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Review

Genomic instability and eye diseases

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ABSTRACT

Background: Genetic information is stored in the bases of double-stranded DNA. However, the integrity of DNA molecules is constantly threatened by various mutagenic agents, including pollutants, ultraviolet light (UV), and medications. To counteract these environmental damages, cells have established multiple mechanisms, such as producing molecules to identify and eliminate damaged DNA, as well as reconstruct the original DNA structures. Failure or insufficiency of these mechanisms can cause genetic instability. However, the role of genome stability in eye diseases is still under-researched, despite extensive study in cancer biology.

Main text: As the eye is directly exposed to the external environment, the genetic materials of ocular cells are constantly under threat. Some of the proteins essential for DNA damage repair, such as pRb, p53, and RAD21, are also key during the ocular disease development. In this review, we discuss five ocular diseases that are associated with genomic instability. Retinoblastoma and pterygium are linked to abnormal cell cycles. Fuchs' corneal endothelial dystrophy and age-related macular degeneration are related to the accumulation of DNA damage caused by oxidative damage and UV. The mutation of the subunit of the cohesin complex during eye development is linked to sclerocornea.

Conclusions: Failure of DNA damage detection or repair leads to increased genomic instability. Deciphering the role of genomic instability in ocular diseases can lead to the development of new treatments and strategies, such as protecting vulnerable cells from risk factors or intensifying damage to unwanted cells.

1. Introduction

Genomic instability refers to an increased tendency to acquire mutations in the genome, which can range from point mutations to structural or numerical alterations of the chromosome. While it is a key source of genetic diversity, it is also related to diseases such as cancer.[1,2] External environmental factors such as UV light, X-rays and pollutants, as well as intrinsic disruptions to DNA activity, can all affect genomic stability. It is estimated that approximately 70,000 lesions occur in each human cell every day with most of the lesions being single-strand DNA breaks (SSBs) caused by factors such as oxidative stress produced by intracellular metabolism.[3] These SSBs can be further converted to double-strand breaks (DSBs), a more dangerous form of DNA damage. Multiple DNA repair pathways have been identified to fix these DNA lesions and maintain the fidelity of the genetic materials, including base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), homologous recombination (HR), and nonhomologous end-joining (NHEJ). These five major pathways for DNA repair play crucial roles in counteracting the environmental damages and intrinsic disruptions that threaten the integrity of the genome.

Although the relationship between genomic instability and cancer has been extensively studied, its association with ocular disorders is not well-defined. Understanding this association can shed light on the development of new treatments. For example, retinoblastoma (RB) treatment commonly depends on DSBs induced by chemotherapeutic agents. While RB1-deficient cells prefer the micro-homology-mediated end-joining repair pathway (MMEJ) to repair DSBs, inhibiting MMEJ and inducing DSBs synergistically can be more effective in killing RB cells and reducing

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the side effects of chemotherapy on healthy cells.[4] In this review, we explored the relationship between five ocular diseases - RB, sclerocornea, Fuchs' corneal endothelial dystrophy (FECD), pterygium, and age-related macular degeneration (AMD) - and genomic instability to illustrate their underlying mechanisms.

2. Main text

2.1. Retinoblastoma

RB is a malignant tumor that arises from photoreceptor precursor cells and seriously threatens to the vision and lives of children (Fig. 1A). It is caused by the inactivation of the *RB1* gene and loss of function of the RB protein (pRb). The global incidence of RB is estimated to be 1 in 16,000 to 18,000 live births, and around 8000 new cases are predicted each year.[5] RB is the most common intraocular cancer of childhood.[6] It can occur in an inherited or sporadic manner, with inherited and sporadic RB accounting for approximately 45% and 55% of all cases, respectively.[7] RB presents in two clinical forms: bilateral RB, which is hereditary and accounts for 25% of all cases, and unilateral RB, which accounts for 75% of cases, 90% of which are non-hereditary.[8] About 5% of bilateral RB cases are associated with intracranial tumors, a condition known as trilateral RB.[9] Patients with hereditary RB have a higher chance of developing a second cancer, even after the original RB has been cured.[10]

