Ocular Cancer Stem Cells: Advances in Therapeutic Interventions

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Upasna Upadhyay, Raaghav Sen, Swathi Kaliki, and Jaganmohan R. Jangamreddy

Abstract

Cancers affecting the eye are rare and can be either initiated in the eye, primary intraocular cancers, or invaded into the eye as a malignant tumor started elsewhere, secondary intraocular cancers. Melanoma and non-Hodgkin lymphoma in adults and retinoblastoma and medulloepithelioma in children are the most common intraocular cancers. Similar to other cancers, cancer stem cells are reported among retinoblastoma, lymphoma, and melanomas that can be malignant even though are very rare in occurrence. Here, we explore the cancers of the eye and cancer stem cells with the perspective of advanced therapeutic applications for vision and globe salvage.

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U. Upadhyay · R. Sen
Prof. Brien Holden Eye Research Center, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India

Operation Eyesight Universal Institute for Eye Cancer, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India
e-mail: upasna@lvpei.org

S. Kaliki
Operation Eyesight Universal Institute for Eye Cancer, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India

J. R. Jangamreddy (✉)
Prof. Brien Holden Eye Research Center, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India

Operation Eyesight Universal Institute for Eye Cancer, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India

The Cornea Institute, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Banjara Hills, Hyderabad, India

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Keywords

Cancer stem cells · Ocular tumors · Eye cancer metastasis · Retinoblastoma · Ocular melanoma

7.1 Introduction

Despite the current advancements in cancer treatment, the recurrence and metastasis of tumor at site or at distant site is prevalent. The available treatment options besides eliminating the cancer cells also target the normal healthy cells, resulting in the tissue damage and recurrence of the tumor due to residual cancer cells. Similar to the stem cell population, existence of cancer stem cell (CSC) subpopulation initiating the tumor and driving its proliferation are widely reported. Like normal stem cells, CSCs have the ability to self-renew, preserve the undifferentiated stem cells, and regulate their quantity, generate a range of tumor cells at different stages of differentiation. Within the tumors, the CSC can be characterized using specific markers and differentiated from those of normal stem cell population. These CSC subpopulations exhibit similar pluripotency and proliferation characteristics mimicking normal stem cells [1]. The current approach to chemotherapy demands a strategy inclined toward targeting specifically the CSC population to prevent the recurrence of the tumor. The CSC differentiates into different tumor components through the stemness pathways that control many important biological processes. In CSC these stemness pathways are not strictly regulated resulting in differentiation of various tumor components [2, 3].

This book chapter outlines ocular stem cells and cancer stem cells emphasizing on marker characterization with genetic mutations affecting cancer stem cells, their regulation via various signaling pathways, and resistance to chemotherapy.

7.2 Stem Cells

Stem cells are ascribed for their extensive self-renewal, differentiation, and clonally regeneration properties within tissues they inhabit [4, 5]. Stem cells undergo repeated divisions producing undifferentiated stem cell and differentiated progenitor cells with not all stem cells having infinite self-renewal potential (see [6]). Like stem cells from trabecular meshwork, orbital and sclera whose regeneration potential is not completely understood experimentally. On the other hand, limbal, corneal, conjunctival, and retinal stem cells have been exploited for their application in regeneration and treating degenerative disorders in animal and human clinical trials [1]. Limbal stem cells are widely recognized for their repair and regeneration of cornea-related diseases [7].

The repair and regeneration process of stem cells involves replenishing the lost cells with healthy regenerated cells. The injury caused at the site reduces stem cell population resulting in many diseases associated to its deficiency [8]. Stem cell population involves many intricate interactions of cytokines and growth factors regulating modulation of fibroblasts and epithelial cells.

7.3 Cancer Stem Cells (CSCs)

A tumor is an abnormal indefinite growing mass of cells. The rapid indefinite proliferating ability of cancer stem cells through accumulation of mutations leads to tumor development [9]. CSCs exhibit similarities of normal stem cells with regard to ability to proliferate, self-renew, and trigger epithelial to mesenchymal transition, giving rise to differentiated cells. Similar to normal cells, CSCs also undergo aberrant differentiation due to continuous accumulation of mutation leading to heterogeneity of cells. The heterogeneity also arises through the clonal origin with diverse phenotypic expression of tumorigenic cells. The phenotypically variable expression of tumorigenic cells with CSCs to possess indefinite as well as limited or no proliferative potential explains the self-renewal and differentiation properties, respectively, as retained by the normal stem cells [10]. The occurrence of such combined subpopulation of CSCs in a tumor makes tumor targeting difficult and thus leaving the subpopulations of CSC's undisturbed during chemotherapy sessions. Thus the CSC subpopulation retained would maintain and reinitiate the tumor growth exhibiting metastasis to distant areas and attaining resistance to chemotherapy [11] (Table 7.1).

