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Applications of stem cell biology to oculoplastic surgery

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Abstract

Purpose of review—This review examines the utility of stem cell biology in ophthalmology and oculoplastic surgery.

Recent findings—The applicability of stem cell biology varies across a range of different subfields within ophthalmology and oculoplastic surgery. Resident stem cells have been identified in the lacrimal gland, corneal limbus, orbital fat, and muscles of the eye, and can potentially be applied for *in vitro* cell and organ cultures with the intent of disease modeling and transplants. The discovery of adipocyte derived stem cells (ADSCs) offered a potentially powerful tool for a variety of oculoplastic applications, such as wound healing, skin rejuvenation, and burn therapeutics. Several groups are currently identifying new uses for stem cells in oculoplastic surgery.

Summary—The need for stem cell treatment spans a wide array of subfields within ophthalmology, ranging from reconstruction of the eyelid to the generation of artificial lacrimal glands and oncological therapeutics. The advent of induced pluripotent stem cells (iPSCs) opened the realm of regenerative medicine, making the modeling of patient-specific diseases a possibility. The identification and characterization of endogenous stem cell populations in the eye makes it possible to obtain specific tissues through iPSC differentiation, permitting their use in transplants for oculoplastic surgery.

Keywords

Stem cells; oculoplastic surgery; translational medicine; regeneration; regenerative medicine

INTRODUCTION

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are both pluripotent cells that can self-renew and differentiate into multiple lineages. Clinical applicability of these cells ranges from *in vitro* disease modeling using patient-specific

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Conflicts of interest

None

iPSCs to cell replacement therapy for diseased or damaged cells, such as in defects in hematopoiesis [1]. The ability to generate iPSCs through overexpression of a minimal set of transcription factors (TFs) instigated a paradigm shift in stem cell biology, and established the field of regenerative medicine [2, 3]. Since the advent of this technology, the field has developed to the point where ocular tissues can also be repaired or replaced by either patient-specific stem cells or differentiation products from these cells. This technology provides the benefits of cell sources that can be replenished, cell products that do not cause immunological complications, and platforms to study diseases *in vitro* [4]. Though they possess their own limitations, such as differentiation protocols producing cells not 100% identical to target *in vivo* cells and low efficiency of cell generation, the evolution of this field and its application to the clinic can revolutionize general and personalized medicine.

In the context of ophthalmology, stem cell biology and stem cell treatment (SCT) benefits from ease of access in the eye, as its immune-privileged status allows injection of stem cells into the eye within the extracellular matrix microenvironments [5]. Different fields of ophthalmology, such as cornea, retina, and glaucoma, have all benefited from the application of stem cell biology. To this end, corneal epithelial cell transplantation is the second most common type of SCT, behind bone marrow transplant [6]. Corneal epithelial stem cells reside in the basal limbal epithelium, and damage to these populations (as in chemical burns) can result in corneal conjunctivalization [7]. Transplantation of corneal limbal stem cells that are expanded *ex vivo* shows great promise in treatment of cornea associated disorders, and tissue engineering with human ESCs to generate corneal epithelial-like cells is also progressing [8, 9]. In the retina, diseases include macular degeneration, retinopathy and optic neuropathy which causes damage to the retinal ganglion and amacrine cells [10]. Success has primarily been seen only through mouse models, showing promising outcomes. The extent of these results, however, remains unclear [11]. SCT has the potential to be applied to glaucoma treatment as a method to replace lost retinal ganglion or trabecular meshwork cells, or to protect these damaged cells by secreting neurotrophic factors [12, 13]. As the field of iPSC biology and direct cell conversion develops, we will see an increased focus on patient-specific care, and new treatments for various disorders in ophthalmology.

While translational development in ophthalmology has recently erupted through the use of stem cell biology, there is great potential for application of this new field of regenerative medicine to oculoplastic surgery. This encompasses a variety of subfields such as reconstruction of the eyelid, lacrimal gland development, repair of tissue after tumor resection, and cosmetic surgery (Fig. 1). Patient-specific stem cells may possibly provide: 1) a model system for diseases that afflict these structures, 2) sources for cell replacement therapy, and 3) platforms to generate 3D organ systems for whole organ replacement therapy. As with other studies, this application of stem cell biology to oculoplastics is still in its infancy, but with time will become a key tool in personalized and regenerative medicine.

