

OCULAR LYMPHATICS: STATE-OF-THE-ART REVIEW

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ABSTRACT

Research involving the lymphatic system has experienced an exponential progression during the past decade largely because of advancement of modern technology and discovery of several lymphatic specific molecules. The eye provides an excellent site for lymphatic studies due to its accessible location and the unique feature of tissue heterogeneity – while some tissues are lymphatic-rich, others are lymphatic-free or -inducible. This review provides an update on our current understanding of ocular lymphatics and possible associated eye diseases.

Keywords: lymphatics, lymphatic pathway, lymphangiogenesis, eye/ocular disease

The lymphatic system was first described in the 17th century (1) at almost the same time as the blood circulation. However, compared to blood vessels which have been studied intensively in the past, lymphatics have suffered centuries of ignorance. Unlike blood vessels, lymphatics are not easily visible. Anatomically, the lymphatic network differs from that of blood circulation in that a) it is a unidirectional channel rather than a circuit; and b) lymphatic capillaries have large interendothelial gaps without tight junctions, pericytes, or a continuous basement membrane. These anatomical features have been used heavily to identify the lymphatics, particularly in earlier studies. The recent

discovery of several lymphatic endothelial molecules and the advancement of modern molecular and imaging technology have ignited intensive research with rapid progress in the field (2-7). Among these lymphatic-specific molecules are VEGFR-3 (vascular endothelial growth factor receptor-3), LYVE-1 (lymphatic vessel endothelial hyaluronan receptor-1), podoplanin (a transmembrane glycoprotein), and Prox-1 (a transcription factor) (8-11). The list of lymphatic factors and markers will continue to expand as more investigations are carried out in the field.

In parallel to the blood circulatory system, the lymphatic network penetrates most tissues in the body and plays critical roles in many functions, which include but are not limited to immune responses, cancer metastasis, fat and vitamin absorption, and body fluid regulation. Numerous diseases and conditions are therefore associated with lymphatic dysfunctions, such as inflammatory diseases, transplant rejection, diabetes, autoimmune diseases, AIDS, and lymphedema (2-4,12,13). To date, there is little effective treatment for many of these disorders, and these remain fields with continuing and increasing demand for new therapeutic protocols.

Unlike most tissues in the body which are normally endowed with lymphatic vessels, ocular tissues are by nature heterogeneous: while the conjunctiva is rich in lymphatics, the cornea and the retina are devoid of them. However, lymphangiogenesis is induced in

TABLE 1
Lymphatic Characteristics of Ocular Tissues

Category	Tissues
Lymphatic-rich	Eyelids, lacrimal glands, conjunctiva, limbus, optic nerve sheath, extraocular muscles, connective tissues of the extraocular muscle cones, choroid (avian eyes)
Lymphatic-free	Cornea, lens, iris, ciliary body, retina, choroid, sclera
Lymphatic-inducible	Cornea, iris, ciliary body
LYVE-1 ⁺ cells	Cornea, conjunctiva, limbus, iris, ciliary body, choroid, retina, sclera, extraocular muscles, optic nerve sheath

the inflamed cornea. It was also recently reported that a large population of non-endothelial LYVE-1⁺ cells resides in most ocular tissues (14,15). This tissue heterogeneity is summarized in *Table 1*.

Due to its accessible location and the unique feature of tissue heterogeneity, the eye provides an excellent site for lymphatic studies. A broad spectrum of lymphatic disorders has also been identified in the eye, whether they are local forms or ocular manifestations of systemic diseases. While some ocular tissues have been intensively studied and others are yet to be elucidated, this review provides an update on our current understanding of ocular lymphatics and possible associated eye diseases.

TISSUE HETEROGENEITY

Cornea

The cornea is the most well studied and characterized tissue in ocular lymphatic research. As the forefront medium in the passage of light to the retina, it by nature maintains transparency and is devoid of any vasculatures. The presence, longevity, and importance of lymphatic vessels in the cornea under pathological situations were questioned for a long time, but it is now known that: (a)

lymphatics are induced in the cornea after inflammatory, infectious, traumatic, chemical or toxic insults (*Fig. 1*) (14,16-24); (b) corneal lymphatics can be induced independently of blood vessels (23); and (c) the lymphatic pathway is absolutely critical for the induction of corneal transplantation immunity (4,22,25,26).

Corneal transplantation is the most common and successful form of solid-tissue transplantation in humans with a two-year survival rate of 90 percent on uninflamed (low-risk) corneas. However, this rate is greatly reduced to less than 50 percent on inflamed and vascularized (high-risk) corneas (4,27-30). Unfortunately, many patients who are blind as a result of corneal diseases fall in this high-rejection category. To date, there is no effective management of this situation. The pharmacotherapy of corneal transplant rejection has changed little over the past decades with corticosteroids of limited efficacy and fraught with side effects such as glaucoma, cataracts, and opportunistic infections.