RB1 was the first tumor suppressor gene discovered in humans.[11,12] The protein encoded by *RB1*, pRb, acts as a cell cycle monitor, regulating the G1 to S phase transition.[13] During the G1 phase, pRb remains non-phosphorylated or hypo-phosphorylated and binds to the transcription factor E2F to inhibit the transcription of a series of cell cycle progression genes.[13] Cyclin D, a member of the cyclin protein family, binds to the cyclin-dependent protein kinases CDK4 and CDK6, which then phosphorylate pRb. Once pRb is phosphorylated, E2F is released, and the expression of genes necessary for DNA replication and cell division is activated.[14]

Mutations in tumor suppressor genes can lead to uncontrolled cell division, ultimately resulting in cancer. The two-hit theory, proposed by Knudson in 1971, explains the development of RB as the successive inactivation of both *RB1* alleles during retinal development.[15] In hereditary RB, the first *RB1* gene mutation is inherited from a parent, theoretically occurring in all cells, while the second mutation occurs after birth in retinal photoreceptor precursor cells, leading to RB. In non-hereditary RB, patients spontaneously gain *RB1* mutations in both alleles, and the onset of the disease is relatively late compared to the

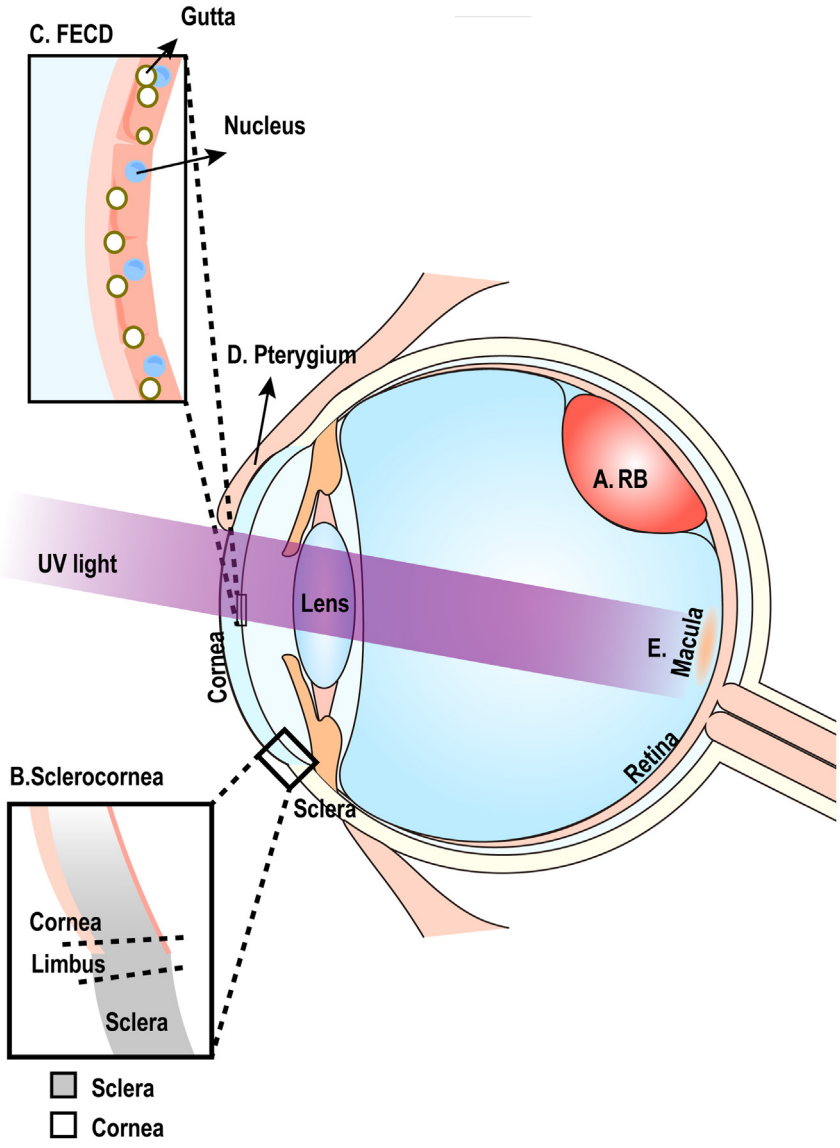

Fig. 1. Schematic description of the relationship between ocular diseases and the potential risk factor UV light.

