



电离辐射致晶状体损伤：暴露特征、剂量-效应关系及分子机制*

胡成昊 任韶涵 张海涛 战景明**

(中国辐射防护研究院放射医学与环境医学研究所, 太原 030006)

摘要 眼晶状体是电离辐射敏感性极高的组织之一, 放射性白内障虽被列为确定性效应, 但其致病阈值与分子机制尚存争议, 是当前放射防护领域的关键科学问题。本文系统综述了电离辐射致晶状体损伤的流行病学特征与生物学机制进展。在暴露特征与剂量-效应关系方面, 文章基于多维暴露特征, 分析了剂量率、辐射品质及个体遗传背景对损伤的修饰作用, 并探讨了现行 0.5 Gy 阈值与线性无阈值模型间的学术争议。在核心机制层面, 重点阐释了电离辐射诱导晶状体混浊的四大驱动路径: 一是 DNA 双链断裂修复能力受损, 损伤在缺乏细胞更新的晶状体中持续累积; 二是核转录因子红系 2 相关因子 2 (Nrf2) 抗氧化防御系统失调, 出现氧化应激与晶状体蛋白聚集; 三是生长因子介导的细胞增殖异常与早衰; 四是 Wnt/ β -catenin 通路激活致使细胞迁移增强与黏附分子下调, 引起上皮细胞异位积聚。本综述提出未来应整合分子流行病学与多组学技术, 构建全景式机制模型, 旨在为确立更科学的辐射防护限制及开发靶向干预策略提供理论支撑。

关键词 电离辐射, 放射性白内障, 剂量-效应关系, DNA 损伤与修复, 抗氧化系统, 细胞增殖与衰老, 细胞迁移与黏附
中图分类号 R146, R148 **DOI:** 10.3724/j.pibb.2025.0438 **CSTR:** 32369.14.pibb.20250438

已知多种因素可导致白内障发生, 包括衰老、电离辐射暴露及代谢紊乱等^[1-2]。眼晶状体被认为是对辐射敏感性最高的组织之一^[3]。国际放射防护委员会 (international commission on radiological protection, ICRP) 在其最新报告 (ICRP 2012) 中, 已将电离辐射诱发的白内障明确为一种确定性效应^[4], 但目前关于晶状体混浊的剂量阈值仍处于建议阶段。深入阐明电离辐射在晶状体中的作用机制, 对于确立更准确的剂量阈值及辐射防护暴露限值, 并为放射防护实践提供科学依据具有重要意义。

迄今为止, 大量研究聚焦于电离辐射诱发白内障的发生机制, 主要探讨其电离辐射对白内障关键靶组织——晶状体的影响。早期研究显示, 辐射可引起晶状体上皮细胞的调控异常, 涉及转录及生长因子、金属蛋白酶等, 以及参与细胞周期调控和脱氧核糖核酸 (deoxyribonucleic acid, DNA) 损伤应答的信号通路^[5-7]。还有研究假设, 电离辐射暴

露后晶状体上皮细胞的分化及增殖/迁移过程异常, 导致细胞在晶状体后囊下区域异常积聚, 从而引发混浊^[8]。此外, “致白内障负荷”概念的提出^[9]进一步揭示了白内障形成的多因素累积特征: 生活方式、遗传因素及环境因素 (尤其是电离辐射) 共同作用, 导致 DNA、蛋白质及脂质损伤持续累积, 当这些损伤超过晶状体维持透明性与功能的阈值时, 即引起白内障的发生。然而, 目前仍缺乏系统、完整的机制模型以解释电离辐射如何导致晶状体混浊的形成与进展。

总体而言, 放射性白内障的研究主要集中在两个方面: 一是剂量阈值的界定, 二是作用机制的解析。本文旨在综述目前放射性白内障发生发展机制的相关研究进展。

* 中央引导地方科技发展资金 (YDZJSX2025D087) 资助项目。

** 通讯联系人。

Tel: 0351-2202265, E-mail: zhanjingming@cirp.org.cn

收稿日期: 2025-10-09, 接受日期: 2026-02-05

1 电离辐射致眼晶状体损伤的暴露特征与剂量-效应关系

1.1 电离辐射的暴露特征

从流行病学角度, 电离辐射的暴露特征主要从“量、时、空、人”4个维度进行评估(表1)。

在剂量维度上, 多项研究提示放射性白内障可能存在线性剂量-反应关系^[10-11], 但剂量率对其发生发展的具体影响尚未明确。在时间维度上, 放射性白内障通常具有较长的潜伏期, 往往在电离辐射暴露数年后才会出现临床症状^[12-13]。无论急性暴露还是长期慢性暴露, 均可显著增加白内障发生风险, 尤其是皮质性及后囊下白内障^[14-16]。在空间维度上, 只要眼晶状体受到电离辐射照射, 无论是全

身暴露(如原子弹爆炸幸存者)还是局部暴露(如医疗影像学计算机体层成像(computed tomography, CT)检查), 均会显著提高放射性白内障的发生风险^[13, 15]。在人群维度上, 主要暴露群体包括原子弹幸存者、宇航员和飞行员、某些核及制造业工人、介入放射科医务人员, 及接受放射治疗的患者等^[17-18]。个体易感性方面, 研究表明, 遗传背景在皮质性或后囊下白内障的发生中起显著作用^[19]。此外, 性别、年龄、紫外线暴露、代谢状态及生活方式等因素可能通过协同或混杂作用影响个体风险^[20-21]。因此, 电离辐射所致晶状体损伤的发生机制极为复杂, 其风险评估体系尚未完全建立, 亟需更系统的流行病学与分子生物学研究加以完善。

