Insights into ocular cancer oncogenesis (Review)

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Abstract. Ocular cancer refers to a cancerous growth in any part of the eye. Ocular cancer primarily manifests as one of four types: Uveal melanoma, conjunctival melanoma, retinoblastoma, or ocular surface squamous neoplasia. It can arise in three key areas of the eye: The orbit, the adnexal structure and the eyeball. In cancer, oncogenes are activated from proto-oncogenes. An oncogene is a malfunctioning gene in a cell caused by mutation or gene fusion (a proto-oncogene) or overexpression. There are certain specific oncogenes implicated in ocular cancer, such as the retinoblastoma (Rb) gene, guanine nucleotide binding protein alpha 11 (GNA11), G protein subunit alpha Q (GNAQ) and tumor protein 53. Of note, >90% of instances of uveal melanoma are caused by activating mutations in GNA11 and GNAQ. Oncogene activation occurs through several mechanisms involving genetic, epigenetic and environmental variables. Biomarkers trigger the activation of this type of oncogene. A biomarker is a quantifiable trait or indicator that can be used to test or measure biological functioning, disease states, or therapeutic responses. Certain target therapies (such as radiation therapy, gene therapy, surgery, combination therapy, and immunotherapy) are used in cancer treatment. The present review aimed to provide a more thorough understanding of the involvement of oncogenes in ocular melanoma. It is hoped that this may aid in the treatment of several forms of ocular cancer. Understanding the mutated gene may assist in the discovery of a cure or treatment for the cancer caused by that particular gene.

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Key words: retinoblastoma, uveal melanoma, conjunctival melanoma, retinoblastoma gene, TP53 gene, G protein subunit alpha Q, guanine nucleotide binding protein alpha 11

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1. Introduction

Ocular or eye cancer is defined as a malignant development (uncontrolled cell proliferation) in any area of the eye. Cancer can occur in various regions of the eye, including the orbit, adnexal tissues and the eyeball. A previous study on 80 cases of ocular cancer discovered that eyelid tumors were the most common (53.75%), followed by intraocular (21.25%), conjunctival/corneal (20%) and orbital (5%) cancers (1). The three primary layers of the eyeball are the sclera, uvea and retina. Cancer typically affects the iris, ciliary body of the uvea and the choroid. The orbit is the tissue that surrounds and protects the eyeball. Orbital malignancies are tumors that reside in these tissues. Adnexal structures cover the area containing tear glands and eyelids. These are referred to as adnexal malignancies (2).

Types of eye cancer

Uveal melanoma. The uvea is the term for the central layer of the eyeball. The ciliary body, choroid and iris are its three main components. Uveal melanoma tumors originate from melanocytes in the uveal or middle layer of the eye, where the choroid is most frequently found, followed by the ciliary body and iris (3). This is the most prevalent and peculiar type of cancer, affecting primarily adults, and up to half of its victims succumb due to liver metastases, although it can also affect the skin, bones and lungs (4).

Retinoblastoma. Retinoblastoma affects the retinal cells of the eye. It is an uncommon childhood eye cancer that is usually hereditary and bilateral, resulting from a mutation. Individuals who suffer from unilateral retinoblastoma do not pass the illness on to their progeny, whereas people with bilateral retinoblastoma have tumors that induce cancer in other areas (5).

Conjunctival melanoma. Conjunctival melanoma is derived from melanocytes and is an extremely uncommon type of cancer, similar to uveal melanoma. Cancer spreads to other parts of the body due to its rapid growth and propensity to migrate through lymph and blood arteries (2,5).

Ocular surface squamous neoplasia (OSSN). OSSN may culminate in basic dysplasia, invasive squamous cell carcinoma and dysplastic and carcinomatous lesions in the cornea or conjunctiva (6). It is most typically detected in the limbal region, particularly in elderly persons who live near the equator, where UV-B radiation is excessive, making it a major etiological cause. The condition can cause symptoms ranging from no pain to severe pain and vision loss, emphasizing the significance of early diagnosis and treatment (7).

Oncogenes and their types. A broad category of disorders known as cancer is defined by genetic instability and altered DNA activities, which can cause abnormalities in the cell cycle as well as unchecked proliferation, dedifferentiation, and cellular immortalization. The proto-oncogene group is a unique gene that controls the cell cycle. They function as growth factors by acting as messengers, and they are crucial for healthy cell division and growth (8,9). When proto-oncogenes interact with environmental carcinogens, they undergo mutations and ramifications that activate or alter the new, modified genes known as oncogenes (Fig. 1 and Table I).

2. Epidemiology

Ocular cancer is a relatively rare form of cancer compared to other types of cancer. It involves tumors that form in or around the eye. The epidemiology of ocular cancer varies depending on the specific type of cancer and geographic region; below are some general insights:

Age and sex. Some forms of ocular cancer, such as retinoblastoma (a childhood cancer), primarily affect infants and young children. Retinoblastoma often presents prior to the age of 5 years (10). However, other forms of ocular cancer, such as uveal melanoma, typically occur in adults. There may be variations in incidence based on gender and age groups for different types of ocular cancer (11).

