cellular nucleotide pool

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Cells are constantly exposed to reactive oxygen species (ROS), produced either endogenously or exogenously by environmental factors and drugs. It is well known that ionizing radiation as well as UV radiation is amongst the exogenous agents producing ROS. While ionizing radiation ionizes intracellular water molecules leading to the formation of ROS, UVA radiation excites photosensitizers leading to the formation of ROS. ROS in turn exerts its effect by modifying DNA base in the DNA and nucleotide pool (dNTP), which may lead to mutations during replication. Oxidatively modified DNA bases will be repaired mainly by base excision repair pathway. ROS can modify dNTP. The modified dNTP can be incorporated into the DNA during replication and give rise to mutation. The dominant forms of ROS induced dNTP modification include 8-oxo-dGTP and 8-oxo-dATP. Different types of mutations can arise depending on which dNTP has been modified in the nucleotide pool and incorporated in to the DNA. The cells are equipped with the nucleotide pool sanitization enzymes (ex. hMTH1) to avoid incorporation of modified dNTP into the DNA. Mutant frequency, mutational spectra, clonogenic survival, the level of micronuclei and the levels of 8-oxo-dG in cytoplasm and in the cell culture medium in TK6 cells with normal as well as with low level of hMTH1 in order to understand the mutagenic effect of ROS-induced dNTP modifications were studied. The mutagenic role of nucleotide pool in the cells exposed to UV (UVA, UVB and UVC) and gamma radiation will be discussed.

Biography

Siamak Haghdoost is Associate Professor of Radiation Biology and PhD in genetic Toxicology, working at the Department of Molecular Bioscience, The Wenner-Gren Institute, Stockholm University, Stockholm, since January 2006. He has published 35 peer reviwed artiles in the international journals. He has been leading the work in the Laboratory of Centre for Radiation Protection Research, Stockholm University, Sweden. His research focuses on the role of nucleotide pool modifications and nucleotide pool sanitization enzyme in mutagenecity and sensitivity to radiation.

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