As demonstrated in *Fig. 2*, the immune reflex arc in corneal transplantation mainly consists of the following components (i) the afferent pathway of lymphatic vessels through which antigens and antigen presenting cells migrate to the draining lymph nodes, (ii) the

lymph nodes where T cell priming occurs, and (iii) the efferent pathway of blood vessels through which the primed T cells are homed to the targeted corneal grafts. Once induced, corneal lymphatics enhance the high-volume delivery of antigens and antigen-presenting cells and accelerate inflammation and transplant rejection (4,29). Interestingly, it has been shown that surgical severing of the lymphatic pathway leads to 100 (low-risk) and 90 (high-risk) percent transplant survival in mice (25,26). However, surgical lymphadenectomy for promoting transplant survival is not practical in humans. It is therefore essential to understand the molecular mechanisms underlying this pathway - a prerequisite to discover new therapeutic targets. It is becoming increasingly evident that a variety of factors are involved in lymphatic processes and their molecular blockade promotes corneal transplant survival (22,24,31-33).

From a broader perspective point of view, the cornea provides an ideal tissue for lymphatic studies due to its accessible location, transparent nature, and lymphatic-free and -inducible characteristics. A variety of corneal models have been designed for lymphatic research including models of chemical burns, suture placement, micropocket implantation, and transplantation. It is anticipated that results from corneal studies will also shed light on our understanding of other lymphatic related diseases. The fruitfulness of using the cornea for lymphatic studies can also be predicted from the fact that during the past decades, more than one third of our basic knowledge on blood vessels is derived from studies with the cornea (personal communication, Judah Folkman).

Conjunctiva

In contrast to the cornea, normal conjunctiva is endowed with both blood and lymphatic vessels (14,34-39) which support the essential metabolic functions of the tissue as well as provision of cellular immune

effectors to the anterior compartment of the eye. Little is known about the mechanisms by which the clear vascular distinction between the two neighboring tissues is achieved and what resources are utilized to transform the cornea into a lymphatic-rich tissue when the system is challenged under patho-inflammatory conditions. Two recent studies demonstrated that normal conjunctiva is endowed with a large population of bone marrow-derived LYVE-1⁺ cells of macrophage lineage (*Fig. 3*) (14,15). Although there has been no clear evidence, it is plausible to hypothesize that these cells might contribute to corneal lymphangiogenesis during inflammation. The close link between these two systems was also indicated by a recent study demonstrating that the conjunctival lymphatics dilated during corneal inflammation after mustard gas insult (40).

Uveal Tract

Consisting of three major structures, the iris, ciliary body, and choroid, the uveal tract is normally devoid of any lymphatics in vertebrates. However, lymphatics are present in avian choroid, and they drain into the venous system (41-43). Additionally, lymphatic dilation is also found in avian models of myopia (44,45).

Distinctive from the alymphatic cornea, which is also devoid of blood vessels, the uveal tract is rich in blood supply. It also contains numerous LYVE-1⁺ cells (15,46), among which a unique population also co-express Sca-1 in the iris root, indicating that they are lymphatic progenitor cells (15). It is speculated that these cells might supply uveal lymphangiogenesis under pathological situations. Allied to this are two recent studies illustrating that lymphangiogenesis was induced in the iris after lens pricking (47) and in the ciliary body in melanomas with extraocular extension (48). However, the sources of the cells contributing to the active lymphangiogenesis were never elucidated, and clear evidence linking the

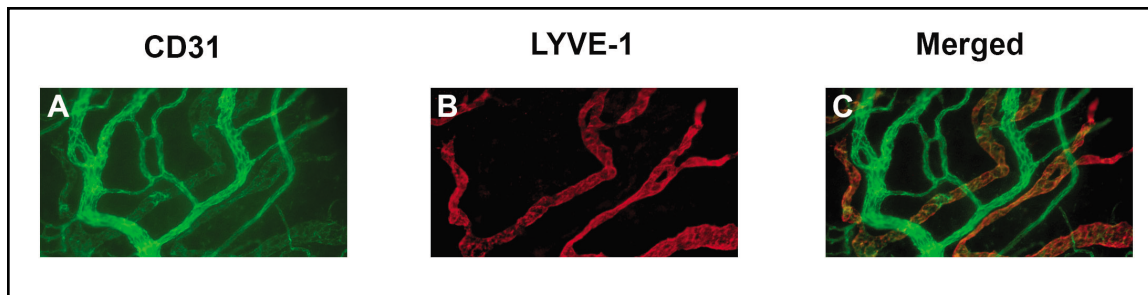


Fig. 1: Representative micrographs showing newly developed lymphatics ($LYVE-1^{high}CD31^{low}$) in the inflamed cornea. Red: LYVE-1 (a lymphatic marker); Green: CD-31 (a panendothelial marker); Merged: yellow. Original magnification: X100.