Risk factors. Several risk factors are associated with ocular cancer, including exposure to ultraviolet (UV) radiation, certain genetic factors (e.g., a family history of retinoblastoma), and possibly, environmental factors, such as blue light exposure (12) and human papilloma virus (HPV) type 16 in synergy with UV exposure (13).

In individuals who have a fair skin and are light-colored, the eyes may have a greater vulnerability to UV light (14), which increases the risk of developing ocular melanoma. Exposure to certain chemicals, such as formaldehyde (15) and pesticides such as acephate and bromacil (16) has been shown to be associated with an increased risk of developing ocular cancer (17).

Geographic variation. The incidence of ocular cancer may vary according to the geographic region. For instance, uveal melanoma is more common in populations with lighter skin tones and may have higher rates in regions with greater sun exposure (12,18-19).

Diagnosis and treatment. In cases of ocular cancer, prompt identification and treatment are essential for optimal results. Depending on the type and stage of the cancer, treatment options may include chemotherapy, surgery, radiation therapy, targeted therapy and immunotherapy (2). Due to the relative rarity of ocular cancer and the diversity of its types, ongoing research is essential to better understand its epidemiology and risk factors, and develop optimal treatment strategies. Early detection through regular eye examinations and the awareness of risk factors can also contribute to improved outcomes for individuals at risk of developing ocular cancer.

Epidemiological studies conducted by researchers and institutions often include assessments of ocular cancer incidence, risk factors and outcomes within specific populations. These studies may use various methodologies, including surveys, medical records reviews and population-based cancer registries. The fact that uveal melanoma affects populations differently depending on their place of residence is one of its main characteristics. Over the past 30 years, the incidence of uveal melanoma has remained constant, in contrast to that of cutaneous melanoma, which has exhibited a notable increase in frequency (20). Examples of disparities in incidence rates across Europe include Portugal, Spain, and Italy at two cases per million, and Denmark, Sweden and Norway at nine cases per million (21). While these sources contribute to the understanding of ocular cancer epidemiology, the study design, population characteristics and data quality all need to be taken into consideration when interpreting the results. Researchers continue to explore new methods and collaborate internationally to improve cancer surveillance and advance knowledge about ocular cancer prevention, diagnosis, and treatment.

3. Oncogenes and their role in ocular cancer

Oncogenes. An oncogene is a malfunctioning cellular gene (proto-oncogene) caused by mutation, fusion with another gene, or overexpression. Typically, oncogenes are considered to cause cancer by inhibiting apoptosis or deregulating cell growth (22).

Oncogenes are genes that, when expressed abnormally, can cause tumorigenic conversion. Under normal circumstances, their proteins play essential roles in cellular signaling, growth, and differentiation. Proto-oncogenes are the typical, appropriately controlled forms of these genes. On the other hand, constitutive activation of proto-oncogenes results in unchecked cell growth and proliferation, which ultimately causes the development and spread of cancer (23). Physical mutations that cause changes in the structure of the encoded protein and those that alter the appearance of proteins are two well-known types of physical mutations that trigger proto-oncogenes (24).

Function of oncogenes. Oncogenes are physically and functionally diverse. They regulate the cell cycle, apoptosis and the growth, differentiation, and proliferation of cells. Growth factors, growth factor receptors, signal transducers, transcription factors, apoptotic regulators and chromatin remodelers are among the by-products of oncogenes (25).

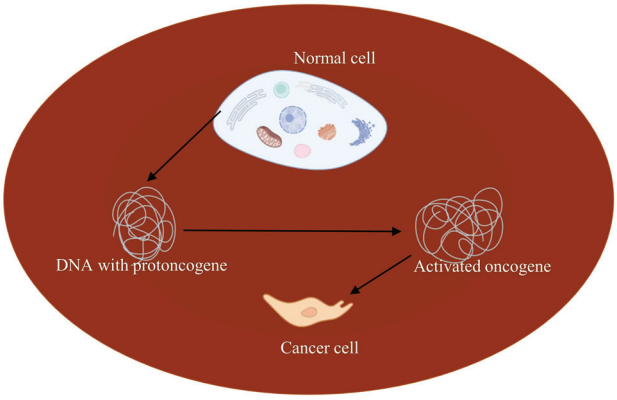

Figure 1. Image illustrating that activated Oncogenes change normal cells into cancer cells.

Table I. Certain oncogenes implicated in cancer.

