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Review

Iron homeostasis and eye disease

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ABSTRACT

Background: Iron is necessary for life, but excess iron can be toxic to tissues. Iron is thought to damage tissues primarily by generating oxygen free radicals through the Fenton reaction.
Methods: We present an overview of the evidence supporting iron's potential contribution to a broad range of eye disease using an anatomical approach.
Results: Iron can be visualized in the cornea as iron lines in the normal aging cornea as well as in diseases like keratoconus and pterygium. In the lens, we present the evidence for the role of oxidative damage in cataractogenesis. Also, we review the evidence that iron may play a role in the pathogenesis of the retinal disease age-related macular degeneration. Although currently there is no direct link between excess iron and development of optic neuropathies, ferrous iron's ability to form highly reactive oxygen species may play a role in optic nerve pathology. Lastly, we discuss recent advances in prevention and therapeutics for eye disease with antioxidants and iron chelators.
General significance: Iron homeostasis is important for ocular health.

1. Iron metabolism in humans

Iron is an essential component of cellular metabolism; however, excess iron can be damaging to tissues. Dietary iron is absorbed through the small intestine and is lost in sweat, shed skin and intestinal cells, and menstruation. However, the body is unable to actively excrete excess iron [1]. As a result, iron stores in certain tissues increase with age. It is thought that excess iron may be toxic due to the release of reactive oxygen species via the Fenton reaction. In this reaction, ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}) by hydrogen peroxide (H_20_2) producing an hydroxyl ion ($OH-$) and the dangerous hydroxyl radical ($OH^{\cdot}$). The hydroxyl radical is very reactive and can cause oxidative damage to lipids, DNA, and proteins. It is hypothesized that iron may contribute to the pathogenesis of ocular diseases through oxidative damage [2].

In order to understand the evidence linking iron metabolism to ophthalmologic diseases, it is important to review the proteins involved in iron homeostasis. Both He et al. [3] and Wong et al. [2] describe iron homeostasis in detail in their reviews of iron toxicity and the retina. The following is a summary of relevant aspects of iron homeostasis. Dietary iron is reduced from the ferric to the ferrous state in the lumen of the duodenum and proximal jejunum. The free ferrous iron is transported across the luminal surface into the enterocytes by a proton symporter, divalent metal transporter-1 (DMT1). Mice with a mutated Nramp-2/DMT1 gene have decreased iron absorption across the gut and severe microcytic anemia [4]. In order for iron to reach the bloodstream, it is transported across the basolateral membrane of the enterocyte by the transporter protein, ferroportin (Fpn). Ferroportin is also expressed in many other tissues including placenta, tissue macrophages in the liver, lung, brain and retina [5–9]. Ferroportin works in conjunction with ferroxidases ceruloplasmin (Cp) and hephaestin (Heph) that oxidize ferrous iron to its ferric state facilitating iron export. Additionally, a recently-discovered serum peptide called hepcidin regulates iron absorption [10] by triggering degradation of ferroportin. Hepcidin knockout mice have severe iron overload [11] and mice overexpressing hepcidin have iron deficiency [12]. Ultimately, once iron is absorbed by the enterocytes and exported from the cells, the majority of the non-heme iron in the circulation is bound to the serum protein transferrin.

The circulating iron is carried by transferrin, but requires a special mechanism to cross the blood–brain barrier (BBB) since transferrin alone cannot cross. Transferrin carrying two molecules of iron binds to a transferrin receptor on a cell of the BBB. After endocytosis, the ferric iron is released from transferrin within acidified endosomes [3]. Transferrin and transferrin receptor complex are then returned to the cell surface.

The intracellular iron can be stored by ferritin, a 450 kDa multimeric protein complex capable of carrying approximately 4500 ferric iron atoms [13]. Ferritin exists as a combination of heavy, or H-ferritin (21 kDa), and light, or L-ferritin (19.5 kDa) polypeptides. In addition to size, H-ferritin differs from L-ferritin in that it contains a ferroxidase allowing it to rapidly convert ferrous iron to ferric iron. Interestingly, it has been shown that increased expression of H-ferritin in lens epithelial cells decreases the amount of intracellular free iron and improves cellular defenses against oxidative stress [14].

Balanced iron homeostasis is necessary to provide adequate iron for cellular functions and simultaneously avoid the toxicities from

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excess iron. As a result, iron-handling proteins are exquisitely responsive to vacillating iron levels. This iron-responsive mechanism is mediated by iron regulatory proteins (IRPs) that control the levels of the iron related proteins. This is accomplished by IRP binding to iron-responsive elements (IREs) on mRNAs when intracellular labile iron levels are low. For example, a state of relative iron deficiency would require decreased expression of iron storage proteins like ferritin and increased expression of transferrin receptor to augment uptake. To accomplish this, the IRPs bind to the IRE on the 5′ end of ferritin mRNA and obstruct translation; however, in the case of transferrin regulation in iron deficiency, the IRP binds to the IRE on the 3′ end of transferrin receptor mRNA protecting the mRNA from degradation leading to increased protein levels [3]. Also, the various iron-handling proteins are differentially regulated depending on their location in different cell types. For example, iron depletion results in downregulation of ferroportin in the liver, but increased production in the duodenum [5].

In sum, iron is necessary for cellular metabolism, but excess iron can be toxic through the formation of oxygen free radicals. Iron levels are delicately regulated and perturbation of iron homeostasis has been implicated as a potential cause of eye disease. Following an overview of basic ocular anatomy, this paper will explore the evidence for iron's potential role in the development of eye diseases.

