Understanding Retinopathy through ROP
The Friedenwald Lecture

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Retinopathy is a common cause of blindness in all age groups. There are 15 million people in the United States with age-related macular degeneration (AMD)—20% of those aged 65 to 74 years and 50% aged >74 years—and 1.6 million of those have neovascular (wet) AMD. In the working age population there are >20 million (>7% of the population) with diabetes, and 50% of patients with diabetes mellitus have diabetic retinopathy (DR) after 25 years. In children, retinopathy of prematurity (ROP) is a major cause of vision loss. Approximately 460,000 (11%) of infants per year are born prematurely, and there are ~2,000 infants per year with severe ROP, even with treatment. There is a high impact of blindness in children (0–70 years).

Although fewer children are affected by retinal neovascularization than adults, ROP offers a window into understanding the pathophysiology of retinopathy. The study of ROP has helped to develop nondestructive therapy for retinopathy. Research in ROP is easier in theory than that in DR or AMD, as there are clear and distinct comparisons to be made: normal in utero development versus development after premature birth. If we understand what factors change between the in utero retina where vascularization proceeds normally without retinopathy and the retina of infants born prematurely, then we may better understand normal vascular development, vessel loss, vessel repair, and neovascularization. ROP occurs over a much shorter time line (~10–20 weeks) than does DR or AMD.

ROP and other ocular diseases with pathologic neovascularization have two phases. The first phase consists of cessation of vessel growth and loss of vessels. In ROP, this phase has its onset at the time of premature birth and is associated with the loss of factors normally provided by the mother in utero. Phase I is also precipitated by the addition of factors in the extraterine environment, notably oxygen that is above intrauterine levels even in room air. The relative hypoxia is exacerbated by supplemental oxygen. This shift from the environment in utero leads to cessation of normal retinal vessel growth and vaso-obliteration, leaving peripheral retina avascular.

In phase I, oxygen-regulated growth factors are suppressed by higher than normal levels of oxygen and others are lacking because they are normally provided by the mother in the third trimester of pregnancy. As the retina matures after birth, it becomes more metabolically active, and the avascular retina becomes hypoxic, leading to phase II of ROP. The hypoxia of phase II induces a rapid increase in hypoxia-inducible factor (HIF)-regulated growth factors that were suppressed in phase I.

Factors missing from the mother may rise slightly if the fetal liver and other organs that produce them have matured sufficiently but still may be lower than in utero levels.

To study both phases, we developed a mouse model of oxygen-induced retinopathy to take advantage of the genetic manipulation possible in mice. Proliferative retinopathy in the mouse model develops reliably (and quantifiably) over 10 days, unlike rodent models of diabetes, in which proliferative disease does not develop. Neonatal mice are exposed to 75% oxygen from postnatal day 7 until day 12. Hypoxia causes vessel regression, and the cessation of normal radial vessel growth occurs mimicking the first phase of ROP. The extent of vaso-obliteration can be determined by measuring the nonperfused area in retinal wholemounts. On return to room air, the nonperfused areas of retina become hypoxic, thereby inducing the expression of angiogenic factors and resulting in retinal neovascularization. The neovascular phase in the oxygen-induced animal model is similar to the second phase of ROP in humans and, in addition, mimics many aspects of proliferative diabetic retinopathy and some aspects of neovascular AMD. Neovascular tufts are measured by quantifying endothelial cell nuclei extending into the vitreous in cross sections of retina, or by quantifying the area of vascular tufts in retinal flatmounts. The mouse model has been useful in delineating the molecular changes in both phases of the neovascular eye diseases.

OXYGEN-REGULATED FACTORS

The Complex Role of Vascular Endothelial Growth Factor (VEGF) in ROP

Excessive oxygen use has been associated with development of ROP since the 1940s when retrolental fibroplasias, the early name for ROP, was first noted after the onset of the use of closed incubators, which caused supplemental oxygen concentrations to rise to unprecedented levels. Although it was not initially known that such unregulated oxygen use was toxic to the neonatal retina, it has become widely accepted that hypoxia-induced vessel loss results in retinal hypoxia, which stimulates the release of factors that influence blood vessel growth. It had been proposed by Michaelson in the 1940s and by Ashton et al. that oxygen-regulated factors would be involved in retinal neovascularization—phase II of retinopathy—but none had been found for many decades since the description of a possible oxygen-regulated “factor X.” Vascular endothelial growth factor (VEGF) was a good candidate for such a molecule.

