New modeling approaches to investigate cell signaling in radiation response

by

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Ionizing radiation damages individual cells and tissues leading to harmful biological effects. Among many radiation-induced lesions, DNA double-strand breaks (DSB) are considered the key precursors of most early and late effects [1] leading to direct mutation or aberrant signal transduction processes. In response to damage, a flow of information is communicated to cells not directly hit by the radiation through signal transduction pathways [2]. Non-targeted effects (NTE), which includes bystander effects and genomic instability in the progeny of irradiated cells and tissues, may be particularly important for space radiation risk assessment [1], because astronauts are exposed to a low fluence of heavy ions and only a small fraction of cells are traversed by an ion. NTE may also have important consequences clinical radiotherapy [3]. In the recent years, new simulation tools and modeling approaches have become available to study the tissue response to radiation. The simulation of signal transduction pathways require many elements such as detailed track structure calculations, a tissue or cell culture model, knowledge of biochemical pathways and Brownian Dynamics (BD) propagators of the signaling molecules in their micro-environment. Recently, the Monte-Carlo simulation code of radiation track structure RITRACKS was used for micro and nano-dosimetry calculations [4]. RITRACKS will be used to calculate the fraction of cells traversed by an ion and delta-rays and the energy deposited in cells in a tissue model. RITRACKS also simulates the formation of chemical species by the radiolysis of water [5], notably the ‘OH radical. This molecule is implicated in DNA damage and in the activation of the transforming growth factor beta (TGFβ), a signaling molecule involved in NTE. BD algorithms for a particle near a membrane comprising receptors were also developed and will be used to simulate trajectories of signaling molecules in the micro-environment and characterize autocrine and paracrine cell communication and signal transduction.

References:
New modeling approaches to investigate cell signaling in radiation response

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Introduction

• Following radiation exposure, a flow of information is exchanged between cells in tissues, and cells not directly hit are also affected [1].

• These so-called non-targeted effects (NTE) may have important consequences. Therefore, several elements should be included in irradiated tissue models:
  - Stochastic track structure and dosimetry
  - Tissue or cell culture model
  - DNA damage and repair models
  - Brownian dynamics algorithms for the simulation of signaling molecules in the micro-environment
  - Cell signaling pathways

Tissue or cell culture model

• Most tissue and cell culture models are based on Voronoi tessellation (in 2D and 3D)
• A Voronoi cell is the space closest to a given point (than the other points)
• Some rules are added:
  - Diameter limits (min and max)
  - Contact energy: harmonic oscillator

Models derived from microscopic images can also be used

Top: a Voronoi cell in 2D
Bottom: a cell culture simulated with modified Voronoi cells

Simulation of radiation track and dose calculations

• The energy deposition by the radiation is highly dependent on the radiation type and energy and leads to the formation of the track structure.
• The radiation track structure is dependent on the radiation type and energy.
• Many radiolytic species (H, OH, H₂, H₂O₂, e−aq etc) may be formed during this process.
• The track structure is simulated using the Monte-Carlo simulation code RITRACKS [2].

Image of a cell culture (120 µm x 120 µm) irradiated with 30 ⁶⁶Fe²⁺ ions, 1 GeV/amu, LET ~150 keV/µm. Dose: ~5 cGy

Signaling molecules: TGFβ

• Among signaling molecules involved in the response of cells to ionizing radiation, TGFβ is of particular interest
• TGFβ is secreted as an inactive form (the Large Latent Complex “LLC”) [3]; it is released from the LLC by several factors, notably the OH radical [4].

• TGFβ binds to its receptors and initiate several actions mediated by the SMAD proteins; it has been shown to suppress apoptosis in irradiated cell culture and also to mediate cellular response to DNA damage [5].

DNA damage models

• The chromosomes are simulated by random walk
• The dose to the nucleus is calculated with the code RITRACKS
• The intersection voxels with energy deposited and chromosomes are obtained
• The probability of DSB is obtained by applying the equation

\[ \psi = 1 - e^{-QD} \]

where D is the dose in a voxel, and Q is a parameter which may depend on the radiation type [6]

Discussion

• We are working on a model combining stochastic radiation track simulations, cell culture or tissue models, DNA damage and repair models, cell signalling pathways and BD algorithms.
• These models and simulations should help understand the role of cell signalling in the response to ionizing radiation

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