Table 1 Dimensional analysis of exposure characteristics for ionizing radiation-induced lens damage

表1 电离辐射致晶状体损伤的暴露特征维度分析

维度	核心特征	临床与流行病学观察要点	参考文献
剂量	剂量-效应关系	多项研究提示可能存在线性关系; 剂量率的具体影响尚不明确	[10-11]
时间	潜伏期与暴露时间	具有较长潜伏期; 急性或长期慢性暴露均显著增加风险(尤其是皮质性与后囊下白内障)	[14-16]
空间	暴露范围	无论全身暴露(如原子弹幸存者)还是局部暴露(如计算机体层成像检查), 均显著提高发病风险	[13, 15]
人群	高危群体	原子弹幸存者、宇航员/飞行员、核工业/制造业工人、介入放射科医务人员、放疗患者等	[17-18]
	个体修饰因子	遗传背景起显著作用; 性别、年龄、紫外线暴露、代谢及生活方式等可能产生协同或混杂影响	[19-21]

1.2 剂量-效应关系

剂量-效应关系是辐射流行病学的核心科学问题之一, 它定量描述健康风险随辐射剂量变化的规律, 是将个体暴露水平转化为群体风险预测并制定防护标准的重要科学依据。

放射性白内障作为电离辐射引起的确定性效应^[4], 普遍认为存在剂量阈值。该阈值是剂量-效应关系的关键参数。基于现有流行病学证据, ICRP建议将0.5 Gy作为导致1%白内障发生率的单一阈值剂量, 并据此显著下调了职业照射的年剂量限值^[4]。然而, 也有部分研究认为, 白内障发病风险与吸收剂量呈近似线性关系, 即不存在明显阈值^[13-14, 22]。

除剂量外, 其他修饰因子亦显著影响放射性白内障的发生, 如辐射品质、剂量率与照射时间等(表2)。从辐射品质而言, 高传能线密度(linear energy transfer, LET)辐射(如质子或中子)诱发白内障的相对生物学效应显著高于低LET辐射(如X射线或 γ 射线), 且眼晶状体对高LET辐射的

敏感性尤为突出^[23-25]。一项以远交系小鼠为模型的研究显示, 与对照组相比, 暴露于0.4 Gy太空高LET粒子辐射或3.0 Gy γ 射线后, 白内障发生风险平均增加约2.5倍^[23]。剂量率对白内障形成的作用目前尚无一致结论。研究表明, 剂量率与晶状体混浊的严重程度尚未发现直接关联^[4, 26-28]。剂量率常与照射时间密切相关, 后者对辐射生物效应的影响日益受到关注。近年来的研究指出, FLASH放疗(FLASH radiotherapy, 即超高剂量率瞬时照射, ≥ 40 Gy/s)可能显著降低正常组织的放射性毒性, 但其分子机制尚未明了^[29-30]。值得注意的是, 部分体内外研究提示, 晶状体组织可能存在反向剂量延长效应, 即延长照射时间(由单次急性照射改为分次照射或低剂量率持续照射)反而可能增强辐射生物学效应^[31-34], 这一现象与经典放射生物学理论存在明显差异。总体而言, 急性单次暴露与分次暴露在晶状体生物效应上的差异仍需进一步验证, 慢性暴露的阈值亦尚不确定。

综上所述, 当前关于放射性白内障的剂量-效

应关系研究虽已揭示大致的阈值范围,但仍缺乏精确的阈值估算方法、标准化的剂量-效应曲线及剂量率/分次照射的量化修正因子。未来研究应聚焦于特定职业暴露人群(如核工业工作者及介入放射

科医务人员),开展长期、系统的随访研究,以进一步完善放射性白内障的剂量-反应模型和防护标准。

Table 2 Comparative modulation of radiation exposure characteristics on lens damage effects

表2 不同辐射暴露特征对晶状体损伤效应的修饰作用对比

暴露特征维度	参照组	对比组	效应特征	参考文献
辐射品质	低LET辐射	高LET辐射	晶状体对高LET辐射敏感性高, RBE显著升高	[23-25]
剂量率	常规剂量率	超高剂量率瞬时照射	超高剂量率可能降低组织毒性, 机制待解	[29-30]
时间分布	单次急性照射	分次/低剂量持续照射	部分证据显示延长照射时间反而增强生物学效应, 与经典理论相悖	[31-34]
剂量模型	阈值模型	线性无阈值模型	模型尚存争议, 尽管ICRP设定阈值, 但低剂量区的线性风险不能完全排除	[13, 22]

LET: 传能线密度 (linear energy transfer), RBE: 相对生物效能 (relative biological effectiveness), ICRP: 国际放射防护委员会 (international commission on radiological protection)。

2 电离辐射导致晶状体损伤的机制

2.1 DNA损伤修复能力下降

电离辐射可通过直接作用于核DNA或通过诱导氧化应激的间接作用,导致晶状体上皮细胞发生DNA双链断裂(DNA double-strand break, DSB)^[35-36]。目前,磷酸化组蛋白变体H2AX(gamma-H2A histone family member X, γ -H2AX)、53结合蛋白1(p53-binding protein 1, 53BP1)和重组酶A同源物51(RAD51 recombinase, RAD51)是被广泛用于评估电离辐射诱导的DSB形成及其修复过程的生物标志物^[37](图1通路a左侧)。DNA修复动力学具有显著的剂量依赖性。与暴露于20 mGy或100 mGy X射线后的外周淋巴细胞相比,小鼠晶状体外周单层上皮区的修复速率明显较慢^[38]。在永生化的晶状体上皮细胞系FHL124中也观察到类似的剂量依赖性变化^[39]。此外,辐射剂量率对DNA损伤修复有重要影响——降低剂量率通常可减少暴露后未修复的DSB数量^[40]。然而,动物实验中观察到“反剂量率效应”:当剂量率降低时,晶状体上皮细胞中53BP1焦点数反而显著增加,这一现象与同一动物的淋巴细胞中观察到的剂量率效应趋势相反^[34]。

