Genetics

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Goals and Projects

The Function of TULP1 in Photoreceptor Cells of the Retina.

Retinitis pigmentosa (RP) incorporates a large number of inherited retinal disorders characterized by photoreceptor degeneration. RP is genetically and phenotypically heterogeneous, affecting over 1 million individuals worldwide. Previously, we identified mutations in a gene called *TULP1* to underlie an early-onset and severe form of autosomal recessive RP. Tulp1 is a protein exclusive to photoreceptor cells and there is evidence from the murine model lacking Tulp1 that it plays a role in intracellular protein movement in multiple compartments of the photoreceptor. Our data indicate that in *tulp1-/-* mice, prior to photoreceptor degeneration, rod and cone opsins are mislocalized, and rhodopsin-bearing extracellular vesicles accumulate around the inner segment (IS), indicating that Tulp1 is necessary for the transport of proteins to the outer segment (OS). These mice also have a synaptic malformation that precedes photoreceptor degeneration and most likely interferes with the proper development of post-receptoral neurons. The absence of Tulp1 results in abnormalities that affect structure and function in multiple retinal sites, as well as causing distinct abnormalities in separate photoreceptor compartments. This suggests that it either performs a general role throughout the photoreceptor or participates in multiple distinct pathways.

Our central hypothesis is that Tulp1 is a component of the molecular machinery involved in the vesicular movement of proteins in two photoreceptor cell compartments. Our long-term objectives are to understand the physiological function of TULP1 and the pathogenic mechanism responsible for retinal degeneration associated with TULP1 mutations. Current studies are designed to identify Tulp1 interacting partners by proteomic analysis, comparing IS-specific to synaptic-specific interactomes. Molecular dissections of the IS and synapse lacking Tulp1 and expressing mutant forms of TULP1 that cause RP will be conducted to probe for structural or spatial disturbances.

Results from this project will position Tulp1 in a functional context and define its mechanism of action. It will provide insight into the functional organization of photoreceptor protein transport pathways, as well as insight into the perturbation of retinal function associated with *TULP1* mutations. Finally, this project will significantly impact an important aspect of photoreceptor biology relevant to human retinal disease.

Pharmacogenetics of Neovascular Age-Related Macular Degeneration.

Age-related macular degeneration (AMD) is the most common cause of irreversible, severe vision loss in the United States, affecting the quality of life for millions of elderly individuals. Approximately 90% of this vision loss is attributable to the neovascular form of AMD, characterized by the invasion of blood vessels into the subretinal space. The treatment of neovascular AMD has been dramatically improved by the development of the anti-vascular endothelial growth factor (VEGF) therapies, bevacizumab (Avastin) and ranibizumab (Lucentis). The Comparison of AMD Treatments Trials (CATT) is a multi-centered randomized clinical trial that evaluated the relative safety and efficacy of Avastin and Lucentis. Results showed that intravitreal injection of Avastin was equivalent to Lucentis in improving visual acuity (VA) of patients with neovascular AMD when treatment was administered either monthly or as needed. However, despite this remarkable clinical effect, there was considerable individual variation in required dosing and treatment response.

AMD is a highly complex disease with a strong genetic component. The contribution of genetics to AMD has been well-documented through reports of familial aggregation, concordant phenotypes in twins, and a higher risk of disease in first-degree relatives of affected individuals. In the past several years, significant progress has been made in identifying genetic loci that contribute to disease development and progression. Several discoveries of AMD-associated single nucleotide polymorphisms (SNPs) in multiple genes have been reported. Remarkably, currently identified variants are estimated to account for 50-75% of the genetic contribution to disease risk. Although the risk associated with these SNPs is well-characterized, the influence

of these genetic variants on response to therapy is unknown. The challenge at hand is to correlate AMD-associated genotypes with response to treatment.   Given the recent rapid progression in AMD genetics research and advancement in clinical treatment, we plan to determine the cause of the observed heterogeneity in clinical response by analyzing the exome of each of the CATT participants and correlate these findings with response to therapy. A comprehensive analysis of genotypic associations with visual and anatomical outcomes is ongoing.

The investigation into potential relationships between AMD genotypes with response to anti-VEGF therapy is timely, innovative and should generate new insights toward offering personalized treatment based on a patient's underlying genetic background. The potential impact of this study is significant because we anticipate that future patients with AMD will benefit from the knowledge gained regarding the relative efficacy of the anti-VEGF agents within specific genotypes.

Genetic Analysis of Inherited Retinal Diseases

One of the main objectives of our lab is to identify and analyze genes responsible for inherited retinal degenerations such as retinitis pigmentosa, Leber congenital amaurosis and juvenile and age-related forms of macular degeneration. These objectives are met through a candidate gene approach involving the collection of DNA samples from patients with inherited retinal diseases, the selection of candidate genes based on a well-established set of criteria and large-scale mutation screening of the DNA samples using high-throughput, semi-automated molecular genetic techniques.

A separate project related to the study of inherited retinal diseases involves the retinal degeneration pathophysiology facility that supports the collection of human tissue from donors with known eye diseases through contacts with the Eye Bank Association of America. Postmortem eye tissues offer a unique opportunity to study the relationship between genotype and disease pathogenesis. In recent years, molecular genetic studies have taken on an increasing role in the study of inherited retinal diseases. There continues to be a paucity of correlation between underlying molecular etiology and clinical and histopathological data from the same individual. Such information obtained from combined analyses becomes even more valuable as it provides a better understanding of the disease process and its clinical manifestations. Projects are ongoing where retinal histopathological changes in the eyes of donors from families with inherited retinal diseases are correlated with the identified genotype. Microscopy, DNA analysis, immunocytochemistry and image analysis are all performed.

Lab Staff members
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