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Review

Iron metabolism in the eye: A review

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ABSTRACT

This review article covers all aspects of iron metabolism, which include studies of iron levels within the eye and the processes used to maintain normal levels of iron in ocular tissues. In addition, the involvement of iron in ocular pathology is explored. In each section there is a short introduction to a specific metabolic process responsible for iron homeostasis, which for the most part has been studied in non-ocular tissues. This is followed by a summary of our current knowledge of the process in ocular tissues.

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1. Introduction

The key roles of iron in cellular metabolism have been studied for over a century and more recently the involvement of iron in oxidative damage has become clear. Reactive oxygen species (ROS) play a fundamental role in the pathophysiology of dozens of diseases. Iron-catalyzed formation of ROS is a major player in these processes (Gutteridge et al., 1981). The oxygen radical superoxide is produced in cells from oxidized reactions in the mitochondria and other redox reactions in cells. Superoxide is detoxified by superoxide dismutase with the resulting formation of hydrogen peroxide, which in the presence of ferrous iron can form the highly reactive and damaging hydroxyl radical. Clearly, careful control of iron availability is central to maintenance of normal cell function. Specifically in the eye, ROS participate in tissue damage which contributes to many diseases (which are covered in the referenced reviews) including cataractogenesis (Lou, 2003; Spector, 1995, 2000; Truscott, 2005), diseases of the cornea (Shoham et al., 2008), retinal degeneration (He et al., 2007), diabetic retinopathy (Feng et al., 2007), glaucoma (Aslan et al., 2008), photoreceptor damage in uveitis (Saraswathy and Rao, 2008), light-induced retinopathy (Siu et al., 2008), and age-related macular degeneration (Beatty et al., 2000; Dunaief, 2006; Dunaief et al., 2005).

The story of iron metabolism continues to evolve with new discoveries including iron regulation of glutamate production and secretion, glutathione (GSH) synthesis and the activity of hypoxia-inducible factor-1 (HIF-1) which will be described below. Despite the importance of iron in these varied roles, our understanding of the control of intracellular iron metabolism has only moved forward conspicuously in the last 10 years. During this time rapid developments in our understanding of iron metabolism were made possible by the discovery of several key iron regulatory proteins. Our current knowledge of iron metabolism in ocular fluids and tissues, especially the lens, cornea, retina and retinal pigmented epithelial cells is the subject of this review and it is clear that it has not kept pace with this rapidly developing field of study of iron physiology in other, non-ocular tissues.

2. Iron content of the eye

2.1. Intraocular fluids (IOFs)

The iron content of the fluids and tissues of the eye of numerous species has been studied since the 1940s (Tauber and Krause, 1943). We and others found very low levels of iron in the normal aqueous and vitreous humors of the eye (McGahan and Fleisher, 1986b). This level was a small percentage (less than 1%) of the iron content of plasma likely reflecting the ability of the blood–ocular barrier to prevent the entrance of the plasma iron transport protein, transferrin, into the eye. Inflammation, which causes a breakdown of this barrier, induced a large increase in the iron concentration in

Abbreviations: IRP, iron regulatory protein; IRE, iron response element; LEC, lens epithelial cells; RPE, retinal pigmented epithelial cells; GSH, glutathione; HO, heme oxygenase; IOFs, intraocular fluids; PCBP1, poly-c binding protein-1; TfR, transferrin receptor; DMT1, divalent metal transporter-1; GPI, glycosyl-phosphatidylinositol; AMD, age-related macular degeneration; Cp, ceruloplasmin.

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both the aqueous and vitreous humors (McGahan and Fleisher, 1988). In the aqueous humor much of this iron was likely bound to transferrin during the course of the inflammatory response due to the availability of iron-binding capacity in this fluid. However, there was some hemorrhage in the posterior segment which resulted in iron concentrations exceeding the transferrin-iron-binding capacity of the vitreous. Such non-transferrin bound, redox-active iron could cause tissue damage due to free radical formation.

2.2. Lens

The iron content of the lens has been determined in numerous species over the years by a variety of methods (Agarwal et al., 1976; Lakomaa and Eklund, 1978; McGahan, 1992; Oksala, 1954; Yamaguchi et al., 1980). Iron concentration in these lenses has been reported to be between 0.18 and 9.6 μg/g wet weight. There is a wealth of evidence linking oxidation of proteins to cataract formation (Spector, 2000; Truscott, 2005). Iron has a central role in catalyzing free radical reactions leading to oxidative damage. Iron-catalyzed reactions have been linked to changes in lens crystallins (Garland, 1990; McDermott et al., 1988), lens DNA damage (Kleiman et al., 1990) and cataract formation (Garland, 1990; Levi et al., 1998; Truscott, 2005). Therefore, it was important to determine if iron levels and reactivity change in the lens during cataractogenesis. A number of studies found increases in lens iron content with cataract formation (Dawczynski et al., 2002; Garner et al., 2000b). Significantly, redox-active iron (not bound in the iron storage protein ferritin) was found at higher levels in cataractous versus non-cataractous lenses (Garner et al., 2000a, 1999).