DNA损伤及修复能力受遗传背景影响。基因修饰小鼠实验显示,遗传背景显著影响DNA损伤应答,不同品系间的DSB修复速率及放射性白内障的发生率存在明显差异。修补同源物1(patch 1, *Ptch1*)和切除修复交叉互补基因2(excision repair cross-complementation group 2, *Ercc2*)突变

小鼠均对放射性白内障高度易感^[41-42](图1通路a右侧)。研究发现,低剂量辐射后,携带*Ptch1*基因突变的小鼠晶状体上皮细胞中53BP1焦点数量更多,而携带*Ercc2*基因突变的小鼠则出现更少的53BP1焦点^[34]。由此可见,DNA修复能力与遗传背景之间存在复杂的交互关系,两者共同影响放射性白内障的易感性。流行病学研究也支持该观点,中国高本底辐射地区居民中,共济失调毛细血管扩张症突变蛋白(ataxia telangiectasia mutated, *ATM*)基因及肿瘤蛋白53(tumor protein 53, TP53)的单核苷酸多态性与皮质性及后囊下白内障的发生风险显著相关^[19](图1通路a右侧)。

晶状体具有独特生理特征——细胞缺乏更新能力,使其对辐射损伤极为敏感。所有晶状体细胞(包括死亡细胞)终生保留于晶状体内,大分子成分如蛋白质与脂质等几乎无代谢更新。因此,辐射诱导的DNA损伤可在晶状体组织中长期积累^[9],DNA修复能力对减少辐射损伤累积至关重要。Barnard等^[33]提出,晶状体上皮细胞的DNA损伤应答与其持续增殖/分化机制之间可能存在动态平衡:在低剂量及低剂量率辐射条件下,细胞增殖分化机制可能占优势,从而抵消部分DNA损伤的负面影响。然而,目前关于DNA修复在放射性白内障形成中的确切作用机制仍缺乏系统研究,其分子调控机制仍需进一步阐明。

2.2 抗氧化系统功能失调

晶状体的透明性依赖于高度有序的蛋白质结构及完善的抗氧化防御系统。抗氧化系统功能缺陷可导致晶状体蛋白质聚集,从而引发晶状体混浊,是

白内障形成的重要机制之一^[43-45]。个体水平的研究^[46]显示,与低分级白内障患者相比,高分级患者房水中总抗氧化水平显著降低;但不同白内障亚型(核性、后囊下性和混合性)患者之间的房水抗氧化水平差异并无统计学意义。

晶状体抗氧化系统受核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)调控。Nrf2可诱导多种抗氧化酶及热休克蛋白的表达,从而维持细胞内氧化还原平衡^[47]。研究显示,激活Nrf2/血红素加氧酶1(heme oxygenase-1, HO-1)抗氧化信号通路可显著增强

活性氧类(reactive oxygen species, ROS)的清除能力,有效保护晶状体上皮细胞免受辐射诱导的氧化损伤^[48](图1通路b)。此外,氧化应激与炎症反应之间存在密切的相互作用。氧化应激源暴露诱导ROS产生,从而激活炎症关键转录因子核因子 κ B(nuclear factor kappa B, NF- κ B)信号通路,进一步导致晶状体上皮细胞凋亡和抗氧化酶活性降低^[49-50](图1通路b)。尽管人晶状体的抗氧化系统功能障碍已被确认为白内障发生的重要机制,但其在电离辐射背景下调控氧化应激的分子机制仍需深入研究。