VEGF was discovered initially as a vasopermeability factor (VPF), and was later found to induce endothelial cell proliferation. VEGF is regulated by oxygen, specifically by HIF and VEGF mRNA increases in response to hypoxia and plays a key role in tumor angiogenesis, and so we investigated VEGF as one of the factors proposed by Michaelson as being critical.
to phase II, proliferative retinopathy, as well as having a role in phase I vessel loss.

**Elevation of VEGF in Phase II of ROP**

In the mouse model of retinopathy, we examined the expression of VEGF mRNA after oxygen-induced vessel loss (P7–P12) and subsequent hypoxia starting at P12. VEGF expression increases in the Müller cells and astrocytes of the inner retina, corresponding temporally to the onset of pathologic neovascularization. More critically, we found that inhibition of VEGF after the intravitreal injection of either an anti-VEGF antisense oligonucleotide or with a VEGF-binding molecule (VEGF receptor/IgG chimera) significantly decreases the neovascular response in phase II, indicating that VEGF is a critical factor contributing to retinal neovascularization. In retinal specimens from an ROP patient, the VEGF expression pattern was similar to that found in the mouse model of ROP. VEGF was found in the vitreous of patients with proliferative diabetic retinopathy.

Based on these and other studies, intravitreal anti-VEGF treatment is now available to treat neovascularization associated with age-related macular degeneration and is in clinical trials for diabetic eye disease. Clinical trials are planned for evaluation of treatment of the proliferative phase of ROP.

**Suppression of VEGF in Phase I of Retinopathy**

VEGF was also found to be essential in the development of the retinal vasculature and phase I of ROP. During normal retinal development, blood vessels grow from the optic nerve to the periphery. As the neural retina develops anterior to the vasculature, the increased oxygen demand of the developing neural tissue generates a wave of “physiological hypoxia” that precedes vessel growth. In response to the hypoxia, astrocyte expression of VEGF stimulates blood vessel growth that follows the astrocyte template. As new vessels form and retinal hypoxia decreases, VEGF expression and further vascular growth are reduced via a local feedback mechanism.

Supplemental oxygen in premature infants, however, interferes with normal VEGF-driven vascular development. In phase I of the murine model of ROP, hypoxia suppresses VEGF expression, resulting in the loss of the physiological wave of VEGF anterior to the growing vascular front. Cessation of normal vessel growth and regression of existing vessels subsequently occurs. The hyperoxia-induced vaso-obliterration is caused by apoptosis of vascular endothelial cells and can be partially prevented by administration of exogenous VEGF or PIGF-1, a VEGFR-1-specific ligand. This finding indicates that VEGF signaling through VEGFR-1 is required for survival of the immature retinal vasculature and explains, at least in part, the effect of hyperoxia on normal vessel development in ROP.

**Neuroprotection Provided by VEGF**

We also asked if VEGF might be important to neuroprotection, and in the ROP model we found that retinal neurons also require VEGF. VEGF was routinely described as a vascular endothelial cell-specific mitogen, and VEGF receptor 1 (VEGFR-1) and VEGF receptor 2 (VEGFR-2) were described as endothelial cell specific, but the developing eye presented a unique opportunity to examine the function of VEGF in neural tissue alone. The peripheral retina is normally avascular at birth and becomes vascularized over the first 2 weeks after birth. This avascular tissue could be evaluated with VEGF blockage without the complication of inhibited vessels contributing to any induced pathology. We localized VEGFR-1 and -2 mRNA and protein to extravascular neuronal tissue during early retinal development. We found that vascular cornea also expressed these receptors. Inhibition of VEGFR-1 and -2 in vivo with a specific small-molecule tyrosine kinase antagonist, SU5416, inhibited development of the nonvascularized immature retina, resulting in cell loss in the inner retina, including the inner nuclear layer containing Müller cells and the ganglion cell layer containing astrocytes. We found that VEGFR-1 and -2 are necessary for normal neural retinal development independent of vascular development.

