Genetic hypersensitivity to ionizing radiation in imaging and treatment

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Background

• Exposure to medical radiation (MR) has increased over the past years significantly
• MR constitutes to a major part of exposure to radiation in medium/high income countries.
• Hypersensitivity to ionizing radiation has been observed in some genetic syndromes in the context of diagnostics and treatment.
• On cellular level specific gene expression seems to correlate with cancer cell sensitivity to radiation.
Material and methods

• Pubmed was searched for studies between the years 1990-2012 reporting *in vitro* or *in vivo* sensitivity to ionizing radiation among genetic syndrome carriers.

• This review summarizes observations on radiosensitive phenotypes and cellular sensitivity based on gene expression.
Genetic syndromes and cancer genes predispose to radiogenic cancers

- Inherited rare pathogenic mutations in genes are associated with human cancer susceptibility syndromes. These subjects are predisposed to radiation induced cancers e.g. Li-Fraumeni, Gorlin, and retinoblastoma.

- The role of BRCA1, BRCA2 and ATM genes in mediating cellular response to ionizing radiation may indicate that germline mutations associated with hereditary cancer may also predispose to radiation induced cancers (Travis et al 2012).

- Two-hit hypothesis describes that somatic mutations are needed before cancer predisposition occurs among subjects with inherited mutated tumor suppressor genes (Knudson 1991).
Sporadic cancer

- Any cancer is always a genetic disease
- Cancer pathogenesis includes inactivation of tumor suppressor genes, alterations in DNA repair genes and immunodeficiency.
- Genetic changes limited to target tissue or accumulated during one’s life time are not inherited (if not in germiline cells)
Hereditary predisposition

- Genetic change is present in all cells (inherited change in germinal cell line)
- Cancer development ALWAYS through tissue level change, mutations, defective repair against carcinogens
Two hit theory

Inherited change + life long exposure changes -> inactivated growth regulation -> cancer

Shorter time to clinical cancer compared to sporadic cancer

Knudson, 1991
<table>
<thead>
<tr>
<th>Human disorder</th>
<th>Major clinical features</th>
<th>Cancer type</th>
<th>Frequency</th>
<th>DNA repair defect</th>
<th>Gene</th>
<th>Pro obs</th>
<th>Is gene-radiation interaction definitive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td>Cerebellar ataxia, immunodeficiency, oculocutaneous telangiectasia</td>
<td>Lymphoma, leukaemia, epithelial carcinomas</td>
<td>1:300 000</td>
<td>Kinase activity</td>
<td>ATM</td>
<td>Avoid mammography, CT. Reduced dosage / duration of RT if not avoidable</td>
<td>Yes</td>
</tr>
<tr>
<td>Fanconi anaemia</td>
<td>Bone marrow deficiency, short stature, intellectual deficiency, thumb / radial hypoplasia</td>
<td>Leukaemia, squamous cell carcinoma of oropharynx, oesophagus and vulva</td>
<td>3:1 000 000</td>
<td>Base excision repair pathway</td>
<td>FANCA, FANCC, FANCG</td>
<td>Haematologic / gynecologic examinations. Reduced dosage / duration of RT if not avoidable</td>
<td>Yes</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Odontogenic jaw keratocysts, palmar / plantar pits, rib / skeletal abnormalities, macrocephaly</td>
<td>Basal cell carcinoma, medulloblastoma</td>
<td>1:40 000</td>
<td>DNA repair defect</td>
<td>PTCH</td>
<td>Dermatologic screening. Risk of basal cell carcinoma development in radiation field</td>
<td>Yes</td>
</tr>
<tr>
<td>Ligase IV syndrome</td>
<td>Growth deficiency, microcephaly, developmental delay, skin photosensitivity, immunodeficiency</td>
<td>Leukaemia, multiple myeloma, lymphoma</td>
<td>Very rare</td>
<td></td>
<td>LIG4</td>
<td>Avoiding RT</td>
<td>Yes</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Cancer usually observed when younger than 45 years</td>
<td>Breast carcinoma, sarcoma, leukaemia, brain tumor</td>
<td>Very rare</td>
<td>Cell cycle control</td>
<td>TP53</td>
<td>Mammography / MRI for breast screening. Minimizing dosage / duration of RT</td>
<td>RT induced cancer observed; gene-radiation interaction has not been found</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Cafe au lait spots, neurofibromas, axillary / inquinal frecklings, Lisch's nodules</td>
<td>Optic glioma, malignant peripheral nerve sheath tumor (MPNST), soft tissue sarcoma</td>
<td>1:3 500</td>
<td></td>
<td>NF1</td>
<td>MPNST observed after RT for optic gliomas; gene-radiation interaction has not been found</td>
<td></td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>Microcephaly, growth deficiency, intellectual deficiency, immunodeficiency</td>
<td>Lymphoreticular malignancy</td>
<td>Rare</td>
<td>Post-replication repair</td>
<td>NBS1</td>
<td>Reduced dosage / duration of RT if not avoidable</td>
<td>Yes</td>
</tr>
<tr>
<td>Hereditary retinoblastoma</td>
<td>Bilateral retinoblastoma</td>
<td>Retinoblastoma, bone and soft tissue sarcoma, melanoma, brain tumor</td>
<td>1:20 000</td>
<td>Cell cycle control</td>
<td>RB1</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

**RT:** radiotherapy, **CT:** computed tomography
"We think it has something to do with your genome."
Guidance to physicians and patients

• Clear description of potential benefits and risks of the intervention is needed
• Assign subjective weight to these factors for an informed choice
• Discuss the choice of tests with the patient or their representatives and with colleagues
• To promote good practice, clinical decisions are to be discussed in clinicoradiological or multidisciplinary meetings
• Meticulous documentation and research

BMJ 2011: 342:589-593
Results and Conclusions

- Eight syndromes with hereditary genetic radiation sensitivity identified
- Genetic profile is linked with increased cancer cell’s sensitivity to radiation (BRCA1, BRCA2, ATM)
- The challenge is optimal diagnostic imaging and radiotherapy in patients with hypersensitivity to ionising radiation - alternative methods
- Techniques used for detecting genetic hypersensitivity to ionising radiation - when widely available - may improve our ability to attribute a cancer to radiation exposure.
Thank you for your attention