PREFACE

Detection and responses to light are common features found throughout the plant and animal kingdoms. In most primitive life forms, a patch of light-sensitive cells make up a region containing a cell sheet devoid of any specialized anatomical structure. With the development of the eyes in more advanced life forms, light-sensing structures became more complex but primitive eyes are still in contiguity with other body tissues and fluids. The evolution of the eyeball promoted an increase in visual acuity and visual processing that, in turn, allowed vision to become the dominant sensory system for many species, including humans. The formation of a totally enclosed structure, however, required a unique set of solutions to enable the eye to control its environment.

Like most organs, the eye evolved a series of homeostatic mechanisms to regulate its environment within tightly controlled limits. Unlike most organs, however, this advanced light-sensing structure has a series of requirements that place a tremendous burden on molecules that are responsible for controlling ocular homeostasis. There are many signaling molecules and pathways that work in parallel or through crosstalk to maintain the normal ocular environment required for visual function. Perhaps none are so critical as the group of membrane molecules that are collectively termed transporters. These molecules are responsible for the controlled and selective movements of ions, nutrients, and fluid across various ocular layers necessary to optimize the internal milieu to preserve visual function.

One of the most critical functions of the eye is to maintain a clear optical path to the retina. The cornea is composed of just two cell types with a stromal layer between them. This delicate structure acts as a barrier to the external environment without the advantage of a protective layer of skin. It must also remain transparent and maintain the right level of curvature to allow refraction of light. Maintaining the correct hydration of the stroma requires coordinated ion and water transport by both the corneal epithelium and corneal endothelium. In many tissues, transport involves regulated movement of molecules from adjacent blood vessels. The cornea must maintain its structure in the absence of any blood supply. In the first three chapters of this volume, the authors explore these transport mechanisms and the ways in which they not only control corneal volume and transparency, but promote epithelial renewal, endothelial migration, and wound healing.

A second structure that must maintain optical clarity over many decades is the lens. Lens epithelial cells undergo a complex terminal differentiation into fiber cells that involves extensive elongation, loss of nuclei and other organelles, and expression of large quantities of specific lens proteins, including the crystallins. Maintenance of this complex tissue organization depends on tightly controlled levels of hydration and carefully controlled fluxes of ions. The roles of specific lens transporters in normal lens physiology, and in the development of cataracts, are discussed in several chapters of this volume.

Because the cornea and lens are avascular structures, they depend on fluid and nutrients transported across the ciliary epithelium. Materials flow from the ciliary processes,

into the posterior chamber, forward into the anterior chamber via the pupil, and finally out through the trabecular meshwork. There is a dynamic balance between the inflow and the outflow of this fluid pathway and the difference gives rise to an intraocular pressure of approximately 15 mm Hg. Too little pressure and the optical path can be compromised; too much pressure and a pathological cascade can be activated leading to glaucoma.

Unlike the cornea and lens, the retina, a thin sheet of CNS tissue that lines the back of the eye, is highly vascularized. Indeed, unlike most regions of the CNS, the retina receives two separate blood supplies. The inner retina of most mammals contains a capillary network that arises from vessels entering the eye through the optic nerve. These vessels spread over the inner surface of the retina and then ramify this stratified structure at the level of the outer plexiform layer. The vasculature and associated glia form a blood-retinal barrier that is similar to the barrier found elsewhere in the CNS. The photoreceptor layer of the retina has an alternative source for oxygen and nutrients, the choroidal blood supply at the back of the eye that allows free passage of molecules across the fenestrated capillaries. Before reaching the retina, molecules have to traverse the retinal pigment epithelium (RPE). The tight junctions between the RPE cells form the second type of blood-retinal barrier. Because of this barrier the RPE cells play a critical role in providing glucose and other nutrients to the retina, removing retinal waste products, regenerating visual pigments as part of the visual cycle, and generally regulating the extracellular environment of the retina. Many of the transporters and channels expressed by the RPE cells show a remarkable asymmetric distribution between the apical and basal surfaces. This results in an ability to separately control the subretinal and choroidal extracellular spaces. It also results in vectorial transport of many molecules into and away from the retina. A group of five chapters in this volume discusses a wide array of RPE transporters and their functions. It is clear that the catalog of molecules is not complete and that there is much to find out about the molecules already identified. For example, we are only beginning to understand the many ways in which circulating molecules, trophic factors, and neuromodulators can affect transport of particular molecules across the RPE.

As with other neural tissues, the function of neurons that comprise the retina requires tight control of levels of ion and neurotransmitters surrounding synaptic terminals. Ion exchangers are important molecules in maintaining synaptic terminal ion gradients, which are essential for normal function. Removal of neurotransmitters from the synaptic cleft regulates the magnitude and time course of synaptic transmission. The transporters that carry out this removal are important molecules that can shape synaptic responses.

One measure of the importance of transporters in the eye is the range of pathological changes seen when these molecules are mutated or dysfunctional. One of the best examples of such dysfunction is found in mutations of the ABCA4 transporter, which can lead to some forms of Stargardt's disease and retinal degenerations. Altered glutamate transport is also associated with various retinal pathologies, a topic discussed in detail in two chapters of this volume.

Ocular transporters are also important targets for drug therapy to the eye and good conduits for drug delivery, a topic explored in three chapters in this volume. Because of its unique properties, the eye is a well-studied experimental model to understand how

drugs penetrate tissues and how enzymatic alterations can affect their bioavailability. It is rapidly becoming a popular model to explore new avenues to deliver drugs by nanotechnology. Drugs such as Timolol™ and its derivatives are potent agents that regulate intraocular pressure and aqueous flow. Delivered as eyedrops, such drugs must diffuse across ocular tissues and work against the direction of ocular fluid flow. Although the exact mechanism of action of the adrenergic drugs at the ciliary epithelium remains poorly understood, they have proved to be effective agents for treatment of many forms of glaucoma. There is less progress in devising ways to deliver drugs to the back of the eye to treat retinal diseases. Given the numbers of patients worldwide suffering from macular degeneration, glaucoma, and diabetic retinopathy, easy and effective delivery systems are urgently needed. A better understanding of ocular transport would certainly facilitate the development of better drug delivery systems to the eye.

Molecules involved in the transport of fluid, ions, micronutrients, metals, and neurotransmitters have been studied for many decades. It is only in the last few year, however, that we have identified the structure of some of these molecules and have only now begun to understand their structure–function relationships. Most of the discussions on transporters have previously been restricted to a specific type of molecule or cell. It is our hope in putting together this volume that researchers working on the front of the eye will read about work going on in the back of the eye, and vice versa. We also hope that clinicians and pharmacologists will also benefit from the excellent reviews in this text by those who have worked diligently in the field to provide information that shows how altering transport of molecules in one part of the eye might affect the physiology of other ocular structures. As molecular, pharmacological, and genetic approaches establish the importance of ocular transporters in physiological and pathological functions, we may have better insight into their regulation and potential for exploitation in delivering therapeutics to the eye.

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