TEXT OF REVIEW

Lacrimal gland

The lacrimal gland plays a crucial role in maintaining the healthy ocular surface through tear secretion. One of the most prevalent eye disorders, dry eye disease, occurs due to lacrimal

gland dysfunction and reduces quality of life because of ocular discomfort and visual disturbance due to the ocular surface epithelial damage [14]. In a developmental context, the lacrimal gland forms similarly to other ectodermal organs such as teeth and hair follicles by reciprocal epithelial and mesenchymal interactions [15]. A thorough understanding of developmental biology and the way different tissues form within these organs is crucial for fully applying stem cell biology for therapeutic intervention. Furthermore, understanding the composition of cells within the tissue can aid us in understanding the mechanisms behind its function or its repair.

It is known that the lacrimal gland contains resident tissue stem cells, which express nestin and Ki67, that repair damaged murine-lacrimal glands following interleukin-1 induced inflammation [16, 17]. These cells can be responsible for restoring the tissue after cell loss, or maintaining the tissue throughout aging. Potential candidates of these resident stem cells have been identified in human lacrimal glands, expressing c-kit, ABCG2, and ALDH1 [18]. Understanding the role of these resident stem cells could reveal mechanisms involved in generation of this tissue, and how the various cell types within the organ arise and function. Some success in studying this tissue has been found *in vitro* with the establishment of functional human lacrimal gland cultures [18]. Bioengineered lacrimal gland organs reconstituted with epithelial and mesenchymal cells from the lacrimal gland of an E16.5 mouse successfully adopted the morphology of lacrimal glands *in vitro* [19, 20]. Growing these cells in culture can provide platforms for studying disease mechanisms, as well as opportunities for organ generation and replacement.

To apply this information regarding lacrimal gland stem cells to oculoplastic surgery, somatic cells from patients suffering from lacrimal gland disorders such as dry eye disease could be reprogrammed to iPSCs, and then differentiated to the lacrimal gland stem cells and/or the damaged cells of the lacrimal gland. These cells could then be corrected and transplanted into the patient's lacrimal gland in an attempt to restore its function. Furthermore, similar to the bioengineered lacrimal gland, iPSCs offer a patient-specific context to study disease mechanisms *in vitro*, and the chance to generate personalized tissue transplants. Further understanding of the developmental biology driving lacrimal gland generation will support iPSC differentiation and SCT.

Oncology

Cancers of the eye and surrounding orbital area is a frequent issue to confront. Multiple different cancers can arise in this area, such as conjunctival squamous cell carcinoma (SCC) [21], basal cell carcinoma (BCC) on the eyelids and periocular skin [22] and sebaceous gland carcinoma on the eyelid [23]. These cancers of the periocular region account for 5 – 10% of all newly documented cases of skin malignancies [24]. Surgery remains the best treatment modality for these periocular tumors, but several reasons may prevent this from being the best choice of action [25]. Therefore, multiple non-surgical treatments have been used for these cases, including radiotherapy, cryotherapy, 5-fluorouracil, imiquimod, photodynamic therapy, and hedgehog signaling inhibitors [26].

If surgical means are chosen for resection of the periocular tumors, defects must be repaired. This responsibility subsequently falls upon the reconstructive surgeon, who must repair the

eyelid so that it can fully protect the ocular surface and be cosmetically acceptable. The eyelid is composed of an anterior and posterior lamella, with the medial and lateral canthal tendons providing support for the eyelids [27]. Surgeries that result in small defects can be allowed to heal through granulation or direct closure, but large resections require reconstruction of the lamellae with either a flap or a graft.

Stem cell biology can be applied to ocular oncology in various ways. Regarding tumor resection, patient-specific cells can be used to generate autologous grafts for transplants without the concern of rejection. This concept is applied to other areas of reconstruction in the “Reconstruction” section of this review. The study of stem cells in the development of ocular cancer remains ongoing, such as in uveal melanoma. Researchers are interested in the mechanisms behind dormant stem cell activation and aberrant proliferation in these melanomas [28]. Other studies have identified the expression of cancer stem cell related markers, including CD44, CD133, and ABCG2, in orbital adenoid cystic carcinoma (ACC) [29]. It was found that expression of these markers can influence the progress of ACC, but this does not help in evaluating cancer prognosis.

Reconstruction

For reconstructive or aesthetic applications, the use of adipose derived stem cells (ADSCs) has recently begun to develop due to their ample supply and their ease of procurement and ability to differentiate to several different cell types [30]. Adipose taken from the majority of the body is derived from the mesenchyme, but it has been found that orbital adipose derives from the neural crest [31]. These cells contain neuronal markers, and it has been postulated that the origin of these cells can prime them for use in ocular surface reconstruction, retinal dystrophies, and other disorders of the eye.