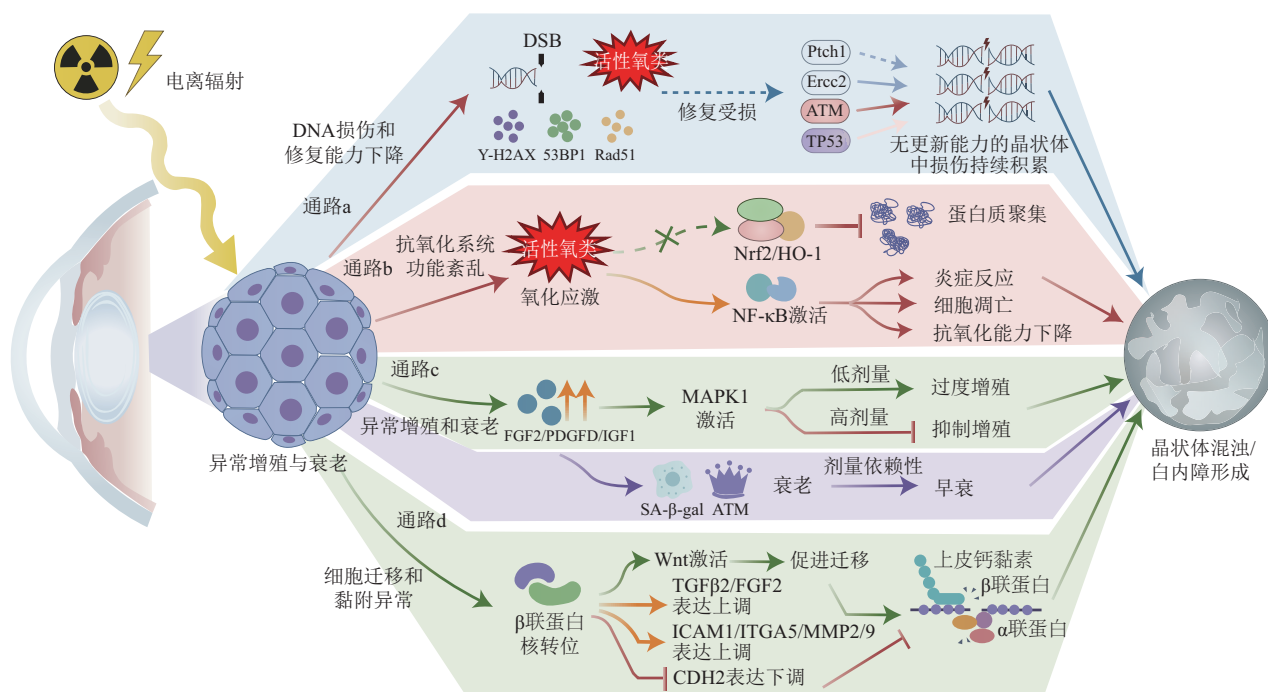


Fig. 1 Hypothesized mechanistic pathways for ionizing radiation-induced lens damage

图1 电离辐射致晶状体损伤假设机制通路

电离辐射激活4条主要通路导致晶状体混浊。DNA损伤和修复能力下降(通路a):电离辐射直接作用于DNA或通过诱导氧化应激的间接作用导致DNA损伤,DNA受损表现为双链断裂(标志物 γ -H2AX、53BP1、Rad51)及修复动力学下降(剂量、剂量率及遗传依赖,如Pth1、Ercc2突变,ATM/P53多态性),无更新能力晶状体中损伤持续积累。抗氧化系统功能紊乱(通路b):活性氧类诱导氧化应激后,Nrf2/HO-1抗氧化信号受损引起蛋白聚集,NF- κ B激活介导炎症/凋亡及抗氧化能力下降。细胞增殖异常和衰老(通路c):低剂量下FGF2、PDGFD、IGF1通过MAPK1上调细胞增殖能力,而高剂量时抑制;电离辐射呈剂量依赖性诱导过早衰老(SA- β -半乳糖苷酶和ATM核周冠状结构可作为生物标志物)。细胞迁移和黏附异常(通路d): β 联蛋白核转位,Wnt激活及TGF β 2/FGF2表达上调,细胞迁移增加;ICAM1、ITGA5、MMP2/9上调及CDH2下调,黏附减弱,E-cadherin- β -catenin- α -catenin复合物(有助于维持细胞黏附并抑制细胞迁移)被破坏。多个机制通路共同作用,导致晶状体混浊白内障形成。DNA:脱氧核糖核酸(deoxyribonucleic acid);DSB:DNA双链断裂(DNA double-strand break); γ -H2AX:磷酸化组蛋白变体H2AX(γ -H2A histone family member X);53BP1:53结合蛋白1(p53-binding protein 1);Rad51:重组酶A同源物51(RAD51 recombinase);Pth1:修补同源物1(Patched 1);Ercc2:切除修复交叉互补基因2(excision repair cross-complementation group 2);ATM:共济失调毛细血管扩张症突变蛋白(ataxia telangiectasia mutated);TP53:肿瘤蛋白53(tumor protein 53);Nrf2/HO-1:核转录因子红系2相关因子2(nuclear factor erythroid 2-related factor 2)/血红素加氧酶1(heme oxygenase-1);NF- κ B:核因子 κ B(nuclear factor kappa B);FGF2:纤维细胞生长因子2(fibroblast growth factor);PDGFD:血小板衍生生长因子D(platelet-derived growth factor D);IGF1:胰岛素样生长因子1(insulin-like growth factor 1);MAPK1:促分裂原活化的蛋白激酶1(mitogen-activated protein kinase 1);SA- β -gal:衰老相关 β 半乳糖苷酶(senescence-associated β -galactosidase);Wnt:Wnt信号通路(Wingless-related integration site);TGF β 2:转化生长因子 β 2(transforming growth factor beta 2);ICAM1:细胞间黏附分子1(intercellular adhesion molecule 1);ITGA5:整合素 α 5(integrin subunit alpha 5);MMP2/9:基质金属蛋白酶2和9(matrix metalloproteinase 2/9);CDH2:钙黏蛋白2(cadherin 2)。

2.3 细胞增殖异常与过早衰老

晶状体细胞增殖与分化的异常均可能导致晶状体混浊。研究表明,低剂量辐射可诱导成纤维细胞生长因子2 (fibroblast growth factor, FGF2)、血小板衍生生长因子D (platelet-derived growth factor D, PDGFD) 及胰岛素样生长因子1 (insulin-like growth factor 1, IGF1) 等生长因子表达上调,并伴随促分裂原活化的蛋白激酶1 (mitogen-activated protein kinase 1, MAPK1) 显著增加,从而刺激晶状体上皮细胞过度增殖^[51] (图1通路c)。然而, Ahmadi 等^[31]报道,在0、0.1、0.25和0.5 Gy 剂量照射后24 h内,细胞存活率呈剂量依赖性下降, Hamada^[52]也发现较高剂量 (3.53 Gy) 辐射可抑制晶状体上皮细胞增殖。

