Blood in the Eye, Diabetes to Blame; You Give VEGF a Bad Name

Westosha Central High School SMART Team
Tyler Andrews, Trevor Millhouse, Connor Muff, Joyce Ripplinger, Elizabeth Van Kammen, Tasia Vassos, Morgan Williams
Advisor: Jonathan Kao
Mentor: Alison Huckepahler - Medical College of Wisconsin

Introduction

Diabetes is a disease characterized by high blood sugar. One of the most serious symptoms of diabetes is vision loss caused by glycosylation and damage to blood vessels. The eye contains some of the most metabolically active tissues in the body and the damage to the blood vessels depletes the eye of oxygen. Therefore, the body reacts quickly to restore oxygen through the growth of new blood vessels. This growth is signaled by a protein called Vascular Endothelial Growth Factor (VEGF).

Consider Diabetes

Glycosylation blocks small vessels in the eye and cause the retina to become a hypoxic environment. As oxygen levels drop, VEGF is produced in large quantities. Low concentrations of VEGF are shown in control patients. Patients with diabetic retinopathy (D), show higher levels of VEGF (Fig 3).

VEGF begins a signal cascade to grow new blood vessels in a process called angiogenesis. New blood vessels are weak and often end up leaking, causing fluid buildup behind the fovea and pushing it outwards. This damage, called diabetic retinopathy, distorts vision over time and can eventually lead to blindness. Patients may at first experience subtle blurriness, which worsens.

Fig 1. Pathway of Light Through the Eye
Light from the image travels through the front of the eye and eventually interacts with the retina. The macula is the region of the retina responsible for the high resolution, color vision.

Fig 2. The Anatomy of the Fovea
The fovea is a small spot at the back of the eye responsible for transmitting light information to the brain using two types of photoreceptor cells: cones and rods. Cones are responsible for color vision and white rods are responsible for night vision. Within the retina, most of our vision comes from an area called the macula and a small depression in the macula—the fovea—contains the highest concentration of cones. When an image is in focus, the light reflected from the image is focused on the fovea. The concave shape of the fovea is essential to developing clear images and determining the level of visual acuity.

See The Light

Fig 3. VEGF Concentrations Increase with Diabetic Retinopathy.

Molecular Pathway

Fig 4. Healthy Eye Compared to Eye with Diabetic Retinopathy
Healthy retina (A) has no leaks. Diabetic Retinopathy (D) is characterized by hemorrhages from newly formed blood vessels. Healthy fovea (C) is concave in shape. Convex fovea (D) results from fluid buildup.

Anatomy of VEGF-R

- Chains (Upper Image)
  - Two mirrored chains of VEGF-R
  - VEGF bound to the receptor
- Domains (Lower Image)
  - 5 extracellular domains shown
  - Domain 6, 7, and intracellular domains omitted due to size constraints
  - Ligand binds to D2-D3
  - Homotypic contacts in 4-7 increase ligand binding and are essential for receptor activation
  - Intracellular kinase domain responsible for signal transduction

Fig 5. A model of VEGF-R based on 5T89 pdb

Citations

2. Lucentis
3. Avastin
4. Eylea

Summary

The ultimate cause of diabetic retinopathy is angiogenesis which is signaled for by VEGF. By targeting angiogenesis, a new treatment option has become available whereas previous treatments were restricted to invasive and potentially dangerous procedures. Drugs that inhibit VEGF signaling have been shown to be an effective treatment for diabetic retinopathy because the reduction in vascular permeability prevents the fovea from becoming distorted. Thus the story of VEGF/VEGF-R has yielded therapeutic applications which are being used currently.

Treatment for Retinopathy

Non-protein based treatments for retinopathy are invasive and potentially dangerous. Laser coagulation involves cauterizing the leaking vessels with lasers. This treatment does not prevent future leaks and burns the retina, causing a partial loss of vision.

In contrast, treatments targeting VEGF/VEGF-R do not damage the retina and can prevent leaks from forming. Medications such as Ranibizumab (Lucentis), Aflibercept (Eylea), and Bevacizumab (Avastin) are drugs that treat treatments which inhibit VEGF signaling. These treatments stop new blood vessels from forming which prevents the resulting leaking fluid from the fovea.

Fig 7: Treatments of Retinopathy
Laser coagulation cauterizes leaking blood vessels leaving visible burn marks and permanently damaging the periphery of the retina.

Fig 8: Lucentis Inhibits VEGF
Lucentis inhibits vascular permeability triggered by VEGF. This figure shows the concentration-dependent inhibition of VEGF in guinea pigs. In this experiment guinea pigs were colored by blue dye to track vascular permeability with different concentrations of Ranibizumab.

Commonly used drugs in treating diabetic retinopathy with VEGF inhibition include Lucentis, Avastin, and Eylea. These drugs prevent VEGF from directly binding to VEGF-R. Lucentis is a VEGF Antibody which binds to VEGF. As a result the new Lucentis/VEGF complex does not fit in the receptor. Avastin is a smaller clone of a fragment of a VEGF antibody that has a similar function to Lucentis. Eylea is a decoy protein that is actually the binding D2-D3 of VEGF-R. As a result Lucentis is likely to bind to Eylea rather than VEGF-R. The end result of all three drugs is that VEGF-R does not continue the signal cascade and thus new blood vessels are not formed reducing vascular permeability.

Fig 9: Schematic Diagram of VEGF Targeting Drugs
Drugs bind VEGF preventing them from binding to VEGFR.