Target gene	Cancers caused
HER2 gene	Breast cancer
BCR/ABL1 gene	Chronic myeloid leukemia
c-myc gene	Burkitt lymphoma
N-myc gene	Small cell lung cancer and neuroblastoma
EGFR and EML4AK genes	Adenocarcinoma of the lung
Kras gene	Pancreatic cancer and lung cancer
GNA11 or GNAQ	Eye cancer (uveal melanoma)
RB1 tumor suppressor gene	Retinoblastoma

Specific oncogenes implicated in ocular cancer

Retinoblastoma (Rb) gene and retinoblastoma. There are 27 exons spread across roughly 200 kb of DNA in the Rb gene. Mutations in the germline Rb gene typically occur at 5'-C-phosphate-G-3' (CpG) dinucleotides and are distributed throughout the whole gene (26). The Rb protein is functionally inactive in nearly all human malignancies in which the Rb gene is not altered, indicating that Rb is a tumor suppressor of fundamental significance in cancer biology (27). Indeed, oncoproteins, which bind to and inhibit Rb, are produced by tumor-causing viruses, such as SV40, adenovirus and human papillomavirus. These proteins play a crucial role in the tumorigenic potential of these viruses. The Rb 'pocket', which is produced by the interaction of the A and B boxes along an extended interface, is essential to the ability of Rb to suppress tumors, as shown by the fact that almost all mutations that cause tumors disrupt it (5).

As the first cloned tumor suppressor gene, the Rb gene is known for its ability to bind to the transcription factor E2F and limit the transcription of genes required for the S phase, thereby functioning as a negative regulator of the cell cycle. The Rb gene is known to have biological impacts on tumor suppression, cell cycle regulation, apoptosis and differentiation. These functions are made possible by the interactions of the Rb gene with a variety of cellular proteins. Of the >100 proteins that have been demonstrated to interact with the Rb protein, most, if not all, include the pocket domain. The transcription factors E2F are the most studied Rb binding partners (28).

G protein subunit alpha Q (GNAQ)/guanine nucleotide binding protein alpha 11 (GNA11) mutations in uveal melanoma. The most frequent intraocular cancer in adults and the most prevalent non-cutaneous melanoma is uveal melanoma (29-31). Uveal melanoma comprises 3-5% of all occurrences of melanoma; it occurs in the uveal tract of the eye and mostly affects the choroid (85-90%), ciliary body (5-8%) and iris (3-5%) (32).

Unlike other forms of melanoma, uveal melanomas do not carry mutations in V-Raf murine sarcoma viral oncogene homolog B1 (BRAF), neuroblastoma-RAS (NRAS), or neurofibromatosis type 1 (NF1) (33). Instead, constitutively active mutations in GNAQ and GNA11, which encode the closely related α subunits GQ and G11, account for >90% of uveal melanomas. They belong to the Gαq family, which also includes G14 and G15/16. To generate heterotrimeric G proteins, individual α subunits attach to β and γ subunits. The signals from Gαq-coupled GPCRs are subsequently sent to effectors by these proteins. The majority of uveal melanoma mutations affect codons Q209 and, less frequently, codons R183 of GNA11 or GNAQ, which functionally reduces their GTPase catalytic activity. In addition to GNAQQ209L and GNAQQ209P having slightly different tertiary structures and developing downstream signaling mutations, GNAQ and GNA11 have somewhat different mutation spectra. Asp630 in phospholipase C β4 (PLCβ4) encoding, which is downstream of Gvq, or codon Leu129 in CYSLTR2, a Gαq-coupled GPCR, were the sites of recurrent mutations in 10% of uveal melanomas without GNAQ or GNA11 changes. Therefore, the key activation of the Gαq pathway brought on by somatic mutations can be considered the disease-defining feature of uveal melanoma. Gαq pathway mutations are also linked to other neoplastic conditions, such as mucosal melanoma, anastomosing and congenital hemangiomas, capillary malformations, hepatic small artery neoplasms, Sturge-Weber syndrome and port-wine stains (31). Additionally, mutations in the Gαq pathway also produce phakomatosis pigmentovascularis and central nervous system melanocytomas.

Alterations in ocular surface squamous neoplasia. OSSN is a term used to describe a variety of tumors that affect the ocular surface. These tumors can range in histology from intraepithelial neoplasia to various stages of squamous cell carcinoma. Early lesions that fluctuate in size typically begin at the limbus, junction point of the cornea, and conjunctiva. Higher or more advanced stages may infiltrate the orbit and affect the eyelids. Oddly, OSSN usually only affects one eye (34).

Various cellular functions are regulated by p53, a crucial function that has been thoroughly investigated. p53 plays a role in several biological processes, such as DNA repair, apoptosis, senescence and homeostasis, in addition to cell cycle arrest. As anticipated, p53 is expressed in every part of the eye and plays a key role in the human body. Modified p53 signaling pathways have been specifically linked to the development of retinoblastoma, intraocular melanoma, uveal melanoma and conjunctival malignancy. Since non-selective cancer chemotherapies that may employ ionizing radiation may be linked to low efficacy or dose-limiting toxicities in the eyes (35).

Other identified oncogenes. Conjunctival melanoma accounts for ~5% of all ocular melanomas. Melanocytes in the base layer of the conjunctival epithelium give rise to it. As an early stage in the development of tumors, up to 50% of conjunctival melanomas are characterized by the V600E mutation in BRAF. Of note, ~30% of conjunctival melanomas have NF1 mutations (36).