衰老同样是放射性白内障的重要影响因素^[8],但其机制研究受限于缺乏可靠的辐射诱导衰老生物标志物。一项研究基于 ATM 蛋白核转运机制建立了个体辐射反应模型,发现 ATM 蛋白在持续应激条件下聚集于细胞核周形成冠状结构,可能为辐射特异性衰老标志物^[53]。目前,细胞衰老表型的鉴定主要依赖经典衰老标志物衰老相关 β 半乳糖苷酶 (senescence-associated β -galactosidase, SA- β -gal)。基于该标志物的研究表明,辐射照射后晶状体上皮细胞早衰比例显著增加,并呈剂量依赖性^[31, 52] (图1通路c)。综上,细胞增殖异常与早衰在放射性白内障的发生发展中起重要作用,但其分子机制仍需要进一步研究。

2.4 细胞迁移和黏附异常

细胞迁移与黏附改变亦被视为辐射诱发白内障的潜在途径之一^[6, 38] (图1通路d)。细胞骨架蛋白 β 联蛋白 (β -catenin) 主要定位于细胞膜胞质侧,与上皮钙黏素 (E-cadherin) 及 α 联蛋白 (α -catenin) 结合形成 E-cadherin- β -catenin- α -catenin 复合物,维持细胞间黏附并抑制细胞迁移^[54]。研究显示, β 联蛋白缺失的小鼠晶状体上皮细胞排列紊乱,晶状体形态异常,提示 β 联蛋白对维持细胞黏附至关重要^[55]。Wang 等^[56]报道,小鼠眼晶状体在0.05~0.2 Gy 剂量照射后3个月,后囊下区域迁移细胞数量显著增加,其中0.1 Gy时增幅最大,同时,晶状体前囊上皮细胞中 β 联蛋白表达增加并向细胞核转位,激活 Wnt (Wingless-related integration site, Wnt) 信号通路,提示 Wnt/ β -catenin 信号通路可能介导低剂量辐射后的晶状体上皮细胞迁移。此外,

0.25 Gy 照射可显著增强细胞迁移能力,并伴随转化生长因子 β 2 (transforming growth factor beta 2, TGF β 2) 及成纤维细胞生长因子2 (fibroblast growth factor 2, FGF2) 表达上调;而细胞黏附能力随剂量升高而下降,细胞间黏附分子1 (intercellular adhesion molecule 1, ICAM1)、整合素 α 5 (integrin subunit alpha 5, ITGA5) 及基质金属蛋白酶 (matrix metalloproteinase, MMP) (包括 MMP2、MMP9) 表达升高,钙黏蛋白2 (cadherin 2, CDH2) 表达下降^[51]。因此,电离辐射诱导的晶状体上皮细胞迁移增加及细胞间黏附减弱,可能是放射性白内障形成的重要分子机制之一。

3 总结与展望

电离辐射诱发晶状体损伤的核心机制包括 DNA 损伤修复能力下降及其长期积累、抗氧化系统功能失调、细胞异常增殖与早衰,以及迁移增强与黏附减弱,最终导致后囊下细胞异常积聚和蛋白质聚集。关键调控通路涉及 Nrf2/HO-1 抗氧化轴障碍、氧化应激激活的 NF- κ B 炎症通路、Wnt/ β -catenin 介导的迁移促进,以及生长因子 (如 FGF2、TGF β 2) 驱动的增殖与基质重塑。这些机制相互交织,受遗传因素 (如 ATM、P53 变异等)、辐射品质及剂量率调控,体现“致白内障负荷”的累积特征。目前剂量-效应关系趋向线性无阈值模型,但精确分子机制与阈值估算仍有待阐明。

未来研究应整合多组学方法构建系统性机制模型,重点揭示关键通路 (如 Wnt/ β -catenin 与 Nrf2/HO-1) 的动态交互及剂量率效应的分子基础。同时,针对高危职业人群开展前瞻性队列研究,结合遗传易感性评估,进一步优化晶状体剂量阈值与个体化防护标准,并探索潜在干预靶点 (如 Nrf2 激活剂),以有效降低放射性白内障风险。

参 考 文 献

- [1] Delcourt C, Cristol J P, Tessier F, *et al.* Risk factors for cortical, nuclear, and posterior subcapsular cataracts: the POLA study. *Pathologies Oculaires Liées à l'Age. Am J Epidemiol*, 2000, **151**(5): 497-504
- [2] Criner G J, Gayen S, Zantah M, *et al.* Clinical review of non-invasive ventilation. *Eur Respir J*, 2024, **64**(5): 2400396
- [3] Poppe E. Experimental investigations on cataract formation following whole-body roentgen irradiation. *Acta Radiol*, 1957, **47**(2): 138-148

