MEDDOCS Open Access Publisher

Annals of Ophthalmology and Visual Sciences

Open Access | Review Article

Radiation damaging effects on ocular tissues

Yuan-Hao Lee[1*]; Randolph D Glickman[2]

[1]Department of Ophthalmology & Visual Science, University of Texas Health Science Center at Houston, Houston, TX

[2]Department of Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX

***Corresponding Author(s): Lee Y**

Department of Ophthalmology & Visual Science, University of Texas, Health Science Center, Houston, TX, USA

Email: gugu610@msn.com

Received: June 18, 2018

Accepted: Aug 02, 2018

Published Online: Aug 09, 2018

Journal: Annals of Ophthalmology and Visual Sciences

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Cataract; Radiation damage; Radiosensitivity; Retinopathy

Abstract

The human eye, composed of specialized tissues, has unique functions to admit or receive certain wavelengths of electromagnetic radiation. In order to integrate information from the entire visual field, visible light is collected and focused by the spherical lens onto retinal neurons. Excessive light exposure, however, not only mediates photoreceptor activation but also induces photodamage effects. With respect to radiation-induced oculopathy, this review describes key components that influence cell radiosensitivity (or photosensitivity) and discusses other potentiating risk factors. Finally, this review provides preventive and therapeutic information for reducing radiation-induced retinal and lenticular damage.

Introduction

Through the unique process of photon transduction in retinal photoreceptors, along with the associated synaptic activity of the other retinal neurons, optical radiation (i.e., light) is transformed into electrical signals and perceived by our visual association cortex, while the optical structures of the eye function as analogues of camera parts [1-3]. Excessive radiation or high-energy radiation, however, is potent in inducing DNA damage and post-translational modification of proteins [4-6]. Examples include solar retinopathy caused by excessive sun gazing or even from reflected light from snow or sand, as well as radiotherapy incurred or cosmic rays-induced blindness [7-10]. In this respect, it is important to know the differential photo- and radio-sensitivity of various types of ocular cells for preventing and repairing radiation-induced oculopathy. This review focused on mechanistic descriptions of how radiation induces lens opacification and retinopathy apart from the structural complexity and cellular plasticity of the ocular system.

Radiation-induced insults

DNA damage

Radiation-induced reactive oxygen species can result in DNA breakage, cross-links, and nucleotide modification, which require DNA repair pathways, including homologous recombination, non-homologous end joining, and nucleotide excision repair [4, 11-15]. Generally, radiation-induced double-stranded breaks in proliferative cells are predominantly repaired through homologous recombination when cell cycle propagates through

Cite this article: Lee Y, Glickman RD. Radiation damaging effects on ocular tissues. Ann Ophthalmol Vis Sci. 2018; 1: 1002.

the DNA synthetic phase [16]. If DNA damage remains unrepaired, proliferating cells will be rendered apoptotic due to the failure of accomplishing cell mitosis [17].

Radiation-induced protein malfunction

The denucleation of lens fiber cells, essential for the maintenance of lens clarity, is mediated through the activity of DNases that readily cleaves DNA and hence degrade nuclei. If this process is stalled then cataract is induced following cell differentiation defects [18]. Excessive light exposure of retina induces protein oxidation and polyubiquitination and renders cells apoptotic [19,20]. The radiation-induced impairment in protein degradation can lead to lenticular and retinal degeneration as well as vision loss.

Cell radio sensitivity

Responses of ocular tissues to radiation are associated with the turnover rates and differentiation levels of cells [21-23]. The higher a tissue turnover rate is, the less tissue function is impaired after irradiation. While most of the ocular tissues are constituted of differentiating intermitotic cells and present moderate radio sensitivity [22,24-26], radiation-induced lens opacification, which underlies high radio sensitivity of the lens itself, is different than the effect of cell killing.

Dividing cells

Studies have shown that the Lens Epithelial Cells (LECs) and retinal neuroblasts are more proliferative and less differentiated than lens fiber and retinal neurons, respectively [27,28]. The high turnover rates of LECs render them susceptible to radiation-induced DNA damage [29]. In the development of cataracts after cell exposure to ionizing radiation, LECs uncontrollably proliferate and migrate to the posterior pole of the lens on the anterior surface of the posterior capsule [30]. Studies have shown that radiation revokes contact inhibition and promotes FGF-2-triggered lens fiber cell differentiation through Wnt signaling [31-33]. Radiogenic oxidative stress and DNA double-strand breaks can cause LECs migration backward to the posterior capsule, leading to hindrance of light penetration (posterior subcapsular opacification) [34, 35]. Therefore, the control of cell expansion and migration becomes critical to the mitigation of radiation cataractogenesis. It is proposed that chemo attractant receptors of LECs, such as IGF (insulin-like growth factor) and TGF-β (transforming growth factor) receptors, are activated by radiation and mediate cell migration toward the source of attractants [36].