hereditary form.[16] As *RB1* is not only in the eye but also in other tissues, its mutation has the potential to induce a wide spectrum of cancers. However, the annual occurrence of cancers associated with germline *RB1* mutations other than RB is only 0.5%.[17] This ocular tropism is due to the higher sensitivity of cone precursor cells to the loss of pRb function.[18] RB can develop as early as 21 weeks after pregnancy[19] and researchers linked this observation with the retinal development.[18] Studies have shown that RB originates from human L/M cone precursor cells,[20] and the proliferation of pRb-deficient cone precursor cells depends on cone-specific proteins such as RXRγ and TRb2. This suggests that cone precursor-specific circuitry collaborates with pRb loss to initiate retinoblastoma genesis.[21]

ARF, also known as $p14^{ARF}$ in human and $p19^{ARF}$ in mouse, is an alternative transcript of *INK4bARF-INK4a* locus.[22] It is an important tumor suppressor that plays a vital role in the p53 tumor monitoring network. The absence of pRb induces the expression of *ARF* via the E2F transcription factor.[23,24] High *ARF* expression is observed in both *RB1*-deficient retina and precancerous retina,[25] indicating that the $p19^{Arf}$-mediated apoptotic response may be impaired in the early stages of RB tumorigenesis.[18] MDM2, a proto-oncogene that encodes a protein that can bind to and inactivate p53, leads to the abrogation of the anti-proliferative and apoptotic effects of p53. MDM2 is specifically enriched in cone precursors during embryonic development, and its high expression inhibits $p19^{Arf}$ -mediated apoptosis,[23] supporting the cone-genesis of RB. Additionally, MiR-24, a non-coding RNA that blocks the synthesis of ARF, compromises the function of p53 in tumor surveillance during RB development.[26]

Several studies have demonstrated that the biallelic inactivation of *RB1* is necessary but insufficient for RB development.[27] Additional genomic alterations are required to drive the onset of malignancy. In a cohort study of RB, Rushlow et al. found that 2.7% of patients did not have *RB1* mutations, but 52% of them exhibited abnormally high amplification of the *MYCN* oncogene.[28] Similar observations were reported in subsequent studies,[29,30] suggesting that high amplification of *MYCN* may represent a new genetic subtype of RB. *In vivo* experiments have shown that the *MYCN* amplification alone is insufficient to initiate RB-like tumors in mice, but when combined with deletion of both *RB1* alleles, it induces tumor formation.[31] The inactivation of *RB1* and the overexpression of the human *MYCN* gene increase the expression of *MYC*, *E2F*, and ribosome-related genes, eventually leading to RB. *MYCN* is primarily expressed during the development of the central and peripheral nervous system.[32–34] As a member of the proto-oncogene MYC family, it contains a helix-loop-helix (bHLH) domain, which binds to DNA with the bHLH protein as a dimer. Epigenomic analysis showed that *MYCN* knockout altered nucleosome assembly in the promoter region of genes involved in DNA repair, leading to DNA damage. MYCN target gene *FACT* (facilitates chromatin transcription) was downregulated upon *MYCN* knockout, resulting in a significant increase in DNA damage in neuroblastoma cells.[35] In *MYCN*-related RB, *MYCNOS* (MYCN opposite strand) is amplified along with *MYCN*.[36] It encodes several RNA variants, including long non-coding RNAs (lncRNAs) and coding RNAs. Deletion of the variant *MYCNOS1* can reduce MYCN protein level but not transcript expression, thereby inhibiting rhabdomyosarcoma and neuroblastoma cell growth while enhancing the RB cell response to topotecan[36,37]

pRb has long been known for its role in cell cycle regulation, but emerging evidence suggests that it also plays a critical role in maintaining chromosomal stability and preventing aneuploidy.[38] Epigenetic changes, which refer to heritable changes in gene expression and activity without alterations in the gene sequence,[39] have been implicated in driving genomic instability. In addition to directly binding to E2F, pRb interacts with chromatin regulator enzymes, such as histone deacetylases, H3–K9 methyltransferases, H4–K20 methyltransferases, ATP-dependent helicases, and DNA methyltransferases, via the LXCXE peptide motif to modulate the structure of nearby nucleosomes.[40–42] Point mutations in the mouse *Rb1* LXCXE binding site have been found to compromise H4–K20 trimethylation in pericentric heterochromatin, resulting in centromere fusion and missegregation of chromosomes during mitosis.[43] Additionally, the loss of pRb compromises centromeric cohesion, particularly during the S phase, leading to an increase in DNA damage.[44] In *Drosophila*, pRb regulates chromosomal structure by interacting with dCAP-D3, a component of the condensin II complex.[45] Inactivation of pRb leads to an accumulation of DSBs,[46] which can be caused by UV radiation or cancer treatments such as the topoisomerase poison etoposide and camptothecin. Traditional treatments for RB such as radiation therapy and chemotherapy, are prone to inducing DSBs in the genome. DSBs are repaired via two major mechanisms, NHEJ and HR,[47] both of which have been implicated in pRb's role in maintaining chromosomal stability.[48–50]