- [4] Authors on behalf of ICRP, Stewart F A, Akleyev A V, *et al.* ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs—threshold doses for tissue reactions in a radiation protection context. *Ann ICRP*, 2012, **41**(1/2): 1-322
- [5] Chang P Y, Bjornstad K A, Chang E, *et al.* Particle irradiation induces FGF2 expression in normal human lens cells. *Radiat Res*, 2000, **154**(5): 477-484
- [6] Chang P Y, Bjornstad K A, Rosen C J, *et al.* Particle radiation alters expression of matrix metalloproteases resulting in ECM remodeling in human lens cells. *Radiat Environ Biophys*, 2007, **46**(2): 187-194
- [7] Chang P Y, Bjornstad K A, Rosen C J, *et al.* Effects of iron ions, protons and X rays on human lens cell differentiation. *Radiat Res*, 2005, **164**(4 Pt 2): 531-539
- [8] Ainsbury E A, Barnard S, Bright S, *et al.* Ionizing radiation induced cataracts: recent biological and mechanistic developments and perspectives for future research. *Mutat Res Rev Mutat Res*, 2016, **770**(Pt B): 238-261
- [9] Uwineza A, Kalligeraki A A, Hamada N, *et al.* Cataractogenic load - a concept to study the contribution of ionizing radiation to accelerated aging in the eye lens. *Mutat Res Rev Mutat Res*, 2019, **779**: 68-81
- [10] Hamada N, Fujimichi Y. Classification of radiation effects for dose limitation purposes: history, current situation and future prospects. *J Radiat Res*, 2014, **55**(4): 629-640
- [11] Ainsbury E A, Bouffler S D, Dörr W, *et al.* Radiation cataractogenesis: a review of recent studies. *Radiat Res*, 2009, **172**(1): 1-9
- [12] Azizova T V, Hamada N, Grigoryeva E S, *et al.* Risk of various types of cataracts in a cohort of Mayak workers following chronic occupational exposure to ionizing radiation. *Eur J Epidemiol*, 2018, **33**(12): 1193-1204
- [13] Little M P, Cahoon E K, Kitahara C M, *et al.* Occupational radiation exposure and excess additive risk of cataract incidence in a cohort of US radiologic technologists. *Occup Environ Med*, 2020, **77**(1): 1-8
- [14] Chylack L T, Peterson L E, Feiveson A H, *et al.* NASA study of cataract in astronauts (NASCA). Report 1: cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. *Radiat Res*, 2009, **172**(1): 10-20
- [15] Minamoto A, Taniguchi H, Yoshitani N, *et al.* Cataract in atomic bomb survivors. *Int J Radiat Biol*, 2004, **80**(5): 339-345
- [16] Chylack L T, Feiveson A H, Peterson L E, *et al.* NASCA report 2: longitudinal study of relationship of exposure to space radiation and risk of lens opacity. *Radiat Res*, 2012, **178**(1): 25-32
- [17] Hamada N, Azizova T V, Little M P. An update on effects of ionizing radiation exposure on the eye. *Br J Radiol*, 2020, **93**(1115): 20190829
- [18] Hamada N, Sato T. Cataractogenesis following high-LET radiation exposure. *Mutat Res Rev Mutat Res*, 2016, **770**(Pt B): 262-291
- [19] Gao Y, Su Y P, Li X L, *et al.* ATM and TP53 polymorphisms modified susceptibility to radiation-induced lens opacity in natural high background radiation area, China. *Int J Radiat Biol*, 2022, **98**(7): 1235-1242
- [20] Villeneuve P J, Frangione B, Talarico R, *et al.* Occupational exposure to low dose ionizing radiation and the incidence of surgically removed cataracts and glaucoma in a cohort of Ontario nuclear power plant workers. *Radiat Res*, 2025, **203**(4): 271-283
- [21] Barnard S G R, Hamada N. Individual response of the ocular lens to ionizing radiation. *Int J Radiat Biol*, 2023, **99**(2): 138-154
- [22] Neriishi K, Nakashima E, Akahoshi M, *et al.* Radiation dose and cataract surgery incidence in atomic bomb survivors, 1986-2005. *Radiology*, 2012, **265**(1): 167-174
- [23] Kleiman N J, Edmondson E F, Weil M M, *et al.* Radiation cataract in heterogeneous stock mice after γ -ray or HZE ion exposure. *Life Sci Space Res*, 2024, **40**: 97-105
- [24] Hamada N. Recent insights into the biological action of heavy-ion radiation. *J Radiat Res*, 2009, **50**(1): 1-9
- [25] Hamada N, Imaoka T, Masunaga S, *et al.* Recent advances in the biology of heavy-ion cancer therapy. *J Radiat Res*, 2010, **51**(4): 365-383
- [26] Neriishi K, Nakashima E, Minamoto A, *et al.* Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat Res*, 2007, **168**(4): 404-408
- [27] Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000-2002: a threshold analysis. *Health Phys*, 2006, **90**(2): 154-160
- [28] Worgul B V, Kundiyeve Y I, Sergiyenko N M, *et al.* Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res*, 2007, **167**(2): 233-243
- [29] Loo B W, Verginadis I I, Sørensen B S, *et al.* Navigating the critical translational questions for implementing FLASH in the clinic. *Semin Radiat Oncol*, 2024, **34**(3): 351-364
- [30] McGarrigle J M, Long K R, Prezado Y. The FLASH effect—an evaluation of preclinical studies of ultra-high dose rate radiotherapy. *Front Oncol*, 2024, **14**: 1340190
- [31] Ahmadi M, Barnard S, Ainsbury E, *et al.* Early responses to low-dose ionizing radiation in cellular lens epithelial models. *Radiat Res*, 2022, **197**(1): 78-91
- [32] Matsuya Y, Sato T, Yachi Y, *et al.* The impact of dose rate on responses of human lens epithelial cells to ionizing irradiation. *Sci Rep*, 2024, **14**(1): 12160
- [33] Barnard S G R, McCarron R, Moquet J, *et al.* Inverse dose-rate effect of ionising radiation on residual 53BP1 foci in the eye lens. *Sci Rep*, 2019, **9**(1): 10418
- [34] Barnard S G R, McCarron R, Mancuso M, *et al.* Radiation-induced DNA damage and repair in lens epithelial cells of both Ptc1(+/-) and Ercc2(+/-) mutated mice. *Radiat Res*, 2022, **197**(1): 36-42
- [35] Alexander P. Division of biophysics, on the mode of action of some treatments that influence the radiation sensitivity of cells. *Trans NY Acad Sci*, 1962, **24**(8 Series II): 966-978
- [36] Feng K, Guo H K. Eaf2 protects human lens epithelial cells against