Molecular pathways and signaling cascades. Oncogenic signaling in ocular malignancies encompasses a wide spectrum of pathways and molecular changes. Mutations in the GNAQ, GNA11, CYSLTR2, or PLCB4 genes increase G protein-coupled receptor signaling in uveal melanoma, activating the MAPK and protein kinase C pathways downstream (33). Other genetic alterations, such as chromosome 3 monosomy and BRCA1 associated deubiquitinase 1 (BAP1) mutations, also influence the risk of metastasis. MERTK, a receptor tyrosine kinase overexpressed in a number of malignancies, promotes cell migration and survival by activating the PI3K and MAPK pathways (34). Chromosome changes and oncogene mutations affect specific signaling pathways in ocular cancers, such as retinoblastoma, uveal melanoma and squamous cell carcinoma (39).

Cell cycle regulation. Cell cycle dysregulation is crucial for ocular oncogenesis, particularly in retinoblastoma and uveal melanoma. RNA sequencing in retinoblastoma has revealed that cell cycle disruption plays a crucial role in carcinogenesis (40), with six genes (BUB1, RRM2, TPX2, UBE2C, NUSAP1 and DTL) identified as possible targets for innovative therapeutics. Both retinoblastoma and uveal melanoma rely on the retinoblastoma gene (RB1) and its protein product (pRB) to suppress tumors and govern the cell cycle. Cyclins D1 and E, as well as CDK inhibitors p16 and p27, are overexpressed in primary uveal melanoma cell cultures, suggesting aberrant cell cycle regulation (41) (Fig. 2).

Apoptosis. Ocular homeostasis and disease processes depend heavily on apoptosis, a genetically programmed type of cell death. Glaucoma, retinitis pigmentosa, cataract, retinoblastoma and diabetic retinopathy are among the ophthalmological disorders in which it is implicated (42). According to Tempestini *et al* (43), there are two primary apoptotic signaling pathways: The intrinsic (depending on mitochondria) and extrinsic (dependent on death receptors) pathways. Both pro- and anti-apoptotic factors are found in mitochondria, and the main cause of cell death is the mitochondrial permeability transition pore (43). Novel treatment approaches for ophthalmology that prevent cellular death may result from an understanding of the molecular pathways of apoptosis in ocular illnesses (42) (Fig. 3).

Angiogenesis. Angiogenesis, or the formation of new blood vessels, is required for ocular tumor growth and spread (44). The 'angiogenic switch' enhances tumor vascularization when pro-angiogenic factors exceed anti-angiogenic factors. Tumor blood vessels have a different structure, permeability and maturation compared with normal vessels (45). VEGF is a key component of ocular angiogenesis (44). Anti-angiogenic medicines, particularly anti-VEGF drugs, have shown promising results in the treatment of ocular malignancies as they inhibit growth, reduce the risk of metastasis and improve the effects of radiation therapy (44,46). These therapies are being tested for retinoblastoma, von Hippel Lindau disease and uveal melanoma, among other ocular tumors (46) (Fig. 4).

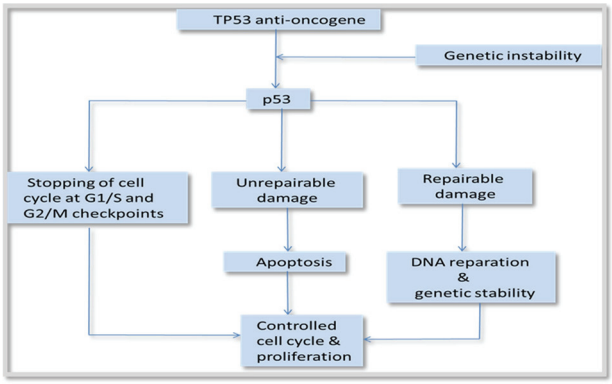

Figure 2. Cell cycle regulation. Tp53 is involved in cell cycle regulation, in the G1/S and G2/M phases of cell cycle. Tp53, tumor protein 53

4. Mechanisms of oncogene activation

Epigenetic modifications. This type of mutation occurs in uveal melanoma. It includes DNA methylation, histone modification and microRNAs (miRNAs/miRs) (47).

DNA methylation. DNA methyltransferase (DNMT)3A mediates the insertion or removal of a methyl group from a DNA sequence. Transferases are responsible for writing DNA methylation and are used as therapeutic targets to treat various types of cancer (48,49).

i) The Ras association domain family 1 isoform A (RASSF1A) gene, located on chromosome 3p21.3, significantly affects the development and spread of uveal melanoma tumors when it is absent or inactivated. It is essential for the control of the cell cycle, apoptosis, and microtubule stability. RASSF1A methylation may play a role in uveal melanoma carcinogenesis (3).

ii) Preferentially expressed antigen in melanoma (PRAME) can occur regardless of the cancer progression stage. In the instance of uveal melanoma, the hypo-methylation of locations near the PRAME promoter has been demonstrated to promote PRAME activation, with a concomitant increase in the risk of metastasis (47-49).

c) DNMT1 and DNMT3B are key players in the suppression of P161NK4A (also known as CDKN2A). It has been demonstrated that P161NK4A and P14ARF gene epigenetic modifications were frequently linked to uveal melanoma in addition to cutaneous conditions (3).

d) The methylation of the telomerase reverse transcriptase (TERT) promoter falls under uveal melanoma. The oncogene human TERT has been shown to be overexpressed in uveal melanoma (50).