Periocular reconstruction, including the tarsus and the conjunctiva, can be challenging due to the limitation of these tissues. Grafting of these tissues could thus lead to graft versus host disease, resulting in donor site morbidity. For grafting, surgeons have relied on either human acellular dermis or bioengineered materials with porcine dermal collagen [32]. These materials, however, have various restraints, such as a limited range of function or increased fibrosis of the grafts. Patient-specific tissues generated either from ADSCs or somatic cells via reprogramming to iPSCs (fibroblasts, adipose, etc) would be used for transplants and avoid all of these potential issues.

In the context of reconstruction, stem cell biology can be applied for the events that result in poor wound healing, such as in facial burns, infection, and advanced age [33]. ADSCs were previously found to increase rate of wound closure without scar formation [34]. To further demonstrate the utility of ADSC transplant for wound therapy, cells injected into radiation-induced wounds showed significant increase in healing [35]. To fully integrate these discoveries to the clinic, we need to establish patient-specific cells to avoid immunological complications. Using iPSCs would circumvent these issues, and allow for this area of reconstruction and wound healing to rapidly grow for treatment of patients.

Cosmetic surgery

Over the course of typical aging, the skin throughout the body can become much less elastic, as well as erratically pigmented. Several risk factors and environmental conditions can contribute to this, such as smoking and excessive sunlight. Application of stem cell biology to this subfield has already been successful, with ADSC conditioned culture media inducing dermal fibroblast migration as well as type I collagen secretion [34]. This mechanism occurs through secreted cytokines and growth factors from the ADSCs, which matches with other studies with mesenchymal stem cells (MSCs) and the effect of their secreted factors in mitigating the appearance of aged skin [36]. Subcutaneous injection of ADSCs to mouse models of UV light induced wrinkles demonstrated a thickening of the dermis and decrease of wrinkling [37]. In humans, injection of ADSCs to photoaged periorbital skin of a patient led to a subjective improvement of wrinkling, and increased dermal thickness by 10% [38].

The first application of stem cell biology in burn management began with cultured epithelial autografts (CEA) for epidermal regeneration. These CEAs contained keratinocytes and epidermal stem cells (EpSCs), and help constitute this well established therapeutic measure for burn victims [39]. Though this method can be applied early after the burn and functionally shows epithelialization, it has been criticized due expense, the time it takes to create, and concerns of immunological complications and infection. Stem cell biology with CEA could improve the setting of CEA into the wound, as the wound bed quality will affect the quality of the graft. Stem cells in the wound bed can improve neovascularization, growth factor production, and wound contraction [40].

This field can be expanded once patient-specific iPSCs become more integrated into the clinic. The ability to create patient-specific tissue grafts and/or injections for improvement of wrinkled or other affected skin would highlight the utility of stem cell biology in this context. The selection of the various stem cell sources, such as MSCs, umbilical cord blood stem cells, etc. can have a great impact on the generation of appropriate therapeutics for cosmetic surgery.

CONCLUSION

Stem cell biology has been applied to various areas of oculoplastic surgery, and has a lot of room to grow. Its use in generating tissue grafts for cell/organ replacement therapy as well as reconstruction/cosmetic surgery demonstrates its utility. The advent of iPSC technology revolutionized the field of regenerative medicine, and its application to oculoplastic surgery would mitigate the limitations of transplantable cell availability, immune complications, and provide a platform to study multiple diseases whose mechanisms remain unknown.

In the future, focus will need to be placed in the developmental mechanisms driving generation of the several tissues of interest in oculoplastic surgery, as this information will assist the creation of differentiation protocols to obtain cell types of interest from iPSCs. Difficulty remains in disease modeling of various disorders, owing to genetic and functional variation between patients as well as the complexity of several diseases. Though iPSC technology will continue to evolve, 3D organ culture still must become further developed, as diseases involving cell monolayers are significantly easier to study at present. As the field

grows, however, these questions will find answers, and personalized regenerative SCT will become a staple of modern medicine across several fields.

