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Age-related cataract and macular degeneration: Oxygen receptor dysfunction diseases

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ABSTRACT

Age-related cataract and age-related macular degeneration (AMD) is the leading cause of vision impairment and blindness in developing and developed countries, respectively. Oxidative stress and oxidation products have been verified to play important roles in these two aging diseases. Recent research has demonstrated that there are significant oxygen gradients in the eye. Therefore, we propose a new hypothesis that these two diseases could be summarized as oxygen receptor dysfunction diseases of which the main points are as follows. Oxygen in the retinal and choroidal vasculature is transferred into the vitreous cavity by a special switching valve or oxygen receptor that might exist in the internal limiting membrane, vascular endothelium or posterior vitreous surface. It is then transported from the posterior segment to the anterior segment by vitreous collagen fibrilla networks, which work similar to a gas pipeline. Posterior vitreous detachment is the starting point of these two diseases by inducing formation of the local hyperoxia region, which results in the occurrence of age-related cataract and macular degeneration. Thus, an innovative anti-oxidative therapy should be added to the traditional treatment of age related macular degeneration. Some associated experimental and clinical approaches are suggested in our paper to test this hypothesis.

Background

Age-related cataract, which results in opacification of the lens, is the most common cause of vision impairment and blindness in developing countries in persons beyond middle age and the elderly1. Age-related macular degeneration (AMD) characterized by the abnormal growth of new blood vessels under or within the macula is the leading cause of irreversible blindness among the elderly in developed countries [2].

Oxidative stress and oxidation products have been verified to play important roles in these two age-related diseases [1,3–5]. In our previous study, we invented a new vitreous substitute, foldable capsular vitreous body (FCVB), which was prone to result in cataract (Supplemental Fig. 1) [6]. In subsequent clinical trials of FCVB implantation in Guangzhou, there was a very notable clinical case of a young male patient with a good prognosis in the first one and half-year follow-up (19th, August, 2011, FCVB implantation). But the patient presented with a sudden anterior chamber hemorrhage and iris neovascularization in the ipsilateral eye around the second year follow up. (27th, April, 2013) After the diagnosis, the young man was given a peripheral iridotomy and then the new vessels on the iris were found to extinct quickly (30th, April, 2013) (data not shown). This suggested that the oxygen supply might flow from the posterior segment to the anterior chamber, while the artificial FCVB might block the channel of oxygen output, leading to ischemia of the eye's anterior segment, thus requiring prevention by peripheral iridotomy. Actually, due to the use of mydriatics of the operative eye after implantation of FCVB in the early phrase, there was just incompletely pupillary block in this case. The formation of iris neovascularization might be due to the double effects of block of oxygen transportation and incompletely pupillary block by implantation of FCVB.

An earlier study from Shui et al. used the fiber optic optical oxygen sensor (optode) to measure the oxygen levels in different regions of the rabbit eye and the oxygen flux across the posterior of the lens [7]. They found that oxygen levels were highest near the retinal vasculature, the iris vasculature and the inner surface of the central cornea. There were obvious oxygen gradients in the vitreous body and oxygen levels closer to the lens were generally lower. Lange et al. found significant intraocular oxygen gradients in proliferative diabetic retinopathy with high oxygen tensions at the posterior pole, steep gradients towards the periphery, and low oxygen tensions in the vitreous [8]. An axi-symmetric, steady-state, finite element model of the oxygen transport and

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consumption model was developed by Filas et al. at Washington University [9]. The model was basically constructed on the experimental data from humans and animals, which reproduced experimental data in humans, including PO_2 gradients (≈15 mm Hg) across the anterior-posterior extent of the vitreous body, higher oxygen levels at the pars planar compared to the vitreous core, increased PO_2 near the lens after cataract surgery, and an equilibrium state of PO_2 in the vitreous cavity following vitrectomy. The loss of the anti-oxidative capacity of ascorbate increases the oxygen exposure levels to three-fold at the lens surface. Complete vitreous degeneration (liquefaction), but not partial posterior vitreous detachment, greatly increases oxygen exposure to the lens and the incidence rate of cataract.

Hypothesis

From what we have learned from the previous research results about oxygen concentration distribution in the vitreous cavity, regardless of whether animals [7], humans [8] or mathematical models [9] were used in the studies, we can deduce that there are significant oxygen gradients in the eye, and that the oxygen is mainly supplied by the huge retinal and choroid vasculature. In addition, the oxygen gradients extend from the posterior pole of the retina to the core of the vitreous and peripheral retina, and from the core of the vitreous cavity to the posterior lens surface. Thus, it is reasonable to postulate that there may be special oxygen switching valves (a kind of oxygen receptor) and convection channels in the eye. In our hypothesis, the main points are as follows. (1) A kind of special oxygen receptor may exist in the internal limiting membrane, vascular endothelium or posterior vitreous surface, and that the oxygen absorbed from the huge vascular system in the retina and choroid could be transferred into the vitreous cavity by this special oxygen receptor, and then transported into the hypoxia districts though vitreous collagen fibrillar networks, which work similarly to a gas pipeline. The oxygen transported by the collagen fibrillar network from the retinal and choroidal vasculature may arrive at the posterior surface of the lens and then diffuse into the ora serrata mixing with the oxygen secreted by the ciliary body vasculature. Then, a proportion of the oxygen is transported to the anterior chamber, the anterior chamber angle and the trabecular meshwork (Fig. 1A). (2) Posterior vitreous detachment may be a starting point of age-related cataract and AMD as the oxygen transmission pathway is blocked and a local hyperoxia region is formed by degeneration