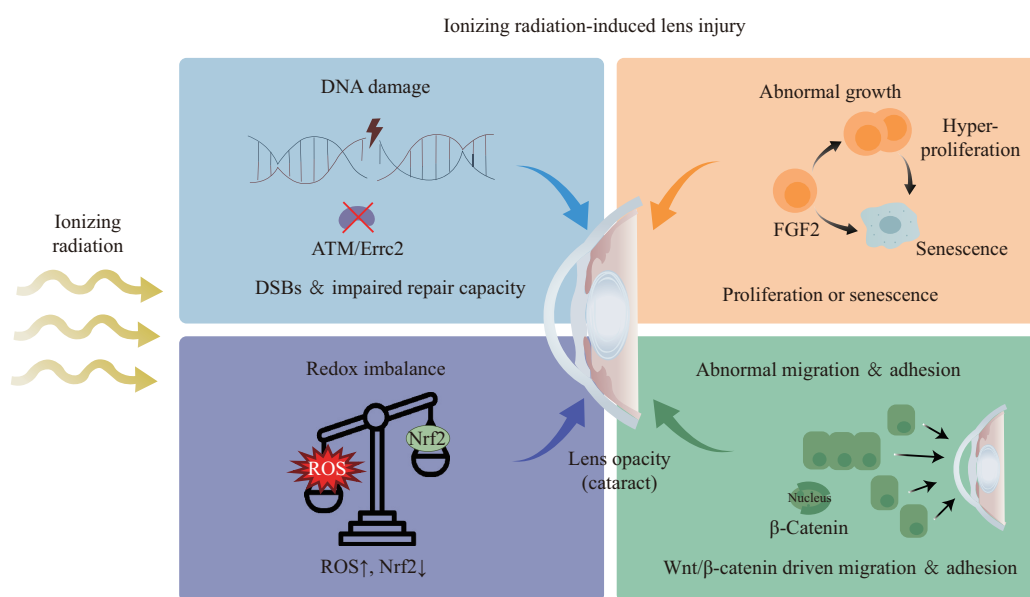
- oxidative stress-induced apoptosis by Wnt signaling. *Mol Med Rep*, 2018, **17**(2): 2795-2802
- [37] Horn S, Barnard S, Brady D, *et al.* Combined analysis of gamma-H2AX/53BP1 foci and caspase activation in lymphocyte subsets detects recent and more remote radiation exposures. *Radiat Res*, 2013, **180**(6): 603-609
- [38] Markiewicz E, Barnard S, Haines J, *et al.* Nonlinear ionizing radiation-induced changes in eye lens cell proliferation, cyclin D1 expression and lens shape. *Open Biol*, 2015, **5**(4): 150011
- [39] Wang L, Wormstone I M, Reddan J R, *et al.* Growth factor receptor signalling in human lens cells: role of the calcium store. *Exp Eye Res*, 2005, **80**(6): 885-895
- [40] de Almodovar J M R, Bush C, Peacock J H, *et al.* Dose-rate effect for DNA damage induced by ionizing radiation in human tumor cells. *Radiat Res*, 1994, **138**(1): S93
- [41] Kunze S, Dalke C, Fuchs H, *et al.* New mutation in the mouse Xpd/Ercc2 gene leads to recessive cataracts. *PLoS One*, 2015, **10**(5): e0125304
- [42] de Stefano I, Giardullo P, Tanno B, *et al.* Nonlinear radiation-induced cataract using the radiosensitive Ptch1(+/-) mouse model. *Radiat Res*, 2016, **186**(3): 315-321
- [43] Masuda T, Shimazawa M, Hara H. Retinal diseases associated with oxidative stress and the effects of a free radical scavenger (edaravone). *Oxid Med Cell Longev*, 2017, **2017**: 9208489
- [44] Ahmad A, Ahsan H. Biomarkers of inflammation and oxidative stress in ophthalmic disorders. *J Immunoassay Immunochem*, 2020, **41**(3): 257-271
- [45] Zhang M, Zhang R, Zhao X, *et al.* The role of oxidative stress in the pathogenesis of ocular diseases: an overview. *Mol Biol Rep*, 2024, **51**(1): 454
- [46] Atalay E, Oğurel T, Derici M K. The role of oxidative damage in cataract etiopathogenesis. *Ther Adv Ophthalmol*, 2023, **15**: 25158414231168813
- [47] Liu X F, Hao J L, Xie T, *et al.* Nrf2 as a target for prevention of age-related and diabetic cataracts by against oxidative stress. *Aging Cell*, 2017, **16**(5): 934-942
- [48] Chen Y, Zhu L, Meng H, *et al.* Ferulic acid protects human lens epithelial cells against ionizing radiation-induced oxidative damage by activating Nrf2/HO-1 signal pathway. *Oxid Med Cell Longev*, 2022, **2022**: 6932188
- [49] Richardson R B, Ainsbury E A, Prescott C R, *et al.* Etiology of posterior subcapsular cataracts based on a review of risk factors including aging, diabetes, and ionizing radiation. *Int J Radiat Biol*, 2020, **96**(11): 1339-1361
- [50] Guo C, Ning X, Zhang J, *et al.* Ultraviolet B radiation induces oxidative stress and apoptosis in human lens epithelium cells by activating NF- κ B signaling to down-regulate sodium vitamin C transporter 2 (SVCT2) expression. *Cell Cycle*, 2023, **22**(12): 1450-1462
- [51] Vigneux G, Pirkkanen J, Laframboise T, *et al.* Radiation-induced alterations in proliferation, migration, and adhesion in lens epithelial cells and implications for cataract development. *Bioengineering (Basel)*, 2022, **9**(1): 29
- [52] Hamada N. Ionizing radiation response of primary normal human lens epithelial cells. *PLoS One*, 2017, **12**(7): e0181530
- [53] Al-Choboq J, Mathis T, Restier-Verlet J, *et al.* The radiobiological characterization of human and porcine lens cells suggests the importance of the ATM kinase in radiation-induced cataractogenesis. *Cells*, 2023, **12**(16): 2118
- [54] Valenta T, Hausmann G, Basler K. The many faces and functions of β -catenin. *EMBO J*, 2012, **31**(12): 2714-2736
- [55] Kreslova J, Machon O, Ruzickova J, *et al.* Abnormal lens morphogenesis and ectopic lens formation in the absence of beta-catenin function. *Genesis*, 2007, **45**(4): 157-168
- [56] Wang P, Li Y W, Lu X, *et al.* Low-dose ionizing radiation: effects on the proliferation and migration of lens epithelial cells *via* activation of the Wnt/ β -catenin pathway. *Mutat Res Genet Toxicol Environ Mutagen*, 2023, **888**: 503637