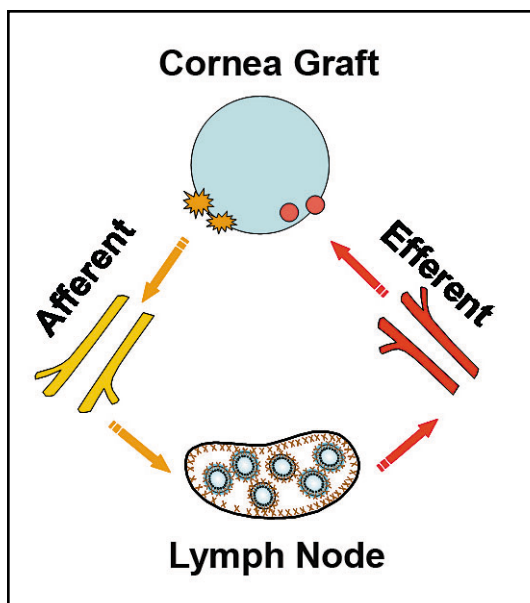


Fig. 2: Importance of lymphatic and blood vessels as entry and exit processes of the immune reflex arc involved in corneal transplant rejection. Yellow: lymphatics of the afferent pathway facilitating antigen-presenting cell trafficking; Red: blood vessels of the efferent pathway facilitating T cell infiltration to the graft.

progenitor cells in the iris root to the newly formed lymphatics is still missing.

Retina

Similar to the uveal tract, the normal retina is rich in blood vessels but absent of lymphatics. Though it was reported previ-

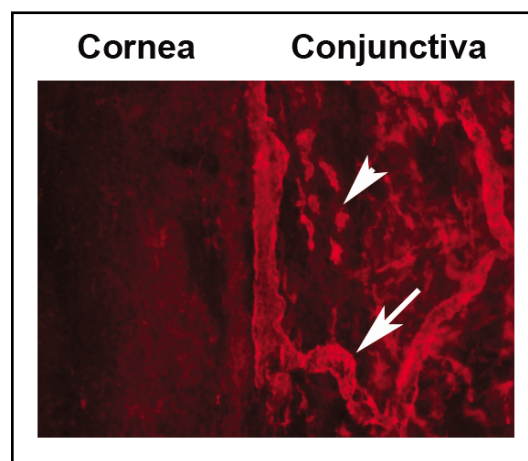


Fig. 3: Representative micrographs demonstrating the lymphatic-rich (arrow) conjunctiva and the lymphatic-free cornea. A number of LYVE-1⁺ cells (arrowhead) also exist in the limbus and conjunctiva. Original magnification: X100.

ously that cervical lymphostasis resulted in lymphostatic retinopathy (49), there has been no definite demonstration of inducible lymphangiogenesis in this tissue. It was also recently found that the retina is normally endowed with a number of LYVE-1⁺ cells (15), of which the functional roles are yet to be determined. It will be interesting to investigate whether the retina maintains a lymphatic status under all circumstances. If this turns out to be true, this tissue will provide a superb site to explore potentially powerful mechanisms of lymphatic inhibition.

