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Mini-review

Role of carcinogenesis related mechanisms in cataractogenesis and its implications for ionizing radiation cataractogenesis

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ABSTRACT

Ionizing radiation is a proven human carcinogen and cataractogen. The crystalline lens of the eye is among the most radiosensitive tissues in the body. A clouding of the normally transparent lens (i.e., cataract) is very common. Conversely, the lens continues to grow throughout life without developing tumors, suggesting that the lens possesses strong anti-carcinogenesis mechanisms. There is mounting evidence that mutations of oncogenes, tumor suppressor genes, DNA repair genes involved in base excision repair, nucleotide excision repair, and DNA double-strand break repair, and genes involved in intercellular interactions (e.g., via connexin gap junctions), and inflammation affect cataract development. Associations of these factors with cancer have long been recognized, highlighting that cataractogenesis shares some common mechanisms with carcinogenesis. This paper briefly overviews the current knowledge on the potential involvement of tumor related factors, DNA repair factors, intercellular interactions and inflammation in spontaneous cataractogenesis, and discusses its implications for cataractogenesis induced by targeted and nontargeted effects of ionizing irradiation.

Abbreviations: A-bomb, atomic-bomb; Acvr1, activin A type 1 receptor; AP, apurinic/apyrimidinic; APE1, apurinic/apyrimidinic endonuclease 1; AQP, aquaporin; Arf, alternative reading frame; ATM, ataxia telangiectasia mutated; BER, base excision repair; Bin3, bridging integrator 3; Brca1/2, breast cancer susceptibility gene 1/2; Brg1, Brahma-related gene 1; BLM, Bloom syndrome RecQ helicase-like; BS, Bloom syndrome; BubR1, budding uninhibited by benzimidazoles-related 1; CKO, conditional knockout; c-Maf, cellular homologue of avian retrovirus musculoaponeurotic fibrosarcoma oncogene; CNS, central nervous system; CNV, copy number variation; Cox-2, cyclooxygenase 2; Cry, crystallins; CSA, Cockayne syndrome group A; CSB, Cockayne syndrome group B; CSF2, colony stimulating factor 2; CtIP, C-terminal binding protein-interacting protein; Cx, connexin; DLAD, DNase II-like acid DNase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; 5′-dRP, 5′-deoxyribose-5-phosphate; DSB, DNA double-strand break; E2F1, E2F transcription factor 1; EphA2, Eph receptor tyrosine kinase type A2; ERCC6, excision repair cross-complementation group 6; FasL, Fas ligand; FEN1, flap endonuclease 1; FGF, fibroblast growth factor; γH2AX, phosphorylated histone H2AX; GJIC, gap junctional intercellular communication; GJ, gap junction; GST, glutathione S-transferase; GSTM1, glutathione S-transferase μ 1; GSTP1, glutathione S-transferase π 1; GSTT1, glutathione S-transferase ζ 1; GZ, germinative zone; HMGA1, high-mobility group AT-hook 1; HPV16, human papilloma virus type 16; HR, homologous recombination; Hsf4, heat shock transcription factor 4; HSP, heat shock protein; ICRP, International Commission on Radiological Protection; IFI27, interferon α inducible protein 27; IL, interleukin; Ink4a, inhibitor of kinase 4a; IR, ionizing radiation; Kip1/2, kinase inhibitory protein 1/2; KO, knockout; LEC, lens epithelial cell; LET, linear energy transfer; LFC, lens fiber cell; LIG1, DNA ligase I; LIG3α, DNA ligase IIIα; LLR, long-lived radical; LTCC, L-type calcium channel; MCP-1, monocyte chemoattractant protein 1; mgRb, retinoblastoma minigene; MMP-2, matrix metalloproteinase 2; MΦ, macrophage; NanogP8, Nanog homeobox pseudogene 8; Nbn, nibrin; NBS1, Nijmegen breakage syndrome 1; Ncoa6, nuclear receptor coactivator 6; NDRG2, N-Myc downstream regulated gene 2; NEIL1, Nei endonuclease VIII-like 1; NER, nucleotide excision repair; NF2, neurofibromin 2; NHEJ, nonhomologous end joining; NTE, nontargeted effect; OCDL, oxidatively induced clustered DNA lesion; OGG1, 8-oxoguanine glycosylase 1; 3'-P, 3′-phosphate; Pax6, paired box gene 6; PCNA, proliferating cell nuclear antigen; PI3K, phosphatidyl inositol 3-kinase; Polβ, DNA polymerase β; 6-4PP, (6-4) photoproduct; PSC, posterior subcapsular; Pten, phosphatase and tensin homolog; 3'-PUA, 3′-phospho-α,β-unsaturated aldehyde; RANTES, regulated upon activation normal T-cell expressed and secreted; Rb, Retinoblastoma; RFC, replication factor C; RNS, reactive nitrogen species; ROS, reactive oxygen species; RPA, replication protein A; RTS, Rothmund–Thomson syndrome; sCLU, secretory clusterin; SIRT1, silent information regulator T1; SSB, DNA single-strand break; ssDNA, single-stranded DNA; Stat3, signal transducer and activator of transcription 3; SV40, simian virus 40; SWI/SNF, switch/sucrose nonfermentable; TFIIH, transcription factor II H; TGFβ1, transforming growth factor β1; TNF-α, tumor necrosis factor α; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; UV, ultraviolet light; VIC, vision-impairing cataract; Waf1/Cip1, wild-type p53-activated fragment 1/cyclin dependent kinase interacting protein 1; WRN, Werner syndrome helicase; WS, Werner syndrome; XLF, XRCC4-like factor; XPC, xeroderma pigmentosum complementation group C; XPD, xeroderma pigmentosum complementation group D; XRCC1, x-ray cross-complementing group 1.