Suppression of VEGF during the proliferative phase of retinopathy is the first medical treatment for the disease and has changed the way we treat AMD. Though the study of ROP helped define how inhibition of VEGF could suppress proliferative disease in AMD and DR (and ROP), it also suggested the importance of VEGF in vessel and neuronal survival. ROP studies revealed that timing and degree of suppression of VEGF are critical. Excess VEGF suppression during vessel loss may worsen disease.

**A Second Oxygen-Regulated Factor: Erythropoietin**

VEGF is clearly important in angiogenesis but it is not the only factor controlling blood vessel growth and stability. VEGF suppression does not completely control retinal neovascularization in the ROP model or in patients with AMD. Other factors are clearly involved. We also looked at another oxygen-regulated molecule, erythropoietin or Epo.

Epo is an HIF-regulated hormone produced in the kidney in response to hypoxia, promoting erythrocyte formation in bone marrow. Recombinant Epo is now widely used for treatment of anemia in diabetic patients with chronic kidney failure or anemia in premature infants and anemia in cancer patients with chemotherapy-induced bone marrow suppression. These patients are at risk for diabetic retinopathy or ROP or promotion of cancer growth. Elevated levels of Epo are found in the vitreous samples of patients with proliferative DR. In addition, higher doses of Epo have recently been associated with increased risk of cardiovascular disease and tumor growth. Epo is also a powerful cytoprotective factor that can protect both vascular cells and neurons from apoptosis.

However, the role of Epo in normal vascular stability was largely unknown. Understanding the effect of Epo on vessel stability and angiogenesis is likely to benefit not only patients with retinopathy but also those with diseases that involve angiogenesis, which are also often treated with Epo. Since retinal vessel loss precedes neovascularization and the severity of neovascularization is largely determined by the extent of initial vessel loss, understanding the role of Epo in the development of initial vessel loss in retinopathy is important. We examined the role of Epo in vascular stability and neovascularization in the ROP model.

**Suppression of Epo in Phase I and Elevation in Phase II**

We found Epo and its receptors to be expressed in the retina of the mouse. As with VEGF, retinal Epo levels were markedly suppressed during the hyperoxia-induced vessel loss phase. Administration of exogenous Epo prevented both vessel dropout and subsequent hypoxia-induced neovascularization. Early use of Epo also protected against hypoxia-induced retinal neuron apoptosis. Epo’s early protective effect against vessel loss occurred through both systemic retinal recruitment of proangiogenic bone marrow-derived progenitor cells and activation of prosurvival NF-κB via Epo receptor activation on retinal vessels and neurons. Thus, lack of Epo, a potent cytoprotective factor, may contribute to the initial vessel loss
in retinopathy. Correction of Epo deficiency or anemia treatment during phase I of retinopathy could be of benefit in preventing the initial vessel loss and thereby the devastating proliferative stage of the disease.

In contrast, retinal Epo mRNA levels were highly elevated during phase II neovascularization. Exogenous late Epo treatment did not protect the retina, but rather enhanced pathologic neovascularization. Inhibiting Epo in the proliferative phase in the mouse model of retinopathy inhibits retinal neovascularization and is independent of VEGF, and inhibition of both Epo and VEGF are additive.30 Thus, treatment of anemia in patients with active proliferative retinopathy (phase II) or with the potential for angiogenesis-induced cancer progression should be approached with great care. Indeed, inhibition of Epo may be beneficial during proliferative (phase II) disease. Understanding the role of Epo in ROP helps to clarify that timing is critical to the effect of Epo on pathologic angiogenesis.

**Non–oxygen-regulated Factors**

**Growth Hormone and Insulin-Like Growth Factor in Retinopathy**

Although oxygen, acting in part through VEGF and Epo, plays a central role in the first phase of ROP, premature itself rather than hypoxia is the most important risk factor.35 Thus non–oxygen-regulated growth factors are at least equally as important as oxygen-regulated factors in the development of retinopathy. Clinically, ROP is clearly multifactorial. Despite controlled use of supplemental oxygen, the disease persists, suggesting that other factors related to prematurity and growth and development are also at work in ROP. These are also likely to be factors in diabetic retinopathy and neovascular AMD.

