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Multi-cellular dosimetry of β+-emitting radionuclides used for cell labeling in the context of cell tracking studies with PET imaging

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Introduction

Radiolabeling of cells combined with nuclear medicine imaging provides a potential method for cell trafficking analysis *in vivo*. Besides, the use of β^+-emitting radionuclides is of particular interest given the good intrinsic characteristics offered by PET technology. Generally, a direct labeling approach is applied in which cells are mixed with a radioactive solution and incubated *in vitro* at 37°C to permit the incorporation of the radionuclide intracellularly. Because the procedure implies the use of high amount of radioactivity, various studies have taken interest about the effects of labeling on cell viability and functionality. Though severe cell cytotoxicity was pointed out, *e.g.* reduction of proliferation capacity when labeling with ^{18}F-FDG [1, 2], not clear conclusions has been drawn from these findings. Particularly, comparison and analysis of results are limited because the observed biological effects are often evaluated as a function of added activity rather than absorbed dose delivered to the cell [3, 4, 5]. Accurate dosimetry is required to allow for the establishment of a reliable absorbed dose-effect relationship and therefore to get a comprehensive assessment of the toxicity induced by the labeling procedure. This work aimed to develop a realistic multi-cellular dosimetry and apply the model to the analysis of 3 radionuclides used for labeling in PET: ^{18}F, ^{64}Cu and ^{68}Ga.

Materials and Methods

A program using Python was developed to generate cell coordinates from a set of initial parameters i.e. cell size, cell density, bounding volume size. A cubic cell arrangement was assumed and the calculation approach was based on an analytical formula using pre-determined S factors (absorbed dose per unit time-integrated activity). These S values were calculated by MCNP6 modelling considering radioactivity uniformly distributed in a source

cell placed at variable distances from another cell with the nucleus as the target. The mean absorbed dose to the cell nucleus was determined as a function of the cell density and the intra-to-extra cellular activity distribution considering both the contribution of radioactivity located within the cells (self- and cross-dose) and in the culture medium. To verify the contribution of cellular dosimetry in this study, the results were compared with those obtained using conventional dosimetry which is based on the assumption that the radionuclide is distributed homogenously in the global volume. Dose calculations were also done under realistic conditions of labeling of leukocytes with ^{18}F-FDG on the basis of labeling parameters used in few reported studies.

Results

For all radionuclides, the cellular-to-conventional dose ratios can vary significantly with cell density, reaching important values at low density and approaching 1 at high density. They were also influenced by the activity distribution between the cells and the medium, the highest values occurring when all activity was incorporated in the cells. Such trends were in agreement with previous work [6, 7]. A significant underestimation of mean dose to the cell by conventional model was particularly observed for ^{64}Cu up to 15-fold at low density when source is located in the nucleus. This observation is due to the emission of short-range auger electrons, responsible for a major self-dose, that deposit all their energy in the cell nucleus. ^{68}Ga and ^{18}F presented lower discrepancies between cellular and conventional doses considering the emission of larger-range β^+ that enables to counteract a certain degree of heterogeneity in the source distribution by a more homogenous dose deposit. Finally, the comparison between published data highlighted the high disparity of parameters used for labeling of leukocytes with ^{18}F-FDG. Calculation results showed significant deviations of the actual cell dose from the conventional one up to a factor of 5. We also observed that a same injected activity per cell can result in important different absorbed doses.

Conclusions and Perspectives

The development of a realistic multi-cellular dosimetry offered a better understanding of how absorbed dose to cell is affected as a function of key labeling parameters such as uptake ratio of activity within cells and cell density. The need to use cellular model over the conventional one was highlighted in the case of low cell densities and high activity incorporation into cells, especially when labeling with radionuclides emitting low range electrons such as ^{64}Cu. The establishment of the dose-effect relationship for mesenchymal stem cells is under way through functional tests *in vitro* including clonogenic assay, proliferation ability and senescence induction after labeling with ^{18}F-FDG and external irradiation for comparison.

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