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Review Article

Apoptosis of The Lens Epithelial Cells After Ultraviolet-B Exposure as a Proposed Pathogenesis of Senile Cataract: Literature Review

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ABSTRACT

Cataract shares a major burden causing half of the world's visual impairment and blindness. Ultraviolet light exposure has been associated with a higher incidence of cataracts. UV irradiation causes damage to the ocular tissue through protein crosslinking, enzyme dysfunction, ion pump inhibition, genetic mutation, and cell membrane disruption. Irreversible damage causes apoptosis to the lens epithelial cells, which is the main motor of lens homeostasis. Disturbance to the lens homeostasis will result in the loss of lens transparency and the development of cataracts. Understanding the pathophysiology of UV-induced cataract may bring to better approach to slower progression of the aging of the lens and formation of cataractous lenses.

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INTRODUCTION

Senile cataracts account for a major health problem in the world as they serve as half of the visual impairment and blindness in the world. Population expansion and increasing life expectancy increase the incidence of senile cataracts and the rate of blindness due to senile cataracts. Cataract surgery contributes to an enormous economic burden on society, not to mention the post-operative complications such as posterior capsular opacity, retinal detachment, endophthalmitis, posterior capsular rupture, and other complications that may cause irreversible blindness.[1] Exposure to sunlight is scientifically proven to be one of the risks that is strongly associated with the incidence of cataracts.

Ultraviolet A (UV-A) and B (UV-B) exposure plays an important role in the pathogenesis of cataract formation. It was postulated that cortical cataract formation may associated with the thinning of the stratosphere ozone layer since cataract incidence increased in the equatorial area.[2] Accumulation of a small quantity of radiation may cause damage after decades of exposure. Ultraviolet radiation from sunlight reaches lens epithelium and lens fiber at 0.0006-00.005 mW/cm^2 UV-B and 100-1000 mW/cm^2 UV-A. In vitro, exposure to UV-B irradiation shows DNA damage to the lens epithelial cells. DNA repair mechanism after DNA damage induces changes in specific protein synthesis.[3] Moreover, lens fiber homeostasis and lens clarity depend on the function and intercellular communication of lens epithelial cells. Lens aging and initiation of cataract formation both require the same basis: the accumulation of reactive oxygen species (ROS) due to decreasing repair mechanism, lens epithelial biomolecular damage, and finally induced cellular dysfunction and lens pathology.[4]

The Role of UV-B in the Pathogenesis of Senile Cataract

Sunlight radiation consists of 50% visible light, 40% infrared light, and 9% ultraviolet radiation. Visible light radiation is produced by the light that can be seen by the human eye. Each color of visible light has a different wavelength. Ultraviolet radiation is the most biologically active electromagnetic spectrum and influences human health most.[5] The ultraviolet spectrum is divided into three classes: UV-A at 320-400nm wavelength, UV-B at 290-320 nm wavelength, and UV-C at 200-290 nm wavelength.[6] The human eye absorbs most of the radiation energy with a wavelength of 300 nm. The average dose of UV-B radiation absorbed by the human eye is 0.105 J/cm2.[7] UV-B and UV-C do not pass through the lens because they are mostly absorbed by nucleotide bases and aromatic amino acids in the lens fibers. UV-A and UV-B radiation that reaches the retina vary with age, but it is estimated that in adulthood 2% of UV-A and 1% of UV-B reach the retina.[8]

The damage is caused by UV irradiation through several mechanisms, namely protein crosslinking, enzyme dysfunction, ion pump inhibition, genetic mutation, and cell membrane disruption. Ocular organs such as the cornea, aqueous humor, and lens crystallin proteins absorb UV-B irradiation. The biological effect of UV-B irradiation can be direct or indirect, targeting damage to lipids, protein, and nucleic acid. UV-B rays directly damage DNA by excitation of nucleic bases, which produces dimer products and indirectly by activating free radicals. Radiation energy transferred to oxygen molecules can trigger the formation of reactive oxygen species and other photo-oxidative products.[9]

UV radiation causes modifications that result in direct damage to DNA and lens epithelial cell membrane pumps. Cell membranes damaged by UV radiation cause calcium leakage into the lens

