Radiation damaging effects on ocular tissues

Yuan-Hao Lee¹; Randolph D Glickman²

¹Department of Ophthalmology & Visual Science, University of Texas Health Science Center at Houston, Houston, TX
²Department of Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX

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.

Keywords: Cataract; Radiation damage; Radiosensitivity; Retinopathy

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...
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 denudation of lens fiber cells, essential for the maintenance of lens clarity, is mediated through the activity of DNases that readily cleaves DNA and hence degrades 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 LEC 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 irreversible 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 fibers, 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-crystallinets 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

Annals of Ophthalmology and Visual Sciences
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 or diabetic 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

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


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


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


52. Martini 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


