MELODI Multidisciplinary European Low Dose Initiative

4th International MELODI Workshop

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Helsinki, Finland

Break-out session 2B: Non-cancer effects

Thursday, 13 September at 16-18 hours

Moderator: Jean-Rene Jordan,

Rapporteur: Eeva Salminen, STUK

Non-cancer effects/radiation abstracts pp 77-90

-Target tissue/cells

1) Lens vs lymfocytes Graw J et al, pp 77

2) Neural/mitochondrial/gene expression/microvasculature Samari,N.et al pp86 Quintens, R.et al pp84, Lumniczky K et al pp81

3) Endothelial and/or HUVEC cells Rombouts,C. Et al, pp85, Kiuru,A.et al, pp Nylynd,R.etal pp83, Tapio,S.et al. pp89

4) Inflammatory response/cytokines Wunderlich, R. Et al.pp90

-Experimental vs practical Moignier, A.et al, pp82

- **Hybrid computational phantom to explore coronary dose /cardiac irradiation**

-Modelling-multimodel interference Schöllnberger, H.etal pp87

- Systemic review meta analysis of circulatory disease from low dose exposure Little, M.et al pp79

Structure of the session

Poster presentations

- The endothelium response to low dose ionizing radiation/cell line differences (R. Benotmane)
- Radiation-induced alterations in the proteome and miRNAome of the endothelial cells (S. Tapio) sampling times-novel biomarkers
- Mouse lens epithelial cells and lymphocytes exhibit similar sensitivity to γ-irradiation (J. Graw) strains/doses
- Identification of novel in vivo p53 target genes in the developing mouse brain (R. Benotmane) novel genes-function?
- Maturating neurons exhibits a delay in neurite outgrowth upon exposure to low and moderate doses of ionising radiation (R. Benotmane) dose dependent changes cut-connections
- Towards a better knowledge of cardiovascular doses following radiotherapyusing hybrid computational phantom (A. Moignier) coronary dose-heart dose
- Dose-Responses from Multi-Model Inference for the Non-cancer Disease Mortality of A-Bomb Survivors (H. Schöllnberger)
- Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimated potential population mortality risks (R. Wakeford)/impact of low dose on circulatory disease comparable to cancer.

Research priorities as described in the current version of the SRA: discussion on how updating/improving the document

- 7 questions
  (multiple choice, 1 answer option) N = 42

1. Can realistic cohorts be designed to study association between low dose radiation and non-cancer effects on health?

1. Yes 64,7%
2. No 35,3%

0 sekuntia jäljellä.

2. What could be the most informative study populations for evaluating non-cancer effects of low-dose radiation?

1. Medical exposure: radiotherapy, CT scans, nuclear medicine 43,2%
2. Occupational exposure: Interventional cardiologists, other medical staff; 16,2%
3. Workers exposed to alpha emitters (eg Mayak), Uranium and other miners 5,4%
4. Aircrews 5,4%
5. Environmentally exposed populations (high natural background radiation, domestic radon, nuclear accidents) 5,4%
6. LSS population 18,9%
7. Other 5,4%

0 sekuntia jäljellä.

7. Are the mechanisms causing non-cancer effects more consistent with stochastic/linear than with deterministic/threshold dose response?

1. Yes, this has been shown 5,7%
2. Remains to be determined, an open research question .68,6%
3. Cannot be evaluated with current approaches 5,7%
4. No, such differences appear unlikely to be of relevance ..5,7%
5. I am not an expert 14,3%

0 sekuntia jäljellä.

4. Which genetic and/or epigenetic modifiers/biomarkers available are most promising markers associated with individual susceptibility to radiation-induced non-cancer effects?

1. Polymorphisms of specific genes e.g. DNA damage repair genes 5,0%
2. Exploratory analyses of wide array of genes (GWAS) 20,0%
3. Epigenetic changes of specific candidate genes (e.g. methylation) 7,5%
4. Wide-scale screening of epigenetic changes in multiple genes 10,0%
5. Other 15,0%
6. I do not have an opinion 42,5%

0 sekuntia jäljellä.

5. Can the known genetic predisposition to cancer risk be extended to non-cancer risk of tissue responses at low doses? If so- are there some biological pathways known that are influenced by genetic factors?

1. Yes, this has been shown 2,7%
2. Remains to be determined, an open research question 75,7%
3. Cannot be evaluated with current approaches 16,2%
4. No, such differences appear unlikely to be of relevance 5,4%

0 sekuntia jäljellä.

3. Should studies on the non-cancer diseases after low-dose radiation exposure address also other diseases than cardiovascular diseases?

1. Yes, cognitive effects, neurodevelopment 50,0%
2. Yes, pulmonary disease 2,4%
3. Yes, infectious disease 7,1%
4. Yes, endocrine disease (thyroid, parathyroid, diabetes etc) 4,8%
5. Yes, cataract 11,9%
6. Yes, renal 0,0%
7. Yes, other 7,1%
8. No, we should concentrate on CVD in the near future 16,7%

0 sekuntia jäljellä.