The most well-known epigenetic modification is the DNA methylation of histone proteins. Non-coding RNAs, including short chain non-coding RNAs (miRNAs, siRNAs, and piRNAs) and lncRNAs, are also key epigenetic regulators of gene expression.[51] In RB development, lncRNAs have been found to play significant roles. For example, the lncRNA *GAU1* can recruit the transcription elongation factor TCEA1 to the promoter of *GALNT8* and promote its expression. Knockdown of *GAU1* has shown a therapeutic effect on orthotopic xenografts of human RB cells.[52] The upregulation of the lncRNA *PANDAR* is related to cell growth and apoptosis in RB cell lines.[53] The lncRNA *BRAT1* accelerates tumorigenesis by activating *E2F3* transcription.[54] Additionally, the non-coding RB suppressor lncRNA *CANT1* inhibits RB progression by blocking PI3Kγ promoter trimethylation.[55]

In summary, RB is one of the most severe ocular malignancies, and its onset is regulated by both the genetic and epigenetic factors. Understanding the role of genetic instability in retinoblastoma can help the development of new treatments and therapies for patients with these conditions.

2.2. Sclerocornea

Sclerocornea is a rare disease that belongs to congenital corneal opacity, and its incidence accounts for about 6.4% of congenital corneal opacity.[56] A healthy ocular surface has a clear demarcation between the cornea and sclera, with the limbus serving as the boundary between these two areas. However, in patients with sclerocornea, the transparent cornea becomes white and opaque, and is indistinguishable from the sclera (Fig. 1B). Orderly arrangement of corneal stromal fibres is essential for corneal transparency. Electron microscopy studies have revealed that the arrangement of stromal fibres in sclerocornea patients is disrupted, with varying diameters of these fibers.[57,58] There are two types of sclerocornea: peripheral and total sclerocornea. Total sclerocornea affects the entire corneal area, while peripheral sclerocornea affects only the corneal rim, leaving limited but functional vision in patients.

Congenital corneal opacity encompasses several ocular developmental diseases, including Peters' anomaly, Axenfeld-Rieger syndrome, congenital hereditary endothelial dystrophy (CHED), congenital hereditary stromal dystrophy (CHSD). These diseases present similar eye phenotypes, making it difficult to obtain a precise diagnosis. Genetic screening is a useful tool for diagnosing these diseases. Sclerocornea-related genes that have been reported include *FOXE3*,[59,60] *BMP4*,[61] *SOX2*,[62] *RAX*,[63] *PAX6*,[64] *NDP*[64] and *RAD21*.[65] These genes play critical roles in eye development and patients carrying mutations usually suffer from malformation of the eye.

RAD21 is a subunit of the cohesin complex, which forms a ring structure together with SMC1 and SMC3. Mutations in any of these genes could result in Cornelia de Lange syndrome (CdLS), a disorder that affects multiple organ systems and causes typical facial features.[66,67] In rare cases, ocular abnormalities have also been observed in CdLS patients.[68] RAD21 is essential for maintaining sister chromatid cohesion and mitosis progression.[69] During prophase to metaphase, the cohesin complex binds to the chromosome arms and centromeres to keep the two sister chromatids attached to each other.[70] Separase mediates the removal of cohesin from chromosomes, and the active enzyme cleaves RAD21 by

proteolysis following the arginine at positions 172 (Arg172) and 450 (Arg450).[71] These breaks on RAD21 open the adhesion complex and allow sister chromatids to separate. RAD21 is also important for DSB repair and HR.[72,73] Ionizing radiation is often used in cancer treatment to cause DNA damage. Overexpression of RAD21 in cancer cells enhances their survival, inhibits apoptosis, and mitigates the effects of ionizing radiation.[74]

