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The mechanism of metal nanoparticle-mediated radiosensitization of tumor cells may be independent of DNA damage amplification and DNA repair inhibition

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Selective targeting of radiation effects to tumors represents a fundamental challenge in radiotherapy. Metal nanoparticles, such as gadolinium, gold, or platinum nanoparticles are preferentially internalized by tumor cells and have been recognized to locally amplify the radiation dose upon irradiation. Hence, nanoparticles delivered in tumor cells might increase tumor-specificity and efficiency of radiotherapy at the same time. The physical mechanisms related to the radiation dose amplification by nanoparticles have been already well described; however, cellular structures targeted by nanoparticles remain unknown. The DNA molecule is the most sensitive and critical cell structure in the cell concerning the effects of ionizing radiation. Hence, a crucial question remains open of whether a damage to the nucleus is necessary for the radiosensitization exerted by gadolinium and other nanoparticles.In this work, we studied the effect of 3 nm gadolinium based nanoparticles (GdBNs) on the induction and repair of DNA double-strand breaks (DSBs) in the nuclear DNA of U87 tumor cells irradiated with γ-rays. For this purpose, we used currently the most sensitive method of DSB detection based on high-resolution confocal fluorescence microscopy coupled with immunodetection of two independent DSB markers, γH2AX and 53BP1. Equivalent data for Au and Pt nanoparticles are just being analyzed. Our experiments brought about quite surprising results. In the conditions where GdBNs amplify the radiation effects, they remain localized in the cytoplasm and their influence on DSB induction and repair is only insignificant. This suggests that the radiosensitization mediated by GdBNs and potentially other nanoparticles (of defined parameters) is a cytoplasmic event that is independent of the nuclear DNA breakage (a phenomenon commonly accepted as the explanation of biological radiation effects). Based on recognized intracellular localization of nanoparticles studied, we hypothesize about possible non-DNA targets for (some) nanoparticles.

Biography

Martin Falk has completed his Ph.D from Masaryk University in Brno, CR. He is the leader of the Department of Cell Biology and Radiobiology at the Institute of Biophysics of the Czech Academy of Sciences (Brno, CR). He participated in more than 30 papers that concern the role of chromatin structure in regulation of cellular processes. Other research interests include DNA damage and repair, carcinogenesis, tumor cells radio-sensitization, and radiobiology. Important publications: Falk et al. BBA-MCR 1773/10(2007), BBA-MCR 1783/12(2008), Mutation Research 704(2010), Lukasova et al., BBA-MCR 1833/3(2013); Hofer et al. J Med Chem. 59(7):3003-17 (2016)

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