Lower dose radiation kills retinal neuroblasts and affects visual function; higher dose exposure induces loss of epithelial cells and pericytes in the capillaries of the retina, leading to micro infarcts and lack of perfusion [9]. Radiation treatment for tumors in the eye, orbit, paranasal sinuses and cranial fossa usually results in occlusive vasculopathy, leading to retinal edema, exudates and vision loss [37,38]. Radiation damage to retinal vascular endothelial cells is believed to initiate the development of radiation retinopathy due to the role of the circulation in supplying nutrients and oxygen to the metabolically active retina as well as protecting retina from molecular toxins, microorganisms, and pro-inflammatory leukocytes [39,40]. To reduce the risk of retinopathy following radiation therapy, the accepted upper limit of safe total absorbed dose for radiation retinopathy is 30 Gy [41].

Researchers have found that radiation retinopathy is associated with VEGF production [37,39]. The reduction of VEGF inhibits neovascularization, decreases vascular permeability and maintains visual acuity. Additional risk factors for developing radiation retinopathy include short tumor distance from the optic nerve, preexisting diabetes mellitus, and young age. On the other hand, retinal stem cells reveal radio resistance through Notch and WNT signaling [42,43]. Radiation-induced resistance has been observed in fetal mouse retinal explants [44]. The radio resistance was larger when the dose of radiation was reduced and when being exposed at later times, indicating a correlation between cell radio resistance and radiation dose rate or age [44,45].

Non-dividing cells

Lens fiber cells at higher differentiation levels have no mitotic functions and require very large doses to result in catastrophic cell death. Nevertheless, radiation doses at smaller amounts are readily capable of resulting in irrecoverable cellular damage in lens fiber cells that causes cataractogenesis [34]. The deformation of crystallins, for example, induces cross linking and disrupts the tight packing of fiber cells, resulting in cataractous opacities [38]. Diabetes exacerbates radiation-induced cataract by stalling the metabolic pathway of blood sugar [46]. Studies have shown that glucose can be converted to sorbitol in the lens and forms sorbitol aggregates under the deficiency ofα-crystallin [47,48]. When lenticular α-crystallingets deformed by radiation [49], its protective effect on sorbitol dehydrogenase weakens, leading to inefficient conversion of sorbitol into fructose [47]. In addition, higher blood sugar causes damage to blood vessels in the retina and exacerbates the effect of radiation-induced vessel damage.

Similar to diabetes-associated metabolic stress, radiation-induced water ionization increases generation of superoxide and other reactive oxygen species in the retina, leading to vascular lesions and retinopathy [48]. Studies have shown that highly metabolic photoreceptor cells, cones and rods, can potentiate diabetic retinopathy through the induction of hypoxia and oxidative stress [50]. Nevertheless, it remains unclear whether photoreceptors play a role in radiation retinopathy. Researchers have shown that retinal degeneration is associated with rhodopsin-induced stress signaling and inflammation in photoreceptors [51].

Promotion and mitigation of cell radiosensitivity

Smoking increases cataract formation via two mechanisms. First, smoke-containing chemicals, including arsenic, lead, carbon monoxide and hydrogen cyanide, neutralize reductants that counteract oxidation. Secondly, oxidative stress emerges within the lens via the absorption and accumulation of smoke-containing chemicals [46].

Oxygen levels, on the other hand, are highly associated with radiation-induced free radicals, which damage lenticular fibers and decrease the membrane's ability to transport certain ions. In addition, radiation-induced hydroxyl radicals can further escalate vascular activity and exacerbate radiation-induced damage to retinal capillaries [52].

To decrease the interaction of singlet oxygen (or superoxide ion) with cellular components through photochemical reactions, free radical scavengers, such as vitamin C, sodium a zide and superoxide dismutase may be employed [53]. Recently, the administration of bone-marrow-derived mesenchymal stem cells into neuroretinal tissues has shown some potential

for healing laser-induced retinal injury partially through down-regulation of monocyte chemotactic protein-1 [54]. In addition, intramuscular injection of adherent human placental stromal cells effectively recovered the hematopoietic system following total body irradiation of mice [55]. These observations suggest that stem cell-derived interventions may lead to an effective, versatile treatment for radiation retinopathy.