RAD21 is widely expressed in various tissues and cell types. Knockout of *RAD21* is lethal, indicating its critical role in cellular processes.[75,76] During embryonic development, RAD21 is more enriched in the cornea than in other ocular tissues,[77] suggesting its potential role in corneal development. Our studies have shown that RAD21 is involved in neural crest migration and corneal stroma formation during embryogenesis.[78,79] One possible mechanism by which RAD21 mediates corneal development is through the regulation of chromosomal conformation.[80,81] Cohesin can also facilitates the chromatin looping, bringing the promoter close to its regulatory elements such as enhancers, which can regulate the expression of genes within the loop.[80,81] To investigate the role of RAD21 in sclerocornea, three-dimensional chromosome conformation analysis and transcriptome analysis were conducted on primary cells isolated from sclerocornea patients carrying a heterzygous mutation in *RAD21*. The results showed that the chromosomal interactions around the *PCDHG* gene cluster were significantly altered after the partial loss-of-function of RAD21. The *PCDHG* cluster is closely related to cell migration,[79] particularly during embryonic development, by facilitating axons distribution and specifying synaptic connectivity through regulating mutual exclusion between cells.[82] Further study found knockdown of *Pcdh7* in *Xenopus* resulted in apoptosis of neural crest cells before programmed neural crest migration.[83] We found the *RAD21* mutation influenced the expression of the *PCDHG* cluster and thus affected corneal stromal development.[79] Besides RAD21, further research on the roles of other DSB repair genes in maintaining corneal cell homeostasis is necessary, as the cornea is the outermost tissue of the eye that is directly exposed to the environment.

2.3. Fuchs' endothelial corneal dystrophy

The corneal endothelium is a single layer of hexagonal endothelial cells that resides on the inner surface of the cornea. It maintains corneal transparency by regulating the corneal stroma's hydration through its barrier and pump functions. Human corneal endothelial cells are arrested in the G1 phase with limited proliferative capacity *in vivo*.[84] Thus, a pathological decrease in endothelial cell number can lead to endothelial dysfunction and corneal edema. FECD is a disease characterized by the progressive loss of the corneal endothelium and was first described by Fuchs in 1910.[85] FECD also accompanies by the accumulation of guttae, which are extracellular matrix excrescences produced by endothelial cells, along Descemet's membrane (Fig. 1C).[86] FECD is a complex age-related genetic disease that typically manifests in the fifth or sixth decades of life. FECD also displays gender bias, with females being more prone to the disease.[87,88] In the United States, FECD is the leading indication for corneal transplantation in the older population, with an estimated prevalence of about 5% in people over 40 years.[89] FECD is inherited in an autosomal dominant manner. Several genetic abnormalities have been identified in FECD, including *COL8A2*, *TCF4*, and *SLC4A11*.[90] However, the genotype-phenotype association varies in FECD, displaying significant individual differences in the disease's etiology.[91] This suggests that epigenetic and environmental factors may also play a role in FECD's development.

The direct exposure to UV light predisposes the cornea to lesions due to increased oxidative stress and DNA damage (Fig. 2). Singapore, with one of the highest UV levels in the world, has a significantly higher incidence of FECD (6.6%) than Japan (3.3–4.1%),[88] suggesting a possible association between UV exposure and FECD incidence.

Previously studies have also shown that the corneal endothelium is a highly metabolic tissue, producing tremendous reactive oxygen species (ROS) necessary for ATP generation and maintaining its barrier function through ion pump. The accumulation of ROS can eventually lead to DNA damage, which is a hallmark of FECD (Fig. 2). In fact, the marker of DNA oxidative damage, 8-hydroxy-2′-deoxyguanosine (8-OHdG), was significantly higher in the corneal endothelium of FECD patients.[92] ROS is not only harmful to nuclear DNA but also to mitochondrial DNA (mtDNA), which lacks intron and thus damage to mtDNA can directly affect the coding region of genes.[93] Cells have evolved antioxidant defense mechanisms to repair DNA damage caused by ROS, such as base excision.[94] However, the repair efficiency of the DNA damage repair system in mtDNA is lower than that of nuclear DNA.[95,96] In the endogenous DNA damage test, the FECD group showed lower DNA repair efficiency than the control group, suggesting decreased DNA repair capacity as one of the underlying mechanisms of FECD.[97] Intracellular imbalances between oxidants and antioxidants lead to oxidative DNA damage, abnormal mitochondrial protein synthesis, changes in membrane potential, and eventually endothelial apoptosis. Endothelial cells of FECD patients showed decreased expression of genes encoding antioxidant enzymes, including peroredoxin (*PRDX*), glutathione S-transferase (*GST*), and aldehyde dehydrogenase (*ALDH*) compared to normal subjects.[98] Nuclear factor erythroid 2-related factor 2 (*Nrf2*), a transcription factor that binds to antioxidant response elements and activates antioxidant defense, was down-regulated in FECD endothelial cells.[92,99] In summary, this evidence highlights the critical role of oxidative stress and DNA damage in the development of FECD.