TABLE 2
Clinical Phenotypes and Associated Lymphatic Findings

Clinical Presentation*	Lymphatic Abnormalities
Cancer and tumor metastasis	Lymphatic invasion (48,57-67)
Conjunctival myxoma	Lymphatic dilation (96)
Conjunctival Lymphangiectasia	Lymphatic dilation (97,98)
Chemosis	Lymphatic defects or blockade (74,99)
Mustard gas keratitis	Conjunctival lymphatic dilation (40)
Corneal inflammation	Lymphangiogenesis (14,16-22,24,55,56,100)
Transplant rejection	Lymphatic drainage (4,22,25,26,31-33)
Orbital cellulitis	Impaired lymphatic drainage (101)
Pilomatricoma	Lymphatic dilation (102)
Chalazion	Flattened lymphatics (103)
Dermatochalasis	Lymphatic dilation (103)
Blepharochalasis	Lymphatic proliferation and dilation (104)
Avian myopia	Lymphatic distension (44,45)
Harlequin and Horner syndromes	Lymphatic surgery complication (75)
Hyperthyroidism/Myxedema	Lymphatic dilation (78,83)
Lymphatic filariasis	Lymphatic dissemination (105,106)
Toxoplasmosis	Lymphatic dissemination (101,107)
Tuberculosis	Lymphatic dissemination (108)
Trichinosis	Lymphatic dissemination (101,109)
Conjunctival kaposi's sarcoma	Lymphovascular neoplasm (85,110)
Meige syndrome/Conjunctival edema	Lymphatic structural defects (77)
Milroy's disease/Eyelid and conjunctival edema	Lymphedema (111)
Lymphedema-ptosis syndrome	Lymphedema (87,95)
Lymphedema-distichiasis syndrome	Lymphatic hyperplasia (86,87,93,112,113)
Lymphedema-hypoparathyroidism syndrome	Lymphedema (87,88)
Mucke syndrome/Conjunctival edema	Lymphedema (87,92)
Chorioretinal dysplasia-lymphedema syndrome	Lymphedema (87,94)
Melkersson-Rosenthal syndrome/Eyelid edema	Lymphatic dilatation (82)
Lymphedematous rosacea/Eyelid edema	Impaired lymphatic drainage (79-81)
Turner's syndrome/Conjunctival chemosis	Lymphangiectasis (114,115)
Noonan syndrome/Ptosis and hypertelorism	Intestinal lymphangiectasia (87,89)
Persistent müllerian derivatives	Intestinal lymphangiectasia (87,90,91)
Behcet's disease	Intestinal lymphangiectasia (84)
Venous-lymphatic malformations/Lymphangiomas	Lymphatic malformation (69-73)

*Local forms or systemic diseases with ocular manifestations.

Others

The long held notion that lymphatics are present in ocular tissues of the eyelids, lacrimal glands, optic nerve sheath, and extraocular muscles was also confirmed by modern technology (15,35,37,38,50-54). Not

surprisingly, LYVE-1⁺ cells also populate these sites (15). However, whether these cells function to contribute to active lymphangiogenesis is still a mystery.