Summary

The ocular toxicity of various ionizing and non-ionizing radiation can be exacerbated by diabetes ordiabetic vasculopathy. The following figures recapitulate this point (Figures 1, 2).

Figures

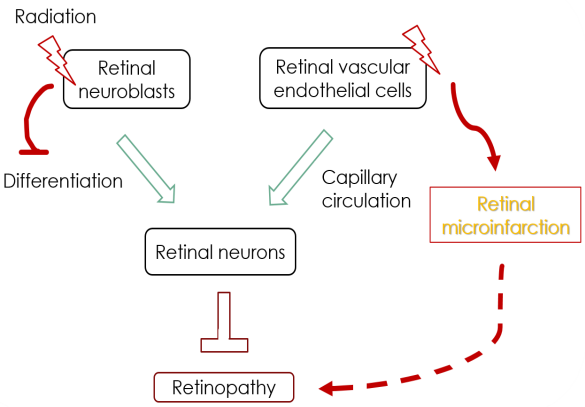

Figure 1 : Schematic diagram showing that radiation elicits apoptosis and blocks the formation of retinal neurons for inhibiting retinopathy evoked by radiation-induced damage on retinal vascular endothelial cells. The yellow highlighted action is associated with diabetic vasculopathy.

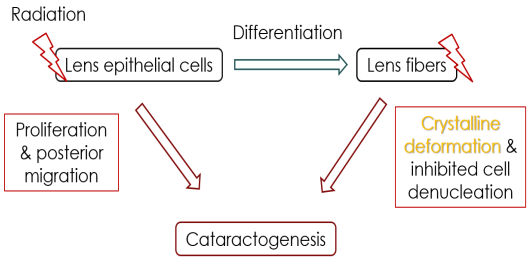

Figure 2 : Schematic diagram showing that radiation elicits cataractogenesis through different mechanisms on lens epithelial cells or/ and lens fibers. The yellow highlighted action is associated with diabetics.

References

1. Szikra T, Krizaj D. The Dynamic Range and Domain-Specific Signals of Intracellular Calcium in Photoreceptors. Neuroscience. 2006; 141: 143-155.
2. Szikra T, Barabas P, Bartoletti TM, Huang W, Akopian A, Thoreson WB, et al. Calcium Homeostasis and Cone Signaling Are Regulated by Interactions between Calcium Stores and Plasma Membrane Ion Channels." PLoS One. 2009; 4: e6723.
3. Jarvis JR, Wathes CM. Mechanistic Modeling of Vertebrate Spatial Contrast Sensitivity and Acuity at Low Luminance. Vis Neurosci. 2012; 29: 169-181.
4. Gordon WC, Casey DM, Lukiw WJ, Bazan NG. DNA Damage and Repair in Light-Induced Photoreceptor Degeneration. Invest Ophthalmol Vis Sci. 2002; 43: 3511-3521.
5. Organisciak DT, Vaughan DK. Retinal Light Damage: Mechanisms and Protection. Prog Retin Eye Res. 2010; 29: 113-134.
6. Zrenner, E. [Light-Induced Damage to the Eye]. Fortschr Ophthalmol. 1990; 87: S41-51.
7. Rocha Cabrera P, Cordoves Dorta L, Gonzalez Hernandez M. Bilateral Solar Retinopathy. Auto fluorescence and Optical Coherence Tomography. Arch Soc Esp Oftalmol. 2016; 91: 391-396.
8. Gibson DC. Terrestrial and Extraterrestrial Space Dangers: Outer Space Perils, Rocket Risks and the Health Consequences of the Space Environment. 2015.
9. Harris JR, Levene MB. Visual Complications Following Irradiation for Pituitary Adenomas and Craniopharyngiomas. Radiology. 1976; 120: 167-171.
10. Millar JL, Spry NA, Lamb DS, Delahunt J. Blindness in Patients after External Beam Irradiation for Pituitary Adenomas: Two Cases Occurring after Small Daily Fractional Doses. Clin Oncol (R Coll Radiol). 1991; 3: 291-294.
11. Téoule R, Duplaa AM. Free Radical and Radiation-Induced DNA Damage to Oligonucleotides. Free Radic Res Commun. 1989; 6: 121-122.
12. Dextraze ME, Gantchev T, Girouard S, Hunting D. DNA Interstrand Cross-links Induced by Ionizing Radiation: An Unsung Lesion. Mutat Res. 2010; 704: 101-107.
13. Bee L, Fabris S, Cherubini R, Mognato M, Celotti L. The Efficiency of Homologous Recombination and Non-Homologous End Joining Systems in Repairing Double-Strand Breaks during Cell Cycle Progression. PLoS One. 2013; 8: e69061.
14. Zhang Y, Rohde LH, Wu H. Involvement of Nucleotide Excision and Mismatch Repair Mechanisms in Double Strand Break Repair. Curr Genomics. 2009; 10: 250-258.
15. Lee YH, Sun Y, Glickman RD. UrsolicAcid-Regulated Energy Metabolism—Reliever or Propeller of Ultraviolet-Induced Oxidative Stress and DNA Damage?. Proteomes. 2014; 2: 399-425.
16. Jeggo PA, Geuting V, Lobrich M. The Role of Homologous Recombination in Radiation-Induced Double-Strand Break Repair. Radiother Oncol. 2011; 101: 7-12.
17. Murray A. Cell Cycle Checkpoints. Curr Opin Cell Biol. 1994; 6: 872-876.
18. Wang W, Li Q, Xu J, Cvekl A. Lens Fiber Cell Differentiation and Denucleation Are Disrupted through Expression of the N-Terminal Nuclear Receptor Box of Ncoa6 and Result in p53-dependent and p53-independent Apoptosis. Mol Bio Cell. 2010; 21: 2453–2468.
19. Nakanishi T, Shimazawa M, Sugitani S, Kudo T, Imai S, Inokuchi Y, et al. Role of Endoplasmic Reticulum Stress in Light-Induced Photoreceptor Degeneration in Mice. J Neurochem. 2013; 125: 111-124.
20. Glickman RD. Phototoxicity to the Retina: Mechanisms of Damage. Int J Toxicol. 2002; 21: 473-490.
21. Liu X, Li F, Huang Q, Zhang Z, Zhou L, Deng Y, et al. Self-Inflicted DNA Double-Strand Breaks Sustain Tumorigenicity and Stemness of Cancer Cells. Cell Research. 2017; 27: 764–783.
22. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist; Lippincott Williams & Wilkins. 2006; 4151-4154.
23. Moding EJ, Kastan MB, Kirsch DG. Strategies for Optimizing the