7.4 The Types of Eye Cancer

In this chapter, the types of ocular cancer shall be broadly categorized into the following:

1. Eyelid tumors.
2. Conjunctival tumors.
3. Corneal tumors.
4. Orbital tumors.
5. Intraocular tumors.

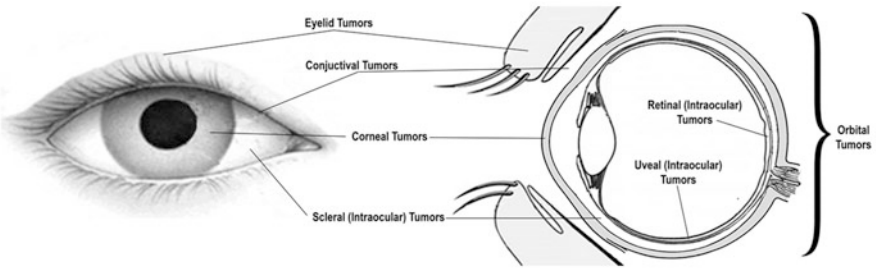

Table 7.1 Markers of ocular stem cell and cancer stem cell of the eye

Ocular cancers (name the cancer and CSC associated)	Stem cell markers	Differentiation markers
Cornea (limbus and stroma)	Limbus: ABCG2 (ATP binding cassette subfamily G member 2) [12], α-enolase, cytokeratin (CK) 19, Musashi-1, vimentin [13]	CK 3/12, connexin 43, and involucrin [14]
	Stroma: ABCG2, Bmi 1, CD166, C-kit, Pax6, Six2, and notch 1	Upon differentiation, stromal stem cells expressed keratocan, ALDH3A1, CXADR, PTDGS, and PDK4 [15]
Conjunctiva	CK19 positive CK3 AND CK12 negative [16]	
Iris	Expression for nestin, Msi, Pax6, Chx10, rho, Otx2, and Olig2 [17]	
Ciliary body	Expresses neuronal/retinal markers nestin, Chx10, Pax6, Sox2, Lhx2, Dach1, and Six3 [18]	
Trabecular meshwork	Expresses mesenchymal cell-associated markers CD73, CD90, and CD105 [19] and stem cell markers ABCG2, notch 1, OCT-3/4, AnkG, and MUC1. AQP1, CHI3L1, and TIMP3 have been differentiation markers [20]	
Retina	Retinal pigment epithelium (RPE)-derived positive markers include nestin, notch 1, CHX2, Map2, CRALBP, tyrosinase, and tyrosine-related protein 1 and 2 [21]	
Choroid	Expressing markers Sca-1, CD90.2, CD44, CD105, CD73, ABCG2, six 2, notch 1, and Pax 6 [22]	
Sclera	Expresses ABCG2, Six2, PAX6, and notch 1 [22]	
Orbit	Epithelial cell markers CD34 and zonal occludin-1 and differentiation markers CK3 and CK19 [23]	
Eye lid (sebaceous gland carcinoma)	ALDH1, CD133, CD44, ABCG2 (cytoplasmic marker) Sox4, Sox9, and slug (nuclear marker) [24]	

7.4.1 Eyelid Tumors

Eyelid tumors are of various types and are the most common type of ocular-related cancers [25]. Most of the neoplasms that originate in the eyelids (between 65% and 85%) are reported benign in nature [25–28]. Eyelid tumors affect all population demographics across the world. Eyelid tumor is a very broad category containing multiple different types of cancers which can be divided on the basis of tissue/cell of origin and as benign or malignant [26]. Some of the benign epithelial tumors are squamous papilloma, seborrheic keratosis, inverted follicular keratosis, etc. Basal cell carcinoma and squamous cell carcinoma are some of the malignant-type epithelial tumors [29]. Many other types of tumors exist which are categorized as eyelid tumors too.

7.4.1.1 Metastasis of Eyelid Tumors

Metastasis of eyelid tumors is very rare. Different reports have studied the occurrence of these tumors and traced it to the point of origin. Most of these reports agree that the most common primary site is breast cancer [30, 31] but list other sites which too cause eyelid metastasis like the lungs [30], gastrointestinal tract, and kidneys [32]. These metastatic eyelid tumors clinically appear as cutaneous nodules and swellings. It is also noted that the upper and lower eyelid may be equally affected [33]. Eyelid metastasis seems to have problems of diagnosis associated with them such as cases where the eyelid tumor became symptomatic before the primary breast tumor was even detected [34] as reported by Ian Hood et al. and issues of misdiagnosis as a chalazion as reported by both J. Kanitakis et al. and G. W. Weinstein et al. [30, 35].

