Energy loss of high-LET α particles and their effect on dose distribution and biological response in glioblastoma cell lines M059J and M059K

Martyna Araszkiewicz

Abstract

Alpha radiation consists of heavy, positively charged particles with a high linear energy transfer (LET). Their interactions cause dense ionization within a short range, leading to complex DNA damage that often exceeds the capacity of cellular mechanisms responsible for repairing double-strand breaks, ultimately resulting in cell death.

Due to these properties, alpha particles are used in cancer treatments such as targeted alpha therapy, which employs isotopes emitting alpha radiation, and boron neutron capture therapy, in which the reaction of the stable nucleus ^{10}B with thermal neutrons produces alpha particles and ^{7}Li ions. Both methods are used to treat, hard to reach, and recurrent tumors, such as glioblastoma multiforme, although a major challenge remains the precise determination of the radiation field and dose within the target tissue.

In this study, alpha particles emitted from a ^{241}Am surface source, an element of a system designed for irradiating biological samples, were characterized. Using Monte Carlo modeling, the energy distribution, LET, and absorbed dose in the sample were determined, and the results were verified experimentally.

The system was used to irradiate two glioblastoma cell lines, M059J and M059K, that differ in *PRKDC* expression, which encodes the DNA-PKcs protein, an essential factor in double-strand break repair. The surviving fraction of cells, alpha particle cytotoxicity, the number of $\gamma H2AX$ foci using immunofluorescence staining, and the expression of 30 DNA repair–related genes using RT-PCR were assessed.

The results indicate that most of the particles α reaching the cell monolayer are characterized by a LET in the range 60–260 $keV/\mu m$, confirming their high biological effectiveness in inducing complex DNA damage. Both cell lines show a dose-dependent decrease in survival, and irradiation with high-LET particles leads to similar survival levels. The number of repair foci increases with dose, with M059J cells displaying more dynamic increase and more complex foci structures.

Irradiation with alpha particles induces a stronger transcriptional response in M059J cells than in M059K cells, reflecting a compensatory adaptation to the absence of DNA-PKcs. DNA repair gene expression profiling and assessment of DNA-PKcs status may serve as a basis for stratifying glioblastoma multiforme patients toward personalized radiotherapy and DNA repair–targeted therapies.