Response of Cancer and Normal Tissues to Radiation. Nat Rev Drug Discov. 2013; 12: 526-542.

24. Beebe DC, Masters BR. Cell Lineage and the Differentiation of Corneal Epithelial Cells. Invest Ophthalmol Vis Sci. 1996; 37: 1815-1825.

25. Rubin P, Casarett GW. Clinical Radiation Pathology. Philadelphia, PA: W. B. Saunders. 1968.

26. Haschek WM, Rousseaux CG. Handbook of toxicologic pathology. 1991.

27. Andley UP. The Lens Epithelium: Focus on the Expression and Function of the Alpha-Crystallin Chaperones. Int J Biochem Cell Biol. 2008; 40: 317-323.

28. Wang SZ, Ma W, Yan RT, Mao W. Generating Retinal Neurons by Reprogramming Retinal Pigment Epithelial Cells. Expert Opin Biol Ther. 2010; 10: 1227-1239.

29. Denekamp J. Cell Kinetics and Radiation Biology. Int J Radiat Biol Relat Stud Phys Chem Med. 1986; 49: 357-380.

30. Aliancy JF, Mamalis N. Crystalline Lens and Cataract. In Webvision: The Organization of the Retina and Visual System, edited by H. Kolb, E. Fernandez and R. Nelson. Salt Lake City (UT). 1995.

31. Dunn SJ, Osborne JM, Appleton PL, Näthke I. Combined Changes in Wnt Signaling Response and Contact Inhibition Induce Altered Proliferation in Radiation-Treated Intestinal Crypts. Mol Biol Cell. 2016; 27: 1863-1874.

32. Chen Y, Stump RJ, Lovicu FJ, Shimono A, McAvoy JW. Wnt Signaling is Required for Organization of the Lens Fiber Cell Cytoskeleton and Development of Lens Three-Dimensional Architecture. Dev Biol. 2008; 324: 161-176.

33. Wei LC, Ding YX, Liu YH, Duan L, Bai Y, Shi M, Chen LW. Low-Dose Radiation Stimulates Wnt/ß-catenin Signaling, Neural StemCell Proliferation and Neurogenesis of the Mouse Hippocampus in vitro and *in vivo*. Curr Alzheimer Res. 2012; 9: 278-289.

34. Wolf N, Pendergrass W, Singh N, Swisshelm K, Schwartz J. Radiation Cataracts: mechanisms involved in their long delayed occurrence but then rapid progression. Mol Vis. 2008; 14: 274-285.