Histone modification- Lysine residues of histone tails are modified by enzymes including histone acetyltransferase (HAT), histone deacetylase (HDAC) and histone methyltransferase via acetylation, deacetylation, methylation, ubiquitination and phosphorylation. Research indicates that the loss of BAP1 has been linked to histone modification. Through the hyperubiquitination of histone H2A, the depletion of the tumor suppressor gene, BAP1, causes cancer cells to lose their ability to differentiate.

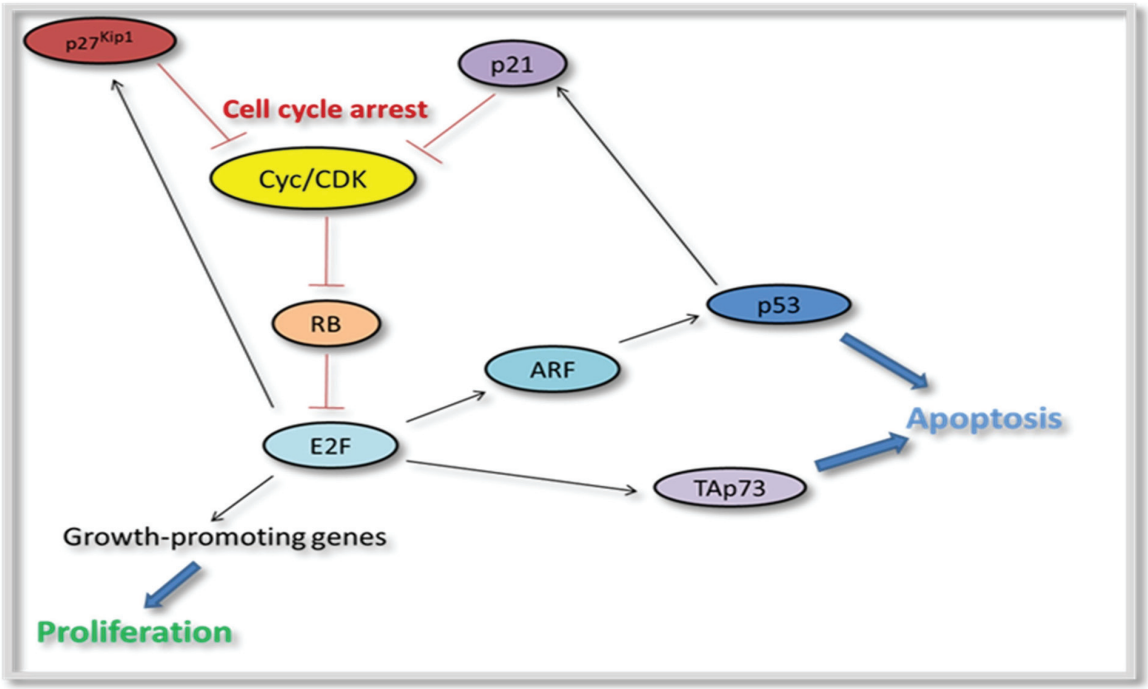

Figure 3. Cell apoptosis and Rb and p53 genes, and E2F (a group of genes that encodes a family of transcription factors) transcription factor. Rb gene, retinoblastoma gene; p53, tumor protein 53.