2. Anatomy of the eye

The anatomy of the eye is organized to optimize its functions: refract light and serve as a portal to the nervous system. In this section the anatomy of the eye will be explored following the path of light: cornea, iris, lens, retina, optic nerve. Similarly, our discussion of iron's potential role in the development of eye disease will be organized anatomically beginning with disease of the cornea, followed by the lens and retina, and, lastly, the optic nerve (Fig. 1).

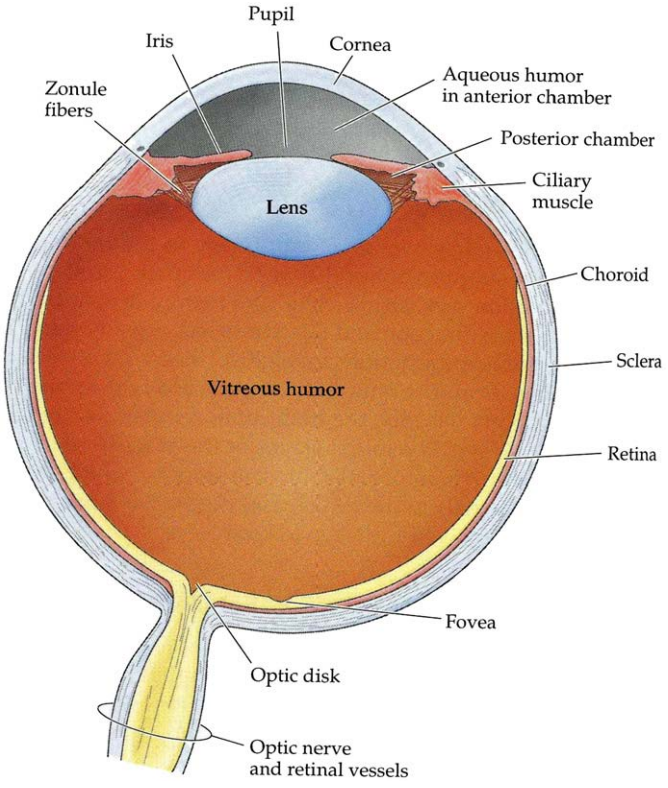

Fig. 1. A schematic drawing of the cross-section of the eye. Reprinted with permission from Sinauer Associates.

2.1. Cornea

The cornea is the transparent dome that covers the anterior aspect of the eye. The cornea functions as the predominant refractive surface as well as protects the inner eye against infections and structural damage. The human cornea is a multi-layered tissue composed of five main layers: the epithelium, Bowman's layer, the stroma, Descemet's membrane, and the endothelium. The outermost aspect of the cornea is composed of 4–7 cells of nonkeratinized, stratified squamous epithelium that is covered by a tear film. Without tears, the corneal epithelium dries out and becomes damaged. Bowman's layer consists of collagen fibers beneath the basement membrane of the epithelium. The stroma is the thickest layer of the cornea and the arrangement of its fibers retains water and allows for transparency. Descemet's membrane is a thin layer lying superior to the endothelium. The endothelium is important in maintaining fluid balance within the eye. The single cell layer pumps excess fluid from the stroma into the anterior chamber to prevent stromal distortion.

A number of eye diseases affect the cornea and some involve perturbations of the epithelium. Evidence for iron's potential participation in corneal disease is demonstrated in the development of iron lines in the cornea. Iron lines develop in the normal aging cornea (Hudson-Stähli line [48,53,54]) as well as in keratoconus (Fleischer's Ring [41,48,62]) and in pterygium (Stocker's line [66–72]). It can also be seen near filtering blebs following surgery for glaucoma (Ferry's line [73]).

2.2. Lens

The lens is a transparent structure behind the iris, suspended in the aqueous humor by the zonular fibers. The zonular fibers are connected to the donut-shaped ciliary body surrounding the circumference of the lens. The ciliary body has a muscular as well as vascular component with blood vessels extending from the choroid layer in the posterior of the eye. The muscles within the ciliary body alter the tension on the zonular fibers changing the shape of the lens. The ability of the lens to change shape alters its refractive power focusing light for high acuity in near and distant vision. In addition to serving the needs of the lens, the ciliary body secretes aqueous humor that fills the space between the cornea and the iris, the anterior chamber, as well as the space posterior to the iris and ciliary body, the posterior chamber. The aqueous humor supplies nutrients to the avascular cornea and lens.

The fiber cells that comprise the lens are uniquely organized and develop from lens epithelial cells. Young fiber cells develop at the expanding periphery of the lens creating new layers throughout the lifetime. As a result, the nucleus of the lens consists of the embryonic cells and the cortex remains metabolically active generating new cells [16].

The most common pathology of the lens is the development of opacities of the normally transparent lens called cataracts. Cataracts can result in vision loss and eventually blindness. Increasing evidence suggests that oxidative damage may play a role in the development of cataracts [16,17]. In his review, Spector offers a detailed description of the development of lens fiber cells as well as presents evidence for oxidative damage's role in cataract development [16]. Iron is implicated in the pathogenesis of cataracts because of its participation in the formation of oxygen free radicals [14,18,19] as well as the fact that iron foreign bodies in the eye cause cataracts [20].

2.3. Retina

The retina is the photoreceptor-containing layer in the posterior segment of the eye that ultimately transduces light into neural impulses. The majority of the cells of the retina can be organized into two layers: the neural layer and the pigment cell layer. The neural