Cataract following low dose ionising radiation exposures: Mechanistic understanding and current research

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CNSC/CRPA Webinar: Lens of the eye – 21st March 2018
Human Lens

Diameter ~9-10 mm, thickness ~4.5 mm

Germinative zone of LEC

Growth factors

-> differentiation

-> lens fibres

Tight temporal and spatial organisation

Deregulation -> cataracts
Cataracts are most frequent cause of blindness worldwide

**Multifactorial aetiology:** Age related effect; Genetic component (congenital cataracts); Also: Sunlight, alcohol intake, nicotine consumption, diabetes, persistent use of corticosteroids, and *ionising radiation*...
Ionizing radiation is generally (but not exclusively) associated with posterior sub-capsular opacities

Well established paradigm: Radiation cataract is a deterministic, late, effect

ICRP, 1990 (and 2007), and others: Thresholds for radiation induced cataracts: 2 Gy acute; 4 Gy or higher fractionated/chronic exposures

ICRP 2011: Threshold ~ 0.5 Gy…
How does ionising radiation cause cataracts?

**Target cells:** Germinative Zone on lens epithelium (?)

**Potential mechanisms might include:**
- Oxidative stress
- DNA Damage/Repair/Mis-repair
- Intracellular signalling
- Gene expression
- Cellular proliferation / mobility / migration
- Damage to proteins/ECM/lipids
- Post translational modifications
- Senescence
- Systemic/Non-targeted effects …

**Modifying factors:** Dose, Dose rate, Age at exposure, Genetic background …
What do we know about oxidation?

**ROS:** Degradation, cross-linking, aggregation of lens proteins, DNA damage

-> Aberrant lens epithelial cell division, cell migration, differentiation…

Hamada et al., 2014
Evidence from a study looking at DNA damage and repair

Markiewicz et al., 2015:
- Low dose, dose-response for DNA damage response in the lens
- Lens (peripheral region) is more sensitive than circulating lymphocytes
Signalling: Tumour related factors

Hamada and Fujimichi, 2015
Data on stimulation of proliferation

Fujimichi and Hamada, 2015: “IR not only inactivates clonogenic potential but also stimulates proliferation of surviving unactivated clonogenic HLE cells”

IR -> abnormal activity

Historical data: Irradiation induces excessive proliferation of rabbit lens epithelial cells; suppression of lens epithelial cell divisions inhibits radiation cataractogenesis in frogs and rats

Markiewicz et al. 2014:
Some publications on lens protein modifications

Abnormal lens protein accumulation -> Aggregation, lens scatters light instead of focusing on the retina

Bloemendal et al, 2004: Lens crystallins: α-,β- and γ-, form the refractive medium of the lens; proteins e.g. αA- or αB- protect from aggregation

Muranov et al., 2010: Protein changes in irradiated lenses similar to those seen in old age

Wiley et al., 2011: Role of abnormal cellular proliferation, e.g. p53 effect?

Fujii et al., 2001: Role of post translational modifications? May reduce solubility to alter transparency
Mouse models: ATM, RAD9, BRAC1 genes control signalling for DNA damage response signalling; Heterozygosity of these genes known to leads to increased risk of cancers

Worgul et al., 2002:
- Cataracts earliest in homozygotes for Atm, then heterozygotes, then wildtype
- Severity and latency proportional to number of damaged cells attempting differentiation
- Atm homozygotes/heterozygotes – genetic predisposition to cataracts

Kleiman et al., 2007: Cataracts develop earlier and in greater numbers in Atm/Rad9 double heterozygotes

Smilenov et al., 2008: Atm/Rad9/Brca1 double heterozygotes showed increased resistance to apoptosis and increased radiation sensitivity

Humans: e.g. Cataractogenic mutations in human crystallin genes
(Very basic) summary of current (incomplete) mechanistic hypothesis

Ionising Radiation

ROS

Dividing cells

Systemic effects

Abnormal differentiation and migration

Antioxidant capacity overwhelmed

Genetic effects

Protein / lipid / ECM damage

Post translational effects

Abnormal accumulation of lens proteins

Radiation cataract
What do we know?

Understanding of lens biology (structure, physiology, process of fibre cell formation)

Radiation causes posterior subcapsular cataracts

High dose responses; impact of RBE, LET, DR

Number of potential competing/parallel mechanisms from wider cataract studies

Cellular and tissue level studies *ex vivo* or *in vitro* support the paradigm of genomic damage of lens epithelial cells as key mechanisms of cataractogenesis

Genetic background (e.g. heterozygosity for *Atm* or *Ptch1*), gene expression

Age dependence, impact of normal aging

Cataract detection/assessment
What don’t we know?

Research model

Questions to be addressed experimentally

- <1Gy IR exposure
- Stochastic vs deterministic (radiation protection)
- Acute vs protracted exposure (dose rate)
- Identify markers of cataract initiation and progression (diagnostic/prognostic)
- Induction of impaired proliferation/differentiation by radiation exposure

Mechanistic targets

- In vivo (ex vivo) models
- Identification of murine strains suitable for endpoints
- Genetic/environmental conditions
  - Diet
  - Circadian rhythm
  - Age/gender
  - Epigenetic altered gene expression
- Opacity monitoring
  - Lens shape
  - Standardized grading
  - Epithelial cell density

Exposed human cohorts
- Medical/occupational
- Accident survivors
- Head/neck RT patients
- Nuclear workers

In vivo relevance

\[\text{Accelerated aging} \quad \text{Nuclear/cellular} \quad \text{Latency period length} \quad \text{Monte Carlo modeling of dose-dep} \quad \text{Confounding factors} \quad \text{Smoking} \quad \text{Alcohol consumption} \quad \text{Background IR exposure} \quad \text{UV exposure} \quad \text{Obesity} \quad \text{Diabetes} \quad \text{Hypertension} \quad \text{Eye injury/inflammation} \quad \text{Asthma} \quad \text{Steroids} \quad \text{COPD}\]
EJP CONCERT LDLensRad: Towards a full mechanistic understanding of low dose radiation induced cataracts

Objective:

“To advance knowledge to solve the question of how radiation causes and/or promotes cataracts.

This will be achieved by providing concrete evidence of the ability of radiation exposure <= 500 mGy to cause cataracts, the impact of dose protraction on the dose response and the biological mechanisms behind cataractogenesis.”
Specific research questions

- Is there a low dose dose-response in radiation cataractogenesis?
- What is the impact of dose rate?
- What is the impact of genetic background?
- What is the impact/involvement with the ‘normal’ aging process?
- How are oxidative stress and intracellular communication, DNA damage, translational, proteomic and lipidomic responses, proliferation and lens morphology impacted by radiation?
- Can the lens be viewed as an indicator of global radiosensitivity?
- Are radiation cataracts most appropriately viewed as a deterministic/tissue reaction or a stochastic effect?

LDLensRad will contribute to answering some of these questions but: 

**Further collaborative research is needed!**
LDLensRad: Towards a full mechanistic understanding of low dose radiation induced cataracts

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Unless otherwise stated, all figures taken from:
Thank you for listening!

Questions/Comments/Suggestions?

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