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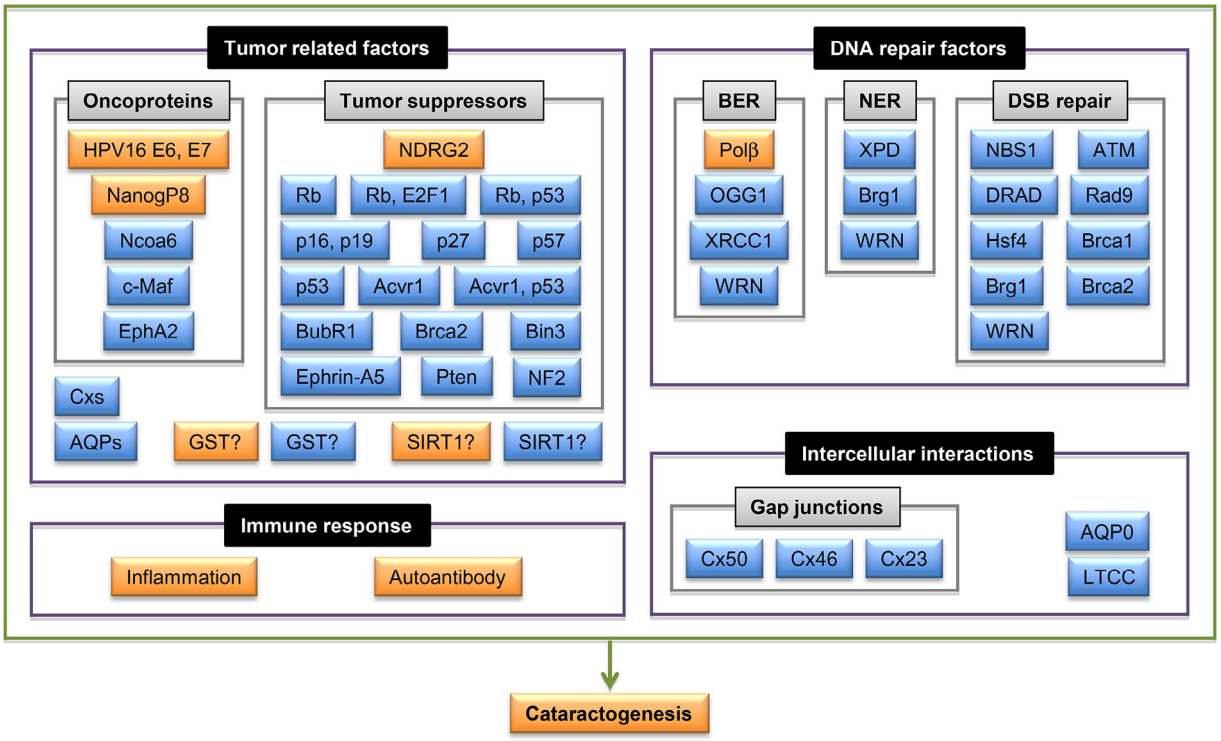