There is a significant gender-related difference in the prevalence of FECD.[100] It has been found that UV light initiates enzymes involved in estrogen metabolism and genotoxicity, resulting in increased susceptibility to FECD development in women.[101,102] The enzyme CYP1B1, which is involved in estrogen metabolism, has been linked to the gender bias in corneal endothelial sensitivity to UV. Women with more severe cases of FECD showed larger mtDNA damage and higher levels of estrogen-DNA adduct formation.[101]

With advancements in sequencing techniques, more detailed information and novel discoveries has been reported on FECD. Single-cell sequencing of the corneal endothelium from healthy individuals revealed one corneal endothelial subgroup showed signatures of DNA replication and cell cycle progression.[103] Although human corneal endothelium has limited proliferation capability, DNA replication-related genes such as *PCNA*, minichromosome maintenance proteins 2–7 (*MCM 2–7*), and *E2F1* were highly expressed in this special cell cluster.[103] These genes are actively involved in DNA repair as well.[104,105] Whether this cell cluster has a higher DNA repair potential remains to be investigated. For the corneal endothelium to function properly, it must maintain a minimal number of cells. In cases of extensive DNA damage, cells with a higher DNA repair capacity have a better chance of survival. Research into DNA repair genes in non-proliferating cells is of particular interest for the development of novel therapies for degenerative diseases. At present, the treatment of FECD is mainly surgical. However, improving the repair ability of endothelial DNA damage by gene editing could be helpful for corneal endothelial protection and regeneration. Thus, the corneal endothelium and FECD serve as excellent cellular and disease models, respectively, for the study of degenerative diseases.

2.4. Pterygium

Pterygium is an aggressive, benign lesion characterised by the overgrowth of the bulbar conjunctiva on the nasal side, with hyperplastic conjunctival fibrous tissue thickening and invading the cornea (Fig. 1D). When pterygium encroaches on the cornea's visual axis, it can cause vision loss. Recurrence is also characterized in pterygium after surgical removal.[106,107] Although the exact etiology remains unclear, it occurs more frequently in geographical areas with stronger UV light,[108] suggesting long-term UV exposure as an important risk factor for pterygium.[109,110]

