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With contributions from: All project partners (HMGU, ENEA, DU, OBU) and Advisory Board members

Reviewer(s): CONCERT coordination team

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Abstract

The lens of the eye is known to be more radiosensitive than previously thought but, despite a substantial reduction in occupational dose limits based on recent epidemiological information and reanalyses, the mechanisms of low dose radiation cataract induction are still unclear. This is an important current public health issue, for instance for medical radiation workers, many of whom will need to amend their working practices despite there being no clear understanding of the effects of chronic, low dose, low dose rate ionising radiation exposure.

The LDLensRad project aims to bring together experts from across Europe to answer a number of key research questions on this topic, including: how does low dose radiation cause cataracts; is there a dose rate effect, and how does genetic background influence cataract development after radiation exposure. CONCERT Deliverable 9.57, describes the final advisory board report presented to the consortium members at the end of the LDLensRad final meeting in Rome in December 2019.

Content

Comments and suggestions from the Advisory Board

Presented on 6th December 2019 by Nobuyuki Hamada (CRIEPI, Japan) on behalf of the Advisory Board: Tamara Azizova (SUBI), Larry Dauer (MSKCC), Joe Dynlacht (IUSOM), Rick Tanner (PHE).

General comments

The project is very well represented on the ResearchGate page (https://www.researchgate.net/project/LDLensRad-the-European-CONCERT-project-starting-in-2017-Towards-a-full-mechanistic-understanding-of-low-dose-radiation-induced-cataracts) – people are paying attention to the project. At the time of the 2019 AM we have posted 33 updates, have 63 followers, and have had 1419 'reads.'

The project is well designed as a whole, but some improvements may further strengthen the merit of the project.

Main comments on the findings

For **WP1 and WP2**: The major assumptions underlying the latest ICRP recommendations include no dose rate effects and progression of minor opacities into vision-impairing cataracts (VIC). ICRP recognizes the importance of mechanistic research to further inform adequate radiation protection (RP).

There is growing epidemiological evidence for radiation cataracts:

- Significantly increased risks for PSC>cortical>nuclear cataracts and females > males in Mayak workers (Azizova *et al.*, 2018)
- US radiologic technologists risks significant < 100 mGy (Little *et al.*, 2018 and 2020)
- Risk of PSC in residents high natural background areas who are thus chronically exposed

LDLensRad data suggest endpoint-dependent impact of dose rates. Various biological changes could be detected including histological data from the eye, biochemical data from bovine lenses, molecular data from next generation sequencing (NGS), cellular data from in vitro cultured human cells. The relevance to manifestation of lens opacities and implications for radiation protection need to be carefully considered.

The epidemiological evidence for progressive nature of cataract is unclear, further attention needs to be paid to this issue, particular in interpretation of the Scheimpflug imaging results.

One of the strengths of LDLensRad is that three institutes (PHE, ENEA, HMGU) used very consistent irradiation conditions for studies with mouse models, which makes inter-laboratory comparisons feasible. However, further description of the similarities and differences in the conditions for radiation, animal facilities, husbandry (bedding, feed, water, etc.), will help identify the potential causes for the 'differences' in the results and make clear the need for consistency in future research.

Discussion of effects as a function of age and time since exposure was a running theme throughout presentation of the results. This poses the question of which population is more sensitive: young or old individuals? At younger ages of exposure, background levels are lower, but onset times can be longer, and vice versa.

For the OCT/histological work: At 12 months post irradiation, there appeared to be a threshold; however, linear dose response was observed at 20 months post irradiation. This resembles the data seen in the Japanese atomic-bomb survivors and Russian Mayak workers; careful interpretation is needed for the radiation protection implications.

Regarding tumor related factors: Evidence is limited but increasing for the possible involvement of various tumor related factors in radiation cataract. This has implications for the stochastic/deterministic (tissue reaction) classification of the radiation effects for radiation protection purposes.

Regarding *WP3*: Integration of the wider systemic effects has been very useful. The biological developments in mice are supported epidemiologically by the Mayak worker and INWORKS studies, and may likely be supported by other studies.

For *WP4*: A clear strength of the project is that the statistical significance can (generally) be tested in a consistent way. AOP is a hot topic, but its practical usefulness is not clear at this stage. Therefore, the position of LDLensRad should be clarified.

For *WP5*: The presence of LDLensRad consortium members and presentations at a large number of international scientific meetings has succeeded in disseminating the work of LDLensRad. Upcoming meetings that we might consider include COSPAR 2020.

Regarding the editorial for the special issue: The introductory paper should clearly mention the objectives of the project including the motivation for pursuing hypotheses that intuitively might not be readily associated with cataracts, also highlights of the main findings, introduction to the key issues in the field of RP and the impact of the main findings. The papers presenting scientific results should clearly reflect the strengths and limitations of assays or tests, e.g., the Scheimpflug imaging (not always detecting PSC), viability assays, and DNA repair assays.

Summary

The initial aims were:

- How does low dose radiation cause cataract?
- Is there a dose rate effect?
- How does genetic background influence cataract development after radiation exposure?

In addition, we intended to look at the shape of the dose response (in time), advancing the debate regarding the nature of cataract (deterministic, stochastic or both), biomarkers or bioindicators of global radiosensitivity. The education of early career scientists was also an important objective. Each of these goals has been met or exceeded very satisfactorily.

For final reporting, we need to stress the education and training aspects as documented by co-authorship of students on papers, student travel and poster awards, etc – the early career scientists have done a great job.

We should also be clear that even 'negative' data should be published and discussed – all the results are valid whether positive or 'negative' in terms of radiation response and could help shape a better understanding of the dose threshold for radiation-induced cataracts.

The field of eye lens dosimetry is advancing, with additional information at low doses, which should in future years yield much more detailed epidemiological data on this issue. The final paper of the special issue should highlight all these relevant issues regarding the landscape of lens research going forward, and outline future research goals.

What we could have done better/what should we look at next time

In order to investigate further the most interesting effects, e.g. the inverse dose rate effects, we should collect additional dose and dose rate points.

The validation we did prior to starting the experiments is important, including the physics of calibration and comparison between the different labs' dosimetry systems, and thus needs to be clearly defined in the relevant publications.

We must keep in mind that while animal models are useful for mechanistic understanding, humans are not the same as mice! For mechanistic modelling, we should rely on the data which are really consistent in order to ensure that the results are high impact and of key relevance for radiation protection. We should also keep in mind the developing epidemiological and other mechanistic data which are emerging, and further work with epidemiologists going forward.

LET and RBE will also be important going forward.