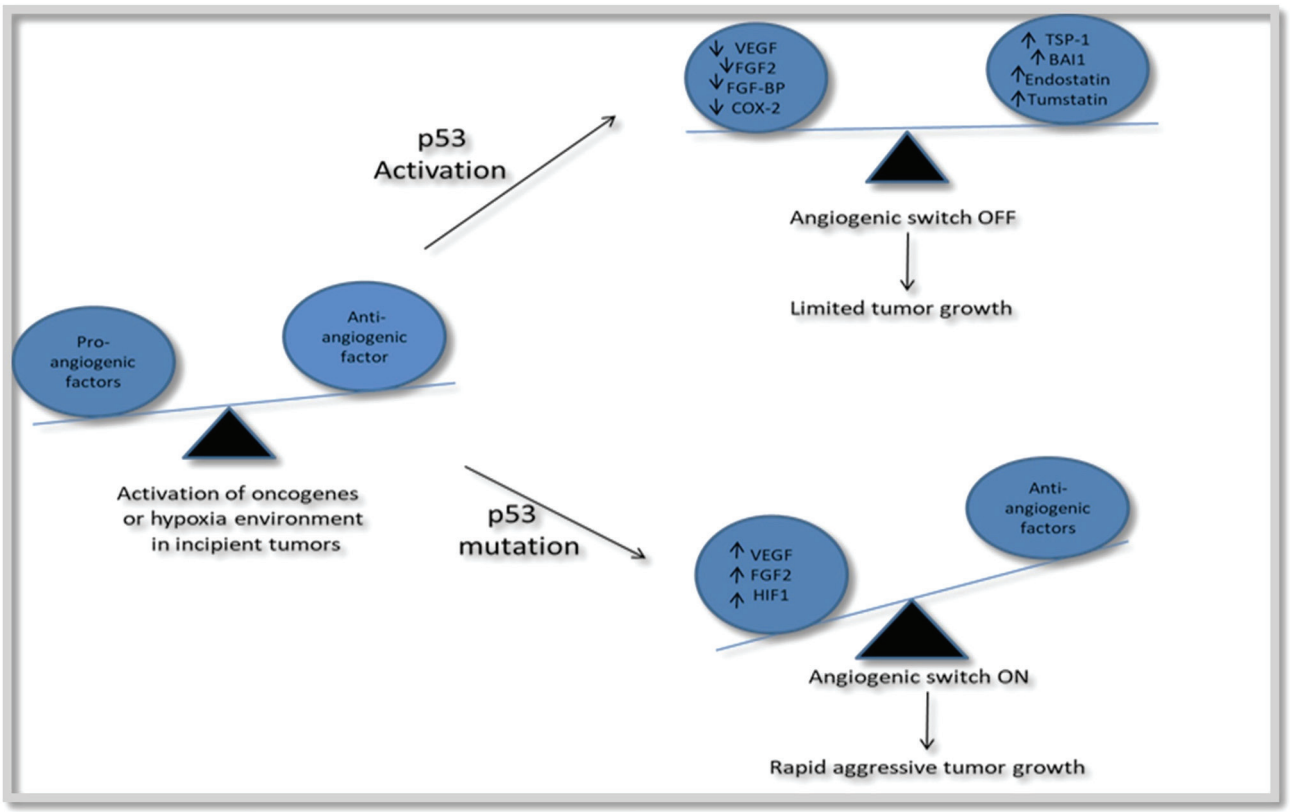

Figure 4. Angiogenesis and p53 oncogene. p53, tumor protein 53; VEGF, vascular endothelial growth factor; FGF2, fibroblast growth factor 2; FGF-BP, fibroblast growth factor-binding protein; COX-2, cyclooxygenase-2; TSP-1, thrombospondin-1; BAI-1, brain-specific angiogenesis inhibitor 1; HIF1, hypoxia-inducible factor 1.

It is associated with other malignancies, as well as an increased risk of developing uveal melanoma (51,52).

miRNAs. Non-coding RNAs known as miRNAs play a regulatory role in the body. They regulate gene expression

in both physiological and pathological processes, including cell proliferation, differentiation, death, organ development, angiogenesis and extracellular matrix remodeling (53). Among the miRNAs involved in cell motility and invasion that have been discovered abnormally expressed in uveal melanoma, 65 were found to be downregulated, 28 were found to be upregulated, and three exhibited a distinct expression pattern as demonstrated by Venza *et al* (54). Additionally, miRNAs control immunological mediators, which can influence uveal melanoma behavior (3,55) (Table II).

Table II. Types of regulatory genes (52).

Upregulated	Downregulated
miRNA-92a-3p	miR-137
miRNA-181b	miR-144
miR-20a	miR-145
miR-155	miR-296-3p
miR-454	miR-23a
miR-367	miR-23a
miR-21	

Genetic mutations. Mutations are defined as any alterations to the DNA sequence of a gene. It is caused by changes in DNA replication that occur during cell division and are exposed to environmental triggers, such as viruses and mutagens. Eye cancer is caused by two different types of mutations, namely point mutations and deletion and insertion mutations (56).

Environmental factors

UV radiation. The mutation spectrum of TP53 has been used as a tool to predict the significance of UV radiation. BRAF mutagenesis results from UV-related mechanisms, including UVA photoreactions or error-prone translesion DNA synthesis following non-specific mutations from UV-induced oxidative stress (57). It has been suggested that UV-induced DNA damage may play a role in the formation of retinoblastoma (58).

Viral infections. One of the elements that affects the eyes and can lead to cancer development is viral infection. As an example, HIV specifically infects helper T-cells, which results in apoptosis. Increased transmission to target cells amplifies the carcinogenic effects of other viruses, including Epstein-Barr virus, Kaposi sarcoma-associated herpes virus and human papillomavirus (59,60).

5. Diagnostic approaches

Molecular profiling of ocular tumors. Molecular profiling involves the use of various technologies to understand the distinctive characteristics that are found in cancer cells. It identifies the specific DNA, RNA, or protein molecule that is associated with the disorder. There are several examples of molecular profiling technologies are as follows:

Next-generation sequencing (NGS). NGS is a technology that enables the simultaneous sequencing of millions of DNA or RNA sequences. It is sometimes referred to as massively parallel sequencing or high-throughput sequencing. Second and third-generation sequencing technologies have been developed as a result of the rapid evolution of NGS technologies. Three steps are involved in all sequencing technology types (52): i) Template preparation, which involves extracting nucleic acids; ii) clonal amplification as part of the library preparation process; and iii) short read alignment and sequencing.

