A Mouse Model for Radiation-induced Thyroid Neoplasia

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kindliche Schilddrüsen-Tumore durch Tschernobyl Fall-out Jod131)

Excess Rel. Risk > 70 in einigen Gebieten der Ukraine und Weißrusslands

Dort diagnostizierte papilläre Schilddrüsentumore bei Kindern sind in etwa 95% aller Fälle strahleninduziert.
2 / 3 dieser Tumore zeigen eine aktivierende Translokation des Ret Protoonkogenes
Purpose: To establish a mouse model for human thyroid carcinogenesis caused by ionising radiation

Background: In the Belorussian and Ukrainian population that was exposed as children to radioactive fall-out the Thyroid Cancer rate increased by a factor of up to 200.

A screen for non-malignant thyroid hyperplasia in asymptomatic person established an even bigger increase for nodules/hyperplasia (C. Land et al 2004)

Are radiation these radiation induced benign tumors early lesion with the potential to progress to malignancy?
Radiation Induction of Thyroid Neoplasia

220 mice treated (F1 hybrids and F2 intercrosses from strain JF1, C3H, C57BL6)

172 control mice

131I injection
14 p.c

day 6 after birth

18 month follow-up

Systematic thyroid necroscopy

3 weeks iodine deficient diet
Dosimetry of maternally transmitted Iodine 131

Injected Activity: 2 x 100 kBq (day 14 p.c. and day 6 after birth)

Whole Body gamma measurement in offspring:

between 8 to 14% of entire activity is transmitted to offspring

resulting thyroid dose: about 2.6 – 4.8 Gy (3.7 Gy average)
Hyperplasia of the Thyroid gland, follicular
Adenoma of the Parathyroid gland, follicular and solid areas
## Thyroid Diagnosis at Autopsy

### F1 Hybrid mice

<table>
<thead>
<tr>
<th></th>
<th>C3H x Bl6</th>
<th>JF1 x C3H</th>
<th>JF1 x BL6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6 animals only)</td>
</tr>
<tr>
<td>Normal gland</td>
<td>31 % (94%)*</td>
<td>76 % (100%)*</td>
<td>0 % (0 %)*</td>
</tr>
<tr>
<td>Simple hyperplasia</td>
<td>32 % (4.9%)*</td>
<td>21 % (0 %)*</td>
<td>0 % (0 %)*</td>
</tr>
<tr>
<td>Complex hyperplasia</td>
<td>31 % (0 %)*</td>
<td>3.5 % (0 %)*</td>
<td>0 % (0 %)*</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>5.2 % (1.2%)*</td>
<td>0 % (0 %)*</td>
<td>100 % (0 %)*</td>
</tr>
</tbody>
</table>

* % in brackets refer to control mice
Strain distribution pattern of Thyroid lesions
**JF1:** suppresses complex hyperplasia and follicular adenoma, simple hyperplasia unaffected

**C3H:** promotes complex hyperplasia

**C57BL6:** promotes progression to adenoma
## Thyroid Diagnosis at Autopsy

### F2 Intercrossed mice

<table>
<thead>
<tr>
<th></th>
<th>JF1 x C3H F2</th>
<th>JF1 x B6 F2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal gland</strong></td>
<td>12.9 %</td>
<td>44 %</td>
</tr>
<tr>
<td><strong>Simple hyperplasia</strong></td>
<td>58 %</td>
<td>24 %</td>
</tr>
<tr>
<td><strong>Complex hyperplasia</strong></td>
<td>16.1 %</td>
<td>20.4 %</td>
</tr>
<tr>
<td><strong>Follicular adenoma</strong></td>
<td>3.2 %</td>
<td>9.2 %</td>
</tr>
<tr>
<td><strong>Follicular carcinoma</strong></td>
<td>6.4 %</td>
<td>1.8 %</td>
</tr>
</tbody>
</table>
Phenotypic classification of F2 mice for QTL mapping

- no pathological alteration: 0
- simple hyperplasia: 1
- complex hyperplasia: 2
- follicular adenoma: 3
- follicular carcinoma: 4
QTL mapping of modifier genes

red: genetic effect assuming additive mode of inheritance
blue: genetic effect assuming dominant mode of inheritance
black: LOD
green vertical lines: threshold for linkage as calculated with permutation test
Fig. 2. Map showing the distribution of 131I ground contamination in Belarus. Annual incidence rates of thyroid cancer in children in different geographic districts are shown per 100,000 children (based on data in ref. 135). (From ref. 103 with permission of the American Association for the Advancement of Science.) (Color illustration is printed in insert following p. 198.)

Note: Highest cancer incidence in regions with the highest contamination

different colours: contamination level

numbers: thyroid cancer incidence
Iodine-131 incorporation by diaplacental and lactational transfer from mother to offspring in JF1 x FVB F2 mice.
Iodine131-incorporation by diaplacental and lactational transfer from mother to offspring in JF1 x FVB F2 mice.
Best defined candidate gene interval on Chromosome 11:
D11Mit313 – D11Mit260 – D11Mit320
Prop1-Ex1f1
\hspace{1cm} JF1
\hspace{1cm} FVB
Best defined candidate gene interval on Chromosome 13:
D13Mit293 – D13Mit178
Activity vs. D11Mit318 + D13Mit78 Genotype

CPS

2xlow
2xhigh
Conclusion

Pre- + postnatal 131I-injection in mice delivers a Mouse-model for simple and complex hyperplasia and Follicular adenoma

Follicular carcinoma arise only in a subset of interstrain Crosses

Majority of neoplasia don‘t exhibit a clinical phenotype But are detected only at autopsie

This is sufficient for quantifying effects (of 131Iodine as well As of modifier genes), allows mapping of QTLs but limits downstream molecular assays.