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and activate apoptosis.[10] Rapid death of lens epithelial cells due to UV radiation will eliminate homeostasis of the underlying lens fiber cells and trigger disruption of lens fiber cell integrity. This reaction coupled with direct DNA damage to lens epithelial cells and damage to the lens epithelial cell membrane will trigger a significant loss of lens epithelial cell viability. The death of lens epithelial cells and damage to the crystallin protein of lens fibers can initiate the rapid formation of cataracts.[5]

Lens epithelial cells that experience DNA damage due to ultraviolet radiation at low doses may not immediately undergo apoptosis. Cells have strategies to deal with DNA damage, first by repairing or tolerating DNA damage, and later by eliminating cells with damaged DNA from the population through apoptosis or other forms of cell death.[11] Cells respond to genotoxic stress such as UV radiation through a very conservative signal transduction cascade, namely the DNA damage response (DDR). Protein sensors will recognize DNA damage caused by UV radiation and replication stress. The sensor protein then sends a signal to the transducer protein, which consists of a protein kinase that is activated through a phosphorylation process. Finally, the signal is conveyed to several effector proteins which function as executors of various cellular functions, including DNA repair, cell cycle checkpoints, cell aging, and apoptosis. DNA damage response (DDR) causes phosphorylation and stabilization of p53 and subsequent upregulation of p21. This cascade triggered a G1/S arrest. Cell damage that cannot be repaired or tolerated, p53 will accumulate and together with other transcription factors will activate proapoptotic factors such as BAX (Bcl-2associated X protein), PUMA (p53-upregulated modulator of apoptosis), NOXA, BID, FAS, death receptor 5 (DR5), and PIDD (p53-induced protein with a death domain (Figure 1).[12]

The p53 protein has been shown to have a target action in mitochondria, where p53 interacts with and activates BAX and BAK.[13] BAX and BAK work by increasing mitochondrial membrane permeability. The space between mitochondrial membranes contains apoptogenic factors, including cytochrome C, DIABLO/Smac, nuclease activator apoptosis-inducing factor, Endo G (apoptotic DNase); HtrA2/ Omni, IAP (inhibitors of apoptosis) which also have proapoptotic serine protease activity) and several procaspases.[11] Cell death via the p53 pathway is then executed by caspase proteinase, where the active caspase (cleaved caspase) gives rise to a typical phenotype for apoptosis. Caspase activation through p53 occurs through the release of apoptogenic factors from mitochondria, including cytochrome C. The release of cytochrome C triggers the formation of apoptosomes, namely molecular complexes consisting of the adapter protein Apaf-1 and caspase-9. Caspase-9 which is active after joining the apoptosome will activate the executor caspases namely caspase-3 and caspase-7 which execute cell death (Figure 2).[10,14]

Lens Epithelial Cells Apoptosis and Development of Cataractous Lens

Epithelial cell apoptosis has been proposed as the initiating event for cataract formation. Evidence that apoptosis plays an important role in the process of lens aging and cataracts has been widely proven, especially in animal model studies. P53 is a phosphoprotein involved in the DNA response mechanism due to ultraviolet irradiation. In contrast, Caspase 3 is one of the executor proteins that play a role in the apoptosis of lens epithelial cells. P53 plays a role in the regulation of cell proliferation and apoptosis in the response to DNA damage. DNA damage activates p53, inducing apoptosis or arrest in the cell cycle. UV irradiation-induced DNA and tissue damage that initiate apoptosis.[15] Apoptosis may be associated with upregulation of p53 expression. Research by Takamura et al. demonstrated apoptosis in rat lens epithelium and stated that apoptosis in a cataractous rat model may be indirectly related to increased p53 protein expression.[16] Research by Ayala et al. found that the expression of p53 and caspase 3 mRNA in the lenses of rats exposed to UV radiation was significantly higher than in the lenses of the contralateral eye.[17] DNA damage and changes in lens epithelial cell protein expression regulate apoptosis through intrinsic and extrinsic pathways that primarily involve the activation of the pro-apoptotic protein Caspase 3.[10] UV irradiation with 300nm wavelength UV ray to rabbit lens shows lens epithelial cell damage, induces apoptosis, and upregulates caspase 3 expression in the lens epithelial cells.[18]

