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BLINDNESS FOUNDATION

VEGF AND COLLAGEN XVIII/ENDOSTATIN IN MACULAR DEGENERATION AND
CHOROIDAL ANGIOGENESIS

This research project asks three questions about what is required for the pigmented cell layer behind the retina to support visual functions in the adult. One question is whether production of a small protein, VEGF, by the pigmented cells is essential for the long-term survival and function of the light sensing cells within the retina and the blood vessels behind the retina. The second question is whether the production of VEGF by the pigmented cells is essential for long-term function of the pigmented cell layer itself. The third question is whether production by the pigmented cells of a connective tissue protein, called collagen XVIII/endostatin, is required for long-term visual function. This protein is a component of thin membranes to which the retinal pigmented cells and blood vessel lining cells are attached, allowing the cells to be organized into thin sheets.

The first two questions are based on recent studies in which it was demonstrated that lack of VEGF production by the pigmented cells during eye development in mice results in blindness after birth and severe defects both within the retina and in the blood vessel layer behind the retina. Given the increasing use of drugs to block VEGF activity in patients with the wet form of age-related macular degeneration, it is essential to determine whether continued production of VEGF plays an important role in the adult eye. This is a particularly significant question to address since there already is some evidence that continued production of VEGF by the pigmented cells in the adult eye may be important for long-term maintenance of visual functions. The third question is based on the finding that patients with inherited defects in collagen XVIII/endostatin lose their eyesight early in life as a result of degenerative changes in the retina. Furthermore, eyes from patients with age-related macular degeneration appear to contain less of this collagen than control eyes of similar age. Finally, mice lacking this collagen exhibit age-related loss of vision and degenerative retinal changes that are similar to those seen in human eyes at early stages of dry macular degeneration.

Thus, the project addresses problems that are at the center of the mission of The Foundation Fighting Blindness. The research does not directly test a new therapy, but the results are key to assessing long-term benefits and risks of current anti-VEGF therapies and will provide a basis for development of new clinical interventions. The proposed experiments use innovative approaches in mice to inactivate the genes that code for VEGF, collagen XVIII/endostatin and VEGF-binding proteins on the surface of retinal pigment cells. The approaches will allow the investigators to inactivate these genes only in the pigment cells and not in other cell types, and to control the timing of the inactivation. In this way, mice can be allowed to develop normally, and gene inactivation can be induced at different stages after birth. Studies of the consequences of such inactivation for eye structure and function will be studied in young as well as adult animals. For example, this approach will make it possible to determine in older mice what the consequences are when VEGF levels in the pigment cells are reduced and what the time course of the effects may be. Furthermore, it will be possible to find out whether eye defects caused by lack of collagen XVIII/endostatin in the pigment cell layer can be prevented by the presence of fragments of this collagen in the circulation. These and other outcomes of the study will provide information about molecules and processes that will need to be monitored in patients with macular degeneration. In addition, mouse models generated by the study will also serve as animal models for testing specific therapeutic interventions in future research.