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REFERENCES

1. Daniel MG, Pereira CF, Lemischka IR, Moore KA. Making a Hematopoietic Stem Cell. Trends in cell biology. 2016; 26(3):202–214. [PubMed: 26526106] *This review highlights efforts that have been made to obtain hematopoietic stem cells *de novo*, and also covers the use of ESCs and iPSCs, as well as stem cell reprogramming technology, in a translational setting. Several medical fields benefit from the application of stem cell biology, ranging from hematology to ophthalmology.
2. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126(4):663–676. [PubMed: 16904174]
3. Takahashi K, Okita K, Nakagawa M, Yamanaka S. Induction of pluripotent stem cells from fibroblast cultures. Nature protocols. 2007; 2(12):3081–3089. [PubMed: 18079707]
4. Singh VK, Kalsan M, Kumar N, et al. Induced pluripotent stem cells: applications in regenerative medicine, disease modeling, and drug discovery. Frontiers in cell and developmental biology. 2015; 3:2. [PubMed: 25699255] *This paper takes a broader look at the use of iPSC technology for translational research, including *in vitro* disease modeling and generation of drug testing platforms.
5. Blenkinsop TA, Corneo B, Temple S, Stern JH. Ophthalmologic stem cell transplantation therapies. Regenerative medicine. 2012; 7(6 Suppl):32–39. [PubMed: 23210809]
6. Dhamodaran K, Subramani M, Ponnalagu M, et al. Ocular stem cells: a status update! Stem cell research & therapy. 2014; 5(2):56. [PubMed: 25158127]
7. Kruse FE. Stem cells and corneal epithelial regeneration. Eye. 1994; 8(Pt 2):170–183. [PubMed: 7958018]
8. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. Ophthalmology. 1989; 96(5):709–722. discussion 22-3. [PubMed: 2748125]
9. Brzeszczynska J, Samuel K, Greenhough S, et al. Differentiation and molecular profiling of human embryonic stem cell-derived corneal epithelial cells. International journal of molecular medicine. 2014; 33(6):1597–1606. [PubMed: 24676408] **This study provides a big leap forward in the use of iPSCs to generate a very relevant cell type to ophthalmology and oculoplastics *in vitro*. The authors followed developmental cues for their differentiation protocols, demonstrating the importance of thoroughly understanding the developmental processes involved in a particular tissue of interest when trying to generate it with iPSCs.
10. Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. Eye. 2011; 25(8):981–988. [PubMed: 21546916]
11. Li N, Li XR, Yuan JQ. Effects of bone-marrow mesenchymal stem cells transplanted into vitreous cavity of rat injured by ischemia/reperfusion. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2009; 247(4):503–514.
12. Sun Y, Williams A, Waisbourd M, et al. Stem cell therapy for glaucoma: science or snake oil? Survey of ophthalmology. 2015; 60(2):93–105. [PubMed: 25132498] *This recent review highlights the applications of stem cell biology to ophthalmology, particularly in glaucoma. This article gives a succinct overview of what has been done in stem cell biology for this specific field.
13. Wein FB, Levin LA. Current understanding of neuroprotection in glaucoma. Current opinion in ophthalmology. 2002; 13(2):61–67. [PubMed: 11880717]