On the other hand, the spread of eyelid cancer has been researched extensively too. Retrospective studies have shown that basal cell carcinoma has very low chances to metastasize with less than 0.5% of cases showing spread [36]. The metastasis is as high as 24% in squamous cell carcinoma of the eyelid or periocular skin with very high incidence of local recurrence (35%), moderate number of regional nodal metastasis (24%), and very few distant metastasis (6%) [37].

7.4.2 Conjunctival Tumors

A thin membrane which covers the eye and the inner layer of the eyelid is called the conjunctiva. Tumors which grow on this membrane are called the conjunctival tumors. The most common of these diseases are squamous carcinoma, malignant melanoma, and lymphoma [38]. These tumors occur in older individuals who have long exposure to sunlight due to outdoor activities [39]. Important factors which seem to play a vital role in the development of this type of tumor include ultraviolet radiation exposure, vitamin A deficiency, ocular injury, exposure to petroleum products, and chronic HIV, HPV, or hepatitis B infection [40].

Conjunctival
<1%
Orbital
9%
Corneal
<1%
Intraocular
2%
Eyelid
89%
Eyelid
Intraocular
Corneal
Orbital
Conjunctival
Metastases
3%
Recurrences
14%
Deaths
11%
Cured
72%
Cured
Deaths
Recurrences
Metastases
Percentages of Cancer
18.00%
16.00%
14.00%
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
15.39%
12.94%
9.91%
0.20%
Breast Cancer
Lung Cancer
Prostate Cancer
Eye Cancer
Cancer percentages compared to total number of cancers
0.18%
0.16%
0.14%
0.12%
0.10%
0.08%
0.06%
0.04%
0.02%
0.00%
0.17%
0.02%
0.004%
0.0006%
Eyelid
Orbital
Intraocular
Corneal and Conjunctival

7.4.3 Corneal Tumors

The sclera and cornea are important barriers which prevent spread of neoplasms to other parts of the body. It is very rare for corneal tumors to arise [41, 42]. Even among the corneal tumor types, epithelial tumors are more common than corneal stromal tumors [43]. These tumors, though rare, are of two types, the congenital and the acquired lesions. Acquired lesions are further subdivided based on the origin of the mass like epithelial, vascular, fibrous, neural, etc. [44]. Exposure to ultraviolet radiation causes growth of carcinoma in the eyelids and neoplasms [45, 46] on the corneal region and is considered the primary cause for acquired lesions.

7.4.3.1 Metastasis of Conjunctival and Corneal Tumors

Metastatic tumors rarely occur in the conjunctiva [43]. Primary sites which cause metastatic conjunctival tumors are again mainly the breast and lung cancer appearing over a very wide window ranging from 8 to 100 months [47]. In cases of advanced stage of organ metastasis, conjunctival masses appear. A study carried out by C. L. Shields showed that the conjunctival primary-acquired melanosis or nevus has lower risk of death and metastasis than de novo melanoma [48].

Conjunctival malignant melanoma is a fatal tumor with recurrence rates at 35%, metastasis reported in 25% patients, and nearly 15% deaths [49]. The same study used the Kaplan-Meier survival estimates, and at 10- and 15-year follow-ups, recurrence rose to 51% and 65%, respectively. The patients who did develop metastasis showed growth in the facial lymph nodes, lungs, brain, and liver. Other research which studied the conjunctival squamous cell carcinoma reported deep corneal invasion, intraocular extensions, and orbital invasions [50]. Hence conjunctival tumors show aggressive capabilities to metastasize.

Very few reports mention any form of corneal metastasis at all. Most studies, which do analyze corneal tumors, mention clearly that no evidence of metastasis ever surfaced in the patients.

7.4.4 Orbital Tumors

Orbital tumors are rare, and metastatic orbital tumors can spread from a variety of different sites like the breast, lung, melanoma [51], etc. Jerry A. Shields et al. have shown that reports which study the orbital tumors are biased toward the interest of the reviewer. For example, neural tumors like meningioma and optic pathway glioma will appear under neurosurgical study. On the other hand, reports from otolaryngology will include mucocele, paranasal sinus neoplasms, and other secondary lesions [52]. Even orbital bone cancer, which constitute between 0.5% and 2.0% of total orbital cancer, is studied under orbital tumors [53]. In this chapter, we shall focus mainly on those tumors which affect the stem cell present in the orbit.

Orbital tumors are a heterogeneous group of neoplasms [54, 55] including cystic lesions, neural tumors, histiocytic tumors, bone and cartilage tumors, etc. and hence

require diagnosis based on clinical analysis, imaging, and other studies before the suitable treatment is administered.