In ROP, any consideration of factors controlling growth must include the growth hormone/insulin-like growth hormone (IGF-1) axis. Growth hormone (GH) has been suspected but not proven to play a role in diabetic retinopathy since the discovery that pituitary ablation can reverse diabetic proliferative retinal neovascularization.37,57 Using the ROP mouse model, we determined that GH acting through IGF-1 is critical to both phases of retinopathy.

**IGF-1 in Phase I of Retinopathy**

Fetal growth and development during all stages of pregnancy are dependent on the IGFs (IGF-1 and -2).40 Serum concentration of IGF-1, but not of IGF-2, increases with gestational age and correlates with fetal size.41,42 IGF-1 levels rise significantly in the third trimester of pregnancy, but fall after preterm birth due to the loss of placental and amniotic fluid sources.49

We hypothesized that IGF-1 is critical to normal retinal vascular development, and that lack of IGF-1 is associated with the lack of vascular growth that sets the stage for subsequent hypoxia-driven proliferative ROP. We found that normal retinal blood vessel development is depressed in IGF-1 knockout mice, a pattern very similar to that seen in premature infants with ROP. In addition, linking IGF-1 and VEGF we found that IGF-1 receptor activation controls maximum VEGF activation of the Akt endothelial cell survival pathway.45 These results help explain how low IGF-1 levels could contribute to the development of phase I of ROP or other retinopathies by preventing the normal survival of vascular endothelial cells.

The results in premature infants corroborated the results in the mouse model of ROP. The mean serum levels of IGF-1 in premature infants are inversely correlated with the severity of clinical ROP.53–56 Low IGF-1 levels in serum appears to be as strong a determinant of risk for ROP as postmenstrual age at birth and birth weight.43,54 Low postnatal IGF-1 levels in preterm infants also correlate with brain development and may account for abnormal neural retinal function in ROP.57 Patients with genetic defects of the GH/IGF-1 axis and a very low level of IGF-1 have decreased retinal vascular density.58 This accumulated evidence suggests that low IGF-1 levels during development are associated with vessel loss and may contribute to early vessel degeneration in phase I that drives late-onset, hypoxia-induced proliferative retinopathy.

These findings also suggest that early restoration of IGF-1 in phase I to normal in utero levels may prevent ROP by preventing early vessel loss. Clinical trials are in progress to supplement IGF-1 and IGFBP-3 to in utero levels in premature infants from birth to evaluate if restoration of IGF-1 to normal levels can prevent or reduce the severity of ROP. They also suggest that low IGF-1 might be used to predict later development of ROP.

**Predictive Nature of Postnatal Growth and IGF-1**

Currently premature infants considered at risk for blinding ROP are screened with eye examinations starting at approximately 30 weeks’ postmenstrual age to identify those who would benefit from laser photocoagulation to prevent disease progression to retinal detachment. The current guidelines for ROP risk are based on the perinatal factors low weight and low gestational age at birth, and they are intended to include 100% of infants requiring treatment. However, only approximately 10% of those examined require laser photocoagulation. If we could more accurately identify those infants who would and those would not develop ROP requiring treatment, it would help clinicians plan appropriately. Since a persistently low serum IGF-1 level (and by implication poor postnatal growth) is associated with the later development of ROP, we developed an algorithm to predict for individual infants the risk of developing threshold ROP using changes in the perinatal factors IGF-1, IGFBP-3, and weight gain, as well as the standard perinatal factors weight and gestational age at birth.

The algorithm was evaluated in a longitudinal study of preterm infants considered at risk by standard criteria (gestational age < 32 weeks) measuring weight gain and serum IGF-1 and IGFBP-3 levels weekly from birth until discharge from the hospital. We monitored deviations from reference models for changes in weight and IGF-1 levels in preterm children who did not develop ROP to detect indications for treatable ROP by Early Treatment for Retinopathy of Prematurity Study criteria. This monitoring method detected 100% of infants in this cohort who required treatment for ROP with a warning signal at least 5 weeks before requiring treatment and at least 3 weeks before developing stage 3 ROP. Most infants not requiring treatment were also identified early,59 suggesting that this algorithm may more clearly delineate infants at high risk and those at low risk for development severe ROP. It also underscores the importance of IGF-1 in the development of ROP and further suggests that replacement of IGF-1 to in utero levels could help to prevent the disease.