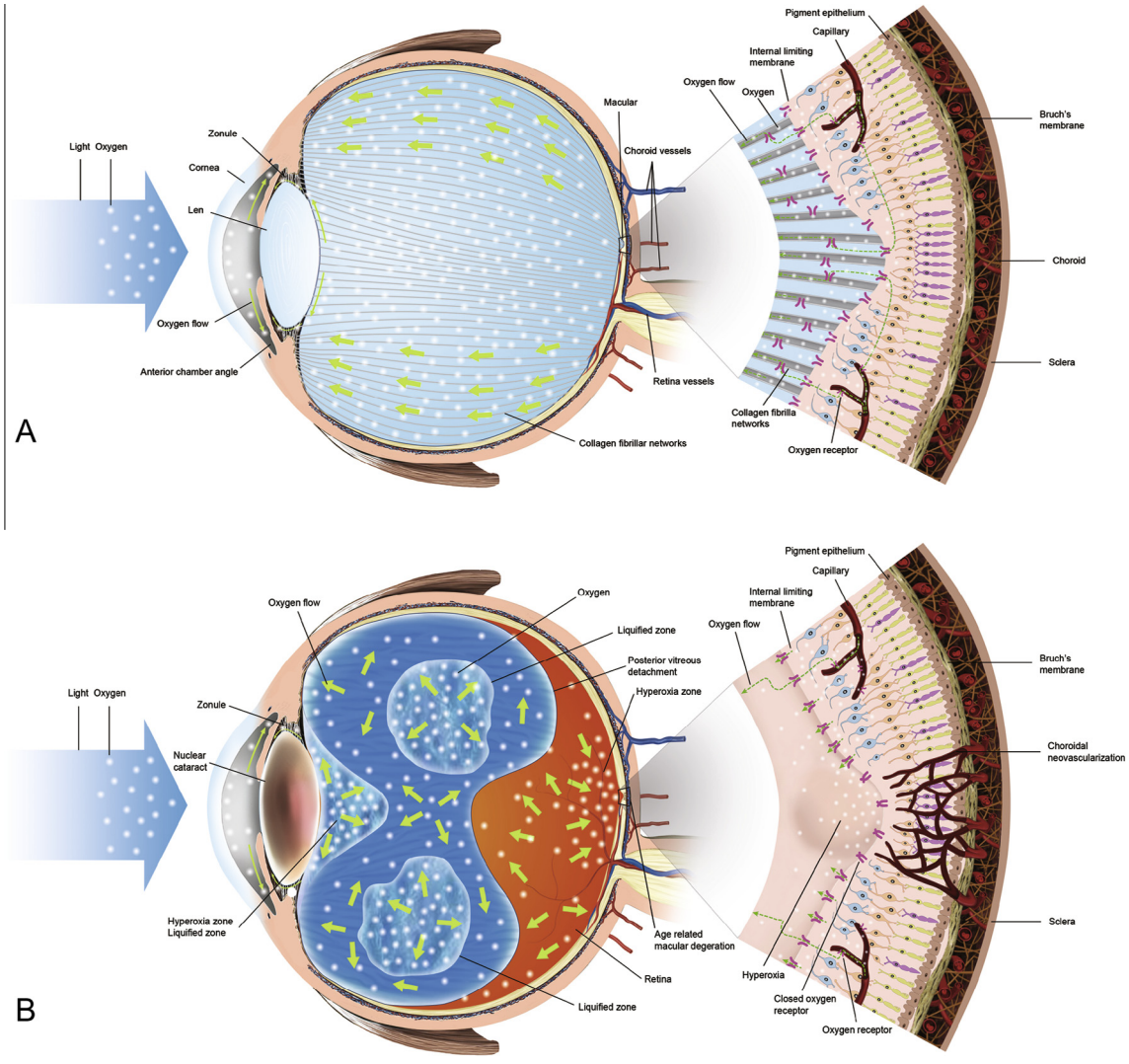

Fig. 1. Illustrations of oxygen convection in normal and oxygen receptor dysfunction eye ((A) Transportation of oxygen from retinal and choroidal vasculature to the vitreous cavity in normal eye. (B) Age-related cataract and age-related macular degeneration onset after posterior vitreous detachment, local hyperoxia and oxygen receptor dysfunction).