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.

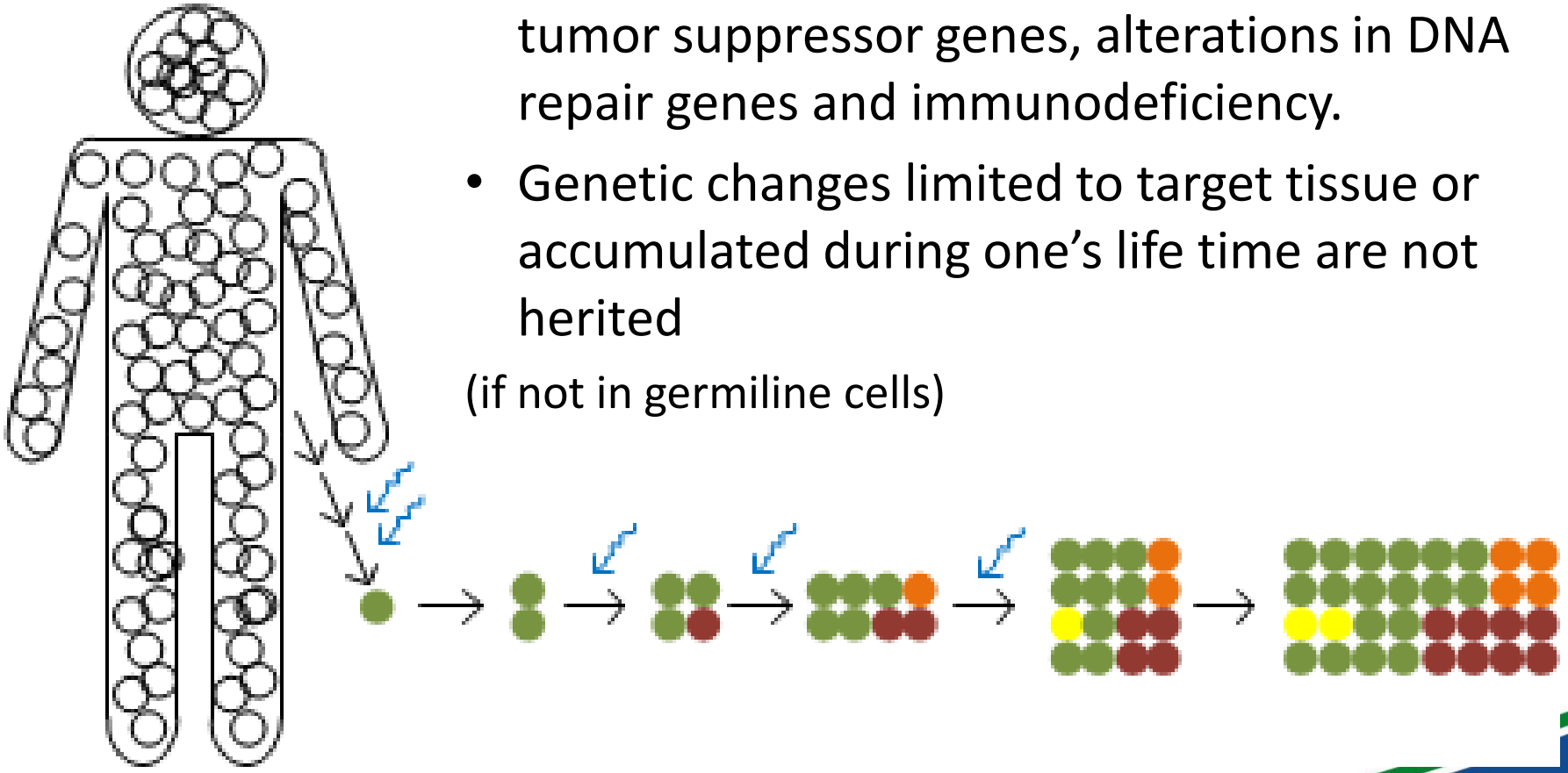
Genetic syndromes and cancer genes predispose to radiogenic cancers