Additional research reveals that short sequence reads that result in sequence gaps, PCR artifacts and pseudogenes are only a few of the disadvantages associated with second-generation sequencing technologies. Single-molecule sequencing-based third-generation sequencing methods were introduced to overcome over these restrictions (61).

This technique has been employed for germline RB1 detection in the majority of studies on NGS in retinoblastoma (51). Furthermore, a pathogenic mutation that is undetectable even by NSG may exist in the gene promoter of RB1, non-coding region, or deep intronic region (52). Although retinoblastomas have not been found to exhibit p53 activity amplification, MDM4 encodes an E3 ubiquitin ligase that functions as a negative regulator of p53 activity. The Rb gene has been extensively studied, and the overexpression of this enzyme is expected to activate the MAP kinase signaling pathway (51). Targeted therapy selection was aided by the identification of several oncogenic driver gene changes by the NSG-based integrative analysis system (49).

Expression profiling. Gene expression profiling (GEP), which assesses the expression of several genes in a tumor, has been proposed as an additional method to categorize patients into prognostic risk groups in order to determine the risk of an individual for developing metastasis (62). In addition to clinical and biopsy data, GEP is a useful tool for classifying patients into low- and high-risk groups. Gene expression analysis predicts the risk of metastasis much more accurately than any other prognostic indicator (48). A predictive strategy for uveal melanoma has been created utilizing GEP. Tumors have been categorized using these techniques into two classes as follows: Class 1 (low risk) and class 2 (high risk) (63). The prognostic capacity of the 31-GEP test to distinguish between class 1 and class 2 CM (62). SF3B1, a gene whose mutation has been found in late metastasizing tumors, is another gene implicated in intermediate-risk uveal melanoma. The PRAME and EIF1AX genes have also been linked to both a higher and lower incidence of metastasis. Metastasizing uveal melanoma has also been linked to a decrease in BAP1 expression. The PRAME gene can be used to determine the percentage of class 1 tumors that result in metastatic illness. Retinoic acid signaling is inhibited by the protein PRAME, which inhibits cell division, proliferation and apoptosis (64).

Biomarkers for oncogene activation. A biomarker is a quantifiable trait or indicator that can be utilized in tests or assessments of disease states, biological processes, or treatment responses. Biomarkers help forecast the prognosis and the likelihood of metastasis, which can be employed for diagnostic purposes. Subgroups of biomarkers include the following: i) Diagnostic; b) prognostic; c) therapeutic; and d) preventative (65). Numerous biological samples, including blood, urine, tissue and even genetic material such as circulating tumor DNA (ctDNA), can contain biomarkers. These may consist

of substances, such as proteins, enzymes, hormones, genetic material (DNA/RNA), or certain features of cells (66).

ctDNA. Tumor cells release highly fragmented single or double-stranded DNA into the bloodstream, which is known as ctDNA. A potent tool for studying the molecular heterogeneity and clonal divergence of malignancy is the ctDNA assay. Tumor DNA (ctDNA) in the circulation function as a substitute DNA source for genomic research (67). It has been suggested that ctDNA in retinoblastoma originates from the aqueous and vitreous humor of the eye (68). When tumor cells undergo apoptosis, or necrosis, or are actively secreted from their bodies, ctDNA is formed. In metastatic uveal melanoma, ctDNA has been proven to be a superior marker of survival prediction (69). Mutations that are mutually exclusive and recurrent in GNA11, GNAQ, PLCβ, or CYSLTR2 are observed in patients with uveal melanoma (70). Early-stage melanomas typically do not exhibit any detectable ctDNA. The later stages of the disease are linked to an immunotherapy response when BRAF and NRAS mutations are present (69). Within 8 weeks of commencing treatment, ctDNA in cutaneous melanoma also exhibits a response to immunotherapy and combined BRAF and MEK inhibition (69).

6. Therapeutic implications

Targeted therapies. Advanced-stage eye cancer may occasionally be treated with targeted therapy. Drugs used in targeted therapy aim to target molecules in cancer cells (71). Standard chemotherapy medications do not function in the same way as targeted drugs. These drugs are used in cases of chemoresistance and severe side-effects associated with chemotherapy. Various types of therapies are described below:

Surgery. Surgery for ocular melanoma may involve removing only the tumors, removing parts of the eye, or removing the entire eye in the event that it is severely damaged by the tumors (72). Surgical options include the following: i) Iridectomy (part of the iris is removed); ii) iridocylectomy (removal of the iris and ciliary body); iii) endoresection (removal of the choroidal tumor); iv) enucleation (removal of the entire eye); v) orbital exenteration (eye and some tissues are removed).

Radiation therapy. High-energy radiation is used in radiation therapy to destroy cancer cells. It is currently frequently selected over enucleation surgery for melanomas of the right size and location for treating uveal melanoma (73). Proton beam radiation therapy, stereotactic radiation therapy and plaque radiation therapy (also known as plaque brachytherapy) are the three primary forms of radiation therapy (74).