Ionizing Radiation-induced Lens Injury: Epidemiology, Dose-effect Relationship, and Molecular Mechanisms*

HU Cheng-Hao, REN Shao-Han, ZHANG Hai-Tao, ZHAN Jing-Ming**

(Institute of Radiation Medicine and Environmental Medicine, China Institute for Radiation Protection, Taiyuan 030006, China)

Graphical abstract



Abstract The crystalline lens of the eye is recognized as one of the most radiosensitive tissues in the human body. While the International Commission on Radiological Protection (ICRP) has classified ionizing radiation (IR)-induced cataracts as a tissue reaction (deterministic effect) and subsequently reduced the occupational equivalent dose limit for the lens, significant uncertainties remain regarding the precise dose threshold and the complex biological pathways driving lens opacification. This review provides a comprehensive synthesis of current knowledge concerning radiation-induced lens damage, integrating epidemiological exposure characteristics with dose-response modeling and mechanistic molecular insights. First, we analyze exposure characteristics through four epidemiological dimensions: dose, time, space, and population. Clinical evidence suggests that radiation cataracts—particularly posterior subcapsular opacities—exhibit a distinct latency period that is inversely correlated with dose. We highlight that risk is not confined to acute high-dose scenarios (such as

* This work was supported by a grant from the Central Government Guides Local Science and Technology Development Fund Project (YDZJSX2025D087).

** Corresponding author.

Tel: 86-351-2202265, E-mail: zhanjingming@cirp.org.cn

Received: October 9, 2025 Accepted: February 5, 2026

in atomic bomb survivors) but is increasingly relevant in chronic low-dose occupational settings (*e. g.*, interventional radiology) and medical diagnostics (*e. g.*, CT scans). Crucially, individual susceptibility is modified by genetic background, age, and environmental co-factors, complicating risk assessment. Second, we critically examine the dose-effect relationship. Although the ICRP suggests a threshold of 0.5 Gy, emerging data challenge the traditional threshold model, with some studies advocating for a linear non-threshold (LNT) relationship. We further discuss the critical roles of radiation quality and dose rate. High linear energy transfer (LET) radiation demonstrates a significantly higher relative biological effectiveness (RBE) for cataractogenesis compared to low-LET radiation. Paradoxically, and unlike many other tissues, the lens may exhibit an “inverse dose-rate effect,” where fractionated or protracted exposures potentially enhance biological damage—a finding that challenges classical radiobiological paradigms. Third, drawing upon the “cataractogenic load” hypothesis and the unique physiological constraints of the lens, this review elucidates the multidimensional molecular mechanisms driving radiation-induced opacification. Key mechanisms include four aspects. (1) DNA damage and repair: IR induces DNA double-strand breaks (DSBs) that, due to the lens’ limited repair capacity (modulated by genes such as ATM, Ptch1, and Ercc2), lead to the accumulation of damage. (2) Antioxidant defense system: dysfunction of the Nrf2/HO-1 antioxidant axis results in redox imbalances, triggering NF- κ B-mediated inflammation and protein aggregation. (3) Cell proliferation and senescence: IR disrupts cell cycle regulation, causing a dichotomy of effects—driving premature senescence in some cell populations (evidenced by ATM nuclear foci) while inducing aberrant proliferation *via* growth factor upregulation (FGF2, TGF β) in others. (4) Cell migration and adhesion: activation of the Wnt/ β -catenin pathway and alterations in the E-cadherin complex promote the abnormal migration of epithelial cells to the posterior capsule, a hallmark of radiation-induced cataracts. In conclusion, radiation-induced cataractogenesis is a multifactorial process in which genetic susceptibility and environmental stressors converge to overwhelm the lens’ homeostatic thresholds. Future research must prioritize longitudinal cohort studies to refine dose thresholds and employ multi-omics approaches to map the crosstalk between DNA damage responses and matrix remodeling. Establishing a robust mechanistic model is essential for developing targeted radioprotective strategies and optimizing radiation protection standards for occupational and medical safety.

Key words ionizing radiation, radiation-induced cataract, dose-effect relationship, DNA damage and repair, antioxidant defense system, cell proliferation and senescence, cell migration and adhesion

DOI: 10.3724/j.pibb.2025.0438

CSTR: 32369.14.pibb.20250438