Researchers report a critical role for the complement system in early macular degeneration

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In a study published on line this week in the journal *Human Molecular Genetics*, Drs. Donita Garland, Rosario Fernandez-Godino, and Eric Pierce of the Ocular Genomics Institute at the Massachusetts Eye and Ear, Harvard Medical School, along with their colleagues, reported the unexpected finding that in mice genetically engineered to have an inherited form of macular degeneration, turning off the animals' complement system, a part of the immune system, prevented the disease.

Macular degenerations, which occur in several forms, are important causes of vision loss. Juvenile or early-onset macular degeneration includes several inherited disorders that can affect children and young adults. In contrast, age-related macular degeneration (AMD) affects older individuals; it is the leading cause of blindness for individuals over 65 years of age in developed countries, and its prevalence is increasing worldwide. Both inherited macular degeneration and AMD lead to the loss of central vision. While therapies exist for some forms of late AMD, and nutritional supplements can slow the progression of early AMD for some patients, improved therapies to prevent vision loss from these disorders are needed.

This is the first report to demonstrate a role for the complement system in an inherited macular degeneration. Previous genetic studies have shown that variants in the genes that encode several complement system components are important risk factors for AMD. Based on this, drugs

that inhibit specific complement system activities are being tested clinically as treatments for AMD. However, it is not entirely clear how alterations in complement system components lead to AMD.

The new results reported suggest that complement activation by abnormalities in the extracellular matrix or the scaffold secreted by retinal cells plays an important role in the formation of basal deposits, one of the earliest stages of macular degeneration. Basal deposits are precursors of drusen, which appear as spots in the retina on clinical examination, and are accumulations of proteins and lipids outside the retinal cells; their presence is the first clinical indication of a risk of developing macular degeneration.

The findings are important because they suggest that inherited macular degenerations share common features with AMD, such as a complement-mediated response to abnormal extracellular matrix. The results also suggest that alterations in the activity of the complement system are involved in the earliest stages of disease pathogenesis. This finding has important implications for the use of drugs that modulate the complement system for treating macular degenerations.

For these studies, the investigators used a mouse model of the inherited macular dystrophy Doyne Honeycomb Retinal Dystrophy/Malattia Leventinese (DHRD/ML) which is caused by the p.Arg345Trp mutation in the EFEMP1 gene. This mutation leads to extensive drusen in patients with DHRD/ML, and the gene targeted Efemp1R345W/R345W mice develop extensive basal deposits.

As a first step in their studies, Dr. Garland and colleagues used proteomic techniques to identify the proteins present in the basal deposits of the Efemp1R345W/R345W mice. Like they do in people, these deposits form between the retinal pigment epithelial cells and their basement membrane, which is called Bruch's membrane and is

composed of extracellular matrix. These studies showed that the basal deposits are composed of normal extracellular matrix components that are present in abnormal amounts. This is logical because the EFEMP1 protein is secreted by retinal cells and is thought to be required for maturation of elastin fibers, which are part of Bruch's membrane.

The proteomic analyses also suggest that the altered extracellular matrix stimulates a local immune response, including activation of the complement system. The complement system is part of our innate immune system, and helps fend off infections, but under certain circumstances can also lead to cell and tissue damage.

More information: hmg.oxfordjournals.org/cgi/con … ZIXSQ182&keytype=ref

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