6. Are there examples where one can well describe the impact of synergistic and interactive radiation effects with other agents?

1. Yes, this has been shown 55,0%
2. Remains to be determined, an open research question 42,5%
3. Cannot be evaluated with current approaches 2,5%
4. No, such differences appear unlikely to be of relevance 0,0%

0 sekuntia jäljellä.

Research priorities as described in the SRA
Non-cancer effects

- **Combined epidemiological and fundamental mechanistic studies** are needed to determine the dose-effect relationships for the induction of **cardiovascular, lens opacities and neurological (cognitive) impairments**. (Here, the question of the presence or absence of thresholds is important). *For this, suitable cohorts (some retrospective, but most prospective) with sound dosimetry and medical control should be identified and set up*

- For these pathologies, **age and developmental specific effects** should be determined (including the involvement of tissues, metabolic, hormonal, immunological, inflammatory responses)

- Research on **cardiovascular effects** should include low (<100mGy) and medium doses (>100mGy). *Of particular interest here is the interaction between elevated cholesterol and radiation-induced arteriosclerosis and clarification whether the mean heart dose or the dose distribution to main arteries are the most relevant parameters (F.A. Stewart, Rome)*

Discussion ensued

How can we meet research targets described in the SRA?

How to make the SRA document more comprehensive?

The 3 entities (circulatory, cognitive, lens opacities) remain valid,

- **are there priorities where dedicated programme could help to understand the mechanism or do we just 'fish in this basket?'**

OR

Is there indication that if we concentrate on one of these we get some specific tools for protection?

However, the poll shows that there is no consensus. We need scientists to discuss what are the arguments to go more in one direction than in the other.

Perhaps we have to go separately to meet these targets, lumping endpoints can be misleading to policy makers.

Discussion continues…

Vascular effects are seen beyond cardiovascular-so why to concentrate on that only- you have to deal with other factors too (radiation, smoking, socioeconomic factors).

-there are cohorts with data on blood pressure etc and these factors should be delt with in epidemiological studies.

Lens is important in point of radioprotection, at least in interventional medicine; to combine etiology and do animal experiments for dose-response questions.

We still lack data to make the choice between research areas. There are not enough studies –work should continue on these 3 fields.

There may be a target which is not yet found, mitochondrial dynamic and functionalism; so also new endpoints should be explored.

-will radiation affect the mitochondrial function in immune system?

DoReMi to organize a meeting on the role of mitochondria with the epigenetics.

EU is already funding cardio and cerebral-molecular epidemiology, mechanistic components, <u>these projects should mature prior we make decision on future.</u>

The endpoints are different but mechanism might be more common.

Should we concentrate on these three or add immunological diseases or …?

- **It might be important to target immune system, apart of targeting the 3 entitites.**
- **If there is a deficiency in immune system the susceptibility to… is affected, and so is inflammatory response.**
- **Inflammation is just a normal response of the body so it may not be such a good target. Overall, the issue of immune system should be addressed.**
- **If the immune system does not work efficiently the response to radiation is different and it affects also cardiovascular diseases etc.**
- **Immune system is critical to all major diseases.**

Dose, Dose rate, Source

- **Dose and dose rate, source of radiation /not given in all abstracts**
- **Low dose, medium dose, high dose/ DoReMi criteria**

Low dose: 100mGy or less, medium 0.1-1 Gy for low LET
Low and medium dose rate 0.1Gy/h or less for low LET radiation

Dose- dose rate – one has to think critically how the dose is being received;
The cellular response is very different when the dose rate is different

X-rays; kV 30-300, standardized dose rate?

Dose, dose rate, source

Way forward

GUIDELINES / CONSENSUS needed for dose/dose rate description for comparability between studies

ALTERATIONS in different biomarkers at different timepoints; where should the research focus on?? Tools and endpoints

STANDARDS for endpoint analyses?

MODELLING consider multiple model approaches

COHORTS: future: medically exposed, confounding factors, radiation protection

LABORATORY: adapted research, radiation protection

ONGOING programms - CONSIDER refresh the SRA

2B conclusions

- **Studies on the key target areas are ongoing. Combined epidemiological and fundamental mechanistic studies** are needed to determine the dose-effect relationships for the induction of **circulatory diseases, lens opacities and neurological (cognitive) impairments.**
- **It might be important also to target immune system,**
- **DoReMi to organize a meeting discussing the role of mitochondria with the epigenetics.**
- **Dose- dose rate – one has to think critically how the dose is being received; cellular response is different when the dose rate is different. Is there is a need for refreshing the SRA?**
- **EU is already funding cardio and cerebral-molecular epidemiology, mechanistic components, these projects should mature prior we make major prgrammatic changes.**