35. Nagamoto T, Hara E. Lens Epithelial Cell Migration onto the Posterior Capsule *in vitro*. J Cataract Refract Surg. 1996; 22: 841-846.

36. Lee EY, Chung CH, Khoury CC, Yeo TK, Pyagay PE, Wang A, et al. The Monocyte Chemoattractant Protein-1/CCR2 Loop, Inducible by TGF-beta, Increases Podocyte Motility and Albumin Permeability. Am J Physiol Renal Physiol. 2009; 297: F85-94.

37. Finger PT. Radiation Retinopathy is Treatable with Anti-vascular Endothelial Growth Factor Bevacizumab (Avastin). Int J Radiation Oncology Biol Phys. 2008; 70: 974-977.

38. Gall N, Leiba H, Handzel R, Pe'er J. Severe Radiation Retinopathy and Optic Neuropathy after Brachytherapy for Choroidal Melanoma, Treated by Hyperbaric Oxygen. Eye (Lond). 2007; 21: 1010-1012.

39. Giuliari GP, Sadaka A, Hinkle DM, Simpson ER. Current Treatments for Radiation Retinopathy. Acta Oncologica. 2011; 50: 6-13.

40. Bharadwaj AS, Appukuttan B, Wilmarth PA, Pan Y, Stempel AJ, Chipps TJ, et al. Role of the Retinal Vascular Endothelial Cell in Ocular Disease. Prog Retin Eye Res. 2012; 32: 102-180.

41. Gupta A, Dhawahir-Scala F, Smith A, Young L, Charles S. Radiation Retinopathy: Case report and review. BMC Ophthalmol. 2007; 7.

42. Del Debbio CB, Balasubramanian S, Parameswaran S, Chaudhuri A, Qiu F, Ahmad I. Notch and Wnt Signaling Mediated Rod Photoreceptor Regeneration by Muller Cells in Adult Mammalian Retina. PLoS One. 2010; 5: e12425

43. Silva AK, Yi H, Hayes SH, Seigel GM, Hackam AS. Lithium Chloride Regulates the Proliferation of Stem-Like Cells in Retinoblastoma Cell Lines: A Potential Role for the Canonical Wnt Signaling Pathway. Mol Vis. 2010; 16: 36-45.

44. Smalheiser NR, Crain SM. Radiosensitivity and Differentiation of Ganglion Cells within Fetal Mouse Retinal Explants *in vitro*. Brain Res. 1984; 315: 159-163.

45. Tronov VA, Vinogradova YuV, Loginova MYu, Poplinskaia VA, Ostrovskii MA. Mechanisms of Radioresistance in Terminally Differentiated Cells of Mature Retina. Tsitologiia. 2012; 54: 261-269.

46. Muchnick BG. Clinical Medicine in Optometric Practice. Mosby Elsevier. 2008.

47. Marini I, Moschini R, Del Corso A, Mura U. Complete Protection by a-Crystallin of Lens Sorbitol Dehydrogenase Undergoing Thermal Stress. J Biol Chem. 2000; 275: 32559–32565.

48. El-Kabbani O, Darmanin C, Chung RP. Sorbitol Dehydrogenase: structure, function and ligand design. Curr Med Chem. 2004; 11: 465–476.

49. Fujii N, Uchida H, Saito T. The Damaging Effect of Uv-C Irradiation on Lens Alpha-Crystallin. Mol Vis. 2004; 10: 814-820.

50. 50. Kern TS, Berkowitz BA. Photoreceptors in Diabetic Retinopathy. J Diabetes Investig. 2015; 6: 371–380.

51. Landfried B, Samardzija M, Barben M, Schori C, Klee K, Storti F, et al. Digoxin-Induced Retinal Degeneration Depends on Rhodopsin. Cell Death Dis. 2017; 8: e2670.

52. Hartnett ME, Lane RH. Effects of Oxygen on the Development and Severity of Retinopathy of Prematurity. J AAPOS. 2013; 17: 229.

53. Horspool WM, Lenci F. CRC Handbook of Organic Photochemistry and Photobiology. CRC Press LLC. 2004.

54. Yu B, Shao H, Su C, Jiang Y, Chen X, Bai L, et al. Exosomes Derived from MSCs Ameliorate Retinal Laser Injury Partially by Inhibition of MCP-1. Sci Reports. 2016; 6: 34562.

55. Gaberman E, Pinzur L, Levdansky L, Tsirlin M, Netzer N, Aberman Z, et al. Mitigation of Lethal Radiation Syndrome in Mice by Intramuscular Injection of 3D Cultured Adherent Human Placental Stromal Cells. PLOS ONE. 2013; 8: e66549.