LYMPHATIC ASSOCIATED EYE DISORDERS

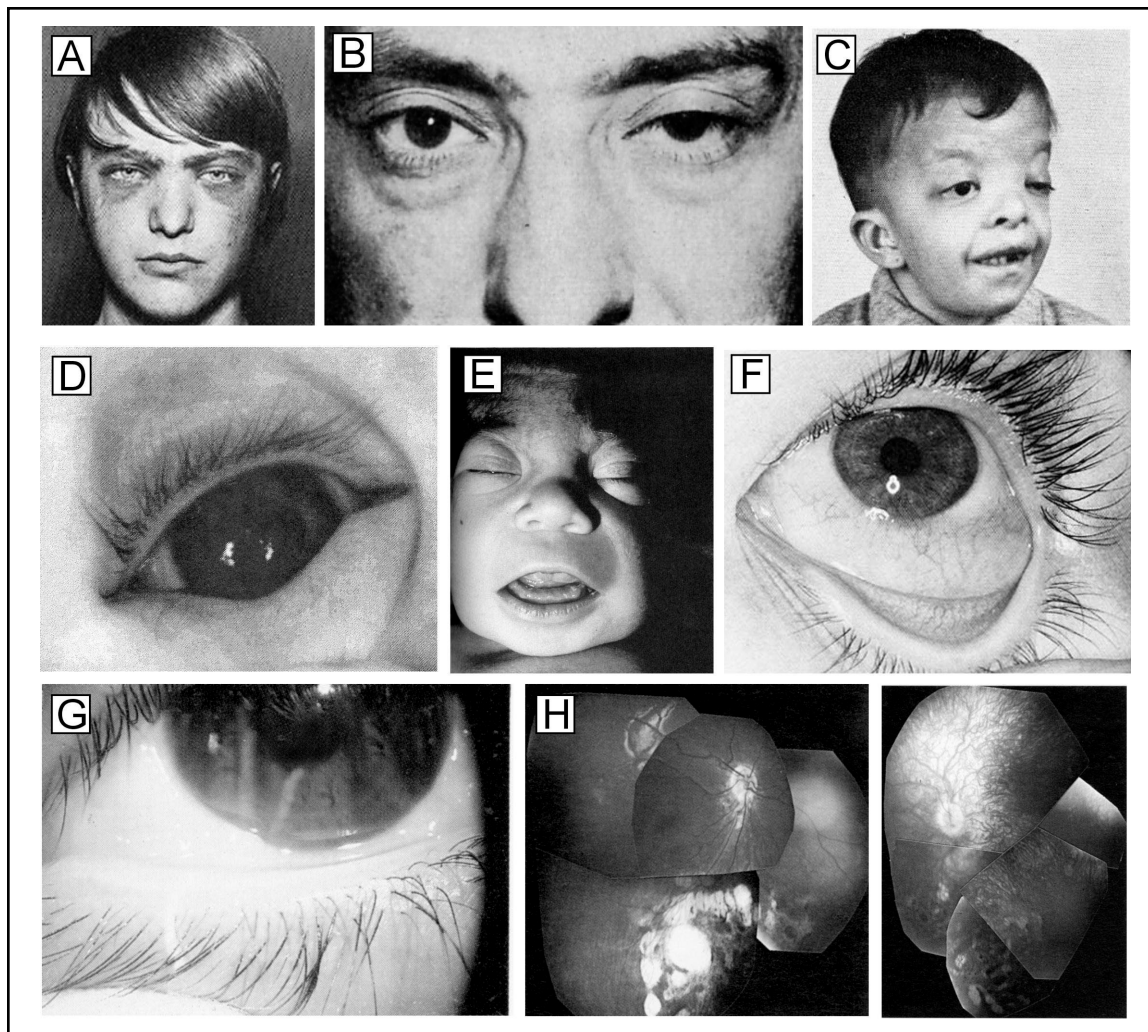


Fig. 4. Ocular abnormalities in hereditary lymphedema syndromes. **A.** Ptosis, conjunctival edema, and medial eyebrow flare in Lymphedema-hypoparathyroidism syndrome. **B.** Unilateral ptosis in Lymphedema-ptosis syndrome. **C.** Ptosis and hypertelorism in Noonan syndrome with intestinal lymphangiectasia. **D.** Ectropion uveae and **E.** Bilateral subepicanthal folds with facial edema in Persistent mullerian derivatives with intestinal lymphangiectasia. **F.** Conjunctival edema and chemosis in Mucke syndrome. **G.** Distichiasis and chemosis in Lymphedema-distichiasis syndrome. **H.** Punched-out lesions in the retina of siblings with Chorioretinal dysplasia-lymphedema syndrome. Composite reproduced with permission from Northup et. al., *Lymphology* (87) with original permissions and citations.

Vision is the most vulnerable of our five senses. A wide array of ocular disorders have been identified to be associated with lymphatic dysfunction. Among them are inflammatory diseases (4,16-21,24,55,56), tumor and cancer metastasis (48,57-67), transplant rejection (22,25,26,31,32,68), venous lymphatic malformations (69-73),

surgical complications (74-76), and ocular manifestations of numerous systemic diseases (77-95). These clinical phenotypes and their lymphatic abnormalities are summarized in *Table 2*. Several examples of ocular abnormalities in hereditary lymphedema syndromes are also illustrated in *Fig. 4* (87).

Not included in *Table 2* are several other phenotypes for which the lymphatic association is neither conclusive nor fully understood. For example, we recently discovered a distinctive LYVE-1⁺ cellular network in the hyaloid vascular system (HVS), a transient structure nourishing the embryonic lens and the primary vitreous of developing eyes (96). It is known that failure of HVS regression leads to several serious blinding ocular pathologies such as persistent hyperplastic tunica vasculosa lentis (PHTVL), persistent hyperplastic primary vitreous (PHPV), and persistent prepupillary membrane (PPM) (97). Glaucoma represents another example of ambiguity: while one study failed to detect the similarity between lymphatics and aqueous drainage channels (98), another concluded that the inner wall of the Schlemm's canal shared endothelial characteristics of initial lymphatics (99). Allied to this latter study were results from several earlier studies demonstrating that (i) months after trabeculectomy, lymphatic vessels were identified in the newly formed transscleral channel (100); and (ii) the lymphatic drainage partnered with the veins to enable aqueous humour outflow after filtering operations (101,102). In the case of sympathetic ophthalmia, there has been no clear-cut evidence on its lymphatic association. However, it was indicated that the exposure of ocular antigens to subconjunctival lymphatics might play an important role in its pathogenesis (103,104).

CONCLUSIONS

Great progress has been achieved in ocular lymphatic research during the past few years. However, our knowledge differs greatly among ocular tissues and is still rather limited in many areas. With improvements in technology, increased knowledge, and joint efforts from diverse disciplines, we expect to witness many exciting discoveries in the near future.

Given its unique feature of tissue

heterogeneity and the vast arrays of study models that can be derived from it, the eye will continue to serve as an excellent site for lymphatic research. It is anticipated that beyond its contributions to ocular diseases, research on the eye, a window to the body, will additionally shed light for the discovery of new therapeutic protocols for other lymphatic related diseases.

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