Editorial

Editorial on photoreceptor glucose metabolism determines normal retinal vascular growth

Amy C. Lo

Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

Correspondence to: Amy C. Lo. Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. Email: amylo@hku.hk.

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Retinopathy of prematurity (ROP) was first described as a disease of prematurity (1). There was then a worldwide epidemic of ROP, which contributed to 50% blindness in 1950. Later vigorous research showed a correlation between the use of supplemental oxygen and the incidence and progression of ROP. This led to a close monitoring of supplemental oxygen given to premature infants, which helped to decrease the percentage of ROP-related blindness to 4% in 1965. Yet, the incidence of ROP increased in recent years, presumably due to great improvement in neonatal care, which in turn resulted in increased survival of very-low-birth-weight premature infants. The most recent estimates from the National Eye Institute showed that 14,000–16,000 premature infants (≤1.25 kg, <31 weeks of gestation) born annually are affected by ROP. Although most of them (~90%) are fortunate enough to develop mild ROP without the need for medical treatment, about 1,100–1,500 infants develop severe ROP where medical treatment is essential. Despite treatment, 400–600 infants (up to 40%, a sizable minority) become legally blind. Moreover, ROP patients have a higher incidence of astigmatism, high myopia and retinal detachment and should be followed routinely afterwards. As these ROP patients age, their long-term disability and severely affected quality of life increase workload and pose intense burden on the pediatrics, adolescent and adult healthcare systems. This makes ROP a major public health issue and therefore a need for of new treatments or improvements in those currently available is warranted.

ROP is a biphasic disease; there is an initial phase of vessel loss, which is followed by a second phase of vessel proliferation with retinal ischemia, retinal neovascularization (retinal capillaries proliferate abnormally from pre-existing vessels) and neuronal degeneration as common pathological features. During the first ischemic phase, exposure to high oxygen (hyperoxia) induces cessation of normal vessel growth and pruning of existing immature vasculature. This occurs when the infant is placed in high supplemental oxygen that inhibits production and secretion of pro-angiogenic factors e.g., vascular endothelial growth factor (VEGF), which in turn leads to retinal avascularity. The retinal response during this phase may also be mediated by hyperoxia-induced free radicals, although their roles remain unclear. In the second vaso-proliferative phase when oxygen supplementation is discontinued, relative retinal hypoxia occurs due to high oxygen demand from the maturing neural components. This triggers a compensatory release of pro-angiogenic factors e.g., VEGF, leading to unregulated vessel growth and neovascularization. These fragile neovascular tufts will in turn lead to intravitreal hemorrhages, retinal detachment and subsequent vision loss.

The severity of ROP is inversely proportional to gestational age (2), which is the greatest risk factor (3). Although STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity, a multi-centered national study) (4) found that oxygen (96–99% saturation) neither causes additional progression of prethreshold ROP nor significantly reduces the number of infants requiring ablative surgery (4), there was absolutely no data to suggest that high oxygen level is safe for early

immature eye that has not yet established ROP. If preterm infants require supplemental oxygen due to cardiopulmonary reasons, withholding oxygen for fear of causing ROP is not recommended.

VEGF is shown to be a critical factor contributing to ROP (5) in driving neovascularization. Recent advances have introduced bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA), a humanized anti-VEGF monoclonal antibody and the first anti-angiogenic agent for the treatment of metastatic colorectal cancer (6). The drug has shown promising results in treating many retinopathies with VEGF up-regulation e.g., age-related macular degeneration (7) and diabetic retinopathy (8-10), showing its potential benefit for the treatment of ROP. Until now, there have been a few case reports, small case series and a multicenter study of bevacizumab use in ROP (11-13), showing some promising results yet with limitations. Further controlled studies with longer follow-up are necessary to determine the long-term ocular and systemic safety of this anti-VEGF agent when used in the rapidly developing neonatal eye.

Treatment of ROP is unsatisfactory. There have been 2 mutli-center trials: the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial and the Early Treatment for Retinopathy of Prematurity (ETROP) trial. Laser photocoagulation as in surgical ablation of peripheral retina is the preferred treatment of choice but is not always successful in halting ROP progression (14). If laser is not available, cryotherapy may be performed. With cryotherapy, unfavorable 15-year structural and visual acuity outcome persist in the treated eyes (15), suggesting an on-going cost of long-term, regular follow-up.