**IGF-1 in Phase II of ROP**

IGF-1 is also more directly critical to phase II of ROP and proliferative retinopathy. Retinal neovascularization is substantially reduced in transgenic mice expressing a GH receptor antagonist or normal mice with a somatostatin analogue that decreases GH release.60 This inhibition of neovascularization by GH is mediated through inhibition of IGF-1, since systemic administration of IGF-1 completely restores neovascularization in mice with decreased GH. The role of IGF-1 in the proliferative phase of ROP in mice was corroborated using an IGF-1 receptor antagonist, which suppresses retinal neovascularization without altering VEGF levels induced in mouse ROP.61
ω-3 PUFA levels will remain low. When the IGF-I level reaches a threshold at ~34 weeks gestation, with high VEGF and Epo levels in the vitreous, endothelial cell survival and proliferation driven by VEGF may proceed. Neovascularization ensues at the demarcation line, growing into the vitreous. (D) There are two ways to prevent the neovascular proliferation: (1) Inhibition of the neovascular phase. If elevated VEGF and Epo vitreal levels are suppressed and IGF-I is normalized and ω-3 PUFA is provided, normal retinal vessel growth can proceed. (2) Inhibition of the vessel loss phase. If IGF-I, Epo, and VEGF levels are increased to normal in utero levels in phase I, then vessel loss is suppressed, and the neovascular phase II will not occur. With normal vascular growth and blood flow, oxygen suppresses VEGF expression, and so it will no longer be overproduced.

ω-3 PUFAs are likely to be important in other retinopathies and AMD as well. Specifically, ω-3 PUFAs are often lacking in Western diets. A recent report based on AREDS 1 data showed a correlation between fish intake and decreased incidence of “wet” AMD suggesting a link between ω-3 PUFAs which are found in fish and neovascularization. Therefore, it seemed that these pathways were worth evaluating in the oxygen-induced retinopathy model system.

The major polyunsaturated fatty acids (PUFA) found in the retina are docosahexaenoic acid (DHA) a major ω-3 PUFA and arachidonic acid (AA) a major ω-6 PUFA, both primarily found in neural and vascular cell membrane phospholipids. Eicosapentaenoic acid (EPA), an ω-3 PUFA, is the precursor to DHA, and is found in the retinal vascular endothelium. Dietary sources of ω-3 and ω-6 PUFAs, released as free fatty acids by phospholipase A₂, contribute to a pool of substrates for enzymes that convert them to vaso- and immunoregulatory lipid mediators. These include bioactive intermediaries such as eicosanoids from AA, neuroprotecin from DHA, D series resolvins from DHA, and E series resolvins from EPA.

Given that ω-3 PUFAs are important structural elements in the retina, we evaluated whether retinal composition reflects differences in dietary intake of lipids. In the retinas of mice on a completely defined isocaloric diet enriched with 2% of total fatty acids from either ω-3 PUFAs (DHA and EPA) or ω-6 PUFA (AA), modeled after Japanese and Western diets, respectively, all the principal ω-3 PUFAs increased in the ω-3 PUFA enriched diet. There was also a decrease in retinal ω-6 PUFAs, resulting in a twofold increase in the total ω-3/ω-6 PUFA ratio. Thus, a 2% change in lipid dietary intake from ω-3 to ω-6 PUFAs caused a twofold change in retinal ω-3/ω-6 ratio in the retina, a remarkable shift.

In the ROP mouse model, we found that an increased retinal ω-3/ω-6 PUFA ratio had ~50% protective effect against patho-

\[\text{FIGURE 1. Schematic representation of IGF-I, VEGF, Epo, and } \omega-3 \text{ PUFAs}\]

\[\text{control of blood vessel development in ROP. (A) In utero, VEGF is found at the growing front of vessels. IGF-I is sufficient to allow vessel growth, Epo is normal, and } \omega-3 \text{ PUFAs are provided by the mother. (B) With premature birth and loss of the \textit{placenta}, IGF-I and } \omega-3 \text{ PUFAs levels fall, and the relative hyperoxia of the ex-}