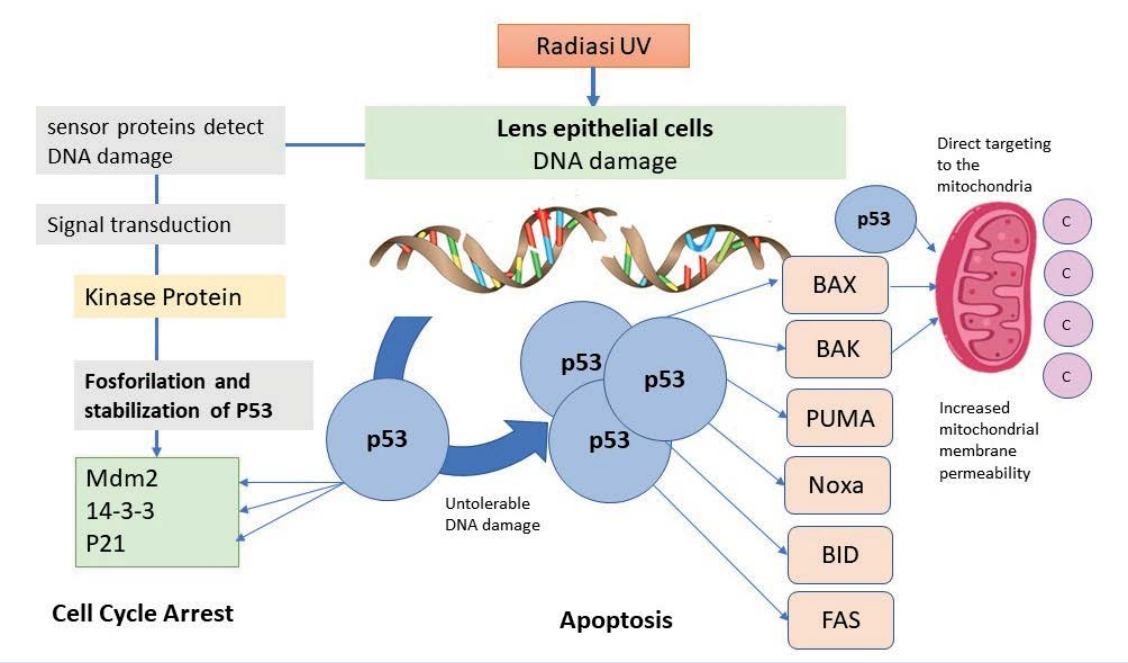

Figure 1: DNA damage response (DDR) due to UV radiation leads to cell cycle arrest and P53-dependent apoptosis.

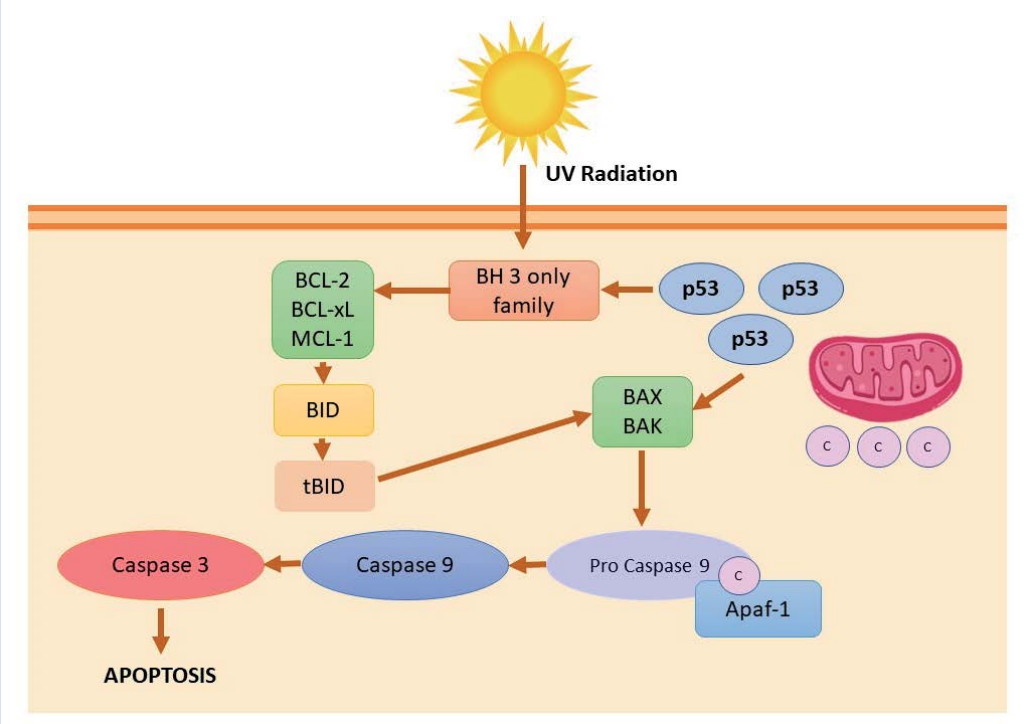

Figure 2: Intrinsic apoptotic pathway of the lens epithelial cells due to UV radiation.