Laser treatment (transpupillary thermotherapy or photodynamic therapy). The actions of photodynamic therapy are is based on the selective elimination of cancer cells or diseased arteries. The photodynamic therapy method employs light to activate photosensitizers, which produce reactive oxygen species that destroy cells (75). Photodynamic therapy reduces harm to normal cells due to its unique methodology. It is a widely utilized method for treating a variety of eye diseases, including uveal melanoma (76).

Combination therapy. It has been demonstrated that epigenetic medications, such as DNMT inhibitors, HDAC inhibitors, histone methyltransferase inhibitors, such as enhancers of zeste homolog 2 inhibitors, and modifiers of miRNA expression, such as antagomirs, can reduce the resistance of tumor cells to cytotoxic T-cells and natural killer cells, while also improving the activity of antigen-presenting cells (77). In order to increase the effectiveness of cancer treatment, more focus is currently being paid to recently developed combination therapeutic techniques that use new molecular inhibitors or epigenetic medicines in addition to other therapies (78).

Immunotherapy. A new, exciting area of cancer drug development is immunotherapy. Immunotherapies aid in boosting the immune system to invade cancer cells. Cytokines, monoclonal antibodies, cancer vaccines and various other immunotherapies are considered highly promising treatments for uveal melanoma (79). Among these, immune checkpoint inhibitors and adoptive cell therapies stand out as notable immunotherapy strategies.

Immune checkpoint inhibitors. Immune checkpoint inhibitors are used to boost the immune response of the body. It is helpful in the treatment of eye melanomas. It exhibits great effect in advanced-stage cutaneous melanoma. However, it exhibits minimal efficacy in metastatic uveal melanoma. Bispecific T-cell engagers (BiTEs) are drugs that link T-cells to melanoma cells, boosting the immunological response of the body. Tebentafusp is one example of this type of medication (80).

Adoptive cell therapy (ACT). Treatment for metastatic melanoma, particularly ocular forms, has shown promise using ACT. Although tumor-infiltrating lymphocytes (TILs) have been effectively employed for ACT, their restricted availability has prompted the creation of other strategies (81). The technique that has demonstrated efficacy in patients with cutaneous and ocular melanoma, is the *ex vivo* growth of circulating antitumor T-cells from peripheral blood mononuclear cells. A phase 2 trial has shown that the adoptive transfer of autologous TILs can mediate remission of metastatic uveal melanoma (82). ACT is a highly tailored cancer treatment that targets somatic mutations unique to each tumor, resulting in long-term, entire regressions for patients with melanoma. The efficacy of ACT in the treatment of cancer has been increased further by the ability to genetically engineer lymphocytes (83).

7. Future directions

It appears that a wide range of medications and treatments are helpful for ocular cancer. It is not required for every treatment to be fully effective for each case of ocular cancer. While some tumors may only operate locally, others may specialize or become resistant to the treatments they receive. Advances in diagnostic technique, such as NGS, expression profiling, immunotherapy, biomarkers, targeted medicines, etc. have come across relatively effectively in recent years. These implications are applied not only to treatment, but also to the identification of cancer linked to treatment resistance. Although ocular cancer cannot be avoided, consuming a balanced diet can reduce the risk of developing the disease.

Resistance is another issue that develops along with the explosive expansion of therapies. The resistant gene renders therapies or treatments ineffective. In such scenarios,

preventive medicine loses its significance. The challenges associated with evaluating blood and tissues for biomarkers can be addressed with concepts, such as liquid biopsy. Additionally, combination medicines are employed when targeted therapy is ineffective. Upon rational screening, certain drug combinations can provide synergistic effects. In conclusion, knowledge of the role of oncogenes in the genesis of ocular cancer and their applications in the treatment of eye cancer is beneficial.

8. Conclusion

In conclusion, the present review aimed to provide a detailed discussion of the role of oncogenes and summarizes genetic predispositions, environmental factors and molecular pathways that lead to the development of ocular cancer. The most prevalent eye malignancies in children and adults, respectively, uveal melanoma and retinoblastoma, have deepened the knowledge of researchers of cell cycle mechanisms and cancer biology. Genetic similarities between conjunctival and cutaneous melanoma, such as mutations in the BRAF, NRAS and TERT genes, point to the possibility of immunotherapy and targeted treatments. Early detection and personalized treatments are the areas that hold vast potential in terms of improved treatment strategies and efficacy from the perspectives of patients and physicians. Collaboration among researchers, physicians and patients may enhance the current knowledge and management of ocular cancers, improving the prognosis and standard of living for affected individuals. The combination of customized medical procedures and cutting-edge genomic technologies may also significantly improve future therapeutic possibilities.

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Authors' contributions

RP was involved in the conceptualization of the study, in the writing of the original draft of the manuscript, and in the writing, reviewing and editing of the manuscript. AD, KT, PT and PS were involved in the writing, reviewing and editing of the manuscript. PKS was involved in the conceptualization of the study, in the writing of the original draft of the manuscript, in the writing, reviewing and editing of the manuscript, and in study supervision. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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