The lens has remarkable control over its iron content. During inflammation, the lens accumulates iron most likely by taking it up from the increased plasma transferrin and non-transferrin-bound iron present in the IOFs after breakdown of the blood–ocular barriers (McGahan, 1992). Importantly, the iron concentration of the lens declined to control levels upon resolution of the inflammatory episode. Therefore, the lens may not only provide a buffer for removal of potentially damaging intraocular iron, but must have carefully controlled mechanisms for release of iron in order to maintain iron levels within a narrow range. These mechanisms may change with age and such changes contribute to the accumulation of iron and to oxidative damage seen in cataractogenesis. Regulation of systems responsible for iron metabolism in the lens is the subject of active investigation in our laboratory.

2.3. Retina and retinal pigmented epithelium (RPE)

It is well known that intraocular foreign bodies containing iron cause retinal degeneration (He et al., 2007). However, the normal functions and regulation of iron in the retina have only recently come under study. The largest amounts of iron in the normal retina, as determined by proton induced X-ray emission, were in the RPE, choroid and inner segments of photoreceptors. Iron stored in ferritin was detected on the disc membranes of intact photoreceptors as well as in RPE phagosomes (Yefimova et al., 2000).

Retinal iron levels increase with age in humans (Hahn et al., 2006) and rodents (Chen et al., in press) and with disease (Dunaief, 2006; He et al., 2007). In addition, iron deposits were found in the macula of humans with age-related macular degeneration (AMD) (Dentchev et al., 2005). In a model of retinal degeneration, the Royal College of Surgeons (RCS) rat, non-heme iron deposits accumulated with time in a debris field resulting from the pathological manifestation of this genetic model, the inability to phagocytose photoreceptor outer segments. Neither the iron-binding protein transferrin, nor the iron storage protein, ferritin, was found associated with this accumulated iron. It was hypothesized that the accumulation of debris disrupted normal movement of iron from the RPE to the retina. Since this iron was apparently not bound to proteins that normally block its ability to catalyze oxidative damage (ferritin and transferrin), it was hypothesized that iron accumulation could contribute to retinal degeneration in the RCS model (Yefimova et al., 2002). Finally, alterations in the levels of proteins involved in iron metabolism, i.e. decreased transferrin and increased transferrin receptor, ferritin, ferroportin, and ceruloplasmin in the neural retina of aging rodents, suggest that dysregulation of iron metabolism and the resulting accumulation of iron could be a causative factor in age-related retinal degenerations (Chen et al., in press).

3. Mechanisms for maintaining iron homeostasis in cells

3.1. Iron regulatory proteins (IRPs)

3.1.1. IRP-1 and IRP-2

Two IRPs have been described, IRP-1 and IRP-2, which bind stem loop structures, called iron responsive elements (IREs), in the 3′ and 5′-untranslated regions of mRNAs of several proteins involved in iron storage and metabolism (Muckenthaler et al., 2008). While they perform similar tasks, their activities are regulated in different ways. IRP-1 can exist in two different conformations. When iron is abundant IRP-1 assumes aconitase activity (cytosolic aconitase, or c-aconitase) and cannot bind to mRNA (Fig. 1). IRP-2 is degraded by the ubiquitin-proteasomal system in an iron-dependent manner. Abundance of iron also decreases the ability of the IRPs to bind to IRE allowing for translation of ferritin and ferroportin (Fpn) as well as the destabilization of transferrin receptor mRNA. When iron is scarce, IRP-1 and IRP-2 have the ability to bind to the various mRNAs, preventing the translation of ferritin and Fpn and stabilizing mRNA for transferrin receptor and DMT1. It has recently been hypothesized that IRP-2 is the major iron sensor in most cells and that under physiological conditions IRP-1 functions mainly as a c-aconitase (Rouault, 2006). This is clearly an elegant system for controlling iron levels and storage within cells.

3.1.2. The dual role of IRP-1

IRP-1/c-aconitase regulates glutamate production and glutathione (GSH) levels in lens epithelial cells (LEC) and RPE. The function of a c-aconitase (the non-mRNA binding form of IRP-1) has been a matter of investigation. While mitochondrial aconitase clearly plays an important role in the mitochondrial citric acid cycle, the cytosolic form has no known function. In one study, it was determined that the conversion of citrate to isocitrate by c-aconitase, with the subsequent metabolism of isocitrate to α-ketoglutarate resulted in the production of the important antioxidant, NADPH. These investigators hypothesized that NADPH was formed as a protective mechanism in response to an increase in iron load (Narahari et al., 2000). However, we were unable to show that there was increased NADPH formed as a result of an increase in iron levels. In our studies in LEC, RPE and neurons, we found that NADPH, formed in response to increased iron levels, was used in the subsequent metabolism of α-ketoglutarate to glutamate by glutamate dehydrogenase (McGahan et al., 2005). Glutamate is an important neurotransmitter in the brain and the retina. Our findings are the first to show that glutamate synthesis and secretion are directly regulated by iron. Since both iron and glutamate are dysregulated in neurological and retinal disease, a physiological link between these two is quite significant.

In a subsequent study aimed at determining the physiological basis for lenticular secretion of glutamate, we found that iron-regulated glutamate production and secretion were functionally linked to increased cystine uptake (by both LEC and RPE) by a cystine/glutamate antiporter. The increase in transporter activity provided cysteine to these cells. Cysteine is the rate limiting amino acid for glutathione production and the iron-induced increase in

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