Effect of Neuron-Glial Antigen 2 on Retinal Microvascular Remodeling in a Murine Model of Chronic Whole Body Hypoxia

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Introduction: Diabetic retinopathy is the leading cause of blindness in working age adults and currently afflicts an estimated 101 million people globally. The image to the far right shows the perspective of a diabetic retinopathy patient. Current treatment options do not target the underlying mechanism of the condition, nor do they prevent the disease. An early marker of this disease is the loss of pericytes, which are cells that wrap around microvessels in the retina. We studied the role of pericytes in retinal microvascular remodeling, a process in which blood vessels in the retina undergo structural changes. Neuron-glial antigen 2 (NG2) is one protein expressed by pericytes that allows them to attach to blood vessels and is involved in microvascular remodeling in other tissues.

Hypothesis: Knocked down NG2 expression levels in the retina decrease pericyte recruitment during microvascular remodeling in response to hypoxia.

Methodology: Hypoxia (low oxygen) stimulates microvascular remodeling. Exposing NG2 transgenic mice to hypoxia for 1-3 weeks allowed us to determine if decreased NG2 expression levels in the retina would decrease pericyte recruitment and/or function during microvascular remodeling. Below on the left is a harvested retina of an NG2 knockout mouse, and on the right in higher magnification, pericytes are shown in red wrapping around the blood vessels labeled in blue.

There is a dropout of pericytes, cells that wrap around blood vessels and regulate leakage, in diabetic retinopathy, which causes blindness. We investigated the effect of different expression levels of neural-glial antigen 2, a protein expressed by pericytes, in response to low oxygen conditions which stimulate blood vessels to remodel.

Quality. Students were trained practicing retinal harvest for past two years. Trials were conducted in accordance with Institutional Animal Care and Use Committee at UVA.

Potential impact. The development of a pericyte-deficient model will aid in the process of developing a stem cell therapy as a potential cure for diabetic retinopathy.

Advance in Knowledge. NG2 knockout mice serve as a pericyte-deficient model for studying diseases like diabetic retinopathy.

Innovation. This is the first time anyone has observed and quantified the microvascular remodeling response to hypoxia in NG2 transgenic mice.

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Results:
- Pericyte coverage was significantly lower in NG2 knockout (KO) mice compared to wild type (WT) controls as shown on the right.
- NG2 knockout mice trend toward decreased pericyte coverage with continued hypoxia.
- Vessel loop density was significantly increased in NG2 knockout mice over wild type controls.

Conclusions:
- NG2 knockout mice have fewer pericytes in the retina compared to wild type mice.
- Quiescent microvascular structure depends on NG2 expression.

Future Work:
Inject mouse adipose-derived stem cells into NG2 knockout pericyte-deficient mouse model. Evaluate the potential for stem cells to differentiate into pericytes and replenish depleted pericyte population, which could be used as a treatment in diabetic retinopathy.

References: