Cell culture tests and electron boost effect in Nano-IRT with synchrotron radiation

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Indirect radiation therapy inactivates cancer cells by secondary radiation products evolving from incorporated target material upon specific absorption of a therapy beam. The power of the method depends on the absorption cross section, the physiological acceptable concentration of the target material and the intracellular location after incorporation. We have developed heavy metal chelate entrapped nanoparticles for indirect radiation therapy with synchrotron radiation, neutrons and gamma-photons.
Nanoparticles are suitable for local deposition and uptake of absorption material at high concentration level, i.e. > 10 mM in tissue. As nanoparticles systems we use a modular combination of liposomes for water soluble and lipid-bound metal complexes, solid lipoid particles for hydrophobic drugs, and Ferrofluids for magnetic manipulation. The metals Lutetium, Erbium, Gadolinium and cis-Platinum were entrapped, and tested with cell cultures and some animal tests.
Target liposomes from DOPC entrapping Gd-, Er-, Lu-DTPA, cis-Platinum and a cis-Pt-lipid depicted a size of 100-200 nm. The entrapped lumen contained up to 300 mM Lanthanide chelate at an entrapping rate of 10%. A part of the nanoparticles was prepared in a formulation braking the blood-brain barrier, as required for treatment of brain tumors.

For the cell culture tests we have developed an irradiation setup and a protocol for a late apoptosis test. In the setup a multiple collection (96) of submerse cells is irradiated in multiwell plates, which are located in a closed environment (bio-container with filters). The protocol provides the proliferation rate, which is the equivalent of tumor growth and its inactivation. Thus we follow up growth curves rather than cell inactivation, which is the equivalent to unfavorate early tumor disruption (necrosis). The complete growth curve is estimated with samples of a single cell plate, which is harvested and developed in sections using an improved MTT-test. This technique reduces the experimental errors to 10% of a triple sample. A proliferation inhibition, i.e. the equivalent of a tumor growth stop, was detected as time shift or stop in the growth curve.
From clinical therapy tests with gamma sources (linear accelerator, 0.1 - 6 MeV photon spectrum) it is known that the tissue before the tumor produces an electron cloud upon gamma irradiation, which enhances the radiation therapy effect significantly (electron boost effect by Compton scattering and pair formation). In a part of our experiments, the tissue before and after the tumor in the tentative therapy client was simulated by Agarose gels in tight, air-free contact with the cell cultures. With F98 cancer-cells the radiation and metal-specific growth inhibition increased significantly upon irradiation above the K-edge of the Lutetium-liposome target (63 keV, 10 Gy). A smaller boost effect was detected with the gel placed after the cell culture. Minor effects were detected below the K-edge, and in controls.

The result indicates the presence of a significant electron boost effect in indirect radiation therapy with synchrotron radiation (PAT), equivalent to that known from gamma photon therapy (PT). Thus the effect has to be observed in future IRT experiments in order to avoid a possible underestimation or loss of therapy effects. The effect is now optimized by cell culture tests, especially for improved cellular uptake, and for different kinds of radiation and beam application.

References

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Specific WEB-site: www.mpsd.de/irt/