7.4.4.1 Metastasis of Orbital Tumors

Orbital metastasis occurs mainly due to primary growth in the breasts, lungs, gastrointestinal tract, and prostate [30, 56, 57] with nearly 45% of orbital tumor cases presenting signs of systemic cancer. The orbital tumor conditions in children are shown to be very different by a case study done by Daniel M. Albert et al. They found that children with orbital tumor metastasis were either suffering from neuroblastoma or Ewing sarcoma which affects bones and had no occurrence of intraocular metastasis from a solid tumor [58]. The findings were very different in adults, who frequently had cases of intraocular metastasis [59, 60].

The metastasis of orbital tumors is well documented by multiple studies. Robert A. Goldberg et al. found that in around 25% patients, the onset of ocular cancer is the manifestation of systemic disease and displacement of the eyeball due to change in its volume (enophthalmos) was frequently seen in patients [51]. A study done by Gunalp et al. showed that the average detection time for secondary site was shortest for lung cancer (2 months) and longest for breast cancer (34 months) making follow-up checks extremely important for these patients [61]. In senior adult population, orbital tumors were malignant in up to 65% of the cases with 25% developing systemic problems.

7.4.5 Intraocular Tumors

Intraocular melanoma is a malignant form of cancer which happens in the tissues of the eye. These occur in the wall of the eye. The wall comprises of three parts, the sclera (outer layer), the uvea (middle layer), and the retina (inner layer).

The uveal tract is divided into three parts too, the iris, ciliary body, and choroid. Iris melanoma is generally a small neoplasm and hardly ever spreads. These are very rare with occurrences as low as 3% of all uveal melanomas, and reports show that an elevated intraocular pressure influences the iris melanomas [62]. The ciliary body gives rise to neoplasms which are larger and more capable of spreading, while the choroidal neoplasms are the largest and most likely to spread [63, 64].

Retinal neoplasms are of different types. The most common of these is retinoblastoma, an aggressive childhood affliction with occurrence 1 per 15,000 to 20,000 children [64, 65]. Other retinal cancers exist like vasoproliferative retinal tumor which typically manifests at ages 20 to 25 [66] and retinal hemangioblastoma which is usually detected between ages 40 and 60 [67]. Exposure to sunlight and ultraviolet rays seem to be the primary reason for the cause of these intraocular malignant melanomas [68].

7.4.5.1 Metastasis of Intraocular Tumors

Intraocular tumors usually arise in the uveal tract and the choroid due to their high vascularity, making uveal and choroidal neoplasms the most common malignancy in

adults. Patients with this kind of posterior choroidal metastasis have low life expectancy, but over the last few decades life expectancy has progressively improved [59, 60]. Primary cancers which lead to choroidal metastasis are mainly breast (40–47%) and lung (21–29%) cancer [59, 69, 70] which cover two third of reported cases. The remaining one third of patients shows no sign of primary cancer at the time of diagnosis [70].

As for spread of intraocular tumors, 45% of patients develop metastasis in the liver, often many years later. Most cases show the liver growth within 5 years, but frequently the cases arise 20 years after the initial diagnosis [71]. The progress of this metastasis is rapid, and hence this remains the most common cause for death in patients with uveal melanoma [60, 71]. In cases of retinoblastoma, if the patient shows optic nerve invasion, then metastasis is expected. If invasion is beyond the lamina cribrosa layer, there is a far greater risk of metastasis [72, 73].

7.5 Regulation of Stem Cells and Cancer Stem Cells

Normal stem cells and cancer stem cells have the self-renewal capability with many common classical pathways regulating the stem cell and cancer stem cell development [10]. Signaling pathways such as Notch, Sonic hedgehog, and Wnt associated with tumor regulation and development are also associated with normal stem cell regulation [74]. These signaling pathways when dysregulated result in tumorigenesis. The CSC attracts the normal stem cells through cytokine secretion, further enhancing the cancer cell metastatic movement and risk of tumor formation [75].

Signaling pathway	Normal stem cell/progenitor cells—pathway regulated	Cancer stem cells—pathway dysregulated
Wnt	Development of epidermal and other tissue	Epidermal tumors
Sonic hedgehog	Neural development	Basal cell carcinoma
Notch	Neural development	

7.6 Conclusions

Compared to other cancers in the rest of the organs, cancers related to the eye are at lower percentage, and the metastasis both intraocular and spread to other organs is at lower percentage. While melanomas constitute melanomas among eye cancers, other cancers such as retinoblastoma, eye lid cancers, and choroidal cancers are also frequently observed. The presence of cancer-specific stem cells among eye cancers as of now reported is very few except for the retinoblastoma, melanoma, and squamous carcinoma. While common markers CD44, CD133, and SOX2 and other cancer stem cell-specific markers are reported, further studies are needed to

propose the aggression of tumors and the ambivalence of the currently established markers in tumor progression in eye cancers.

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