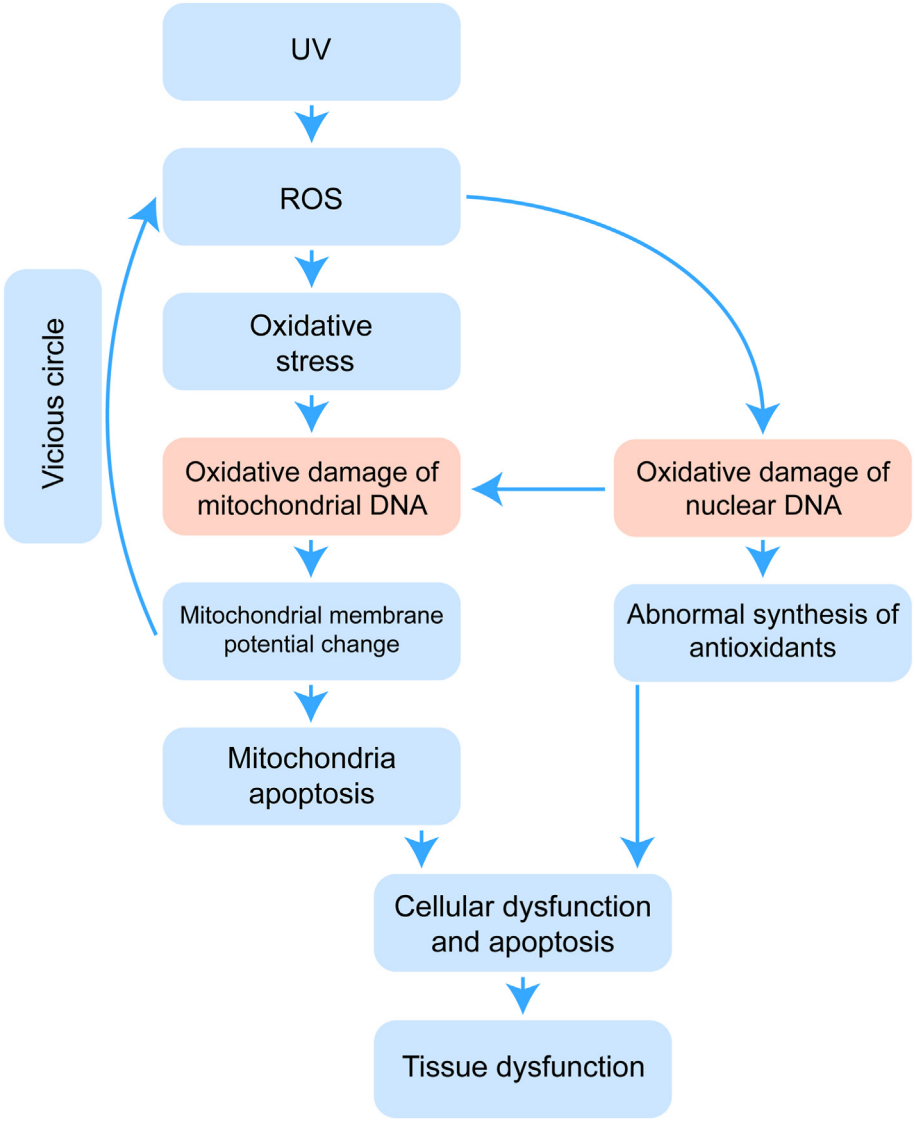

Fig. 2. Brief diagram of oxidative stress process.

Due to the tumor-like properties of pterygium tissue, research on pterygium mainly focuses on the cell apoptosis and hyperplasia imbalance.[111,112] The level of the photo-oxidation product 8-OHdG in pterygium tissues is 4.7 times higher than in normal conjunctiva tissues.[113] 8-OHdG can induce the G:C to T:A switch in the *p53* gene.[114] P53 plays a key role in maintaining genomic stability by detecting DNA damage or replication errors and promoting apoptosis to prevent the accumulation of potentially carcinogenic DNA mutations. G1 phase arrest is the most well-known p53-mediated response to stress. Studies have shown that pterygium patients have monoallelic *p53* mutations.[115] Thymine dimers stained in primary and recurrent pterygium sections revealed positive staining in pterygium tissues and blood vessels, suggesting that DNA damage is involved in the disease.[116] Interestingly, while p53 is a tumor suppressor, overexpression of *p53* was detected in more than one third of a pterygium cohort[116] and in more than half of all examined cases in another cohort,[117] indicating that its overexpression may exert functions other than inducing apoptosis. Indeed, p53 can participate in DNA damage repair by serving as a transcription regulator binding to genes close to a p53 response element,[118] or by exhibiting 3′–5′ exonuclease activities.[119] This overactivation of DNA damage repair may contribute to the tumor-like property of pterygium.

Survivin, a member of the inhibitor of apoptosis protein family (IAP), is involved in inhibiting apoptosis and regulating the cell cycle. It is overexpressed in almost all types of human malignancies.[120] In pterygium patients, survivin was found to be positively stained in about half of the examined samples and was co-expressed with 8-OHdG.[121] Overexpression of survivin in pterygium patients inhibits the apoptotic mechanism triggered by DNA damage, which acts synergistically with the loss of function of p53.

Cyclooxygenase 2 (*COX-2*), another gene inhibited by p53, has abnormal expression in pterygium due to the loss of function of p53.[122] In pterygium, COX-2 was positively stained in the cytoplasm of the epithelium, while it was negative in both normal conjunctival and limbal tissues.[123] The overexpression of COX-2 plays a crucial role in promoting angiogenesis and formation of fibrovascular tissue during the development of pterygium.[124] COX-2 is expressed at low levels in healthy tissues but can be induced by UV and ROS through activation of the NF-κB signalling pathway.[125]

At present, the chemical Nutlin can be used to target MDM2-p53 pathway and activate p53 to kill pterygium cells.[126] In summary, UV-induced oxidative DNA damage and the loss of p53 function are the major contributors to pterygium.

