Effects of Chronic Low-dose Gamma Irradiation on Gastrointestinal Tumorigenesis (CLOGIGAT)

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DoReMi Meeting Munich 8 July 2014
Radiation induced alimentary tract cancers in humans

Natural and man-made sources of ionising radiation are a recognised hazard for human health.

Risk estimates for radiation-induced cancer are based on atomic bomb survivor data.

Previous animal studies have concentrated on quantitative effects of x-ray and fission neutron exposure – high dose-rate and total doses up to 5 Gy.

Little information on effects from chronic exposures to low-dose rate radiation.
Apc<sup>Min/+</sup> mouse

Induced in C57BL/6J mice by ENU (Moser et al, 1990)

Nonsense mutation in codon 850 - truncated Apc polypeptide (~95 kDa)

Heterozygotes Apc<sup>Min/+</sup> develop multiple intestinal tumours

C57BL/6J Apc<sup>Min/+</sup> mice have an average lifespan of 150 days and develop an average of 85 tumours in the GI tract - mostly in the small intestine (SI)
<table>
<thead>
<tr>
<th>Radiation Type</th>
<th>Description</th>
<th>Tumour Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays</td>
<td>Increase in very small tumours (&lt;0.5 mm$^2$) in proximal small intestine (duodenum)</td>
<td>Total tumour numbers increased by factors of 2.7 at 2 Gy and 9 at 5 Gy</td>
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<tr>
<td>Fission neutrons</td>
<td>Increase in tumours of all sizes in proximal small intestine and larger tumours (1.0-5.0 mm$^2$) in distal small intestine</td>
<td>Total tumour numbers increased by a factor of 6 at 1 Gy</td>
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</tbody>
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Project outline

The effect of chronic low-dose rate gamma irradiation on intestinal tumorigenesis in the $Apc^{Min/+}$ mouse will be examined at different doses and compared with effects of acute high-dose rate gamma irradiation.

Task 1. Breeding of CHB6$^{Min/+}$ and CHB6$^{+/+}$ mice
Task 2. Irradiation of mice
Task 4. Gastrointestinal tumour counting.
Breeding of F1 mice for tumorigenesis studies

CBA/H ♀
+/+

×

C57BL/6J ♂
+/min

F1
CHB6


+/+

+/min
Chronic low-dose gamma irradiation experiment – 1.6 mGy h\(^{-1}\)

F1
CHB6

+/-/min

Groups of 50

Total dose
0, 1, 2 & 3 Gy

Groups of 10

+/+

+/+
Acute gamma irradiation experiment – 3 Gy h$^{-1}$

Groups of 50

F1
CHB6

+/min

Total dose
0, 1, 2 & 3 Gy

Groups of 10

+/+
Blood taken from groups of 10-12 mice at two time points:
4-7 days before irradiation ends – isolation of serum for miRNA profiling.
3 days after the end of irradiation – genotoxicity assays:
  Flow-cytometry based MN analyses
  Pig-a assays
Gastrointestinal tumour counting - PHE
Deliverables

Breeding of \( \text{CHB6}^{\text{Min/+}} \) & \( \text{CHB6}^{+/+} \) mice and shipment to UMB

Exposures of mice

Blood sampling for genotoxicity studies

Return of mice to PHE

Analysis of blood samples

GI tumour counting

Final report

PHE Jan 2015

UMB Feb 2015

NIPH Feb 2015

UMB March 2015

NIPH Sept 2015

PHE Nov 2015

All Dec 2015