A Comparative Modeling Study on Intestinal Crypt Dynamics of Steady State and After Irradiation

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Background
- The epithelium lining the small intestinal tract of mammals consists of a layer of columnar cells folded into villi and crypt that are renewed every few days and are sensitive to radiation.
- Over decades of study on the small intestine of BDF1 mice accumulated a large database of both cell kinetics and radiobiological response to various kinds of radiation exposure.
- Apoptosis can be observed in the proliferative cells at the bottom of crypt at dose of 0.01 Gy (Potten 2004), therefore the small intestine is an ideal target to study the effects at extreme low dose of radiation in space exploration.

Specific Aims
- Compare two modeling approaches to analyze the crypt dynamics of BDF1 mice in steady state and after acute radiation, so that the validated models can be extrapolated to other species.
- Incorporate the governing biological processes occurring at the subcellular, cellular, and tissue levels of crypt organization, to validate a multiscale tissue modeling framework for radiation research.
- Correlate the biological parameters in compartmental model with biological processes in spatial model of crypt dynamics, to investigate the parameter estimation procedure through experimental measurement.

Methods

Compartmental model

- X: dividing cells
- Y: maturing cells
- Z: functional cells
- N: dose rate
- D0: radiosensitivity parameter

Multiscale spatial model

Key assumptions for spatial model
- Each cell is equipped with a cell cycle model governing proliferation and differentiation, and a mechanical model specifying interactions with neighbors.
- Extracellular Wnt concentration determines stem cell niche structure and the fate of each cell.
- Radiosensitivity parameters decide dose-dependent cell killing rates of proliferative cells.

Parameter changes due to irradiation

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Steady state</th>
<th>After radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transit cells G1, S, G2, M duration</td>
<td>3.5+1.5×N(0,1), 7.0+1.5×N(0,1), 0.75, 0.75 (h)</td>
<td>2.0+1.5×N(0,1), 6.0+1.5×N(0,1), 0.75, 0.75 (h)</td>
</tr>
<tr>
<td>Mitotic inhibition (G2 duration)</td>
<td>0.75 (h)</td>
<td>0.75 + 1.0×Dose (Gy) (h)</td>
</tr>
<tr>
<td>Colcemidogenetic cell Wnt threshold</td>
<td>0.91</td>
<td>0.91</td>
</tr>
<tr>
<td>Delayed apoptosis</td>
<td>N(0,1) Dose (Gy) &lt;24.0 (h)</td>
<td></td>
</tr>
</tbody>
</table>

Results

Labeling index dynamics after irradiation

<table>
<thead>
<tr>
<th>Time after irradiation (h)</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plm</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>0.75</td>
<td>0.75 + 1.0×Dose (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Simulations snapshots of crypt dynamics after irradiation

Conclusions and future work
- The “proof-of-concept” multiscale spatial model can simulate results compatible to experiments, however, the parameters governing various processes at different levels of crypt organization need to be finely tuned.
- Population kinetics and proliferation indices simulated by the simple compartmental model are consistent to those observed in chronically and acutely irradiated experiments.
- Spatial model has the potential to further incorporate the radiation effects at other biological scales such as radiation induced genetic mutation, chromosomal aberration, DNA damage, and radiation track structure.
- Both models can be extended to model radiation induced tumorigenesis at lower doses in colon and other organs.

References
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