- 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

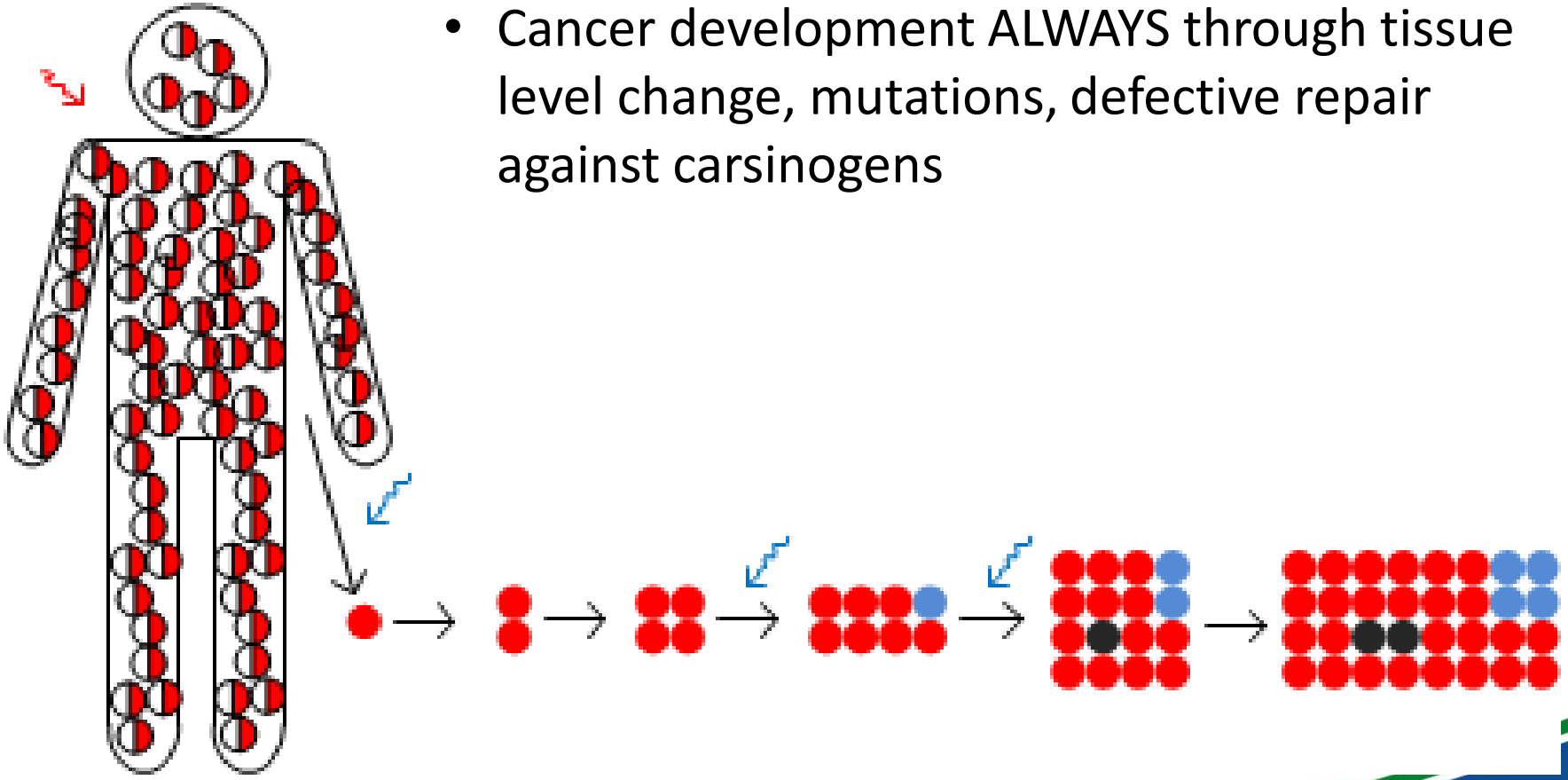
- Any cancer is always a genetic disease
- Cancer pathogenesis includes inactivation of tumor suppressor genes, alterations in DNA repair genes and immunodeficiency.
- Genetic changes limited to target tissue or accumulated during one's life time are not herited