The Role of P53 in Lens Epithelial Cell Apoptosis due to UV-B Irradiation

The p53 gene is a cancer-suppressor gene located on chromosome 17p13.1. The p53 gene produces a phosphoprotein with a molecular weight of 53-kDa which plays a role in the regulation of cell proliferation and apoptosis in the cell's response to DNA damage.[19] The p53 protein exists in both wild-type and mutant forms. Wild-type p53 without mutations is present in normal cells and has an important role in repairing DNA damage. Wild-type p53 acts as an anti-oncogene with its ability to maintain genome stability and normal cell growth by triggering G1 cell cycle arrest or inducing apoptosis in response to cellular stress. The p53 protein in cells will accumulate in response to DNA damage to inhibit cell division and trigger DNA repair. P53 acts as a molecular sensor in cell reactions to UV radiation by mediating cell cycle arrest and apoptosis in damaged epidermal keratinocytes.[20]

UV radiation induces stress at the cellular level. Low doses of stress do not directly cause cell death, but can damage DNA, cell membranes, or other cell organelles. This damage can be repaired if the cell successfully enters cell cycle arrest or experiences cell death or apoptosis. The apoptotic pathway can be related to p53 or not related to p53 at all. P53 also has a close relationship with lens epithelial cell apoptosis. There is evidence that the p53-related apoptotic pathway is involved in adult lens development. p53 expression was found in central and pre-equatorial zone lens epithelial cells, as well as in lens fibers in the nuclear bow area. Apoptosis of lens epithelial cells after UV exposure has been demonstrated in vivo and in vitro.[10,21,22] Takamura et al. (2003) demonstrated increased expression of P53 in lens epithelial cells of mice with galactosemic cataracts associated with lens epithelial cell apoptosis. Ayala et al. (2007) showed that p53 was localized in lens epithelial cells that experienced cataracts after exposure to UV-B radiation in albino mice. P53 expression was quantitatively found to be significantly higher in the lenses of albino mice exposed to UV-B radiation compared to the lenses of albino mice that were not exposed.

The Role of Caspase-3 in Lens Epithelial Cell Apoptosis due to UV-B Irradiation

Caspase-3 is an important protein in the execution of apoptosis. Exposure to UV radiation with a wavelength of 300nm damages lens epithelial cells, induces apoptosis and increases the expression of the active protein caspase-3 in lens epithelial cells in in vivo and in vitro studies.[10, 23,24] Expression of active caspase-3 in healthy mice suggests that active caspase-3 may play a role in protein turnover induced by incidental UV radiation.[18] Expression of active caspase-3 in healthy mice suggests that active caspase-3 may play a role in protein turnover caused by incidental light radiation. Talebizadeh (2016) also found that exposure to UV-B light in vivo stimulated increased expression of active caspase-3 in the lens, with peak expression at 8-16 hours post-irradiation exposure. A study conducted on albino mice exposed to UV-B radiation for 15 minutes with a total dose of 8 kJ/m2 and a wavelength of 300 nm showed that active caspase-3 was found to be more dominant in the central area of the lens epithelium compared to the nuclear arc. Apoptotic cells are found in the central part of the lens epithelium.[17]

CONCLUSIONS

Recent studies point to chronic exposures to lens epithelial cells as the contributing factor to the initiation and development of senile cataracts. UV exposure damages DNA, cell membranes, and proteins causing apoptosis to the lens epithelial cells through the p53-dependent pathway and caspase-3 activation. Protecting the eye from UV exposure may be an easy and practical method to prevent cataract formation and progression.

AUTHOR'S CONTRIBUTION

The study's concept, design, literature search, statistical and data analysis, manuscript preparation, and manuscript review are all under

the purview of NPA. NS oversees the study's concept, literature search, and manuscript evaluation. DH is in charge of the study's concept and manuscript production.

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CONFLICTS OF INTEREST

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ETHICAL CLEARANCE

Not applicable.

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