\[\text{trauterine environment suppress VEGF and Epo. Vascular growth ceases. Both endothelial cell survival (Akt) and proliferation (mitogen-acti-}

\[\text{vated protein kinase) pathways are compromised. With low IGF-I and ce}

\[\text{ssation of vessel growth, a demarca-}

\[\text{tion line forms at the vascular}

\[\text{front. Supplemental oxygen in some}

\[\text{premature infants may further sup-}

\[\text{press VEGF and Epo, increasing inhi-

\[\text{bition of vessel growth. (C) As the}

\[\text{premature infant matures, the devel-}

\[\text{oping but nonvascularized retina be-

\[\text{comes hypoxic. VEGF and Epo in-}

\[\text{crease in retinal and vitreous. With}

\[\text{maturation, the IGF-I level slowly in-

\[\text{creases. Without an external source,}

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\[\text{vitreous. (D) There are two ways to prevent the neovascular proliferation: (1) Inhibition of the neovascular phase. If elevated VEGF and Epo vitreal levels are suppressed and IGF-I is normalized and } \omega-3 \text{ PUFA is provided, normal retinal vessel growth can proceed. (2) Inhibition of the vessel loss phase. If IGF-I, Epo, and VEGF levels are increased to normal in utero levels in phase I, then vessel loss is suppressed, and the neovascular phase II will not occur. With normal vascular growth and blood flow, oxygen suppresses VEGF expression, and so it will no longer be overproduced.} \]
logic neovascularization due to increased regrowth of vessels after vessel loss. The same protective effect against retinal neovascularization or phase II retinopathy was seen with treatment of mice in the ROP model with downstream mediators of omega-3 fatty acids, resolvins, or neuroprotectin. The protective action against retinal neovascularization of omega-3 PUFAs and their bioactive metabolites is mediated in part through suppression of TNF-alpha. This inflammatory cytokine plays an important role in the disease process, since independent suppression of TNF-alpha suppresses retinopathy. Macrophages/microglia are a critical component of retinal vascular growth and repair. The primary source of TNF-alpha is a subpopulation of CSF-1R+ macrophage/microglial cells that are in close proximity to blood vessels. The omega-6 PUFA (AA), through inflammatory bioactive metabolites, increases activated macrophage/microglia production of TNF-alpha, which is suppressed with omega-3 PUFAs (DHA, EPA) and their anti-inflammatory downstream mediators. The balance between omega-3 and omega-6 PUFAs in the retina will determine the production of TNF-alpha and of retinopathy.

In summary, omega-3 and omega-6 PUFAs significantly influence vascular growth and pathology. The omega-3 PUFAs, EPA and DHA, via bioactive metabolites reduce pathologic neovascularization through enhanced vessel regrowth after vascular loss and injury (enhanced recovery from phase I) as well as directly inhibiting phase II, neovascular proliferative retinopathy. Supplementation of omega-3 PUFA in premature infants is likely to be of benefit. These effects on angiogenesis are likely to be important not just for ROP but for DR and AMD as well as other diseases with abnormal angiogenesis. Omega-3 PUFA’s suppressive effect on retinopathy in the mouse eye is comparable in magnitude to anti-VEGF treatment and is likely to be additive to anti-VEGF therapy.

CONCLUSIONS

The pathways involved in ROP are likely to be important in other retinopathies, as well as in AMD and cancer angiogenesis. ROP lends itself to the discovery of the factors involved in retinopathy, since we can look at differences between the in utero environment and the extraterine environment of the prematurely born child—oxygen and oxygen-regulated factors such as VEGF and Epo as well as the oxygen-independent growth factors IGF-1 and omega-3 PUFAs. An important concept that emerges from ROP studies is that there are two different phases of retinopathy—vessel loss (phase I) and hypoxia-driven vascular proliferation (phase II). Phase II (retinal neovascularization) can be suppressed either directly or through suppression of phase I (vessel loss). Phase I and phase II of retinopathy must be approached differently, with the common goal of normalizing growth factors. However, to achieve that goal, some factors must be increased in phase I (VEGF and Epo and IGF-1). Some of these same factors must be suppressed if the disease is approached later in phase II when they are elevated (VEGF, Epo). Timing and degree of suppression or enhancement are critical (Fig. 1).

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