A majority of our understanding on pathogenesis of ROP comes from animal models. The retinal vasculature of a newborn mouse is comparable to that of infants at gestational age 25 weeks, a period at risk for ROP. Therefore, neonatal mouse becomes an attractive model to study ROP pathogenesis. The oxygen-induced retinopathy (OIR) model (16) (a term used to differentiate experimentally induced retinopathy in animals from human ROP) is the most commonly used mouse model of ROP. Here, neonatal mice at postnatal day 7 are exposed to 75% oxygen for 5 days to induce vaso-attenuation and then returned to room air for variable periods to induce vaso-proliferation and neovascularization. This OIR model has allowed extensive studies on the cellular and molecular aspects of pathological retinal vascularization. Recent studies indicated that OIR is multifactorial, involving pro- and anti-angiogenic factors as well as mediators of oxidative stress similar to that in human ROP.

Earlier studies showed that deficiency of aldose reductase (AR), the first enzyme in the polyol pathway for reducing glucose to sorbitol in glucose metabolism, plays a role in decreasing ischemia-induced oxidative stress and blood vessel leakage in mouse retina (17,18). Similarly, pharmacological inhibition of AR activity with Fidarestat reduced retinal oxidative stress and prevented VEGF over-expression in diabetic rats (19). More importantly, deficiency of AR can reduce both retinal vascular and neuronal changes in the mouse model of OIR (20).

Another anti-oxidant of interest is lutein, a member of the xanthophyll family of carotenoids. Together with its stereoisomer, zeaxanthin, they are the only carotenoids present in both the macula and lens of the human eye (21). Lutein is able to protect the retina from ischemia/reperfusion injury *in vivo* and Muller cells from cobalt chloride ($CoCl_2$)-induced hypoxia *in vitro* (22-24). Recently there are three randomized controlled trial studies of lutein in ROP patients (25-27). Although they reported that lutein appeared to be ineffective in preventing proliferative ROP in preterm infants (25-27), there is a decreasing trend of the progression rate from early ROP stages to threshold ROP (defined as beyond which there is 50% likelihood of the incidence of unfavourable outcomes) (26,28). In fact, lutein may be considered as a therapeutic supplement due to its role in facilitating revascularization of retinal vasculature in OIR (29).

Currently, neonatal hyperglycemia has emerged to be a risk factor for ROP, based on the hallmark abnormal vessel growth that is also characteristic of diabetic retinopathy. In fact, both clinical and basic research support the important role of neonatal hyperglycemia in the development of ROP and OIR. A series of clinical studies have shown that hyperglycemia is an independent risk factor associated with ROP (30-35). In experimental models, hyperglycemia induced by streptozotocin reduced the retinal vascular area, increased the number of Iba+ macrophages/microglia and enhanced apoptosis in the inner nuclear layer in P6 neonatal rat (36). These results strongly supports the role of neonatal hyperglycemia in ROP and OIR, but the cellular and molecular mechanism await further investigations.

Interestingly, hyperglycemia in premature babies instead suppresses retinal vessel growth with an unknown mechanism. To solve this research puzzle, Fu *et al.* first established a new model of retinopathy, namely "hyperglycemia-associated retinopathy" where hyperglycemia was induced by injection of streptozotocin into neonatal mice (37). Using this new

model, Fu *et al.* were able to show delayed retinal vessel growth and photoreceptor dysfunction, mimicking the human situation. Following on their earlier studies on dietary omega-3 polyunsaturated fatty acids and adiponectin (APN) and their roles in retinal neovascularization (38), Fu *et al.* again utilized APN knockout mice in this recent study. It was evident that APN deficiency together with hyperglycemia delayed regression of the hyaloid vessels as well as suppressed formation of deep vasculature in the mouse retina.

Fu *et al.* further identified that activation of the APN pathway modulating photoreceptor mitochondrial function in these hyperglycemia retinae. The levels of enzymes involved in glucose metabolism, the Krebs cycle and the electron transport chain were decreased with APN deficiency. Interestingly, it was the photoreceptors but not the vessels that displayed a decrease in the mRNA levels of the metabolic enzyme *Hk1* and *Cs*, pointing to a major role of photoreceptors in the metabolic alterations that occur in the hyperglycemic APN knockout retina. Most importantly, retinal function could be restored by recombinant APN treatment.

In addition, Fu *et al.* also showed that in premature infants, hyperglycemia positively correlated with low serum APN levels, which in turn positively correlated with delayed retinal vascularization. These results added much value to the clinical relevance of the newly developed "hyperglycemia-associated retinopathy" mouse model. Fu *et al.* has defined a role of APN as a potential therapeutic target for retinal vascular diseases with metabolic disorders.

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