Fig. 1. A schema depicting possible changes in carcinogenesis mechanism-related molecules and events that facilitate spontaneous cataractogenesis. Orange-highlighted areas represent increased gene expression or increased frequency of events, and blue-highlighted areas represent decreased gene expression or decreased frequency of events. For details, see sections 'Role of tumor related factors in cataractogenesis', 'Role of DNA repair factors in cataractogenesis', 'Role of intercellular interactions in cataractogenesis' and 'Role of inflammation and other immune responses in cataractogenesis'. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Recent upsurge of interest in ionizing radiation (IR) cataracts

Ever since the discovery of X-rays in 1895, IR has been indispensable in medicine and industry. Whereas human IR cataracts have been described since 1903 [1], the observation of atomic-bomb (A-bomb) and cyclotron cataracts in the late 1940s brought a surge of interest [2,3]. The International Commission on Radiological Protection (ICRP) listed cataracts as a radiation health hazard in 1950 [4] and recommended the first dose limit for the lens of the eye in 1954 [5]. In 2011, ICRP recommended lowering the thresholds for vision-impairing cataract (VIC) from 5 Gy for a single, brief exposure and >8 Gy for highly fractionated or protracted exposures to 0.5 Gy and the occupational equivalent dose limit for the lens from 150 mSv/year to 20 mSv/year (100 mSv in defined 5 years with no single year exceeding 50 mSv) [6], which were revised 27 and 31 years respectively after the previous revision [7]. Such reductions may affect some medical or nuclear workers (and perhaps patients as well) [8], thereby stimulating a resurgence of interest in cataracts. ICRP concluded that cataract is a tissue reaction with a threshold albeit small, and deduced a threshold dose from epidemiological data documenting no threshold [6]. This stimulated a debate as to whether cataracts are of stochastic nature without threshold [9–11], thus necessitating more mechanistic knowledge to justifiably classify cataracts as tissue reactions or stochastic effects [12].

In radiotherapy, the lens dose is kept to a minimum, where 10 Gy and 18 Gy are judged as tolerance dose that produces cataracts needing surgical intervention in 5% and 50% of patients respectively within 5 years post therapy [13] (c.f., an ICRP threshold of 0.5 Gy producing VIC in 1% of exposed individuals with >20 years follow-up [6]). Notwithstanding, children with retinoblastoma often receive radiotherapy because of its radiosensitive nature, leading to cataracts for which pediatric surgery is a challenge [14]. IR cataract is also a concern for long-term interplanetary manned missions [15], but mitigators have yet to be established because mechanisms behind IR cataractogenesis remain incompletely understood. Its mechanisms therefore need to be further clarified.

Here, we briefly overview the current knowledge on the potential involvement of tumor related factors, DNA repair factors, intercellular interactions and inflammation in spontaneous cataractogenesis (see sections 'Role of tumor related factors in cataractogenesis', 'Role of DNA repair factors in cataractogenesis', 'Role of intercellular interactions in cataractogenesis' and 'Role of inflammation and other immune responses in cataractogenesis', and Fig. 1), and discuss its implications for cataractogenesis induced by targeted effects and nontargeted effects (NTEs) of IR (see section 'Implications for IR cataractogenesis' and Fig. 2).

Cataracts and unique features of the lens

A cataract is a clouding or opacity of the normally transparent lens. Cataract is the leading cause of visual impairment and blindness worldwide [16], among which age related cataracts (hereinafter referred to as senile cataracts) are most common. Inherited childhood/juvenile cataracts (hereafter congenital cataracts) also occur, and several factors such as IR and ultraviolet light (UV) are proven to increase a risk of cataracts.

The lens helps focus light onto the retina to form a sharp image and changes shape to adjust the focal length. Lenticular vasculature regresses prenatally in humans and before eye opening in rodents [17]. The cell nucleus and all other organelles undergo degradation during differentiation from cuboidal lens epithelial cells (LECs) into lens fiber cells (LFCs) that compose the bulk of the lens. Crystallins (Cry) are the major lens structural, water-soluble proteins [18]. The lens is proficient in physical intercellular contacts and physiological intercellular exchanges between adjoining cells mediated by connexin (Cx) gap junctions (GJs), aquaporin (AQP) water channels and various ion channels. Any impairment of these processes causes cataracts [19].

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