Abstract:

Geno- and Cytotoxicity of DNA-associated Auger electron emitters

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Theoretical considerations, Monte-Carlo simulations and experimental findings suggest that DNA-incorporated Auger electron emitters (AEE) cause primarily complex and clustered DNA lesions. It was previously shown that the shape of AEE-induced cell survival curves resembles that of High-LET irradiation and, therefore, poses the question of an increased biological effectiveness and a separate quality factor for Auger electrons. During electron capture or internal conversion an electron vacancy in an inner atomic shell is created. Filling the electron vacancy by a higher shell electron can initiate a process of non-radiative energy transmission, commonly termed as “Auger effect”. During the process numerous low-energy Auger electrons (up to 27 in the case of Iodine-125) with a short range are emitted leading to energy densities and free radical production in the close vicinity of the emitter exceeding that of a 5 MeV alpha-particle traversing the DNA double-helix. Experimental data demonstrate, that the cyto- and genotoxicity of AEE is comparable to low-LET radiation per unit dose when the AEE is exclusively located in the cytoplasm. However, in case of DNA-incorporation RBEs ranging from 5 – 9 are frequently reported. Employing the alkaline and neutral comet assay, the high DSB/SSB ratio of I-125-iododeoxyuridine derived from Monte-Carlo simulations could be experimentally confirmed. The unique properties of AEE and the possibility to target DNA in a sequence-specific manner using AEE-labeled Triplex-forming oligonucleotides (TFOs) enable to study the repair of complex DNA lesions at defined sites in more detail. A transgenic SCL-II p2RT strain carrying the stably integrated recoverable p2RT vector system harboring a specific triplex target sequence for TFO-p2RT will help to analyze the repair efficiency of complex DNA lesions regarding mutation frequency, mutation type and mutation localization.