2.5. Age-related macular degeneration

AMD is a retinal degenerative disease and one of the leading causes of irreversible central vision loss worldwide. AMD accounts for 8.7% of all severe eye sight loss and its global prevalence is still increasing.[127] AMD is characterized by the progressive degeneration of photoreceptors and retinal pigment epithelial (RPE) cells in the macular region (Fig. 1E). RPE plays a crucial role in protecting photoreceptors from photo-oxidation damage, maintaining the blood-retinal barrier, and transporting nutrient, water, and electrolytes from the choroid to photoreceptor cells.[128,129] Therefore, the degeneration of RPE leads to vision loss.

The onset of AMD is multifactorial, with contributing factors including age, UV exposure, smoking, and genetic variations. The occurrence of AMD increases with the extension of lifespan.[130] In aging RPE cell lines, the expression of proinflammatory cytokines IL-6 and IL-8 is up-regulated, leading to inflammation.[131] Additionally, the efficiency of DNA repair machinery is negatively correlated with age. BER protects DNA from the damaging environment and is primarily responsible for fixing small and non-helix-distorting base lesions.[132] DNA glycosylases recognize and excise the damaged base to initiate the repair process. The expression of several BER glycosylases, such as 8-oxoguanine-DNA glycosylase 1 (*OGG1*), mutY homolog (*MYH*), and thymidine DNA glycosylase (*TDG*), is down-regulated with age.[133,134] NER, the most versatile DNA repair pathway, removes damage that distorts the DNA double helix, interferes with base pairing, and blocks DNA replication and transcription. Cyclobutane pyrimidine dimers and UV-induced pyrimidine dimers need to be removed by NER and generate DNA strand breaks as intermediates.[135] Environmental factor such as UV exposure affects phagocytosis, osmoregulation and water permeability of RPE cells.[128] Smoking is another major environmental factor in the development and progression of AMD.[136–138] It increases the production of superoxide anion and reactive hydroxyl radical in the body,[139] depleting natural antioxidants like micronutrients and vitamins.[140] Exposure of human RPE cell lines to cigarette smoke increased ROS levels and induced DNA damage associated with 8-OHdG. Smoking also reduces plasma complement factor H (CFH) levels,[141] which are crucial in regulating complement replacement pathways.[142]

Variations in CFH are the primary genetic risk factor for AMD.[143] The CFH mutation in amino acid Y402H has a dose-dependent relationship with AMD.[141] CFH is synthesized in RPE and choroid and negatively regulates the alternative complement pathway on cell surfaces, thus limiting the formation of membrane attack complexes deposited in Bruch's membrane.[142]

To summarize, the reduced efficiency of DNA repair with aging, combined with increased risk of DNA damage from factors such as UV radiation, smoking and gene mutations, collectively contribute to the genomic instability in RPE cells and consequently, the development of AMD. Enhanced knowledge of the underlying mechanisms of genetic instability can offer improved protection to these vulnerable cells and may provide potential therapeutic targets for the treatment of AMD.

3. Conclusions

This review aims to investigate the association between genomic instability and five ocular diseases that span from the ocular surface to the innermost ocular tissue. Due to its constant exposure to environmental mutagens and intracellular metabolic by-products, the eye is susceptible to DNA damage. Failure to detect or repair such damage leads to increased genomic instability and resultant abnormalities. Manipulating DNA damage detection and repair machinery can have two applications: protecting the vulnerable cells from the risk factors or enhancing damage to unwanted cells. Maintenance of genomic stability is crucial for non-proliferative human corneal endothelial cells, whose loss can result in corneal endothelial decompensation. Similarly, degeneration of photoreceptors and retinal ganglion cells can cause vision loss, highlighting the importance of preserving their genomic stability from metabolites and environmental risk factors. In diseased states such as RB and pterygium, inducing genomic instability in these cells with minimal effects on healthy cells is desirable. Consequently, novel strategies for diagnosis, prevention, and treatment of ocular diseases based on these knowledges are anticipated.

Study approval

Not Applicable.

Author contributions

Conception and design of study: BNZ, JC; Manuscript preparation HL, BNZ; Manuscript revision XZ, FFL; Figure preparation BQ. prepared figures.

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Declaration of competing interest

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