14. Gadaria-Rathod N, Lee KI, Asbell PA. Emerging drugs for the treatment of dry eye disease. *Expert opinion on emerging drugs*. 2013; 18(2):121–136. [PubMed: 23621500]
15. Pispa J, Thesleff I. Mechanisms of ectodermal organogenesis. *Developmental biology*. 2003; 262(2):195–205. [PubMed: 14550785]
16. Zoukhri D. Mechanisms involved in injury and repair of the murine lacrimal gland: role of programmed cell death and mesenchymal stem cells. *The ocular surface*. 2010; 8(2):60–69. [PubMed: 20427009]
17. Kobayashi S, Kawakita T, Kawashima M, et al. Characterization of cultivated murine lacrimal gland epithelial cells. *Molecular vision*. 2012; 18:1271–1277. [PubMed: 22665974]
18. Tiwari S, Ali MJ, Balla MM, et al. Establishing human lacrimal gland cultures with secretory function. *PloS one*. 2012; 7(1):e29458. [PubMed: 22253725]
19. Hirayama M, Tsubota K, Tsuji T. Bioengineered Lacrimal Gland Organ Regeneration in Vivo. *Journal of functional biomaterials*. 2015; 6(3):634–649. [PubMed: 26264034] **This study pushes the field of bioengineering further with the successful generation of a fully functional bioengineered lacrimal gland. The authors have generated a significant advancement in this field and for the treatment of Dry Eye Disease, making novel organ replacement therapy a more feasible treatment for this disorder.
20. Hirayama M, Ogawa M, Oshima M, et al. Functional lacrimal gland regeneration by transplantation of a bioengineered organ germ. *Nature communications*. 2013; 4:2497.
21. McKelvie PA, Daniell M, McNab A, et al. Squamous cell carcinoma of the conjunctiva: a series of 26 cases. *The British journal of ophthalmology*. 2002; 86(2):168–173. [PubMed: 11815342]
22. Margo CE, Waltz K. Basal cell carcinoma of the eyelid and periocular skin. *Survey of ophthalmology*. 1993; 38(2):169–192. [PubMed: 8235999]
23. Wali UK, Al-Mujaini A. Sebaceous gland carcinoma of the eyelid. *Oman journal of ophthalmology*. 2010; 3(3):117–121. [PubMed: 21120046]
24. Cook BE Jr, Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. *Ophthalmology*. 1999; 106(4):746–750. [PubMed: 10201597]
25. Murchison AP, Walrath JD, Washington CV. Non-surgical treatments of primary, non-melanoma eyelid malignancies: a review. *Clinical & experimental ophthalmology*. 2011; 39(1):65–83. quiz 92-3. [PubMed: 21040309]
26. Rene C. Oculoplastic aspects of ocular oncology. *Eye*. 2013; 27(2):199–207. [PubMed: 23196649]
27. Subramanian N. Reconstructions of eyelid defects. *Indian journal of plastic surgery : official publication of the Association of Plastic Surgeons of India*. 2011; 44(1):5–13. [PubMed: 21713158]
28. Kalirai H, Damato BE, Coupland SE. Uveal melanoma cell lines contain stem-like cells that self-renew, produce differentiated progeny, and survive chemotherapy. *Investigative ophthalmology & visual science*. 2011; 52(11):8458–8466. [PubMed: 21896849]
29. Lin TT, Zhu LM, He YJ, Zhang H. [Analysis of expression of cancer stem cell-related markers in orbital adenoid cystic carcinoma]. [*Zhonghua yan ke za zhi*] Chinese journal of ophthalmology. 2011; 47(8):703–708. [PubMed: 22169609]
30. Tsuji W, Rubin JP, Marra KG. Adipose-derived stem cells: Implications in tissue regeneration. *World journal of stem cells*. 2014; 6(3):312–321. [PubMed: 25126381] *This review succinctly overviews the importance of adipose-derived stem cells, and how they can be expanded *in vitro* and used for the generation of several relevant cell types for tissue regeneration.
31. Korn BS, Kikkawa DO, Hicok KC. Identification and characterization of adult stem cells from human orbital adipose tissue. *Ophthalmic plastic and reconstructive surgery*. 2009; 25(1):27–32. [PubMed: 19273919]
32. McCord C, Nahai FR, Codner MA, et al. Use of porcine acellular dermal matrix (Enduragen) grafts in eyelids: a review of 69 patients and 129 eyelids. *Plastic and reconstructive surgery*. 2008; 122(4):1206–1213. [PubMed: 18827657]
33. Cherubino M, Rubin JP, Miljkovic N, et al. Adipose-derived stem cells for wound healing applications. *Annals of plastic surgery*. 2011; 66(2):210–215. [PubMed: 21200308]

34. Kim WS, Park BS, Sung JH, et al. Wound healing effect of adipose-derived stem cells: a critical role of secretory factors on human dermal fibroblasts. *Journal of dermatological science*. 2007; 48(1):15–24. [PubMed: 17643966]
35. Rigotti G, Marchi A, Galie M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plastic and reconstructive surgery*. 2007; 119(5):1409–1422. discussion 23–4. [PubMed: 17415234]
36. Kim WS, Park BS, Sung JH. Protective role of adipose-derived stem cells and their soluble factors in photoaging. *Archives of dermatological research*. 2009; 301(5):329–336. [PubMed: 19396609]
37. Kim WS, Park BS, Park SH, et al. Antiwrinkle effect of adipose-derived stem cell: activation of dermal fibroblast by secretory factors. *Journal of dermatological science*. 2009; 53(2):96–102. [PubMed: 18829265]
38. Park BS, Jang KA, Sung JH, et al. Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2008; 34(10):1323–1326.
39. Wood FM, Kolybaba ML, Allen P. The use of cultured epithelial autograft in the treatment of major burn wounds: eleven years of clinical experience. *Burns : journal of the International Society for Burn Injuries*. 2006; 32(5):538–544. [PubMed: 16777338]
40. Rasulov MF, Vasilchenkov AV, Onishchenko NA, et al. First experience of the use bone marrow mesenchymal stem cells for the treatment of a patient with deep skin burns. *Bulletin of experimental biology and medicine*. 2005; 139(1):141–144. [PubMed: 16142297]

KEY POINTS

- Stem cell biology has been applied to multiple areas of oculoplastic surgery, such as lacrimal gland generation, reconstruction, ocular oncology, and cosmetic surgery.
- Adipose derived stem cells (ADSCs) have been applied to various clinical settings, such as wound healing and skin rejuvenation.
- Continued integration of iPSC biology, ophthalmology, and oculoplastic surgery will lead to successful patient-specific disease modeling and cell/organ transplant.

Figure 1.
Overview of primary oculoplastic fields benefiting from stem cell intervention, and examples of stem cell efforts currently being made towards these fields.