(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 carsinogens

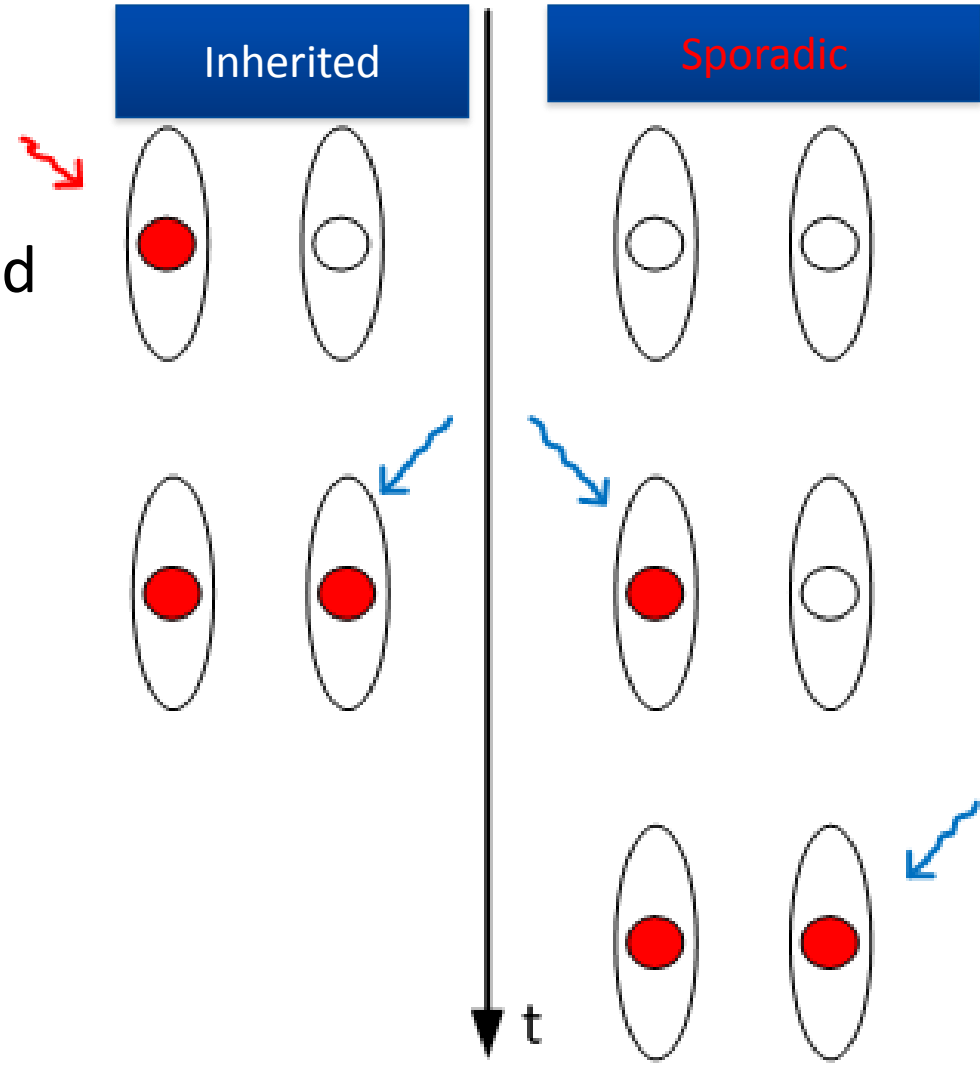


Two hit theory

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

Shorter time to clinical cancer compared to sporadic cancer

Knudson, 1991



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

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 collegues
- 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