Neurovascular Development

Director: Sujata Rao PhD.
Department of Ophthalmic Research
Cole Eye Institute
9500 Euclid Avenue, i31
Office telephone: 216.636.3156
Fax: 216.445.3670
Email: raos7@ccf.org

Goals and projects

Background: The Rao lab is interested in understanding how neurons and vasculature pattern themselves and interact with each other during development as well as in disease

We use the mouse eye as our model system mainly because of the presence of multiple vascular networks and their close association with the neurons. This interface between the neuronal and vascular systems is important for normal function and disruption can lead to pathologies. The two vascular networks that we study are the fetal hyaloid vasculature shown in Fig 1(Top Panel) and the retinal vasculature shown in Fig1 (lower Panel). In mice, the hyaloid vasculature regresses post natally while in humans it occurs in the first trimester. Regression of the vasculature is important to achieve a clear optical axis and when the vasculature fails to regress it results in a condition called Persistent Hyperplastic Primary Vitreous (PHPV), which if left untreated can lead to blindness. Unlike the hyaloid vasculature which has an embryonic origin, the retinal vasculature develops postnatally through a process of angiogenesis and this is the vascular network that provides both trophic and other support to the neurons of the retina. The retinal vasculature is important due its role in many pathological conditions like Diabetic retinopathy and retinopathy of prematurity. Since the retinal vasculature develops postnatally after the retinal neurons have developed, we are interested in understanding how the neuron help pattern this vasculature and in the adults how this neurovascular interactions help to maintain the integrity of both vasculature as well as the retinal neurons. The long term goal of our laboratory is to set up functional assays that we can use to understand the consequences of disrupted patterning to visual function.

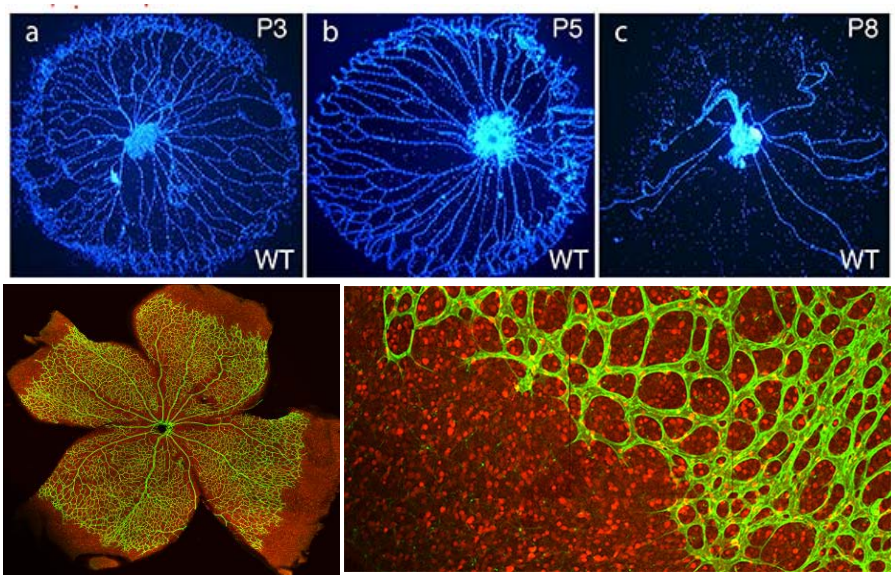

Fig1: Top Panel is a flat mount preparation of the hyaloid vessels at Post natal day (P3,P5 and P8). Note how the vessels are completely regressed by P8. The vasculature is visualized using a nuclear stain.
Lower panel is a low magnification whole mount preparation of the retina at P8 marked with isolectin (green) to visualize the retinal vasculature and Calretenin(red), one of the neuronal cell type of the retina. Right Panel is a higher magnification image to indicate the close association between the neuron and the vasculature. .

Outlined below are some of the projects that we are currently pursuing in the laboratory.

Project 1: Circadian regulation of neuronal and vascular development in the eye.

We have recently demonstrated that environmental light can regulate both neuronal and vascular patterning. Surprisingly, light has a direct effect on the development of the fetal eye and this effect is mediated through the atypical opsin called melanopsin. Light had the maximal effect during the embryonic day 16 and light deprivation at this stage of development result in disrupted neuronal and vascular patterning two weeks later. Based on this analysis we now are investigating why light is required at this stage of development when the animal is incapable of any image forming vision. We hypothesize that light exposure during development As retinal development is a coordinated process of timed cell division differentiation and growth, we hypothesize that early timing cues are important for this process. Not much is known about

circadian clocks and their function at this stage of eye development so we are investigating the role of some of the known genes which are important for generation and maintenance of circadian clock.

Project 2: Role of microglial wnts in neurovascular homeostasis and repair

The hyaloid vasculature and the retinal vasculature are closely associated with resident macrophages and microglial cells. We have previously shown that both macrophages and microglial cells can secrete a number of wnt ligands. We are interested in understanding if wnt ligands secreted from these resident macrophages and microglial cells have a functional role in adult animals for the maintenance of the retinal vasculature and neurons. Deregulated Wnt signaling has been implicated in pathological vascular growth in proliferative retinopathy as well as neuronal degeneration. We will also investigate if these microglial wnts have any function during repair from injuries. We will use mouse genetics along with molecular techniques to identify the Wnt ligands that play a role and if they aid in repair from injuries. The ultimate goal of this project is to define the functional role of Wnt ligands in maintenance and repair of neurons and vasculature

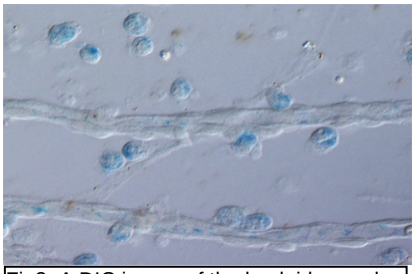

Fig2: A DIC image of the hyaloid vessels and macrophages (blue). These macrophages are LacZ positive as they are from a transgenic animal which is a reporter line for a wnt ligand.

Research & Innovation

Our research was the first analysis that demonstrated a link between environmental light and proper development of the eye. Since then we have demonstrated that light exposure in first trimester is a risk factor for the development of severe retinopathy. We can use the information that we gather from these projects to consider early interventions in treatment of retinopathy of prematurity where it could have an enormous benefit. Furthermore, our current research investigating the role of clock genes which are important in the generation and maintenance of circadian rhythms will uncover novel roles for these genes and will provide us new targets for treatments of proliferative retinopathy. Wnt signaling has been implicated in multiple diseases of the eye. By identifying if certain wnt ligands are involved in maintenance versus repairs from injuries we can begin to target the wnt pathway for specific treatments as opposed to generally blocking the entire pathway which can result in adverse effects.

Lab staff members:

- Sujata Rao, PhD, *Director*
- Meenal Shukla, *Postdoctoral Fellow*
- Onkar Sawant, *Postdoctoral Fellow*